Graham D. Ogg

A Practical Guide to Quality Management in Clinical Trial Research

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Preface

The contents of this book are personal observations and ideas gleaned from many sources too numerous to name. I felt that it would be useful to have a compendium of ideas that appeared to work for us and to give others the benefit of this experience, hopefully so that they can get the same results without the pain of trial and error. Much depends on individual circumstances and company organization, but I believe many of these ideas can be generalized to any small organization.

Specific references to the Good Practice (GxPs) regulations, such as Good Laboratory Practice, Good Clinical Practice, Good Manufacturing Practice, etc., are kept to the absolute minimum in this book as it would defeat the purpose of trying to simplify their implementation. In some cases, specific areas have been missed, but it is not my intention to provide full coverage of the regulations, only to provide some ideas and examples in order to facilitate setting up a quality system. Therefore, this book must not be considered in isolation from the current regulatory framework, and any specific requirements must always be met. It is the purpose of this book to provide the reader with some ideas and examples within an easy-to-read book that they can use to meet their desired regulatory requirements via simple methods. This book should also arm the reader with some of the tools and concepts that can be used to go beyond regulatory compliance and into the realms of business quality improvement.

It should be borne in mind that those who are either "hands-on" involved in research quality systems or are wishing to implement such a system within their own organization are the target audience for this book. Principally, these will be clinicians involved in running clinical trials and those providing laboratory support to them, such as university research departments and hospital-based service departments. This book may also prove useful to clinical research associates (CRAs) and other pharmaceutical industry personnel who wish to have some insight into how the contract research organization (CRO) works within the regulatory framework.

Others who may benefit include quality assurance (QA) personnel who have at least some experience in the field. It is not intended as a manual of "what to do" for those just entering our noble profession, at least, at the start of their career.

The ideas and thoughts presented in this book do not necessarily reflect the way things are done in my organization, nor are they necessarily policies adopted by the company. These are purely personal and no causal relationship should be attributable.

Graham D. Ogg, M.Sc, C.Chem., MRSC, MIQA, FRQA

Author

Graham D. Ogg has been involved in quality assurance within contract clinical research for the past 17 years and has been an active member of British Association of Research Quality Assurance (BARQA) for most of that time. He began his career as a trainee technician in the chemistry department at the University of Dundee, Scotland, where he was given "day release" at local colleges to further his education in analytical chemistry. Finally, with an Ordinary National Certificate (ONC), Higher National Certificate (HNC), and Licentiateship of the Royal Society of Chemistry (LRSC) awarded, he moved to the department of pharmacology and therapeutics in a promoted technical post. There he worked in the field of trace drug analysis for pharmacokinetic studies and was introduced to quality principles and how to put them into practice. He registered for a part-time master's degree (M.Sc.) program in research, which was awarded four years later while he was also doing a distance learning course for the Institute of Quality Assurance's A3 examination in quality management.

A spin-out company (contract clinical research) from the department was established in 1982, and in 1987 he was asked to assume responsibility for the quality assurance function (which had become a necessity in order to get Good Laboratory Practice (GLP) registration). Readily, he said yes. It was also at this point that microcomputers and programmable calculators started to appear on desks, not just in the computing centers or math departments, and the author had a keen interest in these new tools. From this point onward, the involvement with laboratory and clinical QA and business advancement, and now electronic records has been at the forefront of his life. Acting as secretary to the local BARQA forum covering Scotland and Northern England, he has succeeded in maintaining an active chapter, setting meetings with topical themes which are much appreciated by the attendees. For such services to the association he was elected a Fellow and became a recipient of an association award in 2002.

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chapter 1

In the Beginning There was GLP

This book begins by making the assumption that readers either have a laboratory function within their own organization or have an external facility. It is the laboratory-based quality system that will be translated into the area of Phase 1 Good Clinical Practice (GCP). Nearly all the books I have read on quality management within the regulated environment start off with the history and origins of Good Laboratory Practice (GLP). This book makes the assertion that GLP is here and will not consider its origins at all, which hopefully will be a refreshing change for the reader.

If you work in any type of laboratory then you probably work to GLP. I suppose the antithesis is Bad Laboratory Practice (BLP), but nobody considers what they are doing is BLP.

So, by inference, we all must be carrying out GLP! As you will have already guessed, this is not the case, especially when you consider the U.S. Food and Drug Administration (FDA) regulations, the Organization for Economic Cooperation and Development (OECD) guidelines, and the United Kingdom Statutory Instrument. When we met these concepts for the first time and started writing our standard operating procedures (SOPs) in the mid-1980s, I remember an analyst who, being affected by the introduction, joked about the acronym GLP, redefining it as "Great Long Plaster." "Many a true word is spoken in jest" is the saying that comes to mind. The setting up of a GLP environment where none existed before is a very daunting task and getting the staff to write down what they do for every task is a very difficult and time consuming exercise. (We estimated this setting up and documentation stage to account for around 25 to 33% of the working time spent.)

At this point, it may be helpful if I briefly describe my organization — at least as it was back then. The company was set up by my university's department of pharmacology and therapeutics to provide contract clinical research for the pharmaceutical industry, with special emphasis on Phase-I pharmacokinetic studies. This was accomplished by utilizing some spare

space within the department, which was based in a hospital and medical school. The company consisted of three offices, an eight-bed ward, and an analytical facility to carry out the pharmacokinetic studies, along with medical (two), nursing (six), and scientific staff (two). The primary reason for this commercial enterprise was to provide a revenue stream for "blue sky" research within the department and also to support studentships and other worthwhile causes within the university as a whole. This also freed up academic staff to concentrate on their research interests and teaching rather than continually being asked to carry out studies for the pharmaceutical industry. The idea was novel at the time and to some extent still is today, especially regarding the distribution of the company's profits. Since then, the company has now expanded to 36 beds and 50 staff, nursing, medical, analytical, data management, administration and, of course, QA. These facilities are still contained within the medical school but now in a purpose-built building. The ethos of the company has never changed from its initial roots.

Trying to convince the laboratory staff that GLP was a good idea and was going to be well worth the effort was extremely difficult, and without a totally committed backing by management, it would have been impossible. (It must be remembered that as a clinical contract research organization [CCRO], there is no legal requirement for GLP.) As nearly all the staff (except for the managing director) had come from an academic background in universities or the U.K.'s National Health Service (NHS), foundation activities such as documenting "how things are to be done," and regular servicing and calibration of equipment was perceived as a "waste of good research time." If they wasted time on GLP, the thinking was, then the opposition would get ahead of them, because they did not have this administrative burden. I think the killer blow for them was when the sponsors wanted GLP or else there would be no contract; they had to bite the bullet.

Management at this time also needed something to comfort them financially; it was the possibility of obtaining some unexpected contracts from the preclinical phase of drug development, as well. With some preclinical work supplied to us (in retrospect, I suppose with a great deal of trust by the sponsor), we took our first steps on the "yellow brick road" to becoming a registered GLP laboratory. As we had been working to the GLP guidelines, anyway, this was the icing on the cake as far as we were concerned. Obtaining GLP registration for a mainly clinical laboratory (even if only one preclinical study was carried out, registration was mandatory) was far easier then (1988); today, such a registration would be much more difficult to achieve.

Staff Perception of QA

One important aspect of being part of QA is how you are perceived in your role as inspector by the inspected staff. When staff are inspected or, rather, their activities, they can become very nervous, and errors can occur more frequently. At the early stages of QA's existence in any organization, they are seen as "policemen" or "ferrets" always trying to find mistakes, reporting

to management who would then apportion blame. This is one aspect of staff perception that must be changed, because it is not true or, at least, should not be true. QA exists to ensure things are done correctly, efficiently, and in a standardized way to prevent errors from happening in the first place. Such negative attitudes may be modified by meeting and talking to new staff during their induction period. Describing what your function is, what you do, and why you do it can help change such erroneous perceptions. Another persuasive thing you can do is to record the good as well as the bad in a report of an inspection. You must try to strike a balance if at all possible, and give praise when it is due. If an error is noted by the production staff, it is imperative that they come forward and admit it in order to correct it rather than cover it up.

It is my opinion that QA reports should be confidential within the organization; sponsors' QA must not be permitted to see these documents. The main reason for this confidentiality is so that the staff can be forthright with their comments about the QA findings, with the assurance that only internal staff will see them. If, on the other hand, these documents were open to external inspection, then the comments may well be guarded and not so forthright, and, therefore, the QA may not be given a complete answer or, even worse, items may be hidden. You must decide for yourself what your attitude will be toward replies to QA findings.

QA must assist in determining the causes of any issues noted in QA reports and to judge whether it is a simple case of human error, a chance happening, or a deviation from the normal procedures. Such an attitude tends to go against human nature because the first thing you want to do is to blame someone else for the problem. Such attitudes are neither helpful nor productive. Fighting against human nature is always going to be an uphill struggle, getting this message across to all levels of personnel — especially the production line management, who are probably not so enlightened as yourself. In order for this culture change to pervade an organization, there has to be management buy-in from the start or else there is little hope. As a QA professional, you must always try to engender a feeling of trust between yourself and all levels of production staff, from the cleaner to the chief executive officer (CEO) or managing director (MD). This trust must be fostered at every available opportunity and should be considered as a continual cyclical process.

Qualities of a Quality Professional

This topic may seem a little strange when this book is for professionals with a QA interest, but it is still useful to see a distillation of the qualities that you may not even realize you had.

In my role as meetings' organizer for the local British Association of Research Quality Assurance (BARQA) chapter, I have been fortunate in meeting and listening to many presentations by "new starts" in QA. These meetings are designed to provide a venue in which these recruits can practice

their public speaking in a small, friendly environment. They are encouraged to present their observations of the profession and any difficulties they have faced but not necessarily solved. These sessions provide an avenue for such personnel to discuss their problems and try to obtain some solutions from the more seasoned QA personnel in the audience.

There is consistency in what each of them say and these, I feel, can be used to assist in the recruitment of personnel into the "art" of QA. The successful QA auditor is required to have the following qualities:

- Have skin like an elephant. (If anything goes wrong, it is QA's fault.)
- Be a dove of peace (compromise).
- Have god-like qualities (omnipotent, omnipresent).
- Show moral superiority.
- Develop and rely on interpersonal skills.
- The ability to communicate on the same level as those being inspected.
- The ability to communicate throughout the audit or inspection.
- Ability to separate the issues from the detail.
- Protect time in order to keep up to date with regulatory requirements.

Training the Quality Professional

Normally, in the small CRO, there will be perhaps only one person to look after the quality requirements of your operations and to guide management. What qualifications should they have initially? Whether they are primarily for GLP or GCP compliance, life-science- or pure-science-based qualifications are to be preferred. An enquiring mind along with attention to detail, both normally found in science graduates, are required. The main problem here is that in most science degree courses, the study of quality principles is not required. In my opinion, this is a great shortcoming of our university system because those who graduate and stay in science will most likely have to work in a quality-related environment within the industry. However, as you are probably aware, having a degree or other qualification in science is only the base requirement, and training in quality is still necessary. In a one-person QA unit, being trained by another person will not be possible. What is the best way? I suggest some possible solutions below:

- General quality management principles can be studied by correspondence course, such as the Institute of Quality Assurance (IQA) (or equivalent organizations) examinations. The IQA is primarily geared towards engineering and manufacturing, but it does provide some useful tools for quality management programs.
- Though conventional chalk–talk teaching is not common, such courses are available via BARQA and other organizations such as the Society of Quality Assurance in the U.S., and these provide a comprehensive suite of courses for the QA professional. Some of these courses even lead to degrees in research quality assurance. One of

the best things about these professional development courses is that they cover both the regulations and the ways of applying that knowledge in a practical fashion. The course instructors are experienced quality practitioners in their own right and pass on their everyday practical skills.

- There are commercial offerings by consultants and training companies, but these can be very expensive especially for a smaller organization or department and tend to concentrate on the regulations and their interpretation. This sort of training is perfect for keeping you up to date and allowing you to produce your own interpretations and compliance solutions. I suggest that this is not really for those who require basic training, but it can be really useful for the more experienced auditors who wish to hone their skills.
- One of the best ways to learn and obtain advice is to have a buddy system in place. This is where someone in an organization similar to your own agrees to assist someone in your organization. This can consist of regular meetings where both parties can discuss common problems and solutions or, more importantly, contact one another for advice on a problem or interpretation of GxP (all forms of Good Practice regulations) requirements. The local chapters of professional associations can provide the framework for such a system to be set up, if it has not been done already. Initial contact details can be obtained from the association's member directory; this directory is updated and sent to members annually (e.g., BARQA, SQA).

Regulatory Requirements

GLP was a business requirement placed on us by our clinical sponsors who insisted that we be GLP-registered. First contact with sponsor auditors normally comes from their QA department to your organization's QA department. This is helpful as both parties understand each other's requirements and can get the audit underway very quickly and efficiently. The part that really annoyed me as a QA professional was the fact that here were the big pharmaceutical companies and experienced QA auditors coming to insist that any pharmacokinetic work we did for them must be done to GLP and that we must also be part of the U.K. GLP compliance monitoring program if we wanted their work! There must be a lesson for large group QA departments somewhere in this, in that they should look more closely at their requirements and see if the conditions that they specify are really needed. It appears that even today, when QA auditors from these companies perform compliance audits of smaller organizations, they always appear to be much stricter than they would within their own organizations. I still cannot work out why this should be so; perhaps it is a hangover from the days where every aspect of the drug development process was carried out in-house. As preclinical testing and, consequently, GLP already existed, clinical samples were analyzed in the same laboratory.

Another irritation for me is the fact that sponsors' QA insist on carrying out compliance audits of contract facilities even though this is implicit by the existence of a government-supplied certificate of compliance (at least in the U.K.). It is not so much that I mind being inspected by external auditors, it's that they tend to arrive like buses, all clustered together, within a short time frame. Such activity makes it very difficult to get on with your everyday tasks. The reason for these inspections is the implicit requirement in EU legislation that they should do so. Why should there be such a requirement? Perhaps, it is because they cannot delegate their responsibility for GLP compliance when the contract facility is acting as principal investigator (OECD Principles of GLP, Guidelines, Section 2.2.7). However, that is not a requirement as far as I am aware, where the contract facility has the complete study and supplies the study director (OECD, Section 2.2.6). Any such audits, however, are good for the contract facility because they provide a valuable set of "new eyes" over your quality system and can reveal issues that you may not even have considered before. The down side is that these audits tie up personnel for a considerable time, and if several sponsors all want this facility, it mounts up to a considerable amount of lost productivity and, consequently, lost profit for the organization (although I am sure your finance department would be able to recover these costs in any future quotes).

Due to the high throughput of new chemical entities (NCEs) by pharmaceutical companies, the number of specialist CCROs has increased exponentially. This also applies to university departments carrying out clinical research for the industry for a research grant. Such research is seen as very valuable within the industry when carried out by "opinion leaders" (regular publishers of specific topics in medical journals, e.g., hypertension, cardiology, etc.). These latter organizations do not really provide a robust quality service, at least as far as GxP would define and so are most likely to benefit from the ideas presented in this book. It is my opinion, and that of my colleagues in other organizations, that once you have tried the "true way," then you do not want to work in any other fashion. These organizations tend to be those that do not have any preclinical facilities and do not really see why they should be involved in preclinical work at all. These organizations seek regulatory GLP approval but the authorities, at least in the U.K., are resisting these requests. I do not see the problem myself as the members of the U.K. GLP compliance program have to pay a lot for the privilege, and I was always led to believe that it was self-financing, hence the large annual cost of membership for a biennial inspection. However, I suppose we must consider the reasons why GLP was introduced in the first place (trying to prevent fraudulent claims of efficacy for a product). We then have the legal aspects of the compliance regulations and, as with all things legal, you do not seem to be able to extend the boundaries easily, so perhaps this is another reason.

From my recent experience, it seems that the sponsor requirement to have GLP accreditation for your clinical laboratory functions such as biochemistry and pharmacokinetic analyses does not appear to be such a problem today. This suggests that QA within the large pharmaceutical companies

seem to have finally realized (it has only taken them about 10 years to catch on!) that clinical laboratories cannot be part of the GLP compliance program unless they do preclinical analysis as well, which most are not equipped to do, nor do they wish to.

This still does not help with getting your organization accredited by a third party, though, and accreditation is seen as a real requirement for nearly all clinical contract organizations. What is the solution, then, to this dilemma? There are a few national accreditation schemes available such as the United Kingdom Accreditation Service (UKAS), National Voluntary Laboratory Accreditation Program (NVLAP, U.S.), Clinical Pathology Association (CPA) accreditation, National Accrediting Agency for Clinical Laboratory Sciences (NAACLS, U.S.), and also the International Organization for Standardization (ISO) 17025 registration. The first two of these, UKAS and NVLAP, are excellent if you have standardized methods and traceable standards but, normally, this is not the case with analytical research laboratories. CPA or NAACLS accreditation seems promising but falls short of GLP in several important areas. CPA also requires the services of clinical pathologists, something that non-hospital-based and small laboratories do not have and probably cannot afford. That leaves us with the most recent standard, ISO 17025. This is an excellent tool to use as the basis for your laboratory quality system. The rejection criteria presented above may be very simplistic, but I feel that these are the main features that stop such standards being adopted within the CRO environment. It is the difference in the ISO's approach to laboratory quality as opposed to the GLP's that provides the better standard to work to. This is because it extends and encompasses standardized, traceable results, which are really absent in GLP. The specifics of GLP can be bolted onto to this quality management system, and an external consultant can certify these to provide the third-party certification. If you choose a consultant wisely, especially one with experience in GxP auditing (best achieved by recommendation), you can get the best of both worlds. Certification to this standard along with a compliance audit from the sponsors' QA department should allow you to get the work, at least from a quality perspective. I suppose it really depends on your external compliance auditors whether or not they will accept such accreditation, I can see no reason why they should not but, then again, I have no real life experience of this.

As I stated before, I feel that, as a quality standard, the ISO standard is better than GLP. GLP does not require you to use traceable standards, e.g., the laboratory down the road may give plasma concentrations for a drug that are completely different from yours in absolute terms, but both analyses are GLP compliant. However, these results would not be ISO compliant. GLP is a system where you provide the goal posts; ISO says use the standard goal posts.

So, from the scientific point of view, I personally prefer to go with the ISO standard in preference to GLP, because it is better quality standard. If, however, you are tempted to go down the ISO 17025 registration road without having the GLP specifics, you may have problems in obtaining work, so

beware. As I have no experience of this type of registration, I have no idea how the pharmaceutical industry views such a registration of the CROs. The recent U.K. and European GCP legislation may eventually give us what we need, that is, a governmental third party inspection of all clinical and laboratory support facilities based on GLP standards. At the time of writing, the situation is still fluid in the U.K. regarding the extent and nature of clinical laboratory inspections carried out under a regulatory GCP inspection. The implications of the U.K. Statutory Instrument and the expectation among auditors are that the laboratory facilities should be up to GLP standards. So if you aim for and meet that standard, you should not have any problems.

One major complication that, I think, affects all QA personnel is the misinterpretation by others of what QA is all about! This seems to be caused by the mindset that quality control (QC) and QA mean the same thing. From the research QA professionals' perspective, these are entirely different species. QA is the process of assuring that quality control is taking place and is being used effectively. The productive use of quality systems is probably the most important business aspect of QA, and this will be expanded in later chapters. Apart from QC, another contentious issue among scientific staff is that of a QA professional commenting on their "science" rather than sticking to the compliance issues. In my mind, there is not an issue here. If QA is providing a proper value-added service to an organization, and there is a problem with the "science," then they must comment on it and also suggest a correction, if applicable.

A Workable Quality System (Pseudo-GLP)

Let us assume that we cannot get GLP registration as we have no preclinical work. So we must pick a standard to work to; obviously, this must be GLP, so we will work with this system first.

I believe that the following two phrases must be kept at the forefront of any system that is to be implemented successfully, which means everyone buys into the ideals you are putting forward. My tenet, for Good Practice compliance is, "Common sense put into common practice." The other to keep in mind is "Keep it simple (KIS)."

If we are always mindful of these two principles, we will have a system that works for both business and regulatory compliance. This is the goal of all companies who want to compete successfully in the contract world. However, QA is in the middle tier. It has to pull one way with management that wants to save costs by increasing quality, whereas the regulators are pulling the other way with compliance only. Both objectives, at first sight, appear to be excellent ideals to work toward. QA's problem, however, is that the monitoring authority frowns upon the loss of staff focus on compliance, understandably, from a government perspective. What we require is a balanced system that satisfies both points of view and, hopefully, this book will provide possible solutions.

All quality systems must document work instructions, tolerances, and policies. Within our pseudo-GLP environment, we are required to have written work instructions and standard operating procedures (SOPs). These documents are used to define how each process, task, instrument, calibration, etc., will be carried out. These documents form the core of the quality system. The importance of getting them to accurately reflect what is actually done cannot be overemphasized. This is also probably the hardest task to keep on top of because, as a QA professional, you are further removed from the actual processes being described, and you will be asked to evaluate such documentation for quality.

Another aspect of this function of quality system building is the control of such documents. It is of paramount importance that staff are not using outdated, replaced procedures, or unofficial copies.

This can be a task assigned to the QA department, especially in the smaller organization, and it is probably a good idea for this to happen as QA does take a much more responsible position regarding such operations. I personally feel that this is an administrative function and not a QA one, especially the reproduction and physical distribution of these documents.

Interpretation of the GLP regulations and the U.K. Statutory Instrument (SI) is provided by the regulators themselves and via BARQA. The latter is invaluable to someone who wants an answer to a particular regulatory problem. As there is virtually no single correct answer or interpretation of the GLP regulations, BARQA members can provide consensus answers and you can choose which interpretation or combination of interpretations to use. I do not know of another profession in which its members so freely give advice and support to each other. BARQA is to be commended for this, and if you are not a member, I suggest that you correct this omission promptly. We must also remember that although we are speaking about the U.K. compliance program, we should also consider the U.S. Food and Drug Administration (FDA) interpretations and requirements. These are very important in terms of the global nature of pharmaceutical sales and the largest market (sales wise) for these being the U.S. So companies must submit their data there in order to obtain a marketing license for that country. As we are considering the U.S. here, it would be prudent to mention the Society for Quality Assurance (SQA). This organization has the same aims and aspirations as BARQA and should be considered a sister organization. If you are in the U.S., this society should be your first line of support.

Apart from U.K. GLP, we have to add on the OECD, European Economic Community (EEC), and FDA requirements as well. Thankfully, there are not too many differences, and these can be accommodated reasonably easily into your quality system. Details of these differences can be found in various reviews of the topic found on the Web or in print (in any case, the results are too technical and detailed for this work). As BARQA has worldwide links with all other similar professional bodies such as the individual chapters of the European Societies for Research Quality Assurance (FERQAS),

the Japanese Society of Quality Assurance (JSQA), and the American Society for Quality Assurance (SQA), these associations allow the interpretations of any regulatory requirements to be incorporated into the regular information disseminated to their respective memberships and to other bodies such as BARQA. Whether you have GLP accreditation or not, sponsor QA, during compliance audits, will be using those standards to audit and rate your facility. This will normally be to the highest regulatory standard in each geographical area because of the world authority differences which, in turn, depend on where the data is destined to be submitted.

We can implement our system, but we require some projects to work on such as pharmacokinetic profiling or other clinical studies — using two examples from my organization, such as sperm motility or distribution of drugs in breast milk. Some kind of clinical trial is necessary that will generate samples for our pseudo-GLP laboratory. One of the many problems for CROs is that they can have a tendency to obtain the work that others do not want to do or cannot do for various reasons, and it can be quite varied as you can see from the two examples above. This is not quite the simple clinical trial with pharmacokinetic samples we were anticipating, and we will probably need more training and new SOPs to accommodate the new projects to be carried out. This, of course, takes up time and resource in the documentation phase, but on the plus side, it does add to the organization's portfolio of completed work.

Before we can start any study or project, we must have a study plan. It is relatively simple if all you are doing is the laboratory phase, but if the clinical phase is being carried out as well, then is the study going to be carried out under the clinical protocol or will there also be a laboratory plan? This type of decision crops up frequently, and a formal documented solution for your organization should be in place: two studies and one protocol, or two protocols and one study. Neither option is GLP compliant. It should also be noted that clinical protocols tend not to have the level of detail that is required in a GLP laboratory study.

We took the decision very early on that any laboratory phase of a clinical project would appoint a study director, be subject to its own study plan (approved by the sponsor), and have its own audited final report. Such a report, although stand-alone, can be incorporated into the final clinical report as an appendix. Such a system, although requiring more work and administration, has served us well now for many years and is to be highly recommended.

Application of GLP Principles to Phase-I Clinical Trials

The independent QA person in such an environment has a special role to play: They must ensure that the optimum procedures have been followed. This is similar to the passion for "time and motion" studies in the late 1950s and early 1960s. I say this because the first stages of clinical drug development are the most crucial. The first time it is conducted on humans is a

stop-and-go experiment for the pharmaceutical company. Any delays in this process has "knock-on" effects on the whole development program and huge cost implications for any eventual delay in marketing, measured in millions of dollars. This is due to lost revenue in the time before the patent expires and until generic drugs hit the market and reduce the company's market share. Thus, the faster we can get the results to our sponsors the better; hence, the need for quality process improvements.

My particular organization concentrates on Phase-I clinical trials, which are far more applicable to GLP principles. Other clinical phases are much more difficult to control and have a higher level of trust implied in their design and operation. In Phase-I trials, the dosing of subjects can be witnessed for every dose, as subjects are maintained residentially within the unit for the duration of each limb of a trial. The subject's protocol compliance can also be assessed both physically and objectively. As with GLP, an audit trail is produced and centered around a case record form (CRF) rather than the study laboratory notebook.

All equipment used in the clinical trial process is specifically maintained and calibrated where necessary. As with GLP, this maintenance and calibration record is kept up to date for each piece of equipment, and retained for the instrument's entire life within the organization archives, not within the study archives. Again, as with GLP, we maintain log books of calibrations of equipment such as BP machines, ECG machines, and balances, etc., that are similarly archived.

Archive Considerations

You should, of course, be aware that any GxP system must include a secure archive in which all trial-related information will be stored so that any historical study may be reconstructed in its entirety. There is, however, a possibility that your organization may cease trading and the sponsors or regulatory bodies may require access to the information. There have been cases reported in which the data has been dumped in bin bags and left in an unoccupied building, and it was up to the sponsors (if they knew the problem), to locate and retrieve their own study data. This is clearly unacceptable. Such situations arise due to the lack of anyone willing to take responsibility for the material as there is no one to pay them to do so. Such a nightmare scenario is of great concern to sponsors. The contract organization should ensure they have in place something like a guarantee or bond with a firm of solicitors so that if the organization ceases to trade or stops operations, they will handle the regulatory aspects of caring for the data, contacting the sponsor, and assigning it to them, thus guaranteeing the sponsor's data security. With some clinical data, the sponsor removes the original data and you are left with a copy. This does not mean that as you are no longer dealing with raw data, this obviates your archive liabilities. There will always be other nonspecific study records such as maintenance

and calibration details or other non-CRF-based data. As a QA professional, you should ensure that there is some system to protect the data from such circumstances and that the procedure is documented and in operation in your own organization

The core element of any GxP quality system is the use of SOPs, but these must be controlled so that everyone is using the same version and, therefore, doing the same task the same way.

Proper notification to staff of impending changes to procedures and when they will become operational is an implicit requirement. In many organizations, this is normally communicated to the line managers via an e-mail message, and they will communicate the information to their staff. One real problem with this method is ensuring that line managers are aware of the SOPs that affect their areas and staff. People tend to look at the titles or SOP identification mark, say that it is not relevant, and disregard the mail. Thus, subordinate staff are unaware that a change in procedure that may affect them peripherally has taken place. This can be overcome by notifying the line managers of the areas covered by the scope of each SOP. For example, the SOP title and identification number along with a list of applicable areas such as clinic, laboratory, data management, etc., is sent. This minimizes the chances of inappropriate ignorance and the consequential nonimplementation of changes. Staff can then be made aware of these changes via a memo that they can sign and date to indicate their awareness of the change or the new SOP. This record can be filed by the line manager for a specified period, which is then moved to the archive for posterity. Such a system, though not the best, provides the evidence as to how staff are notified of SOP changes, etc., and it works in my organization.

SOP Contents and Design

A SOP can be defined as a document of instructions on how to perform a task. Written documentation rather than oral instruction is necessary because it is less subject to misinterpretation, confusion, and later changes in defining what was meant or agreed upon.

Every SOP must be assigned a unique identification number so that it may be unambiguously referred to in other documents. The other advantage of using numbers is that, nowadays, it is much easier to search for items within a computer system. This becomes much more useful if the identification number is either used directly or within the file name for the SOP. Such a number system may be good for computers but not so for people. Thus, we also provide a keyword for every SOP. In our manual of SOPs, we provide three indices to use for sorting the SOPs by SOP number, title, or keyword. The latter is the most commonly used method in the clinic for locating groups of related SOPs.

The format of SOPs should be consistent and, therefore, it makes sense to have a standard template file. It would also be prudent to store such

documents in a shared, read-only area of your intranet. In order to get this to work properly, only one or two people should be authorized to put the document files onto the shared area and remove the old ones. In my organization, this is done by QA at the same time as the new one is issued. With most network operating systems, the ability to print off your own copy cannot be simply prevented. This must be watched out for. However, such copies are easy to spot if they are being used within the organization, as they are not signed. There should also be a documented organizational policy decision that does not allow users to print out uncontrolled SOPs. One useful tip when creating SOPs is to ensure that you use headers and footers to provide the SOP identification on every page. Also, it is worthwhile inserting the page number and number of pages as well. If for any reason, pages are missing from a SOP, these can be quickly identified.

Within a SOP, a contents section is optional, but should be included in lengthy SOPs as this facilitates access to relevant information. If a large part of a manual is to be included, then such things are best inserted as an appendix to a SOP.

Laboratory Method Operating Procedures (MOPs)

In our particular circumstance of having a laboratory supporting the clinical trials, we decided early on that we had to have two types of SOPs. There is the normal SOP already described, and then there are "special" SOPs that are developed for laboratory use when analyzing for a particular substance.

These tend to be specific to a project and thus are a "one-use document." They contain much more detail than a normal operational SOP. Such details may include the full analytical method, the specific details of the apparatus used, quality control procedures, specific analyte acceptance and rejection criteria, and the validation parameters. As such parameters tend to be specific for each analytical project, using the MOP again, directly, for another study involving the same analyte will invariably result in noncompliance with the original document. To get around such problems, it was felt that a study-specific document was required. Hence, the method operating procedure was devised. These are subject to the same archiving procedures as any SOP, but that may well be with the study data at the end of the project rather than the organization's general GLP archive. These documents are issued and controlled by the laboratory, independently from the SOP issue system. QA is involved with the review and auditing of such documents, but not the actual issue as would be the case with a normal SOP.

Preambles for SOPs

The following statements on purpose, scope, and responsibility should be standard components of your SOPs. They provide a concise statement of delineation.

Purpose

Describe the reason or purpose of the SOP together with any relevant background information. For example: "The purpose of this procedure is to describe how centrifuges must be operated and maintained within the organization."

Scope

Define the organization's operation areas to which the SOP applies. For example: "This SOP is intended to cover the operation of centrifuges throughout the organization and should be read by every member of staff and visitors who may be required to use a centrifuge." Clinical SOPs may contain the statement, "This SOP is compliant with current ICH guidelines on GCP."

Responsibility

This section defines who is responsible for administering the SOP and who is responsible for complying with the instructions contained within it. For example: "QA is responsible for the issue of this document and its administration. All members of staff and visitors to the organization are responsible for complying with the instructions detailed in this procedure."

SOPs should be prepared and compiled only by those who are conversant with the procedure being described. The CEO of the organization must take full responsibility for all SOPs being issued, and this will be documented by their signature and date on the front page. The compiler of the SOP will also sign and date the document. In my organization, QA also signs the document to approve it (this has more to do with the document control function rather than the QA of individual SOPs).

Achieving the Purpose of SOPs

The Details: The Procedure

The procedure should clearly describe the actions necessary to achieve the purpose of the SOP. Note that this must be a set of instructions to be followed, not a set of guidelines that the reader may or may not follow. However, some SOPs may contain reference information, which must be subject to professional interpretation. For some topics that require lengthy SOPs, an introduction should be included.

In some cases, for example, where a SOP is necessary for a complex piece of equipment, the procedure section may simply consist of a paragraph referring the reader to the manufacturer's manual. Any operational limits imposed by the organization should be added to the procedure section.

The manufacturer's manual may be reproduced in full or in part and should be included in the SOP as an appendix. However, this may not be practical if the manual is very large. Even when sections of a manual are

included, the SOP number and version number, together with the SOP page numbers should still appear on the header or footer of each page. This ensures that should any pages come loose or be lost, they can easily be identified.

We have had problems in the past when copying diagrams, etc., from manuals. It was a process of copying, cutting, and pasting on to pages. This task did not easily lend itself to word processing and electronic storage. Such manual systems meant that the electronic copy of the SOP was, therefore, incomplete and could not just be printed off for reproduction. Only the master copy could be photocopied so that the diagrams could be included.

With the introduction of cheap scanners for desktop computers, such "cut out and stick" type of constructions can be consigned to the past. We can now produce compound documents much more easily, store, and modify them electronically, and this latter type of operation is much preferred.

History of Revision

Changes from previous versions of the SOP should be recorded in summary. For example: "Changes from version 1. Typos corrected, maintenance section added."

If the list becomes unmanageable — for instance, after many versions have been made — the SOP should be archived, and the historical record of the new version should contain reference to the version in the archive.

This history section within a SOP is the first port of call for someone rereading the new issue of a SOP, as this is the section that details where the changes have taken place. This section does not require a lot of information, just a sentence for each change or group of changes would do. This is also useful for the line managers to identify key changes that may require some retraining of staff before the document is made active. (Although by this stage in the document life cycle, they should have had more than enough warning to get any training issues sorted.)

Document Control Functions

As with any technical document, it is essential that it is regularly reviewed by the operating personnel to ensure that important changes to procedures are reflected in the documentation. Although the regulations do not specify a review period, we started with a period of yearly review, which was fine with a small number of SOPs. As the quality documentation system increased, it became impossible to review all SOPs within the 1-year period. Thus, we were in noncompliance with our own SOPs — a definite problem with the regulators and external auditors. We then increased the period of review to a 2-year interval; this appears to be common across the industry and has probably become the industry standard. We have found that such a review cycle does allow us enough time to review existing documents by adequately examining them with respect to the systems they cover rather than just a quick read through. There are times when review dates slip. This

is understandable in most busy organizations, but it should not slip by more than 3 months from the review date. Such slippage is always a cause for concern by external auditors and regulatory inspectors; it is also one that is easy to prevent if you keep on top of the review process. Within our organization, this review, collation, and notification stage is carried out by the QA. In order to simplify producing reports, a database management program is used as an administrative tool. This allows us to keep a record of dates of issue and expected dates of review and, with suitable queries, will allow the reporting of SOPs nearing review date, about to be released SOPs, and a whole host of other administrative tasks. Such reports can easily be e-mailed to the appropriate section heads. Another benefit of such a database system is the ability to produce reports of the complete history and evolution of each SOP.

SOP Progression

We have found that, as an organization, setting up a subcommittee of representatives from each of the different areas of activity has allowed us to upgrade the development and content of SOPs. It has been our experience that SOPs designed by a committee have a tendency to sit in the development stage for months if not kept at the forefront of people's attention and SOP committee meetings can help ameliorate such situations. This committee feeds its findings into the regular monthly management meeting for quality review, thus giving it more leverage in getting things done within a reasonable time frame. A similar problem is that of delayed adoption or implementation; this should be avoided at all costs as this situation can drag on for months. A policy should be in place that when a new SOP is required, a base document is produced by one member of staff who will use the procedure. This may not follow the standard rules for SOPs, but at least there is something in place. Such documents still need to be controlled; in fact, more so, as they must be fast-tracked to finalization as soon as possible, and this should certainly be within six months. Such a rapid deployment system does need to be described in your SOP on SOPs and can also be facilitated by your SOP committee.

Building a Quality Assurance System

For any QA system to work, there has to be systematic inspection and audit of all processes to ensure that there is compliance to the applicable regulations and that SOPs are being followed.

How Can You Set Up Such a System?

As stated before, you have to provide yourselves and your organization with a "gold standard" that is used as the basis for your QA system; that is your SOPs!

Table 1.1 Example Titles of QA SOPs

Responsibilities and functions of the quality assurance unit
Project quality assurance
Inspection by regulatory authorities or sponsors
Procedure for subcontracting work
Audit of project reports
Audit of clinical protocols
Audit of laboratory protocols
Audit and integrity of computer systems and software
Inspection of clinical archives
Inspection of laboratory archives
Training of quality assurance staff
Quality assurance of clinical biochemistry results
Preparation and use of standard operating procedures
Audit, storage, and issue of standard operating procedures
Quality control of reports

QA itself requires a set of SOPs that cover all aspects of the units' operations and will consequently form the foundation and bedrock of your system. You will have to define in these documents how you will carry out facility and project inspections and audits. These documents should also provide details on how you will audit reports or parts. Some of our titles are included as examples (see Table 1.1).

As can be seen from this list (not exhaustive), the areas covered by QA within my organization are manifold. Areas of particular deviation from scientific QA are probably the document control function, archiving, and IT system audits. In larger organizations, there are probably highly skilled specialist personnel to carry out these tasks, but in the smaller organization, you have to be prepared to wear many different hats and be something of a jack of all trades. This may result in training gaps for QA personnel: in some cases, only one person is employed in the QA unit. So, someone with wide and diverse experience is required to fulfill such a role. However, specialist training and instruction should be provided for people who are just "keen to learn new things," and also for the people with wider experience who should be eager to learn something new.

It is apparent that some people have difficulty in understanding the difference between *audit* and *inspection* and use the two terms interchangeably. It is my contention that this should not be so, and I propose that we go with the following definition, which I will use throughout this book:

Inspection is the process of looking at procedures to ensure that they match up with those documented in SOPs, protocols, and study plans. This is a live function carried out during the procedure.

Audit is the process of retrospectively looking at a study to ensure compliance with the protocol or raw-data checks and the appropriate regulations.

In short, inspection is "present tense" and audit is "past tense."

Inspection

We can split this into three types:

1. Facility: Examining the fabric, training, and non-study-specific items, routine checks on equipment maintenance, calibrations, and also the archive facility
2. In process: Examining data capture and recording, procedural activities, QC activities, and protocol compliance
3. Ad hoc: QA actioned inspection for compliance with previously reported problem, study director and management requested, non-scheduled inspection

We normally use a checklist (this can also be considered a plan) of items to be examined, but the inspector is not obliged to follow this to the letter; they have the flexibility to curtail an inspection or to expand it, depending upon their findings. The checklist approach is used as an aide-mémoire, so that important things are not missed by the inspector who may be sidetracked by other issues.

Audits

We can divide audits into the following categories:

1. Listings: Tables of data for QA to sample and track back to source data (source-data verification).
2. Protocols: Read protocols to ensure they are within the company's ability to comply; ensure that there are no compliance issues or SOP deviations planned that may compromise a study's integrity and any contractual obligations.
3. Methodology and conclusions: Reading over the textual part of a report to ensure that it supports the tabulated data and conclusions presented. Also confirming that protocol compliance was achieved.
4. Statistical analysis plans: Ensure that the plan matches the protocol requirements and that the tests to be used are appropriate for the conclusions to be expected.
5. CRF (in-house design): Checking the contents to ensure consistency and completeness with the protocol requirements.
6. Audit trails: Ensure that such a trail exists and that there are no unexplained gaps.
7. Archives: Ensure all the study data is maintained in a secure archive, also confirming that all supporting global documentation is maintained in a similar fashion. Finally, ensure that the archives are operated within their SOP requirements.
8. Computer data: Check that completed and archived projects have no data left on the intranet. All such open data files should be archived onto read-only media and be made resident in the archive.

9. SOPs: Ensure that all such documents have appropriate design and approval and that there is document control in operation. There is also the issue of training and notification to staff of these events to be considered.

External Audits

Many of the reports produced by a CRO are intended for submission to regulatory authorities in countries throughout the world. These authorities have to satisfy themselves that the data produced by your organization are reliable and that meaningful decisions may be based on these data. To this end, you may have to anticipate inspections by regulatory authorities from any part of the world. Also, sponsors may be expected to carry out their own inspections or audits prior to, during, or on completion of their projects.

There are two general types of external inspection:

- An inspection of the organization in order to investigate the quality of facilities, staff, procedures, etc., but not to investigate any study in detail. This inspection is intended to give an overall impression of the reliability of data generated within your organization.
- An inspection to ensure that a specific project is being conducted in a competent and proper manner and that the results in a project report correspond to the original data. Before an inspection of this type may be carried out by a regulatory authority, the sponsor's permission should be obtained in writing.

Prior to such a visit by external inspectors, you should ensure that all staff are informed of the impending visit and that, if asked questions, they must only answer those that come within their direct remit. Any questions outside their own knowledge should be passed on to more senior personnel for answer.

You should also ensure that any confidential information is maintained securely and out of sight during any such visits. Any observable breach in another client's confidentiality may result in the loss of a future contract, perhaps, from both parties. Remember, inspectors are trained observers (like yourself), looking for any tell-tale signs indicative of quality or security problems.

Quality Control within Quality Assurance

Whenever one sets up a QA system, it is imperative that some form of quality control (QC) is introduced that monitors a process and has defined limits of acceptance and rejection. There has to be a fine balance with any such system. It must be simple to operate and must not take up an inordinate amount of time on the part of the operator or line manager, i.e., in cases of checking the report against the protocol or checking that QC samples in an analytical

run meet their target or nominal values. It is QA's function to ensure such systems are in place (and perhaps even design them) and are working. This is very much a generalization so I will try to elaborate for you:

It is up to QA to ensure that systems for QC are designed correctly and working. In fact, it is far better if QA are in at the design stage for any such changes to working practices. This will ensure that a set of "independent eyes" are cast over the project to help spot any unforeseen problems. I believe that it is also a QA function to look at all QC operations as an evolutionary process — not a revolutionary one. When defects or problems are noted in a QC system, then the system must be adapted to find, correct the problem, and ensure there is no reoccurrence. It is this cyclic nature of QC that must be introduced as part of a quality culture in any organization.

It is, in my experience, difficult for some management personnel, especially when they have not been trained in management principles, to appreciate quality principles. They tend to be a problem, and it is up to QA to try to educate such naive people. Some of my possible solutions to such educational deficiencies are outlined in later chapters.

chapter 2

Before GCP

In order to accommodate Good Laboratory Practice (GLP) principles within a Phase-I unit, it was convenient to think of volunteers as test tubes and all the clinical procedures as laboratory tests. This may have been a little disrespectful and simplistic, but it did allow us to get a handle on "GLP with ethics." As with any quality system, a series of systems and standard operating procedures (SOPs) were developed to allow us to document all procedures undertaken within the Phase-I arena. The ethical standard by which we operated was that defined in the Declaration of Helsinki (in its various revisions).

Because we were a residential Phase-I unit, the volunteers were controlled to a great extent, and we could be sure that we knew what is "added" to each volunteer and their base line "contents." Other phases, especially the later ones, Phase II and Phase III, of drugs' clinical development are not so well controlled, as these tend to be patient studies, and patient compliance with the protocol can become a significant issue. As I have had little or no real experience of these later phases of clinical trials I shall not develop any more discussion on the issue. I would however say that the general principles presented here do work in any situation, whether you are dealing with patients or volunteers; it is just that the details are different.

As a predominantly clinical research establishment, we could not offer all the laboratory tests required for general hematology and clinical biochemistry screening. These tests are required for each and every study and are fundamental to the safety pharmacology profile for each volunteer. Normally, unless these services are provided in-house, where you can exert a quality assurance function, this may give you some pseudo-GLP compliance problems.

External Suppliers

We did not have clinical biochemistry, hematology, and virology services in-house, so we had to rely on external suppliers. In our case, we used U.K. National Health Service (NHS)-based departments within our local hospital. In most cases, they were happy to provide such a service as it provided a source of flexible research income for them, which is a difficult thing to come by in the NHS. This, on the surface, would appear to be a symbiotic relationship

until you uncover the possible compliance pitfalls. A documented quality system of some sort was expected within the NHS laboratory service, as they provide hundreds of thousands of tests per year on patient samples, but on inspection (using GLP criteria), such a system was not found.

That was not to say that the "quality" of the results they produced was in doubt; in fact, far from it. The laboratories were members of external quality control (QC) checking services and always performed within the top 10% of members. The main problems lay in the absence of documented methods and lack of document control; they were a million miles away from GLP! Over the past few years, things have become steadily better as clinical pathology accreditation (CPA) within the NHS is gradually making its mark. SOPs are now standard documents within such departments, although in my opinion and experience, the document control function could be a little lacking. However, each time we carried out our biennial inspection of these service departments, there was normally a huge improvement of their quality system. In fact, today they (at least the ones in our hospital) have in place everything that you would expect to find in a GLP laboratory except a few important items, such as a lack of archiving or the essential independent quality assurance (QA) function.

One major problem with hospital-based labs is the lack of archive for original test results; these are normally kept for about 1 year before disposal (electronic records). For example, our local clinical chemistry laboratory carries out more that one million tests a year, and maintaining a database of this volume is unwieldy and unnecessary for their NHS work. This, of course, raises the problem of electronic records and FDA 21 CFR Part 11 compliance issues which I will go into later, as this is a topic with a multitude of QA issues (see Chapter 3). Computerized systems are very common in large organizations in order to deal with vast amounts of information and to allow management to keep on top of this mountain of information. It has been my experience that producers of software for handling such data do not have the same requirements for data security and longevity as those of the pharmaceutical industry. Because they do not perceive the need, they tend to ignore the audit trail aspects in their NHS-procured systems. This, of course, causes real additional problems for the continued compliance and acceptance of data from establishments such as NHS laboratories.

It is my opinion that careful guidance by QA here can be invaluable in prevention of misunderstanding of each other's requirements. Because this normal QA advice is very seldom asked for, or acted upon, for various reasons, the chances of good cooperation tend to be problematical at best.

Staffing Issues: Meeting the Needs

Company Needs

Prior to 1992, training of nursing staff was done by "cascade" methods. A few of the more senior staff were trained, normally externally, and this

training was passed down to the ward-level staff. Although the same sort of procedures are employed today, it is done in a much more formalized way, and a record of all training received is maintained. When we record evidence of training, we also try to ensure that the record indicates the level of training provided, such as "competent" or "competent to train." These training methods were also imposed on clinical management, as the record-keeping requirements are the same as in the GLP arena. It was soon noted that the clinicians (management) did not have a similar training record system. They had tended to go their own way and consequently did not keep the same type of records or information. It was felt that they needed to adopt the same system so that a consistency in training records was maintained across the organization. This consistency resulted in a process whereby all members of staff have a training record for which they are individually responsible. These training records can become an integral part of every person's full CV and can be extracted documents, i.e., the tabular list of training can be printed out as a separate stand-alone document. It therefore requires only one master document to be maintained rather than several minor ones and is therefore easier to keep up-to-date.

All training records must be kept up-to-date, and gaps in training require early identification such that there are no possible detrimental affects on any planned studies. Whether or not one individual is made responsible for ensuring records are kept up-to-date is up to you, but I suggest that if you do not, there will always be gaps in your system.

The topic of training will be further examined in a later chapter as this is one of the bedrock requirements of any quality system and therefore requires a thorough understanding of what is required.

SOPs and Training

One real issue that should be mentioned here is the link between SOPs and training. You should be careful with this and not link the SOP documents themselves with training. At first sight, this may appear to be a good idea, linking both together as they appear to go hand in hand anyway. The reason for my caution with this approach is that when an SOP is changed or archived, it could appear that the person is no longer trained for the task. So after every SOP review period, you could end up with a staff with expired training. Clearly, this is incorrect but on paper, to an external auditor, that is exactly what the case seems to be, especially, if your training procedures are referred to as SOPs. You can get around this problem by using the SOP title as a basis for training (but not the SOP identity of the specific document), recording this fact. You must be careful in the way you word your training procedures, otherwise you may fall into this trap.

Sponsor Needs

Before sponsors place any studies with a contract research organization (CRO) such as ourselves, we normally have to supply them with CVs of all

staff to be involved in the study. For most staff who have generous CVs, such a request is an administrative problem. We eliminated the problem by having each member of staff produce a mini CV, which is a single-page document stating their qualifications and a brief summary of experience and job function. Sponsors also want to see documented evidence of the training each staff member receives and proof that the SOPs involved in the study are used and understood, and more fundamentally, that all these staff are familiar with International Conference on Harmonization (ICH) GCP guidelines.

Clinical Staff Needs

Having a good training system in place provides a series of benefits such as improvement of staff confidence and morale, and it also indicates to them that they are valued members of the organization worth investing time and money in. Training helps provide the company with better and more consistent results and, in some cases, the ability to offer more varied services. A bonus for the staff is that they end up with a much more comprehensive CV that can be used elsewhere when, and if, they decide to move on to other employment. An additional benefit of training is the better integration of staff to form teams and thus improve communication between individuals. The key objective of any training system is to ensure that the staff knows exactly what they are permitted to do and the tasks that they cannot perform.

A more detailed discussion on training and some examples of the records will be provided in the training section of this book.

Quality System Evolution

As our GLP clinical system evolved, there was a tendency to produce numerous SOPs for all aspects of work without any real consistency about how they were written or even whether they should have been produced in the first place. Such a situation normally arrives and is driven by an external sponsor QA suggesting to management that you really require a SOP or SOPs on a specific topic. If you immediately get going and produce these new SOPs you could create more problems for yourselves. You may have already covered the topic requested in another SOP at the audit, but could not remember which one, or it was not within your area, and therefore, you were not sure if it had been documented. Consequently, we can end up with different SOPs covering the same areas. On the surface, this may not appear to be a bad thing, but we have been caught out by this on a few occasions during sponsor QA audits. When you cover the same operation in several SOPs, there is a strong probability that you will forget that the topic is included in a different SOP as well, and if you change the procedure, only one version tends to be updated. This problem usually occurs when adjacent-area procedures are being documented, and they have a central common core operation. Because you tend to only go by titles to identify areas

covered, such multiplicity is easily overlooked and usually found by Sod's Law during an external sponsor QA audit. (You said you did it that way but you are doing it this way.)

Prevention of such occurrences is vital in order to save face and to ensure only the correct procedure is being used. This is not normally a real issue as the correct procedure is the one in which the staff would be trained on and would be using, but it does throw up questions for auditors.

How can you minimize such happenings? You can have QA review each SOP, confirm that an SOP topic has not already been covered somewhere else and minimize the number of SOPs you produce. Of course, this really works only in a small organization in which QA is familiar with most of the SOPs in use. Recently, I have been wondering whether we produce SOPs for the benefit of external auditors so that they are there for them to see, rather than for the primary purpose of detailing how to carry out a task. I am sure that this will probably strike a chord with all of you from the CRO environment to some extent.

Clinical Equipment

Within a GLP environment there is a requirement to ensure that there is a maintenance record for each piece of equipment used in regulatory work. The same requirement can be applied to the clinical situation; every piece of equipment must be maintained and documented, and where calibration is required, this is also carried out and recorded. Where this is not possible or practical to carry out in-house, external contractors or manufacturer's service agents must be employed.

In such circumstances, it would be prudent to ensure that your external contractors are registered with some quality standard, e.g., ISO 9001:2000 or UKAS registered or accredited. The frequency of such calibrations or maintenance must, of course, be commensurate with the manufacturer's specification. If there is no such guidance given in equipment manuals, then the SOP for that equipment must be modified to specify your frequency for carrying out such tasks. If you use a GLP practice of using a manufacturer's manual as an SOP, there should also be a section that you write yourself, which includes maintenance and frequency of calibration, if such activities are not already specified.

Ethical Permission to Carry Out a Study

In a laboratory study, the study director has complete control over when a study starts and what the study will do, at least under the terms of the Home Office Project License (U.K.). A clinical study is different in that a copy of the protocol is submitted to an ethical review board consisting of clinicians, other professionals, and lay members of the public who can give an unbiased view of the necessity of the planned study and its effects on any of the subjects used. Standard submission forms are also usually supplied and

CROs become very adept at completing such documents routinely. If only one ethics committee is normally used, there is usually a great deal of mutual understanding of both parties' requirements, which normally allows rapid progression of applications one way or another. CROs are in the unenviable position of trying to get their studies started as quickly as possible, as there is always inherent pressure from sponsors to get the study completed. The ethics committee or investigational review body (IRB) obviously presents an extra hurdle that was not there in a GLP study. It does need to be there, though, to ensure that shortcuts are not taken in regard to volunteer's safety and that medicines are not given inappropriately. These bodies are independent (some were set up by companies for their own use before legislation and standard guidelines) of the organization performing the tests. The local U.K. health board IRBs may have very different timing priorities from those of the CROs, which can be a problem on occasion, trying to fit within the sponsors' time frames. This discrepancy in timing priorities was one of the main reasons that some companies set up their own committees in the first place. Apart from gaining approval from the IRB, there is still another hurdle to be overcome, that of obtaining informed consent from your potential volunteer (also reviewed by the IRB).

Before the European Clinical Trials Directive (ECTD), IRBs showed very little standardization across the country as a whole; there were guidelines, but at best they were "gray" and very much open to different interpretations. Now with the ECTD, we have a set of standardized requirements, which must be met by every IRB and includes the use of SOPs, the foundation of any quality system. From now on, then, it would appear that we should have a lot more consistency in the way approval or nonapproval is communicated. The operations of all IRBs are now subject to regulatory inspection and the same level of transparency of operation as expected from all other groups carrying out pharmaceutical research. This situation is different in the U.S. as the FDA has had such an inspection system in place since 1977, based on regulations in Title 21, Code of Federal Regulations, Part 50 and Part 56. We in Europe and the U.K. are just catching up.

Clinical Protocol Audits

The most important document in any clinical trial is the protocol that describes the objective of the trial, how it will be carried out, and what constitutes the end point. Because this is such an important document, QA, ideally, should be involved during its creation, but normally this does not happen in a small CRO. The main reason for this is that most large pharmaceutical companies produce the protocol in-house, and it is almost "set in stone" by the time it is sent to the CRO. Therefore, the CRO input into such documents is rather limited or nonexistent. Because we have little or no control over such external documents, we have to ensure that when the CRO produces its own, they should be audited carefully to ensure all major points are covered. I have provided a list of the main items I look for when reviewing

a protocol and, of course, those writing protocols can use the same list to ensure they have not forgotten anything major. Thus, it can also be used as the basis for your SOP on protocol production:

General Considerations

Descriptive title of study
Name and address of trial center and names of investigators
Name of monitor, name and address of sponsor, together with the contact telephone numbers
Name and address of any other participant
Specific protocol reference number with the ability to differentiate between different versions of the protocol
Issue date to differentiate different versions
Approval signatures

Study Objectives

Rationale for study
Number of subjects with reasons, diseased or healthy volunteers
Selection criteria and exclusion criteria
Study design, e.g., double blind, parallel group
Description of any randomization methods and blinding techniques

Drug Treatment

Name or code number
Form and strength of dose
Route and duration of administration
Labeling and storage conditions of containers
Number of doses per container
Rules for the use of concomitant therapy
Measures to be implemented to ensure safe handling of drugs
Compliance monitoring
Drug accountability methods
Return of unused medication

Assessments

Prestudy assessments including medical history
Parameters to be measured during the study with findings, specifying special analyses, e.g., pharmacokinetic, clinical, and laboratory method of investigation or examination
Name and address of any laboratory performing analyses if this is not internal

Follow-up assessments with timings
Statement in which results will be recorded

Adverse Events

Method of recording adverse events
Method of evaluating severity
Method of reporting to appropriate persons, i.e., sponsor, ethics committee
Time frame for reporting adverse events to appropriate persons
Information on where trial code will be kept and how this will be broken

Withdrawals

Criteria for withdrawal and method of handling withdrawals
Method of recording withdrawals

Analysis of Results

Methods of analysis, including statistical tests to be employed
Parameters to be included in analysis of data

Monitoring of Trial

Progress and method of monitoring
Handling of trial deviations and other protocol violations

Consent Procedure

Description of information to be given
Description of documentation of consent

Ethics Review

Description of which ethics committee will review the protocol, the information and consent procedure, and how approval will be documented

Declaration of Helsinki

Statement that the study will be conducted in accordance with the declaration and its revision date

Insurance liabilities for volunteer studies with a statement on insurance liabilities
For patients, a statement on compensation for drug-induced illness

Reports

A statement about who is responsible for reporting results of the study and within what sort of time frame
Statement of policy on publications
Style of reports conforming to ICH GCP guidelines

Control of Test Substances

The sponsor normally supplied the test substances either in individual volunteer doses or as bulk supplies to be allocated by the staff. There is always the issue of security with any pharmaceutical material for two reasons: accountability and stability. We kept detailed logs of materials booked into our pharmacy stores, and the products themselves were stored in locked filing cabinets.

The minimum type of information required in any record of receipt should include the following:

- Date of arrival and date of departure
- Drug company
- Shipping agent
- Lot/batch number
- Organization project identification
- Drug identification, i.e., drug name, code number, or both
- Quantity received
- Study period numbers
- Subject numbers
- Date of expiry
- Pharmacy storage area, i.e., details of where the drugs are stored, in a numbered, locked cabinet or refrigerator or controlled-drug cupboard where appropriate
- Signature of person recording the details

However, the system we had in place initially did show up some problems, for example, how were the test substances booked in? Were they recorded as, say, 1 box of drugs, 150 tablets, or 10 x 5 x 3 tablet doses for 3 phases of a trial? Such discrepancies and inconsistencies caused us no end of problems with reconciliation and accountability. The best way we found was to log the test substances into the pharmacy by recording the smallest units of individual dose per subject. It is a lot more time consuming than recording "1 box," but it makes your audit trails much more transparent and

accountability so much easier. Again, such systems need to be documented within SOPs, but it does demonstrate that SOPs are not substitutes for training; they must be seen as complimentary to each other.

Controlled drugs such as opiates, etc., require some special consideration when maintaining logs of use and disposal. Prescribing these drugs should be in accordance with the guidance on prescribing in the section "Controlled Drugs and Drug Dependence" in the current version of the British National Formulary (BNF) or the relevant section in the United States Pharmacopeia and National Formulary (USP-NF). A Home Office license (in the U.K.) and appropriate permission must be applied for prior to receiving or storing controlled drugs. Special locked, secure storage should be made available for such materials. Access to the controlled-drug storage should be made the responsibility of a senior member of staff who will also ensure that a chain of custody of access is maintained where shift staff are involved. Controlled drugs should be checked once every 24 h to ensure that stock records match the physical check. Stock checks should be carried out by two persons to ensure impartiality. Any discrepancy should be reported to management immediately.

In the past, with rather unstable materials, usually liquids, these were dispensed within our pharmacy area by a pharmacist. This dilution or other operation was also witnessed by nursing staff and QA as an independent control. However, these processes were not carried out under aseptic or controlled conditions, as would be the case in a pharmaceutical production environment. These individual doses were then labeled and moved into the clinic for administration to the volunteers. Such simple and risky practices would never be tolerated in today's regulated environment.

Volunteer Issues

The raw material, and one of the most valuable assets of any Phase-I unit, has to be its volunteer panel. These people are the lifeblood (no pun intended) of clinical research in the U.K. and the rest of the world; without them there would be very few new drugs reaching the market place. Ensuring that every subject who is recruited to a study meets the inclusion criteria and does not meet the exclusion criteria is a very difficult task, best assigned to one or two people who can be at the front end in dealing with actual volunteers and potential volunteers. This is normally assigned to administrative staff who handle the volunteer-completed medical history. They also provide the initial contact with volunteers' general medical practitioner (GP), for courtesy, and also for any possible reasons the volunteers should not be used. This type of information is obviously very sensitive and needs to be properly controlled, whether it is held electronically, on paper, or both ways (electronic storage does require significant forethought; see later text). Information such as this needs to be maintained accurately and securely so that personal data are not inadvertently given to the sponsors or anyone else who does not need to have access to the data.

For example, a volunteer's immunological status is a very sensitive issue, and there must be some form of counseling and support for volunteers should either a screening for hepatitis or an HIV test prove to be positive. This type of information is one that clearly illustrates the requirement for the data security elements of whatever system you have in place. Such sensitive information must be transmitted only between persons who need to know: the volunteer, unit medical personnel, the GP, and any councilor, apart from the medical personnel.

Another point to note, especially when there are other clinical CROs in reasonably close geographical proximity, is to ensure that you do not use professional volunteers. These volunteers will enroll in every study available and swear that they have not taken part in any other trials within the last three months, when in fact they have. In the past, this tended to be avoided by circulating lists of volunteers between the different CROs. This practice, at the time of writing, is no longer carried out due to the possibility of breaching the Data Protection Act, 1998 (U.K.). (At this time, the U.S. is not considered to have an adequate data protection provision.) By ensuring that the volunteers give explicit permission for their volunteer status to be provided to other units for the purpose of subject safety, the issue of data protection infringement may be surmounted. The whole topic of data protection is worthy of greater expansion and consideration by the QA unit and will be dealt with later.

After GCP

By this term I really mean the regulations after formalization of the GCP guidelines (the European Union GCP prior to January 1997 and the ICH GCP after January 1997) and not the ECTD or the U.K. Statutory Instrument (GCP SI 2004:1031). Therefore, this section is based on all these considerations and not just simply on the GCP SI and, consequently, precedes the 2004 enactment. My intention is to develop the previous ideas, showing that we had a unit complying with nearly all of the regulations long before the guidelines had any legal status.

The main changes to our procedures were to do with informed consent, ethics committee compliance with GCP, notification of impending trials to the competent authorities, control of test substances, repackaging of trial drug supplies, and a more standardized reporting format.

The regulations provide a basis in U.K. and EU law for the following:

- Standardization of procedures for consideration of and authorization by ethical and competent authority
- GCP standards for starting and conducting clinical trials
- Good manufacturing practice (GMP) standards for medicines used in clinical trials
- Inspections against internationally accepted principles and standards of GCP and GMP, supported by enforcement powers

Prior to the ECTD and U.K. SI, sponsor companies were contractually able to allocate responsibility for particular parts of the study process to third parties such as CROs. The regulations now place overall legal responsibility for initiating and managing trials with the sponsor. Sponsors now not only need to ensure that they are complying with the law, but they must also ensure that any CRO used for a study will not cause them to breach the regulations.

Although sponsors will still be able to allocate contractual liability to their CRO partners, they will still remain primarily responsible by law for the conduct of the trials. Because of this change in responsibility, the monitoring of CROs' performance by sponsors has become much more important.

One of the problems I have with the GCP legislation is that of the ownership of a study with respect to sponsored studies. To my mind, it is a massive deficiency in the regulations. Under GLP, the study director owns the data along with the contract facility, and the latter are responsible for its safekeeping. Under ICH GCP, it appears that this is not the case; data produced are the property of the sponsor, and the integrity of the data is also their responsibility. This appears to fly in the face of logic and can cause CROs a lot of headaches, mainly due to having sponsors' monitors evaluate the collected data and sponsor QA audits. These are not a problem *per se*, but they are an extra burden on the contractor.

As far as I can see, there is no real reasons for this in a Phase-I or Phase-II clinical trial. My experience of the later phases of drug development is rather limited; it may be the case that the necessary controls inherent in GLP are missing, and therefore this type of monitoring is necessary. GCP appears to be set up as a "one size fits all" structure when this is clearly not the case. Perhaps, as experience has shown, the powers that be will realize the problems and modify the legislation with respect to the different requirements of each phase. Perhaps they will even contemplate the requirement to have an independent QAU for each center, which may also help answer the one-size-fits-all problem.

When sponsors provide the case report form (CRF) documentation for a trial, they tend to use no-carbon-required (NCR) multipage documents. On the surface, such action could be considered a good practice. However, because the data belong to the sponsor, and they would want to take the CRF away, the CRO usually ends up with the last copy of about four, which is barely legible. This normally means that someone is assigned to take down the data from the top copies of each CRF before the sponsor takes it. Another consequence is that the source data such as ECGs that are on paper have to be photocopied and authorized as authentic. This is a large burden on a small CRO such as ours, as it does not have a large compliment of support staff, and it usually means assigning a technician or nurse to carry out these tasks. This could have the effect that staff feel undervalued, and such a situation is not good for morale. Granted, the sponsor pays for this privilege, but this does mean that highly trained specialist staff are diverted into areas that could be considered menial, so to speak.

Problems with Nomenclature and Pan-European Consensus

When putting together such complex legislation across Europe, there is an inherent problem of nomenclature and grammar, which must be addressed in order to get a coherent, workable system in place. For example, take the word *protocol*; in English this is a future-related word; however, in German it is a past-related word, which makes interpretation of documents difficult, to say the least. The ECTD is such a compound document and has caused European industry quite a few problems already. Eventually, I suppose, it will evolve into a workable consensus, but at present, care must be taken with interpretation. This is especially true when you are a mixed organization that deals with GLP and GCP. Take, for example, the term *principle investigator* (PI). Under GLP, this is the person appointed at a remote site in charge of some phase of a GLP study. This person is under the direct control of the study director. In the case of GCP, the PI is the clinician in charge of a study but may not take actual part? I do not know how to reconcile this, but it seems to be at variance with what we in GLP used to believe in! The difference in meaning between the two titles is major, and it is my opinion that discrepancies of this sort should have been fixed at the start.

It does now appear that, at last, there is some movement in this area, and the regulators are finally coming round to a standardized type of nomenclature; they always seem to be reinventing the wheel. Perhaps, this is because of the different phases of clinical drug development and the fact that one size does not fit all. Certainly, within the Phase-I and Phase-II arena, these terms need to be more clearly defined; and organizations such as BARQA and the SQA can feed such concerns back to the regulators. However, this is of no avail if the regulators do not listen to well-founded recommendations and act accordingly.

This type of interaction between the regulators and professional bodies has always been the cornerstone of the evolution of GLP, within the U.K. at least. The regulators listen to what organizations like BARQA say and take the appropriate action. It is normally QA who spot any difficulties with proposed changes to old or new regulations and can get compromise solutions in place before they are written into the statute books. This then provides a system built on mutual cooperation between the industry and the monitoring authority and has served us exceptionally well over the years. Why such a system did not appear to be used when setting out GCP, I fail to understand.

Perhaps, the big problem here is the lack of a legal requirement for clinical units to provide their own independent QA function, though this function is implied in the regulations. This is a requirement under all GLPs but does not appear to be mandatory under the ECTD. Without such a guaranteed infrastructure, who is going to represent industry and present the problems to the regulators?

I think this is where the real problems lie with the evolution of European GCP; we need the same tie-up we have with GLP. I realize that in the later stages of drug development, this may be a nonstarter for various reasons. However, an independent QA function, even though not employed by the investigator, could still be made available by using consultants. If this were the recommended practice, I feel that we could be in a much more harmonious position and obtain workable compromises, which at the present appear to be very much lacking.

Test Substances: Controls and Comparators

The doses for any clinical trial must be accountable and stored under appropriate conditions of security and temperature. We accomplish this by having an air-conditioned pharmacy room with locked filing cabinets for the test pharmaceuticals. We have documentation to record how many doses, tablets, etc., are held, who removed what and when, and all the normal GLP controls, along with signatures. Access to the pharmacy itself is controlled, and access to the area where the pharmacy is located is also controlled; thus, three levels of physical security are in place.

In order to ensure the integrity of the test substances, the temperature of the pharmacy itself is monitored using a maximum–minimum thermometer, and the values regularly recorded in a central facility temperature log. However, such a system of temperature logging was discovered to be insufficient for the GMP environment and specific temperature mapping had to be carried out. This entails using multiple probes on a temperature logger, normally with a computer program to download the data, to record the temperature, say, in each drawer of the filing cabinet used to store the test substances. Mapping the temperatures of different shelves and areas of fridges and freezers, you can be absolutely sure of the temperature under which the materials are being stored. This type of operation was new to us, and it did require a significant investment of time and effort to fully temperature-map our pharmacy and its storage arrangements.

Of course, it must also not be forgotten that the fate of drug supplies used in a trial must be recorded even if destroyed or returned unused. A good SOP on this issue, defining all the points stated above, is essential to the proper operation of any pharmacy involved in clinical trials. It has been our experience that external auditors are very concerned about such records, and they should be maintained and documented in as transparent a way as possible. Otherwise, you can end up spending hours explaining your systems and their merits.

Investigational Medicinal Products (IMP) and Good Manufacturing Practice (GMP)

Because we, as a CRO, had been in the past asked by smaller pharmaceutical companies to carry out a Phase-I trial utilizing bulk IMP, it was considered

to be a good idea if we continued to offer such a service, as far as we could. Previously, repackaging and reconstitution of such bulk materials did not pose us a problem; we hired a qualified pharmacist, provided the staff with the appropriate equipment, and they produced the dosage forms for administration during the trial. All this under the watchful eye of QA, of course.

The new ECTD, quite rightly, does not allow such uncontrolled operations; these now must be conducted under U.K. GMP regulations and, in particular, with reference to Annex 13 (which deals with repackaging). Apart from the considerable obstacle of another set of regulations with which we would have to comply and another regulatory inspection, we would also have to apply for a manufacturing license (although a limited one).

This initially did cause us some business problems in that we had a new series of hoops to go through if we were to carry on providing such a full service to our smaller clients. On balance, it was considered that we would apply for a license, but its scope would be deliberately kept narrow and should be limited to the repackaging aspects. All other more difficult operations, such as importing an IMP, encapsulation, preparing parenterals and aseptic operations, would have to be subcontracted to companies who already held such manufacturing licenses.

However, this still left us with the requirement of having a qualified person (QP) "at the manufacturers' continuous disposal." For us, this was not a problem as our QA manager was also a designated QP from a previous assignment; however, for others not in such fortuitous circumstances, this may well be a major stumbling block. Emergency cover for an absent QP had to be taken into consideration here, and this was solved by contracting our local NHS QPs to our organization on an as-and-when basis. Although none of this has a direct bearing on QA *per se*, the action of an organization repackaging and dispensing IMPs and not having them released by a QP would be a clear breach of GCP requirements.

It is only my opinion, but as the demand for QPs increases, as it surely will, there may well have to be a subset of QPs where their remit of certification of product release will be limited to repackaging, etc. The obvious solution of sending staff on specialist QP courses to become QPs will not cover the shortfall as there is still the current additional requirement of professional experience within a manufacturing plant, which in most cases, will not be available in a small clinical CRO environment. There also appears to be an anomaly between mainland Europe and the U.K. regarding the definitions of what qualifications are required to be a QP. For example, in France a pharmacist is automatically defined as a QP, which appears to leave the U.K. in a disadvantageous position. Perhaps, someone will eventually challenge this incongruous situation in the law so that we can have the even playing field we deserve.

From recent conversations with various sponsors, it would appear that they favor CROs who can take over this burden of repackaging. This is

mainly due to the fact that it can be very difficult and expensive for them to change from large-scale production to the small-scale operation that would be required for a small Phase-I clinical trial batch.

It therefore appears that more such manufacturing operations are going to be requested of CROs in the future and, consequently, those with such arrangements in place are in good stead to capture a larger slice of business in an increasingly highly competitive environment.

With the decision made, we obtained our license and now had to apply our quality system principles to pharmacy operations in a way we had not really considered before. In the main, we were only concerned with drug accountability, etc. We now had a different ball game, essentially equivalent to setting up our GCP or GLP system for the first time, a daunting prospect, as it is normally down to QA to get things like this organized and documented on paper. The documentation phase was assisted by the provision of the site master file, Guidance Note 30, from the Medicines and Healthcare products Regulatory Agency (MHRA) via the Web. As with any quality system, all procedures have to be documented within SOPs. One of our first tasks was to identify each individual area of pharmacy operations and to develop a SOP for each. For our situation, which is basically limited to repackaging nonsterile bulk material, this led to the following pharmacy SOPs (GMP) being drafted:

- Monitoring of pharmacy temperature and humidity
- Drug destruction
- Secondary packaging and production of labels
- Manufacture: repackaging or potting of trial medication
- Receipt of IMPs
- Storage of IMPs
- Dispensing IMPs
- Pharmacy equipment and cleaning
- Procedure for dealing with IMP complaints
- Procedure for inspecting pharmacy operations

Some of these areas were new to us and were suggested (by a GMP consultant) as compliance problems should they not be specifically addressed. One key example was that of cleaning the dispensing area; we had not really considered the possibility of cross contamination before, as we tended to deal with only one IMP at a time. It was pointed out to us that we needed to have procedures in place that ensured certification of cleanliness was provided prior to any repackaging. One simple illustration, which clearly indicated the error of our previous ways, was the possibility of manipulations involving antibiotics such as penicillin. Contamination even with trace amounts could have serious consequences for any of the volunteers, if they happened to be immuno-sensitive to such materials.

Other GMP Considerations

Temperature for Shipping

Because we were being supplied with the IMP from the sponsor, it would normally be up to them to provide our QP with the necessary assurance that the IMP was exactly the same as when it left their QP's hands. Large variations in temperature during the shipping stage could have a detrimental effect on the IMP such that it became adulterated. How could our QP be sure nothing had happened en route and therefore preserve the chain of custody? The solution is to add a temperature logging device inside the container in order to take regular samples of the environmental temperatures during the IMPs' time in transit. The output from the logger would normally be downloaded at the sponsors' site (as they would have the adapter for downloading the information) after its return, and the results sent to our QP for information. Provided the temperature ranges were acceptable for the IMP's stability, the QP would be in a position to accept (or else reject) the IMP based on this evidence. This system provides us with confidence in the chain-of-custody records for the IMP between the two sites and both QPs.

Quarantine for IMPs

We had to set up a system that was secure and crystal clear about what IMPs were available for use and those that were not. As a small site dealing with small batches of medication, a separate area would be required for storage of expired or unused materials. We managed to neatly accommodate this by using the same filing cabinet in which the IMP was already stored, and added a series of cardboard labels onto the drawers indicating either the standard project identity or the word "QUARANTINE" visible when reversed. This change in status was accompanied by the QP documenting this change in the file maintained for each IMP in the pharmacy. This system avoided the requirement to have specific separate quarantine areas, which due to our lack of space, would have been impractical.

Expiration Date Problems

In the past we have had some IMP with very short expiration periods, sometimes even extended by the sponsor into the active trial phase. Such situations are no longer permitted, and it is the duty of the QP to check that the dates of expiry fall outside the trial active phase dates before the trial is due to start. Short-dated products can be a real headache for Phase-I as time frames change rapidly, and some of the experimental IMPs can have a very arbitrary and short expiration period. This is a situation that must be kept constantly under review by all pharmacy staff and of course the QA.

Within the U.K. SI, there are a few gray areas, and one that may affect you is the following. For example, let us consider an IMP in which a U.K. marketing license is held; we require to reconstitute the freeze-dried IMP with a diluent, which is a vehicle for administration. Is this a manufacturing operation, which comes under the GMP regulations? According to the SI, it does not fall into the GMP area, a clear and simple answer. However, the "grayness" occurs if we have to label the diluted IMP; this could be a step that requires GMP systems. For safety considerations, such circumstances are best not argued over but simply accepted that it would be better if all operations such as this are carried out under GMP to eliminate all doubt and any compliance issues.

Labels

The production of labels for repackaged material appears to be straightforward at first sight, but again, as with most things, it is a little more complicated. Normally, a computer along with some labeling software would be used, such as one used for labeling blood samples taken for pharmacokinetic analysis. But when dealing with the GMP aspects of labeling, there are a series of criteria that must be met:

- Security of the computer
- Security of label files and materials
- Audit trails

The latter is the most difficult; as is the case with most general commercial labeling packages, files having audit trails are not standard practice. In order to get such compliance, you have to go into the realms of manufacturing software that is compliant. However, the cost of implementing such systems in a small CRO is prohibitively high for the small runs of labels required, so another solution must be sought.

We can approach this from a risk-analysis perspective as follows. If we have a computer, which is not connected to any network, and only user accounts are set up (e.g., Windows® XP/2000, Macintosh® OSX) for people to produce labels (plus the administrator, in case of problems). This will provide the computer security, provided that the computer itself has restricted access from other individuals, i.e., it is in a room, say, the pharmacy with controlled access. If it is, say, a laptop, then the computer itself and the label materials can be further secured by locking them in a drawer or cupboard. (Note: Although the administrator has access to the computer and its files, they do not have unrestricted access to the area in which the system is kept.)

Only authorized persons have access to the physical computer, software, and label materials. The authorized user can produce the template for the label and run off a test set for checking and QP approval. The file will have within the meta data the user name of the last person to use the file. Each time a file is created or modified, a new name is used such that each file is

maintained without corruption, i.e., archived on the hard disk. There is also a record maintained on paper of the acceptance or failure of a particular label batch, which includes an actual copy of the label (see later for an example of a label version and change control logbook). These documents with their approval signatures form the basis of the audit trail in our system. The individual sheets, sheet 1 and sheet 2, can stay with the project data, and sheet 3 stays in the pharmacy as a non-study-specific work record.

Such a risk-based system has been approved by various sponsors' GMP QA auditors, but such an approach has not been given approval by MHRA GMP inspectors. I feel that such a system is adequate to ensure the integrity of labels without the need for actual audit trails, but this is only my opinion and may not represent the best possible approved practice.

Within the GMP environment, one of the difficult things for QA — who is perhaps instrumental in its creation — is the origin of the QC/QA confusion of definitions alluded to early on in this book. The QA department within the manufacturing industry takes samples for analysis to assure the quality of the individual components and finished products. This, by our definition, is QC and not QA. A possible problem now arises from within this confusion with the defined duties and responsibilities of the QP within the designated GMP area, in that they overlap significantly with existing QA activity and responsibility.

The solution I adopted was to prepare a limited QA SOP that provided management with the assurance that the quality systems were in place and working. This also provides QA with the opportunity to look at the "big picture" to consider systems improvements by removing the responsibility for most inspection and audit on to the QP. The other advantage, of course, in our case was that the QA manager was a QP, and therefore another member of the QAU could be used to provide a completely independent assurance of the pharmacy operations, thus completing the quality loop.

To simplify the position and the steps QA takes in these circumstances, I have extracted some of these from our SOP (procedure for inspecting pharmacy operations) below:

- QA should carry out at least one inspection of the pharmacy per year.
- QA should ensure that the company-appointed QP is named in one of the current registers of qualified persons maintained by the Royal Society of Chemistry, Institute of Biology, or the Royal Pharmaceutical Society of Great Britain.
- The QP will only perform the specific functions defined in the pharmacy standard operating procedures. These actions will be documented, and it is this process either during the live or historical phases that the QA auditor will check.
- The following are the documents to be checked by QA:
  - Label reconciliation
  - Label production version control audit trail
  - Record of receipt of study materials

  - Pharmacy record of receipt, movement, and destruction
  - Batch records
  - QP release documentation: suppliers and internal
  - All QC documents that form part of the audit trail
  - Site master file reviews
  - Certificates of analysis
  - Technical agreements
- Any deviations from the pharmacy-operation SOPs or QP's duties should be reported in writing to the CEO for appropriate action. If any apparent problems are noted during the live phase, these should be verbally notified to the relevant operational staff for immediate remedial action, if that is appropriate. After any such verbal report, a confirmatory written summary report should be issued to all parties.
- QA should confirm that suitable training has been applied and the appropriate record of this training is maintained for all personnel involved in the pharmacy GMP operations.

In order to provide you with some idea of the contents of the above documents used for controlling IMPs, I have provided some examples in Form 2.1 to Form 2.7.

Customer Complaints about IMPs

This is a difficult one even to define, but it is necessary in order to comply with the requirements of the legislation.

The following are examples of possible complaints relevant to IMPs:

Sponsor QP release:

- No QP release documentation
- Certificate of analysis not available
- IMP delivered not consistent with certificate of analysis or QP release documentation
- Labeling not GMP compliant (i.e., no expiry date, batch number, etc.)
- Appearance of IMP not consistent with certificate of analysis
- Shipping conditions inappropriate
- Relevant complaints from trial subjects

Organization QP release:

- Certificate of analysis not available
- Labeling of bulk supply not GMP compliant
- Manufacture (repotting or packaging) labels not authorized by sponsor
- IMP not stored as per sponsor instruction
- Errors in manufacture (repotting or packaging)
- Relevant complaints from trial subjects

Form 2.1 Label Reconciliation Sheet

Study Number: ________ **Sponsor Reference Number:** ________

Date	**Subject Number(s)**	**Period/Day**	**Produced by**	**Checked by**	**Used/Unused**	**Destroyed by**	**Witnessed by**
__/__/__		Period: Day:		Signature: Date: ___/___/___		Signature: Date: ___/___/___	Signature: Date: ___/___/___
__/__/__		Period: Day:		Signature: Date: ___/___/___		Signature: Date: ___/___/___	Signature: Date: ___/___/___
__/__/__		Period: Day:		Signature: Date: ___/___/___		Signature: Date: ___/___/___	Signature: Date: ___/___/___
__/__/__		Period: Day:		Signature: Date: ___/___/___		Signature: Date: ___/___/___	Signature: Date: ___/___/___

Form 2.2 Label Version and Change Control Logbook (1) Study-Specific

Original Copy

Study Number: _____

Protocol ID: _____

Date	Version Number	Attach Copy of Label in Box	Produced by	Checked by	Pharmacist Check
____/_____/____			Name: Signature:	Name: Signature:	Name: Signature:

Amendments required? YES ☐ NO ☐ NA ☐

QP approval: _____

Sponsor approval date:_____

If "YES" please comment and complete amendment form.

_____

_____

_____

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Form 2.3 Label Version and Change Control Logbook (2) Study-Specific

Label Amendment Form

Study Number: _____

Protocol ID: _____

Date	Version Number	Attach Copy of Label in Box	Produced by	Checked by	Pharmacist Check
____/_____/____			Name: Signature:	Name: Signature:	Name: Signature:

Amendments required? YES ☐ NO ☐ NA ☐

QP approval: _____

Sponsor approval date:_____

If "YES" please comment and complete amendment form.

_____

_____

_____

_____

Form 2.4 Label Version and Change Control Logbook (3) Pharmacy Work Record Non-Study-Specific

Date	Protocol Number	Project Number	Label	Version	Comments	Produced by	Checked by
Jan/10/06	ABC12345	555555	Treatment A Period 1	1	N/A	Name: Signature:	Name: Signature:
Jan/20/06	ABC12345	555555	Treatment A Period 1	2	Changes made to subject numbering, e.g., from 01 to 001	Name: Signature:	Name: Signature:
__/____/__						Name: Signature:	Name: Signature:
__/____/__						Name: Signature:	Name: Signature:
__/____/__						Name: Signature:	Name: Signature:
__/____/__						Name: Signature:	Name: Signature:

Note: The first two rows have been completed as examples.

Form 2.5 Record of Receipt of Study Materials

Study number: Sponsor reference: Carrier/supply agent:

Certificate of analysis received: YES ☐ NO ☐

QP release documentation received: YES ☐ NO ☐

Item	Batch Number + Expiry Date	Quantity	Date of Receipt	Received by	Checked by	Storage Location

Form 2.6 Pharmacy Record of Receipt, Movement and Dispatch of Clinical Trial Materials

Study Number	Drug Company	Drug Name/Code	Date Received	Received by Checked by QP Signature:	Carrier/ Shipping Agent	Expiry Date
Pharmacy Storage Area	Description Lot/Batch No		Quantity Received	Subject Nos/ Bulk Supply (delete as appropriate)		Period (s) – if applicable

Bulk Supply Accountability (If Applicable)

Subject No(s)	Period (s)	Signatures	Date	Number and Strength Active Medication Before/After Preparation	No Placebo medication before / after preparation	Sponsor Initials:
		Pharmacist: Checked by: QP:	Date: Date: Date:	Before: After:	Before: After:	

		Pharmacist: Checked by: QP:	Date: Date: Date:	Before: After:	Before: After:	
		Pharmacist: Checked by: QP:	Date: Date: Date:	Before: After:	Before: After:	
		Pharmacist: Checked by: QP:	Date: Date: Date:	Before: After:	Before: After:	

For Blinding Purposes, Study-Specific Drug Preparation and Individual Subject Accountability Forms in Possession of Clinical Services Manager until Database Lock

Date Returned/ Destroyed	Sent by/Destroyed by (Two Signatures)	Carrier/Shipping Agent (if Applicable)	Destination and Company (if Applicable)	Quantity Returned/ Destroyed	Used	Unused

Form **2.7** Manufacturing Record

Sponsor Reference Number		**Study Number**	
Drug Name/Code		**Group**	
Batch Number		**Period**	

Subject Number	**Day**	**Number of Active Tablets**	**Number of Placebo Tablets**	**Signed by (Pharmacist)**	**Witnessed by**	**Date**

QP witnessed: YES ☐ NO ☐ QP release issued: YES ☐ NO ☐

QP signature:

Date:_____/_____/_____

Once a complaint has been raised, there are two streams of actions based on where the complaint originates, either sponsor or organization. In order to assist in understanding a possible route of action, I have provided a flow diagram in Figure 2.1 and an IMP complaints form (Form 2.8).

Support Services: What Standard?

As yet, there is no defined standard for clinical laboratories to use, so our standard has to be GLP; this in itself is reasonable but does not go quite far enough. Within clinical laboratory tests, there have to be references to external results, which are used as standard ranges. There is also a requirement to use standardized methods, which belong to an external quality control standard organization (e.g., National External Quality Assessment Service [NEQAS], U.K., or National Accrediting Agency for Clinical Laboratory Sciences [NAACLS], U.S., who will provide information about their performance. This allows such laboratories to see how well they match the national performance and target concentrations. Such systems are not in use or required within a standard GLP preclinical laboratory, as normally the standard is set by the organization itself.

Form 2.8 IMP Complaints Form

Date ____/ _____/_____

Sponsor/Protocol Number:	Study Number:
IMP Identifier:	Chief Investigator Informed by: Date:
QP Release: Organization ☐ Sponsor ☐	Medical Director Informed by: Date:
Complaint: Continue over page if required	
Organization QP Informed by: Date:	Sponsor Informed by: Date:
QP Inspection Performed Y/ N Findings of Inspection: (Continue over page if required) Sign: Date:	Response from Sponsor: (Continue over page if required) Sign:
Actions Taken: (Continue over page if required) Sign: Date:	

Reviewed by: Date:

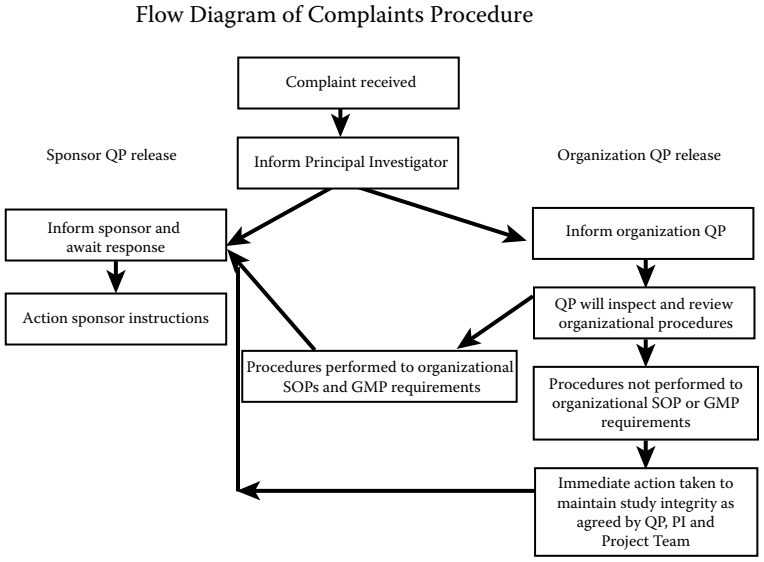

Figure 2.1 Flow diagram of complaints procedure.

Recently, BARQA (2003) has published a quality system for laboratories that undertake the analysis of samples from clinical trials, with the title Good Clinical Laboratory Practice (GCLP). This booklet of guidelines provides the framework for any supporting laboratory to build a quality system. It is based on many different sources of good practice, and of course, GLP is central to the hypothesis presented. The authors have distilled the requirements into an easy-to-digest format that is highly recommended. This publication can be used to provide you with the basis for a set of SOPs for a laboratory that is required to support a GCP trial. It can also be useful as a guide for QA when setting up the criteria you can use when auditing your own clinical support laboratories.

Before awarding a contract, a member of QA should visit the subcontractor. This visit must ensure that the proposed subcontractor is in compliance with the general requirements of good practice regulation (GxP). Special attention should be given to the following:

- Ensuring the subcontractor appreciates what is expected of them in the protocol or study plan and under any GxP regulations
- The adequacy of the staff who will perform the work
- The adequacy of the facilities
- Obtaining a copy or having sight of their health and safety policy
- Ensuring the subcontractor carries the correct level of liability coverage
- A financial check where a private sector contractor is being used
- The record keeping and retention of the original data (minimum of fifteen years)

An inspection plan should be drawn up by QA, which should reflect the services being offered and should be measured against your organizations' SOPs and internal inspection procedures. Where no formal SOPs are available within the external facility, working practice documents can be used as the reference documents.

When auditing or inspecting a clinical laboratory that is a subcontractor, you can use GLP standards in the main, or preferably, the GCLP guidelines previously mentioned. No matter what standard you use, you must also consider the origins of the normal ranges used and any participation in external QC or QA schemes. We have noted that the CPA scheme is an excellent one, and any laboratory that has such accreditation is an excellent provider of information. If you are called on to audit such an organization with respect to GLP, you should find it a pleasure but with a few caveats as mentioned earlier, such as lack of archives, electronic data issues, documentation and its control, and possibly, a formal QAU. Thus, they may not meet your high expectations.

Ethics Committees (IRB) and GCP

Ethical review boards or committees must now conform to the GCP legislation, and they have specific guidelines on how members should be appointed and their business conducted. In the past, the situation regarding ethics committees was a little haphazard and, in some cases perhaps, a little biased for reasons stated earlier — not really what we want when coming from the highly regulated GLP arena. These committees now operate in the same climate as everyone else in that they must have a complete set of SOPs covering all of their activities, and these must be regularly reviewed. All of their operations are subject to audit by the regulatory authorities and, as such, have a much more structured approach to approving or disapproving a trial. As yet, I have not had to carry out an inspection or audit of our local IRB's operations. I suppose this may come in the future.

The IRB now have an obligation to consider the following documents when making their decision:

- The trial protocol
- Protocol amendments
- Written informed consent forms
- Consent form updates
- Subject recruitment procedures (e.g., advertisements)
- Written information supplied to subjects
- The investigator brochure
- All available safety information
- Information about payments and compensation to subjects
- The investigator's current CV
- Any other documents the IRB requires

As can be seen from the above list, the IRB require very comprehensive submissions, so for a CRO, consistency in their submissions can ease the decision making process within the IRB, especially if regularly used.

One of QA's key tasks is to ensure that IRB permission is obtained before any work is started with the subjects. If this is not the case, then you have a clear instance of a GCP noncompliance.

SOPs in the Clinical Area

The technical details in laboratory SOPs are not especially pertinent in the clinical setting, as staff are not scientifically trained. However, this does not mean that the SOPs should be devoid of details but only that more explanations or pictures may be more appropriate. Any system that helps with interpretation of what is required is to be commended and will assist in SOP compliance.

One type of presentation of SOPs for, say, processing blood samples is most effectively prepared as a simple flowchart and displayed in the area of use. If, however, you chose to use such a system, you must ensure that if the flowchart is part of an SOP, it does not become divorced from the original document, and personnel are not using old SOPs. In such circumstances, it is necessary to ensure that the flowchart extract is identified, issued, and controlled in exactly the same way as any other SOP. Inspectors will expect that a robust method of controlling updates and changes to such documents is demonstratably in place.

Planned SOP Deviations

One common problem in the clinical area is that of planned SOP deviations. This is where the sponsor wants the CRO to do things "their way." Their way is normally defined within the protocol and is available to all staff for consultation, but it is a change from the normal, and as QA, you must monitor this closely during inspections to ensure the correct procedure is being carried out. This is really a great source for protocol noncompliance, even with study-specific training, and should preferably be avoided by discussions with the sponsor at the protocol production stage.

Data Protection Act (1988, U.K.) and Freedom of Information Act (2000, U.K.)

Before we go any further with this topic, it is my interpretation that the records we hold via medical histories (speaking for healthy volunteers) are not considered medical records and therefore do come under the scope of the Act. In a situation in which you are dealing with patients and proper medical records, this is probably not the case. If you are in such a situation, please check the requirements of the Act for your particular circumstances.

When dealing with volunteers in Phase-I, there is no such thing as an unsuitable volunteer, as even persons with disease states may be of potential use in some future study. However, maintaining a database of such potential volunteers does fall under the Act. It is therefore necessary for management to come up with a time frame over which such records may be "reasonably" held. This time frame has got to take into account the business aspects and the personal aspects of such data stores; I would suggest a period of 1 to 3 years. It could be kept longer if the volunteer was contacted again and asked for their permission in writing, but if such permissions were not obtained, all records must be purged of the old information. However you may wish to manage all personal data, it must be defined, and the most appropriate place for such a definition is in the relevant SOPs for volunteer recruitment.

As we are dealing with international pharmaceutical companies, we must take into consideration that some personal data may be transmitted to countries (outside the EU) that may not have similar legislation in place to protect the individual (e.g., the U.S.). Provision should be made to ensure that the subjects are aware that their personal data may be transmitted outside the EU, and that they must give explicit permission to allow this to happen. In most cases within the Phase-I arena, we only have informed consents and medical histories. Informed consents are stored with the project data, but the medical histories are not project specific and stored elsewhere. It is unlikely that any such personal information would ever be transferred outside the organization; moreover, it is normally anonymized by using the subject number and therefore not identifiable by third parties.

This type of action works fine for the storage and disposal of personal information, but perhaps more worrying is the fact that it may be possible for volunteers to ask for all information held on them to be made available to them. It is not the fact that this may contain sensitive information that worries me. It is a fact that we may inadvertently not disclose all the information we may have as it may be in several locations and not necessarily easily related. Since January 2005, this may be a criminal offence under the Freedom of Information Act (U.K.) (depending on the type of your organization, public or private), and you may fall foul inadvertently. This may not really be a QA function, but it may fall indirectly at its door in the operation of the quality system relating to an organization's records. It is therefore very important to ensure that all personal information that may be held in various locations for business use is easily brought together for interrogation. If these records are in an electronic database only, then this is made much easier, but we are still far away from the paperless office and will probably end up with paper copies as well. It is in your best interests to ensure there is a tie-up between all of the paper and electronic records of personal data, so that both may be accessed at the same time, which would be synonymous with good practice in any case.

Information Security

When dealing with any electronic data, personal or corporate, the security aspects must be kept at the forefront of your organization's thinking. In 1993,

13 multinational companies realized there was a real problem with data security, so they came together and formulated the document that became British Standard (BS) 7799 Part 1:1995. Most companies have now realized that security of data is not a fix-and-forget task, it is a system of continuous monitoring, action, reaction, and fixes. In fact, it is a culture change for IT staff, similar to the introduction of a quality system. The relevance of data and computer security is evident to us almost every day as the software giants push out fixes for the security flaws in basic everyday software that are exploited by hackers and virus writers.

Small organizations can get caught up in this spiral without any real concept of planning and direction. Such an incoherent situation within the regulated and quality industries just cannot be tolerated; we need some standard or standards on which to base our needs. Fortunately, there is a standard for such systems, that of ISO17799:2000; this standard addresses nearly all of the QA person's questions on data security. The standard is in two parts; Part 1 provides a code of practice for information security management, and Part 2 specifies the requirements for establishing, implementing, and documenting information security management. The standard itself has ten sections, described below, which illustrate the areas covered.

1. Understanding your organization's goals and its dependence on the data it produces or collects
2. Creation of an information security infrastructure
3. Identification and inventory of all IT assets from hardware to software
4. Personnel security
5. Physical and environmental security
6. SOPs for communications and operational management
7. Provision of specific access to data stores
8. System development
9. Business continuity
10. Compliance with regulatory authority standards

Even if your organization does not wish to go down the registration route, you can still apply elements from the standard to show that you have a high regard for data security, in exactly the same way as we have done with our pseudo-GLP clinical lab.

Standardized Reports: Regulatory Submissions

One very good way of ensuring the correct layout for regulatory submission reports is to use the ICH headings from the document Structure and Content of Clinical Study Reports E3, 1995 as your skeleton document. Within the Phase-I area, there are some sections that are difficult to interpret and fill in. In a lot of circumstances, this can mean a lot of duplication of text, but this does not appear to be a problem during the submissions. In my experience, this type of repetition, however, does not engender quality reporting, but

who are QA to argue with the regulators? Such a skeleton framework can be extended to include protocols, so that all the correct questions are asked and in the appropriate order. This has the additional effect of facilitating the IRB review of protocols. If they always use a consistent standard, the whole process is simplified by virtue of the fact that the IRB know exactly where to look in the document for what they wish to know.

At this point it may be useful to state that when producing a supporting-laboratory-based report for human samples, e.g., pharmacokinetic profiles, it is useful to indicate that the results were produced in an environment that used GLP principles. This may be achieved by the insertion of the equivalent of a GLP study director statement (U.K.) without actually declaring GLP compliance.

"No formal claim of GLP compliance is required for this study. Nevertheless, I confirm that study ID was carried out under my direction, that the practices and procedures adopted during its conduct are consistent with the Good Laboratory Practice Regulations, 1999, Statutory Instrument (SI) No.3106, December 1999, amended SI No.994, April 2004, and the OECD Principles of Good Laboratory Practice (as revised in 1997), Paris, 1998 ENV/MC/CHEM(98)17, and that the report represents a true and accurate record of the results obtained."

Of course, you will have to modify the references to the regulations being covered to match those of your own countries' regulations. (It is assumed that an SD is appointed in the laboratory independent of the clinical principal investigator.)

Staff, when writing reports, will always look for the easiest way to do so, using a previous report as a base if working on a similar project, or the protocol, cutting and pasting the required sections. It should be noted that the protocol can be considered a future-tense report without any data or conclusions, especially if the ICH report guidelines have been used, as suggested previously.

With word processors the *de facto* standard, there is great temptation for staff to cut and paste from protocols into the final report, and not change the tense; this can result in real problems with quality. Such practices mean that a report, which must be in the past tense, has some parts in future tense, and this reads badly and provides a totally unprofessional appearance. QC checks must be enforced to ensure that any reports are consistently in the past tense and that no elements are left in future tense. It is not, in my opinion, a QA function to edit poor reports, but to comment on the reasons for such errors, as well as how they can be eliminated, and to suggest modifications to the procedures to prevent future recurrence of the problem. This must be defined as a QC function, but QA should make sure that the sponsor is never allowed to see such problems if they have arisen.

Archived Data Disposal

On the surface, this would seem simple enough. However, it has been my experience that if you have an archive period of, say, 10 to 20 years, there

can be real problems for CROs wanting to do away with files of sponsored data. The principal ones are: (1) the original contact no longer works at the facility, (2) the company no longer exists, (3) the company cannot find any trace of the trial, (4) the company has merged several times, and (5) all trial information has been lost in the mists of time. How can you protect your organization from such problems? One possible way is to define your policy towards these eventualities and operate this within your SOP framework. One outlined example of a policy follows:

At the end of the retention period, the archivist or deputy should inform the study director or principal investigator of this fact and that he or she should notify the sponsor that the retention time has expired. This notification should be done by registered post (up to three consecutive occasions) to the last known address of the sponsor or best estimate thereof. If no response is obtained your organization reserves the right to destroy the data as per item 3 in the following text. You should allow a time frame of approximately 30 days between the notifications, and in case of no response, this should be adequate evidence that you did your best. Your letter of notification should provide the sponsor with three alternatives, 1, 2, or 3, as follows:

1. Retain the data in your archives: If this option is chosen, the new time frame involved will be documented, and this information will be placed in the archive with the retained data. The archive index should also be updated to reflect the new retention period.
2. Return the raw data to the sponsor: If so requested, all raw data should be returned to the sponsor by secure carrier, and the sponsor should supply written authorization that this procedure is required. The documentation for removal of the data and any other relevant receipts should be deposited in the archive using the same study reference. On receipt, the sponsor will be required to supply a certificate that absolves your organization from any further responsibility regarding the data. This certificate should also be archived using the study identification reference.
3. Destruction of raw data: If so requested, all raw data can be destroyed either by secure shredding or secure incineration. In this case, the destruction of the data should be witnessed by independent (QA?) staff, who should be required to sign a certificate of destruction. A copy of this certificate should be sent to the sponsor, where possible, and the certificate itself should be archived using the study identification as reference.

Organization's Policy on Fraud

Intentional fraud is one of the greatest problems in research, as the rewards can sometimes be considerable, although not necessarily financial; fame can also play an important role here, especially in the academic arena. Although intentional research fraud is rare, it is still difficult to detect and quantify, as

the people who perpetrate such acts tend to be very devious characters. It is therefore important that all possible attempts are made to prevent and to eliminate any such activities from the research process. QA is usually the first line of defense or detection for an organization because of the fact that they are involved in source-data verification, and consequently, they have a vital role to play in this regard.

Fraud may be defined in the research process as the generation of false data with the intent to deceive. It must be remembered that any deception can be extensive and difficult to detect, and auditors can frequently be taken in. Moreover, the stigma attached to any accusations of fraud, whether proven or not, can cause an organization the loss of its credibility and may even result in the organization's going out of business.

There are many ways in which research misconduct may be suspected. It can occur in the laboratory, where a colleague can see no evidence for certain conclusions to have been reached. It occurs, as is now well described in the literature, in all manner of ways within clinical research. The monitoring requirements inherent in both GCP and GLP, with all their associated audit procedures, are essential parts of the processes of both detection and investigation of suspected research misconduct. It requires the utmost vigilance from trial monitors and QA to minimize the risk of fraud going undetected.

Because of the nature of the type of work involved in the Phase-I process, fraud is unlikely. My reason for this thinking is that there is little or no reliance on third-party personnel (noninspected) to collect data on our behalf, so that the chances of fraudulent data making their way into a report is minimal. Moreover, there is little or no financial incentive for any individual to falsify data.

However, there is still a possibility that fraud of some type may occur and therefore you must formulate an organizational policy on the topic. As with most aspects of quality, the policy will have to reflect the risks involved within your own organization. A suggested policy is outlined below:

- In the case of suspected fraud by an individual or group of individuals, suspicions must be relayed to the CEO at the earliest possible stage.
- The CEO must arrange for the allegations to be fully investigated.
- The CEO should arrange for a documented report of the investigations and conclusions. This should be made available to the complainant and any other relevant bodies.
- Any person making allegations should not be subject to any disciplinary actions or chastisement for bringing information regarding suspected fraud to the attention of the organization's management. The exception to this rule is a case in which there are no reasonable grounds and the allegations are purely malicious.

The above, of course, deals with only individuals perpetrating fraud. However, you must consider that it could be organization-wide and include

the CEO. Where there is suspicion of fraud or failure of management to fully investigate the claims, the member of staff must have the right to take any or several of the following actions:

- To refer the case to the General Medical Council (GMC, U.K.)
- To refer the case to the GLP Monitoring Authority or GCP Monitoring Authority (U.K.)
- To refer the case to the United Kingdom Central Council for Nursing, Midwifery, and Health Visiting (UKCC), if nursing staff misconduct
- To refer the case to the Royal Society of Chemistry, U.K. (RSC), if analyst's misconduct
- To inform the appropriate ethics committee (IRB)
- To inform the study sponsor
- To refer the case to the police for further investigation of the criminal offence of deception.
- To take out a civil action

These actions, of course, are specific to the U.K., and you should use your own national registration and professional bodies.

As I said before, the likelihood of fraud in a Phase-I unit is not very high, but it is in your best interest to ensure you get commitment and a documented policy in place. Only by clear management and staff commitment to such a written policy, will you be able to convince your sponsors of your position in this regard.

chapter 3

Training in the Regulated Environment

Current thinking of managers outside the Good Practice (GxP) area is that training helps to motivate and retain staff, with the added advantage that absenteeism is also reduced. The concept of "training" is being supplanted by "learning"; this is a shift toward developing learning skills (Chartered Institute of Personnel and Development, CIPD). The main objective of learning is to help an individual become self-directed, with a clear set of objectives and maintenance of records of their progress, such activity is commensurated with the existence of documented procedures in the regulated environment. In order to obtain the maximum benefit from such an approach, it is necessary for the management to build a strategy to determine what skills and knowledge their staff should acquire and how they will do so. Learning is something each individual does, not something that others can do for them. A good learning program will allow individuals to realize their full potential to the benefit of both parties. Such thinking has always been part of the ethos of higher education and, perhaps, university graduates already have such self-learning skills built in. However, we must remember that all staff may not have been so fortunate as to attend university, and management must take this into consideration when designing their training strategy.

In order to facilitate compliance with GxP and business improvement, it is necessary for an organization to provide adequate training to allow staff to carry out their assigned tasks. There needs to be an environment where the trainer–trainee relationship is fostered to provide both positive and negative feedback, which can be used to encourage and motivate the trainee. This helps trainees to assume the responsibility for their own development and to seek out new learning opportunities during and after the formal training period. In our organization, we have separate training modules for different organizational units and have provided standard operating procedures (SOPs) on the topics that we consider essential. I have provided some examples in the following text of the types of topics covered in my organization in the different areas of operation.

These lists also provide the quality assurance (QA) inspectors with audit and inspection targets, which will help them in assessing the completeness of an organization's quality management system as well as the regulatory compliance.

Training of Laboratory Staff

Scientific Staff

- Personnel must be appropriately qualified to carry out their work.
- Management must ensure that appropriate training is given for all procedures so that all personnel are able to fulfill their functions. Detailed training records for each individual should be kept in their personnel file. These training records detail four levels or categories of ability:

  1. Under supervision
  2. Competent to operate
  3. Competent to maintain
  4. Competent to train

  Category C is only applicable to those staff who deal with pieces of equipment that require routine maintenance.
- Certain vocational qualifications (e.g., Higher National Certificate, HNC) require a high degree of practical knowledge, and personnel with such qualifications may be considered as requiring minimum on-the-job training.
- Graduate personnel with extensive laboratory experience may also be considered to have learned the basic laboratory techniques necessary to function as an analyst and, therefore, require minimal on-the-job training.
- New personnel, irrespective of academic achievement or experience, should not be assumed to have the necessary knowledge or ability without first demonstrating their competence to the satisfaction of management.
- Prior to the use of a procedure, management (see following text) will assess the ability of each member of the staff to carry out the work and, if satisfied, will record the competency of the individual for the procedure in the training record. Experienced staff may be assessed and certified directly as being competent for procedures for which they have had previous training or for those that are simple and require no more than a brief explanation, e.g., the use of a hot plate or vortex mixer. In other cases, where specific training is necessary, the "Under Supervision" category (A) of the training record will be signed by the trainer or assessor and the trainee. When sufficient training has been given so that the trainee can use a procedure without supervision, this will be documented by signing of the "Competent to Operate" section B.

- Advanced knowledge of equipment gained through further training or self-learning will be documented under section C — "Competent to Maintain." Individuals who have sufficient knowledge of a procedure to be competent to train others will be signed off to this effect under section D — "Competent to Train."
- Attendance at internal and external training courses on special topics relating to their work should be recorded in the individual's personnel file, along with other pertinent information, including the name of the institution where training was conducted, date of completion, and whether or not a pass was obtained.

Laboratory-Based Non-scientific Staff

Nonscientific personnel must be instructed as to the reasons why work is carried out according to Good Laboratory Practice or Good Clinical Practice and must understand the relevance of their job in the overall compliance program; instruction must include topics such as the way volumetric glassware must be cared for and the level of cleanliness and tidiness expected. Under no circumstances must untrained personnel have access to project-related materials or be expected to do any work whereby the integrity of a study may be placed in jeopardy. A record of any instruction and training given to nonscientific personnel must be kept on file.

Training in Data Management

- Management must ensure that appropriate training is given for all procedures so that all personnel are able to fulfil their functions. Detailed training records for each individual should be kept in their personnel file. These training records detail three levels of ability:
  1. Under supervision
  2. Competent
  3. Competent to train
- New personnel, irrespective of academic achievement or experience, must demonstrate to the satisfaction of management that they are competent, i.e., able to work on a task without supervision.
- Prior to the use of a procedure, management will assess the ability of each member of the staff to carry out the work. Management will record each member's level of competency for the procedure in his or her training record.
- Experienced staff may be assessed and certified directly as competent for certain procedures in which they may have had previous training or experience or for those procedures that are simple and require no more than a brief explanation, e.g., editing a text file.
- When specific training is considered necessary, the "Under Supervision" category (A) of the training record will be signed by the trainer or assessor and the trainee. When the trainee is involved with

project-related work, and an authorization to release data is required, both trainee and supervisor must sign the documentation — the signature of the trainee alone is not sufficient.
- When sufficient training has been given so that the trainee can carry out a procedure without supervision, they will be certified as "Competent" (section B).
- Individuals who have sufficient knowledge of a procedure to be considered competent to train others will be certified as "Competent to Train" (section C).
- Attendance at internal or external training courses on specific topics relating to their work will be recorded in the individual's training record, along with pertinent information, including the name of the training institution and the dates of attendance. Ideally, a certificate of attendance is obtained and a copy kept in the individual's training record. The maintenance of the training record is the responsibility of the concerned individual. This record should be signed by the trainee at least once annually to indicate the completeness of the record.
- Management must ensure that an up-to-date *curriculum vitae* (CV) is maintained on file for all members of the data management staff. All personnel must review their own CV annually and advise management of any significant changes.
- A job description is kept on file for all personnel that defines the general nature of the work they carry out. This job description is signed and dated by both the line manager and the job holder to indicate acceptance of the document.

Training of QA Staff

- Any personnel appointed to serve in the QA unit must undergo orientation to the organization's quality program, including the specific requirements of the U.K. Good Laboratory, Clinical, and Manufacturing Practice (GxPs) regulations.
- All organizational procedures are documented and are freely accessible to all staff, and it is the responsibility of all members of the staff to acquaint themselves with the contents of each relevant SOP.
- QA staff must be familiar with all SOPs in the organization. It is acknowledged that the reading and understanding of the documented procedures does not, in itself, constitute training and, therefore, all QA staff must be given on-the-job instruction and training in order that the highest levels of competence are obtained.

Documentation

- A training record is maintained for each member of the staff, and this is signed by both the trainee and supervisor at the completion of each section.

- Attendance at any external seminars and training courses is also documented in this record of training. These details are appended to this record in chronological order as soon as practicable after the event. Any certificates of attendance or competence is also included in the record.

Training Areas Identified

The following sections are defined as necessary for the complete orientation of new QA staff:

General	GxP guidelines and regulatory requirements To demonstrate knowledge by application	
QA SOPs	Awareness and knowledge application	
Inspections	Analytical lab	Practice and application
	Clinical area	Practice and application
	Biochemistry	Practice and application
	Studies	Practice and application
	Checklists	Production and modification
Audits	Protocols	Practice and application
	Archives	Practice and application
	Systems validation	Practice and application
	Report	Practice and application
Organization SOPs	Document control	
	Approval	
	Production	
	Archiving	
	Awareness of others referenced	
	Review procedures	
Archiving	Organization	
	Procedures	
	Archive operation SOPs	
	QA archives	
QA database system	Summary records	Operation
	Inspections/Audits	Report production
	Statistics	Query creation
		CAR issue and control
		System security
Company QA programme	Quality manual	Production or modification
	Management meetings	Audit findings
	Sponsor meetings	External monitors
	QA system improvements	Project targets
	Staff training	
	ISO 9001:2000	Audits or inspections
		Procedure manual

Training Period

- The expected time for completion of training is 6 months. However, it may be necessary to extend this period to 1 year if all the components cannot be covered in 6 months due to organizational operational requirements.

Supervision

- All study-specific QA duties are carried out under the direct supervision of a relatively senior member of the QA unit. When the individual sections detailed in the training record are completed to the trainee's and supervisor's satisfaction, both persons record this fact and also the date of completion in the training record.
- No study-specific reports or other project documentation may be signed by trainees until they are deemed competent by an entry to this effect in the training record.
- The supervisor countersigns any work carried out by the trainee until the relevant section of the training record is completed and the trainee is documented by the supervisor as being competent.

Ongoing Training

Once the basic training has been completed, an MS Word® table is set up to record all subsequent training that the individual undergoes. This document forms part of each individual's training record. This record has to be printed out on at least an annual basis to be signed and dated by the individual. It is the employees' responsibility to ensure that their training record is up-to-date.

Training for Archivists

Methods

Training is given to cover the following areas:

- Collation of all materials
- Organization of the materials
- Separation of archival materials
- Checking the list of contents
- Anonymizing the records where necessary (as data may be returned to sponsors at the end of the contracted period of archiving)
- Preparing new folders for holding materials
- Packing of materials in plastic
- Packing of folders in plastic
- Recording the addition in the archive register

- Recording information in a computer database
- Obtaining information from the database
- Dispatch of study material to a commercial archive
- Deposits in the on-site GLP archive
- Requesting archived study material from the commercial archive
- Monitoring temperature and humidity; testing of fire detection systems

Implementation

- Adding material to archives
- Access restrictions to the archives
- Maintaining a record of access
- Information retrieval systems
- Maintaining records of temperature and humidity
- Maintaining records of materials removed and returned
- Quality assurance
  - Full acquaintance with all archiving SOPs and adherence to their content is confirmed by on-the-job training, and certification of this capability is acknowledged in the person's training record.
  - All personnel are encouraged to attend any external training courses and seminars to broaden their knowledge of their duties. All such attendances are recorded in their training record.
  - The training record will record the fact that management have accepted that the person named has completed a period of training and is competent to carry out the assigned task. This fact is recorded with a signature in the training record by a management representative.

Let us take as an example the situation of a person who has worked as an archivist in the past but for whom no formal training records have been maintained. You now wish to do so in order to comply with the regulations. You know from experience that the person can do the job with his or her eyes shut, but there is no documentary evidence to show for all the years of experience. (This situation can also sometimes arise within the other service areas of an organization, but this does not normally happen.) Normally, areas such as archiving tend to be overlooked as they are, sometimes, not directly concerned with project work. How does one document this experience and competence? We do it with a statement in the training record, e.g.:

> The organization's archive has been in operation ever since the organization's inception; however, it is now expected to operate in accordance with the requirements of GLP and GCP. There are no formal records of the training undergone by existing personnel prior to this date. In the absence of such records, the general operations of the archive by the archivist(s) is defined by a statement

of competence signed by the CEO and appended in the person's training record.

Such a statement can be used in any training record regardless of the organizational unit and allows one to have a complete set of training records. The statement must be included in the SOP on training to ensure that there is a basis for using it as a policy statement.

Training of Medical, Nursing, and Technical Staff

In the Phase-I drug development process with which we are concerned, it is very necessary to ensure that a comprehensive level of training is provided and documented as this is always required by sponsors and inspectors. Such training must be very specific, otherwise external QA auditors may raise this as an issue (unnecessarily, in my opinion, as it does not seem to be a problem in most other disciplines within the Phase-I drug development process, as is demonstrated by the modified extracts from the training SOPs provided here). However, even if such a level of detail is not required, comprehensive records must be kept for all disciplines.

In Phase-I (or any other phase, for that matter), clinical training may be separated into the following areas:

- Orientation and basic training
- Prestudy requirements
- Basic ward skills
- Extended skills
- Study-specific procedures
- Records of additional training

I have provided a list of the topics covered during our clinical staff training. Of course, these tasks are defined within the clinical SOPs where appropriate. Also, this list should not be considered exhaustive; it is only used here to illustrate the level of detail that is required to satisfy sponsors. This detailed training is especially necessary for nurses whose only experience has been within the confines of the National Health Service (NHS), without the extra quality and regulatory requirements now required in a CRO. The list of topics is as follows:

- Introduction to members of staff
- Confidentiality agreement
- Tour of premises, including security of building
- Basic information about the work of the organization and how it is run
- Existence of SOPs and training records
- Explanations of GLP/GCP and QA
- Organization policy on research fraud
- Volunteer recruitment

- Volunteer confidentiality and the Data Protection Act
- Rules of conduct for volunteers
- Consent and contract forms
- Recording demographics
- Rounding off numbers
- Volunteer travel expenses
- Case record forms (CRFs)
- Clinical request forms
- Adverse events — reporting, recording, and management
- Recording results, corrections, and signatures
- Study information — distribution and communication
- Drugs — prescription and administration records
- Resuscitation — use of the defibrillator
- Use of controlled drugs
- Calibration of balances
- Using e-mail
- Organization's computer network
- Freezers for sample storage
- Testing for drugs of abuse
- Hematology and biochemistry sample handling
- Blood sampling by venipuncture and cannulation
- Urinalysis
- Urine collections
- ECG recording
- Blood pressure recording
- Recording of body temperature and respiration rate
- Breath testing for smoke and alcohol
- Pregnancy testing
- Subject number and treatment code by randomization
- Monitoring Of CRFs
- Recording protocol deviations
- Volunteer withdrawal
- Archiving — documents and drugs

Training for Medical Staff

As would be expected, this training contains the same elements itemized in the previous section, but with a greater emphasis on volunteer and regulatory issues, which are matters that medical staff have to deal with in their day-to-day activities. Noncore activities, e.g., GCP training, advanced life support, preparation of ethics submissions, and writing a regulatory report must also be documented in the experience and training records. It is one of QA's tasks to ensure that there are no large omissions in the medics' training records as medical staff are sometimes guilty of leaving out what they may consider as something that "goes without saying."

Different Training (Learning) Methods for Different Areas?

We must also make allowances for the fact that staff members from the different disciplines involved in the trial process — medics, nurses, scientists, statisticians, etc. — all have their own professional standards, and it can be difficult to have a "one-size-fits-all" approach to training and the maintenance of records. This is clearly evidenced by the types of training records and methods described earlier. Also, as record keeping is chronological, evolution of different record-keeping methods is inevitable and, consequentially, the recording format tends to be disparate across the disciplines and can be lacking in coherence. These individualistic ideas on how records should appear tend to come from those areas considered more academic, such as science or medicine. In these areas, it is normal to include continuing professional development in your CV and not in a training record or, more recently, a record of professional development issued by the appropriate professional body. Breaking down these barriers is somewhat difficult but must be pursued by management and QA in order to get some form of standardization.

It has been my experience that both systems can operate quite happily together as both are trying to achieve the same goal i.e., that of recording your professional competence. Operating several systems may call for differences in SOPs on training as illustrated in the examples provided, but the organizational training records can be in the same format and style across all the various disciplines. Such an approach is consistent with good practice and it is much easier to maintain if only a single way of doing things is adopted. It also makes it a lot easier for QA, both internal and external, to randomly inspect training records if they are consistent in the way data is stored.

Because external auditors always request training records, it makes sense to have a consistent approach to the maintenance and completion of these records. Of course, human nature being what it is, QA still need to "get heavy" with line managers who let their pressure on individuals diminish and fall behind in the updating of records slips. This is one area where an otherwise perfect organization is easily let down; when matters are left to the individual to keep up-to-date, it is always a source of problems. QA should also remember that the sin of omission is very difficult to detect either by inspection or audit and consequently press line managers into taking affirmative action.

In order to assist you in the recording of your organization's training, I have provided an example of an extract of a clinical training record from specific SOP topics. This is just a basic table format produced with a word processor and, therefore, should be simple to reproduce; the difficult part is identifying all the areas that must be covered. This format, of course, should only be used as a suggested layout. I have, however, found that such records are usefully contained in some form of ring binder, with plastic pockets and colored dividers; one binder can be maintained for each staff member with,

perhaps, binders of different colors for different staff categories. The dividers can be used to separate the records into sections such as the following:

Front section: Personal details (full CV) and abbreviated CV
Section 1: List of jobs held, with job descriptions
Section 2: Copies of certificates, registrations etc.
Section 3: General organization orientation records
Section 4: Training and education log, including specific GxP training
Section 5: Competency log, indicating levels of competency
Section 6: Specific SOP training and change notification log
Section 7: Records of management appraisal
Section 8: Additional information

The pockets also allow the insertion of certificates of attendance, competence, etc. or whatever suits the particular situation.

Earlier, I mentioned project-specific training and SOP training. I have provided a flowchart (Figure 3.1) which illustrates the processes that may have to be gone through in order to cover most of the bases with clinical staff training.

Assessment of Training Effectiveness — How?

Assessment of the trainee's theoretical and practical skills is a necessary part of the training experience for both trainee and trainer (Figure 3.2). Trainers should liase with their colleagues to monitor the trainee's development throughout the training period. Continuous feedback from colleagues will assist the trainer and trainee to identify areas that require further development or to identify areas in which the trainee has shown significant skills.

At first sight, assessment may appear to be simple because up to now, I have dealt with tasks which are observed during initial training and assessed directly by the supervisor. The more problematic area is the one that deals with changed procedures. Specific study training can accommodate this, but there will always be gaps, especially in the very basic skills that "everyone knows"; if these change and staff do not regularly use them (or if the staff are part-time or occasional), the situation can be a real problem. In the case of the latter two types of staff, it should be appreciated by management that such staff must come in specifically to read the new or changed SOPs, as well as for training, and they must be paid for this.

In our organization, all procedures are covered by SOPs, and we notify staff when there are new SOPs that they should read and understand. This is done by several methods such as a letter to occasional staff or by attaching a notification to salary advice slips. The staff members sign and return this to their line manager, which indicates that they are aware of the change and will comply. However, human nature being what it is, with people not wanting to do a lot of extra work, these slips may be returned signed without the person's having read or understood the details regarding the changed

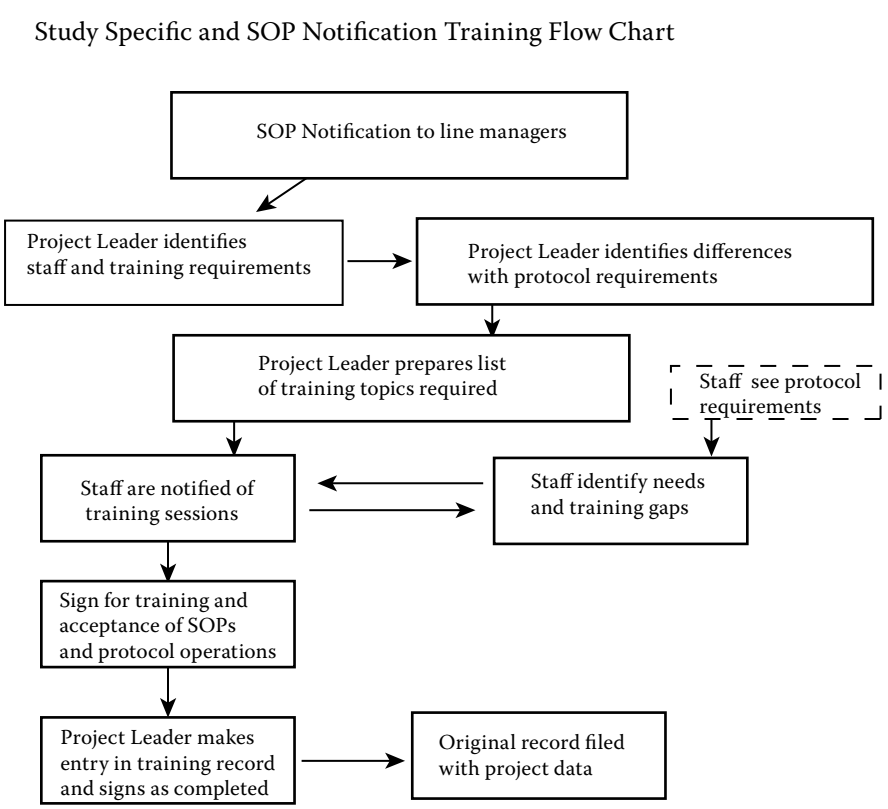

Figure 3.1 Flowchart of suggested training steps for practical topics.

procedure. It is necessary to identify such problems before they become an issue.

There is also an inherent problem here in maintaining a record of who has replied and who has not and, consequently, which staff is available for carrying out work on a study. (No one who is not familiar with the new or SOP changes is allowed to work on a study). This type of operation is time consuming and error prone if carried out manually. If the records of the replies received are entered into a computer database, then it becomes a simpler system to operate. Queries can be run to identify personnel who have completed all SOP training or, more importantly, to establish who are the defaulters and thus target the correct people to prod into some affirmative action. Such a database management system is essentially the same as one that can be used to monitor review status of the SOPs themselves.

When you are sure that your staff are familiar with your new or changed SOPs and training, you will probably note that some form of assessment is required in order to assure yourself (and others) that they are up to speed in the current procedures and not stuck in some time warp. The first method of assessment is obviously provided by observation by the trainer of the

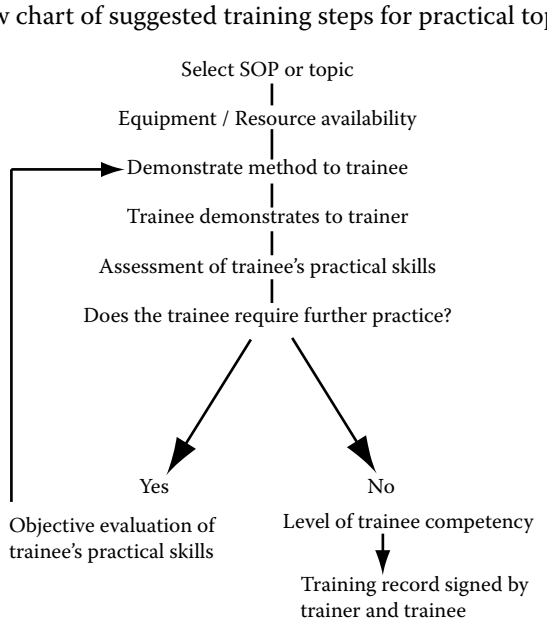

Figure 3.2 Study-specific and SOP-notification training flowchart.

trainee carrying out the task. However, there are areas where observation is not possible or is too labor intensive. In such situations, a couple of assessment options come to mind, such as providing written tests for personnel utilizing questions based on SOPs and techniques. In the larger organizations, "e-learning" is much more useful as a lot of personnel can be trained in their own time or spare time. This type of training is based on interactive multimedia examples of the topic, which is followed by multiple choice questions based on instructional material. There is normally a pass mark set, which could be up to 100% depending upon the material, e.g., health and safety requirements. For the smaller organizations, although this method may be ideal, the costs, time, and skills involved in producing the training material rules out this choice. Of course, for the example given earlier, that of health and safety training, there may well be commercial offerings which will fill the gap. There are also college courses that are available on-line; these are especially useful for nongraduate staff training.

It is clear to me that no matter what the form the training, we must have some robust method of examination or assessment; else we cannot be sure that we have covered all the bases. So we must investigate current commercial offerings to see if they can fit our assessment requirements. There are several vendors of multiple choice questionnaire software in the market place; one of the most comprehensive and simple to implement is the Question Mark® package that is widely used in U.K. universities for both examination and assessment purposes. Of course, paper-based systems can be

used, but these require human resources and considerable time to produce and to mark the responses, whereas the electronic assessment process saves a considerable amount of time and human resource. The electronic method also has the great advantage that it allows the trainee to have "several goes" to get it right, and because they have to reread the SOP or training material to do this, it can also provide a high degree of reinforcement.

Whatever form of assessment is used, it is essential that you maintain records of these operations in the training records. Therefore, it makes good sense to have a system that can automatically produce a written assessment report. This latter component is another bonus that makes an electronic system so much more attractive.

QA Inspection Points

When carrying out facility inspections and checks on personnel and training records, what should you be looking for?

- Evidence of recent entries in training records
- Certificates of attendance, competence, etc.
- Training SOPs with time frames and compliance
- Reasonably detailed job descriptions
- Single-page, condensed CVs
- Full CVs

The last three items should be signed and dated by the person to indicate that the employee is happy with, and confirms, the contents of the documents. The job description should also be signed and dated by management to indicate both parties' acceptance of the details. Catch-all statements should not be allowed, for example, "… any other duties that management wish." As with all Good Practice, management needs to be more definite in their statements regarding what they are employing people to do.

Name_____Training Record for Clinical Staff

	Skills	Instruction Date	Signature of Trainer	Signature of Trainee	Competency Date
	Breath testing by smokerlyser				
	Pregnancy testing				
	Use of automated external defibrillator				
	Drug administration				
	Measurement of blood glucose				
	Calibration of MediSense card sensor				
	Preparation of heparinized saline				
	Alcohol breath testing				
	Urine collection				
	Urine measurements and testing				

Name _____ Training Record for Clinical Staff

	Skills	Instruction Date	Signature of Trainer	Signature of Trainee	Competency Date
	Drugs of abuse testing				
	Hematology and biochemistry sample handling				
	Laboratory normal ranges				
	Blood sampling by venipuncture				
	Blood sampling by cannulation				
	Blood pressure recording and pulse oximetry				
	Recording of body temperature and respiration rate				
	Monitoring of CRFs				
	Protocol deviations				
	Procedure for volunteer withdrawal				
	Use of centrifuges				
	Drug accountability				

chapter 4

Computing in the Regulated Environment

Before 21 CFR Part 11

The early eighties was a period of mass adoption of personal computers, and the enthusiasm continues. The main difference today is that they are cheaper and more powerful. Many instruments of that time, such as the HPLC machines, used the microcomputer to control such things as gradient elution. Today, most such instruments have their logic and processor units built into them. The electronic revolution has provided us with the paperless office that we were promised back then.

It is only now, when using the majority of today's shrink-wrapped, off-the-shelf software, that we begin to see that there are huge problems with this paperless ideal. The major issue with such software is its inherent ability to modify or delete data without any trace — the electronic version of correction fluid. Ironically, this was exactly what we wanted when we purchased a computer in the first place, but it can create problems in some fields.

It is human nature to make mistakes, and we want these errors corrected before we commit our work to paper or allow anyone else to see them. However, it is exactly this process of hiding changes that the regulatory authorities wish to prevent. They want us to provide indelible evidence that can convince them that there has been no deliberate act of deception. All software used to manipulate or store regulatory data must be able to provide this evidence in the form of an audit trail of what was done by whom, why, and when. This was not really seen as a problem until the pharmaceutical companies wanted to submit their dossiers electronically, and this information was required to assure the authorities of their accuracy and truthfulness. They wanted a full electronic submission, warts and all, not at all what the industry had envisaged when they first suggested the electronic route.

The instruments were *black boxes* with paper outputs that were signed by the operator as the raw data and provided a paper audit trail of who, what, why, and when. If these were reprocessed (e.g., chromatograms with

misaligned baselines or peaks), the first printouts were kept and the second printouts considered as the correct results. Both printouts form the raw data. These data were then extracted and read into a computer for summarization or manipulation. Such systems were classed as administrative tools and are not really concerned with the raw data.

Within the Phase-I arena, it was obvious that there was a problem owing to different machines being used in the studies, e.g., portable blood pressure machines and electrocardiograph (ECG) machines, both with printouts. Within the laboratory setting, most of these issues of interfacing with computer systems had been sorted out by the adoption of laboratory information management systems (LIMSs). The clinical area still does not have such evolved systems; however, this is changing rapidly as the market responds to current regulatory requirements.

The quality assurance (QA) unit must ensure that the management defines and documents what raw data is and adheres to it, as everything thus defined must be maintained in the archives for study reconstruction. QA should only concern themselves with the audit and inspection of these data. The workings of the black boxes are outside the QA's remit, but they should have a calibration record if possible.

Although computers can be defined by management as administrative tools, QA should still audit them (especially from a business perspective) to ensure integrity of the data and the system itself. Any data that pertains to a project which is stored on the hard disk of a computer must be subject to regular backup, either to a network server or to a local device such as a disk or tape drive. Backing up the data is important, and testing its restoration capability is crucial. QA has to ensure that the documented procedures for such operations are reviewed and the systems tested for their ability to restore the data regularly.

Proper paper records of this backup restoration process must be kept and inspected frequently to ensure adequate protection. It can prove advantageous to carry out "fire drills" to ensure that data can be recovered from the last documented backup. The frequency of backup should be determined by the amount of data that the management is prepared to lose or repeat. Daily backups may not be frequent enough to prevent a significant data loss. For example, a pharmacokinetic/pharmacodynamic trial may initially collect large amounts of data over a very short time frame, say 1 to 2 h. If this data were lost later the same day, the consequences could be catastrophic. The preferred storage medium in such cases would be network volumes and not local disks. Such storage to high-capacity volumes is to be preferred as the chances of data loss are minimized due to the operating system's inherent security with data storage. An example of this would be the use of Netware® volumes in which deleted files are not overwritten until the volume is full and even then the overwrites are in reverse chronological order. The other big advantage is that with a single investment in high-speed, high-quality backup devices and software, such a system can be centralized and automated to avoid human errors, namely forgetting to do the backup.

The data from machines or manually recorded, say, in a case report form, is entered into the computer using some form of front end such as a form created from a database management program or a spreadsheet. The latter is probably the most frequently used. Several spreadsheets are available, such as Borland Quattro®, Lotus 1-2-3®, or Microsoft Excel®. Today, Microsoft Excel is probably the most common.

Normally, the spreadsheet is set up to provide a calculation template that is copyable but not modifiable as the embedded formulae are contained in locked cells. This should be a priority for QA to check to ensure that a template that has been tampered with is not used to overwrite the master document. One of the easiest and quickest methods of checking is to look at the file details, which always carry time and date stamps that report when the file was last modified. These details can then be compared to the previously recorded creation date. Systems that prevent users from doing anything other than copying a file can be put in place on networks. In fact, it is almost impossible to have a reasonably secure IT system and implement access rights without having a secure network infrastructure. By using a client–server model and a real network operating system rather than a peer to peer one, fine control can be exercised over the users' activities and their file permissions.

If a GCP/GLP system is attached to a network, what level of validation and control over change will inspectors expect of other network servers that are required by the network but may be external to the organization, e.g., Domain Name Servers (DNS), e-Directory®, and Active Directory® servers? This is a case for carrying out an assessment of the possible risk they pose to the regulatory systems. In general, infrastructure associated with regulated work should be qualified and changes controlled and documented. The level of any validation will be determined by the potential impact of such systems or servers on the regulatory work done in an organization.

IT Systems in Organizations

One of the items an inspector will want to see, regarding an organization, is its *organogram*, which is the graphical representation of the management structure and reporting structure for personnel. In IT systems such as computers, servers can be usefully illustrated in such a fashion (Figure 4.1). This is a useful tool in QA's armory to locate and identify any individual PC or server and check data security and file existence. It is also useful to IT as a map of where individual workstations or PCs are attached to the network.(Figure 4.1)

QA in our organization also checks the calculations by producing templates using their own algorithms, which are independently prepared and do not use internal functions for calculations. The functions are all derived from first principles and confirmed manually and by the use of a calculator. The results of such tests with dummy data provide them with an absolute comparator with which to check the project spreadsheet calculations. This

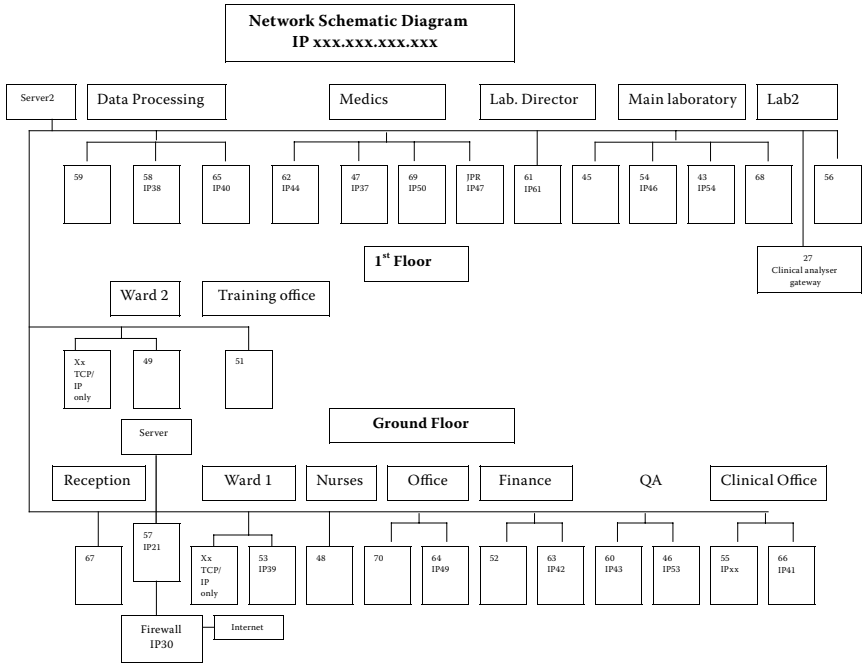

Figure 4.1 Network schematic diagram.

also has the beneficial side effect that the internal functions that are used in the working template are also confirmed.

It was by using such procedures that we were able to spot an error in Microsoft Excel 97's statistical function for a t-test (degrees of freedom were incorrectly applied, but defined correctly in the help system). Just because you buy software shrink-wrapped and off the shelf, you cannot assume that it does all things correctly. You must validate if it is fit for the purpose. Carrying out some library literature searches for similar calculations indicated that Microsoft Excel had been used for their calculations too, as their results also showed the incorrect answer. The error produced was not very significant and, consequently, did not affect the statistical conclusions. Other examples exist in the literature, when using certain hardware or using certain versions of operating systems resulted in erroneous answers being produced. All these examples illustrate just how easy it is to just assume that the computer system is always right. Validation from first principles must be the QA mantra.

This is probably a good point to introduce a QA consensus definition of "validated."

> Validation is the ongoing process of establishing documented evidence that provides a high degree of assurance that a computerized system will consistently perform according to predetermined specifications and quality attributes. It encompasses the

> whole lifecycle. If there is sufficient evidence providing a high degree of assurance that the system is fit for purpose it can be said to be validated.
>
> **BARQA Regulatory,**
> **Compliance and Computing Course, 2004.**

Spreadsheets have a strong presence in most organizations. But these applications do not have any built-in audit functions to record what was changed, why, when, and by whom. The only way around this audit trail problem is to print out paper copies before any modifications are made so that an indelible record is made. This can be signed by the operator, and changes and reasons, etc., appended to such records. This procedure can then be used for each successive generation of the spreadsheet file. All such paper records form part of the raw study data and are maintained in the study archives.

These spreadsheets are normally used to perform intermediate calculations, e.g., interpolating values from a regression line of measurement vs. concentration. Subsequently, the calculated values are used as input for another software package such as a word processor or, more commonly, a statistical package such as SAS®. This will provide tabulation functions based on some simple criteria such as study phase, QC values, and calibration standards. Such software allows the simplification of getting numbers into tables within a word processor, which can end up as several hundred tables in the course of a report production. Any system that simplifies the production of such tables is very welcome from the point of view of accuracy and precision.

Adding other similar software packages, and perhaps even other computers, into the process makes the production of a unified electronic audit trail much more difficult. There have to be QC checks on the source code that is used to extract data from the raw-data files, with more printouts at each stage of the process. Every stage is fraught with the possibility of major errors creeping in, and these have the unfortunate tendency to be systematic, rather than any individual data values.

As can be seen from the previous discussion, what appears on the surface to be a simple system can be a disaster waiting to happen if stringent controls are not in place, including training and Standard Operating Procedures (SOPs). How can we make such systems more error resistant and obtain the Holy Grail of a complete and accurate audit trail? We must also remember that any data errors found within or out of the audit trail must be investigated and corrective actions taken to ensure that they do not recur.

With all computing systems, there is a rapid turnover of versions and security fixes to the basic operating systems, and it should be a considerable worry to QA when such fixes are applied. These questions must be asked: Will this basic change have any effect on my validated system and if so,

how? An example would be laboratory PCs that have patches applied to ensure they cannot be hijacked by some malicious Trojan or worm that provides an access point for some external malpractice. It is vital to ensure that such systems are also protected by the use of antivirus software that requires the regular updating of the virus signatures to provide up-to-the-minute protection from such malware.

Having patched the system and updated the antivirus signature file, how do we check validity? One possible solution is to perform a risk assessment of the changes made to the system and its current status. Revalidation should be proportionate to the level of change being made. QA and management should produce a policy on this process, which can be referred to so that QA does not have to carry out a risk assessment every time a simple change is required.

Validation of Computing Systems

This is always a difficult topic for scientific QA, who, in the main, does not really understand the software and hardware interactions. This is analogous to using a motorcar but not knowing what is going on in the engine compartment. QA has to understand the processes but not necessarily the details of the computing system's operation. Within the small CRO, it is unlikely that you will have to deal with large custom software or hardware systems that are legacy or new systems brought in to improve workflow. Such systems tend to be out of place in the smaller organization. Most of your validation work will be concerned with shrink-wrapped, off-the-shelf software. Sometimes, with scientific data collection or laboratory information systems, there may be other issues that require addressing, but here I will concentrate on the shrink-wrapped type. In any case, these larger system purveyors normally offer to provide most of the validation documentation for you, because they will have experience of such installations within the regulated environment.

What is meant by the term *computer validation*? The software programs, or the hardware, or both, or even the same program running on different computers — what is it that QA should look at?

QA must involve itself with the whole system — software and hardware combined — and within these parameters, the whole software life cycle (General Principles of Software Validation; Final Guidance for Industry and FDA Staff, U.S. FDA, 2002). The topics for consideration here are as follows:

- Quality planning
- Defining the system requirements
- A detailed software requirement specification
- Software design specification
- Construction or coding
- Testing by software developers
- Installation

- Operation and support
- Maintenance
- Retirement

A *system* is defined as the hardware (including firmware), the operating system software, and the functional software. No one item can be independently separated or changed for another, all individual items are considered as one integral unit.

For the shrink-wrapped package we have not got the power nor the ability to carry out some of the life-cycle activities. So what can we do in such cases? We do our best, by carrying out the activities we can do, such as:

Quality Planning

Produce a plan (protocol) that identifies what we are going to do, how problems are to be reported and resolved. Produce a life-cycle definition pertinent to the system being validated.

System Requirements

A written definition of what the system does. A set of documentation that defines the hardware and operating system the software is designed to run on. There should also be a section based on the user requirements, what the user expects the software to do.

Design, Construction, and Coding

This is an area in which we have little or no scope to investigate, because such software code tends to be proprietary and secret to the suppler, e.g., Microsoft®, SAS®, etc. However, if code or macros are built into, say, a Microsoft Excel® template by staff, then it is these aspects that require to be considered, such as definitions of variables, warning messages, systems documentation, and even SOPs for such procedures.

Testing the System

These should be tests carried out using data whose results are already known. There should also be stress tests carried out using extreme data such as nonexistent dates or values that are either too small or too large. This will ensure the proper handling of such errant data. In any case, the outcomes of all tests must meet with the predefined answers in the quality plan.

Installation, Operation, and Support

Once the quality plan objectives have been met, the software should be installed on the target machine if not already there, and some actual test data run on the system, i.e., a normal set of data whose results are known

and are typical of what may be met on a daily basis. Passing such a test would indicate its fitness for the purpose. Support for such systems is probably limited to ensuring that no changes in macros or templates have been allowed without some form of risk assessment being carried out. Normally, it would be the user who carries out such tests but this can be difficult with a user who is short on IT experience. If this is the case, then some IT help should be sought from either inside or outside the organization.

Maintenance and Software Changes

Whenever any software is produced or purchased, it is unlikely to cover all of the specific operational needs of the organization or to be bug free. There has to be some mechanism whereby these errors can be repaired or some changed needs accommodated. Depending upon the extent of such changes to the software, you will have to determine the level of retesting required via a risk assessment. With any changes to the code, e.g., as when deploying service packs, the fact that these have been installed must be documented within the documentation pack for that system.

Retirement

Once a system is to be replaced by, say, a new version of the host software, it is a good idea to take all copies of the software, the added code, the master program, the system documentation and archive these in the same manner as you would do with any paper record. The actual ability to restore such items in 15 to 20 yr is highly unlikely, but you should still make the effort. There is no point at all in archiving the hardware; such a measure would not be expected.

Validation: QA Notes

All validation is of course an up-front process, it cannot be done with a system in operation. It must be done in a similar way as you would produce a study plan or clinical protocol. When auditing or inspecting such a validation, you should expect to have full sets of documentation describing all aspects of the system development and SOPs for the systems operation, which should also provide details of the limits of constraint under which it may be used.

When dealing with more complex systems such as a custom-built software suite such as electronic data capture or scientific data management systems, more complex and detailed documentation is required to describe the validation process. Such systems are outside the scope of this book; for further information and detailed requirements, a search on the FDA and Pharmaceutical Inspection Cooperation Scheme (PICS) Web sites is recommended. For any systems used in clinical trials, a good document to refer to is *Computerized Systems Used in Clinical Trials*. This document was produced as a guidance for

industry by the FDA's Bioresearch Monitoring (BIMO) Program. As a point of information, it should be noted that validation records are outside the scope of 21 CFR Part 11, but you should keep these records for completeness, as these will still be required under the predicate rules.

After 21 CFR Part 11

The FDA regulations 21 CFR Part 11 became effective in August 1997 and has been causing compliance problems for industry ever since. There are several key elements of this legislation, and I will outline these below as they are essential for fully understanding the impact of the regulations and why the industry still finds it very difficult to comply.

21 CFR 11 — Key Elements

Electronic records:

- Trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper
- to records … under any records requirements set forth in agency regulations (predicate rule)
- Different requirements for closed systems and open systems, with additional controls required for open systems
- Validation of systems
- Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records
- Protection of records to enable their accurate and ready retrieval throughout the records' retention period
- Limiting system access to authorized individuals
- Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
  - The printed name of the signer
  - The date and time when the signature was executed
  - The meaning (such as review, approval, responsibility, or authorship) associated with the signature
- Shall be included as part of any human readable form of the electronic record (such as electronic display or printout)

Electronic Records and Signatures

The whole purpose of this legislation was to provide the industry with the ability to submit their registrations electronically. This, of course, allows industry to streamline operations and, consequently, to save money. The unforeseen problems were those of audit trails that are still not implicit in

most of today's shrink-wrapped software packages but was always going to be a regulator's requirement.

It is my assumption that companies thought they could just carry on as before and add on the electronic parts. This was turned on its head when it was realized that you could not mix paper records and electronic records of the same system.

At this point, it would be useful to present my definition of system compliance. If a system captures data directly, automatically, or via an input device then it produces an electronic record and must conform. If outputs to paper are produced, ask the question — which would you use first, the paper or the electronic output? If the electronic output is used in preference (e.g., reading in data) to paper then that system must conform.

Hence, hybrid systems were not allowed; you had to go one way or the other, and this caused the American industry some real headaches in that some hybrid form had been envisaged from the beginning. It now transpired that this was not the case, and that they, as an industry, could most probably not comply. This lead to a confrontation between the FDA and the industry, which was only resolved recently when it was announced that there was to be a slight relaxation of the regulations to allow some paper systems. However, even in this relaxed atmosphere, it must still be borne in mind that the final goal for the FDA is still the implementation of totally paperless submissions, and its e-record-gathering definitions are used to support this aim.

Electronic Signatures

The first real issue with any form of electronic data was with definitions of recording who did what and what comprises an electronic record. Taking the first definition first, that of electronic signatures or e-signatures, this placed the requirement that individuals be provided with an electronic signature. This could take many forms such as a token or smart card, etc., which is used to authenticate the user at the point of joining or storing data on a system. Still, the most common system in use today is that of usernames and passwords, which is the simplest to implement. However, this can cause problems because of the problem of people sharing passwords or allowing someone else to access their account and files. This is especially a problem when several people are feeding data into the same computer file, and the same rights are granted to several people. Normally, it is just laziness or the inability to remember an infrequently used or rapidly changing password that causes such breaches of security. In the e-signature environment in which usernames and passwords are used, excuses on the inappropriate use of passwords cannot be tolerated, and it is up to management to severely discipline any such abuse of the system.

How do we set up such a system? Firstly, management must define its position regarding usernames and passwords and make any abuse such as sharing passwords a disciplinary offence. Usernames and passwords must be regarded on the same level as bank debit cards and Personal Identification

Numbers (PINs). Would you give these away to a colleague without any restrictions? Of course not, you do not trust them enough!

1. Users must be made to sign a declaration stating that they will allow the use of their username and password to be their personal identifier in exactly the same way as they would with their written signature. Then, if an audit trail indicates that they modified or created a datum point, this fact will be indelible proof that they are responsible.
2. An *electronic record* (e-record) can be simply defined as the first recording of data in a computer file, and this information is assigned to an individual and at a particular time. This data can either be keyed in manually or captured from a device; it makes no difference.

To facilitate the coordination of large amounts of shared information within and outside the organization, network operating systems are commonly used. These systems themselves now tend to have open access to the Internet for external transfer of information to sponsors and, more usually, for research purposes such as downloading information. The regulations accommodate such situations, in that tighter security systems, such as fire walls and even encryption of the data, must be in place. This text will only deal with computer systems within an organization and not connected to the outside world. Any such aspects of security are outside the scope of my experience and will not be further expanded upon.

We are now beginning to see a convergence of the Organization for Economic Co-operation and Development (OECD) guidelines and 21 CFR Part 11 regulations, and many companies are asking which of these standards to adopt. Such a convergence will ultimately result in the clarification of the regulations for all concerned. The actual convergence of OECD guidelines and 21 CFR Part 11 regulations are not foreseen in the near future. However, it must be remembered that the 21 CFR Part 11 regulations are still in place and will be enforced. If your organization (especially CROs) submits data to the FDA directly or indirectly and you have records stored or manipulated electronically, you must comply with the 21 CFR Part 11 regulations.

Risk Assessment Considerations

It may be of interest to indicate here the type of findings the FDA inspectors were filing in regard to 21 CFR Part 11 compliance, mainly in GMP, but they apply for any element of GxP, in the period 1999–2002.

Similar things are still being found in organizations today.

- Failure to validate off-the-shelf software for compiling clinical trial data.
- There is no documentation covering Microsoft Excel application software or any procedures instituted covering the protection of electronic records or an established backup system.

- Lack of proper validation of computer system software.
- Failure to establish and implement adequate security in allowing the software vendor unrestricted modem access.
- Not conducting secondary review of computer software modifications.
- Lack of a computer hardware and software change control SOP.
- Lack of verification that software modifications validated on test systems are identical to modifications implemented later in the "live" system.
- Failure to maintain the integrity and adequacy of the laboratory's computer systems used by QC in the analysis and processing of test data.
  - Lack of a secure system to prevent unauthorized entry.
  - Reports sent via e-mail differed from versions in official management reports.
  - Network module design limits support to four HPLC systems but five were connected without validation.
- "Your firm failed to implement appropriate controls over your HPLC to ensure that only authorized changes can be made. It was noted during the inspection that there is an option on the HPLC that allows analysts to delete results after they are processed."
- "The computer software … is deficient. It has no security measures to prevent unauthorized access of the software, no audit trails, … data can be copied or changed at will … . There is no documentation to indicate that analysts are trained in the software and its application."
- "Lack of proper validation protocols, the maintenance of complete and accurate documentation of the performance of the validation protocols, and an analysis of the results for the computerized system … ."
- "Failure to establish and implement adequate computer security to ensure data integrity … an employee was found to have utilized another person's computer access to enter data … ."
- "… the laboratory is using an electronic record system for processing and storage of data from the atomic absorption and HPLC instruments that are not set up to control the security and data integrity in that the system is not password protected, there is no systematic backup provision, and there is no audit trail of the system capabilities."

To summarize these findings, they can be allocated to the following types:

- Data issues.
- Computer systems do not comply with Part 11.
- Access controls are not in place or not followed.
- No control over system replacement/retirement.
- E-mail issues.

We can imply from this that:

- Lack of application of system access controls could be seen as fraud.
- Data from many labs may be unacceptable to regulators.
- E-mails could facilitate investigations in some areas.
- Precedents will drive the rate of change.

Who should be involved with the risk assessment process? The simple answer is, whoever is competent to do so. It should be someone who knows what the system is for and how it works. It should also be someone who can authorize the decisions made regarding such risk. Therefore, it would be simpler to form a risk-analysis committee that has the required broad-based knowledge and not leave it to one individual. It is my opinion that QA should not be directly involved in any such decision-making process. However, within the small CRO without specialist IT support, you may find that your opinion and advice is sought. It would be wise to be conversant with the requirements of the regulatory agencies and also have some idea of how software is put together and what documentation is required.

There is an international standard for risk assessment that can be of help here — ISO 14791:2000 (amended in 2003 to accommodate medical devices). This is the only standard that is referred to by the FDA in relation to risk assessment for compliance with 21 CFR part 11. How can it help here — in the nondevice category? The reference to this standard is somewhat of a change from the FDA's apparent normal stance of trying to prevent fraud to one of consumer protection, a much more useful perspective. If we look at the standard definition of risk we can see how this focus has changed.

Risk: combination of the probability of occurrence of harm and the severity of that harm. [ISO/IEC Guide 51:1999, definition 3.2].

We can summarize this interpretation of risk as follows: the risk management document is to be maintained throughout the entire life cycle of the system, and the risks associated with the corrective action or proposed changes should be analyzed, evaluated, and controlled. Such ideas of life-cycle management are central to the quality management ideals, and should be at the forefront of your thinking. (Some tools for establishing models of processes are presented in Chapter 6). The current revision of the standard proposes to move away from risk analysis towards risk management. Not only do you require to initially assess the risks in each of your processes that comprise the system, you must also justify why you think there is a risk and introduce control measures to minimize these risks if necessary. You are then required to periodically review these risks.

Assistance with Validation and Risk Assessment

A good deal of useful ideas and concepts have been developed by the pharmaceutical industry over the years culminating into the guidelines for Good Automated Manufacturing Practice (GAMP). This book defines the

best methods for ensuring compliance with worldwide regulatory bodies and has evolved through four versions into its current incarnation as GAMP 4 (2001). This may be based around the requirements for GMP but it has great benefits for any computing system being used in the general GxP arena. The guidelines provide the following benefits:

For organizations in general:

- It provides you with validated and compliant systems using the concept of prospective validation and a life-cycle model.
- It provides procedures to ensure that the system remains in a validated state at all times.

Benefits of using GAMP 4:

- It provides cost benefits by aiding the production of systems that are fit for purpose, meet user and business requirements, and have acceptable operation and maintenance costs.
- It provides systems that meet mutually agreed quality standards.
- It provides a simplification of the terminology, leading to increased understanding of the subject matter.
- It reduces the time and effort required to get a compliant system.
- It provides a solution to regulatory compliance and expectation by providing a total life-cycle model.
- It provides a clearer allocation of responsibility between the user and supplier.

There are several sample SOPs and other documents available on the Web that can give you a start in setting up your validation strategy and IT quality system without having to spend a great deal of money. The GAMP 4 guideline book is still a very good investment because it provides a wealth of invaluable information.

Electronic SOPs (E-SOPs) vs. Paper SOPs

The ability to control and distribute all your documentation (such as SOPs and templates) electronically is surely a good one. Within a global or multisite organization, I can see this as a good thing. However, for the smaller organization, it is probably much more difficult to implement and also not cost effective.

Let us take a small organization such as mine. At present, the SOPs are all produced on paper and signed in three places — the compiler, management, and QA — for approval and notification. As QA is in charge of SOP control, this makes sense. It should be noted here that QA does not audit the SOP for the actual content, only format or compliance issues. It is normally the case that they can cover procedures that QA may not fully understand anyway.

QA duplicates the master SOP copy and stamps the copy with red ink stating "CONTROLLED COPY" and "Copy No. X of Y." The SOP is then taken to the point of issue, and the person responsible is supplied with a copy. They sign a register to say that they have received it. If there was a previous version in place, QA will require it to be returned to be destroyed (only master copies are archived). Thus, there is a central record of all SOPs issued and to whom and when.

Doing such a task electronically is much more difficult, but it does allow the distribution directly to many more people, which is especially attractive to multinational companies. It does mean that only current versions are available. However, there is the difficulty of ensuring that there are no uncontrolled printed copies of the old ones in existence. This situation would only be evidenced by careful QA inspections, and this may not be done each time an inspection is carried out. One way around such a system is to ensure that the SOP has only a limited lifespan, of say 24 h from date of printing. For example, providing there is a clear printing date, say in 30-point text, across the printed page, then it is easy for staff and QA to spot any expired documents. Of course, e-SOPs are supposed to be referred to on a computer screen and can therefore utilize the search features of the reader program. This of course presupposes that everyone who needs access to an SOP has access to a computer and the network in their work space (e.g., field workers). There are specific guidelines for the use of any such system, and one very good one is provided by BARQA (Electronic Standard Operating Procedures, BARQA position paper). I will not go into any more detail here as it does become rather complex, and because we are talking about small organizations, it is possibly not worthwhile trying to implement such a system in a regulated environment with all its incumbent validation. It is probably better and easier to stick to the old-fashioned paper.

E-Archives

When we move into the e-record area, we must also consider archiving electronic information. How can we do this ?

Paper records are not really a problem. Apart from the space aspects, we know that it is stable for years, as is evident from library archives. Electronic data, on the other hand, has specific problems. Media stability is really unknown, as we are only given estimates. Also, there is a sense of built-in obsolescence. For example, we were using 5.25-in. low-density floppy disks (360 Kb) when we first started — in fact, generally only one per project (How times change!). We then progressed to high-density (1.25 Mb) 5.25-in. floppy disks, then to the 3.5-in. floppy disk with its 1.44-Mb capacity, and then to the computer's internal storage with its 20-Mb hard disk.

Archiving materials was no problem — just put the disk in the archive. We had not even considered the evolutionary aspects of computing and data storage at that point in time. We can illustrate this nicely with the example of the 5.25-in. drive — try to get one now to read the data. The demise of

the 3.5-in. disk was similar. These are no longer offered by some mainstream manufacturers. Because this data collection process was carried out less than 15 yr ago, we can see the problem of maintaining data access and security.

In our particular case, it was not all that significant as the computer files only facilitated report production. The raw data was still stored on paper and could be retyped in if necessary. It does, however, illustrate the requirement for the archivist to be conversant with data recovery and migration techniques so that the data can be migrated onto current media.

Another consideration you must take is when dealing with the specific case of tailored or specifically written software for your organization's use. Most suppliers are not willing to supply the source code for you to hold in your archives, irrespective of the media it is written on, although this is a requirement of the GLPs. How can we get around such problems?

Well, one way is to allow the source code to be held by a trusted third party such as a firm of solicitors or an organization who specializes in such agreements (National Software Escrow, Inc., Brecksville, Ohio). Should there be a regulatory requirement to access such material, it will be permitted. Such agreements are called *escrow agreements* and should be considered and used when any archiving issue arises during the initial contracts with the software supplier in case you plan to use custom software.

Today, optical media (CD and DVD) is the mainstay of many organizations but the stability of the materials used in the manufacture of some disks has been recently brought into question by some experts. The current estimate could be as low as 3 to 5 yr, depending on the quality of the media. The original perceived life span was apparently about 20 yr. This was normally determined by the manufacturer and based on the average storage conditions under which the media would be kept. It would therefore seem prudent to give archivists the extra responsibility whereby they must regularly confirm the readability of such data in the same way as they do with thermal paper printouts (very short shelf life). If there is a problem with readability, it would be up to the archivist to put remedial action into operation, such as migrating to new media, photocopying, etc.

Larger organizations may wish to consider using the more robust storage medium of magneto-optical (MO) disks because these provide large capacity and reliable storage. This type of media has had many more years of real-world storage reliability with their operation as archive media. There is also the availability of disk "juke boxes," which allow the storage and quick retrieval of hundreds of gigabytes to terabytes of data. These are especially used in document imaging and storage fields, where capacity, speed of access, and reliability are of paramount importance — just what we require for archiving.

Migration of any data does require independent checking by someone, normally QA, to ensure that a certified copy is obtained. Moving data from floppy disks to optical media, for example, is a common exercise and so is the archiving of data from server disks. Normally, this is to WORM (write once, read many) disks such as CD-R. One caveat you should note is the limitations on the number of file name entries on a CD-R disk. This is

particularly a problem when archiving chromatographic mass spectrometry data from a server disk at the end of a study. There can be tens of thousands of very small files. If you exceed more than about 10,000 files, irrespective of the total amount of data, the files appear to be written to the disk but are inaccessible. Hence, even though there may still be considerable space on the disk and it will appear to accommodate more files, none will be readable if any more are added. Make sure you validate what you have written to ensure that it is really accessible by confirming that you can open the file with either a simple text editor or the application that created the file in the first instance (if available). A similar situation may occur when using DVD media, but as we have not yet required such large capacity per project, I do not know for sure if this is the case. For further information with a specific regulatory perspective, I suggest you have a look at the Swiss guidelines for electronic archiving provided by Arbeitsgruppe Informationstechnologie (AGIT).

Server Backup Considerations

Along with the storage benefits of electronic data comes the other pitfall. It is very easy to lose everything accidentally or through physical damage or malfunction. Backup media such as tape cartridges also require special consideration in that they must be kept secure and, preferably, at least one copy be maintained off-site. Again, depending on your documented procedure, you should be regularly archiving your server data at least on a monthly basis so that you can roll back a system to its previous state to facilitate data recovery or study reconstruction. I am perhaps a little paranoid about data backup but I have been involved with the retrieval of lost data on so many servers and hard disks that I am familiar with the anguish and frustration that ensues; I feel a certain amount of paranoia is justified.

A tip that I can pass on here is one of the "belt-and-braces" approach to data security that I endorse fully as it has saved my skin several times. Using tapes to back up and archive your disks is perfect and very cost effective; however, if your disks die, tapes are not very useful in fast data recovery. Your tape catalog has also gone south as it is on the dead disk; how can you get back to where you were? One solution to this dilemma is to use disk imaging software and copy the entire disk as an image onto an external disk. (The costs of external disks has fallen considerably and their storage capacities increased dramatically over the last few years.) Such disk imaging/cloning software is available for stand-alone computers and server operating systems. When the faulty disks are replaced, the external image clone can be written back to the new hardware quickly, without the need and pain of trying to reinstall the operating system and its patches. At this point, you can recover the rest of the system from the last tape backup. In my experience, a crashed system can be recovered within 8 h, provided spares are on-site. Of course, such disk images must be regularly updated. They do not have to be updated every day, but only when system changes are made and

not when data is changed, as these latter changes will be covered by the regular tape backups anyway.

A Suggested Tape Backup/Archive Routine (With 22 Tapes for an Annual System)

Week 1
Monday to Friday — full backup of the entire system
Store previous day's tape off-site
Week 2
Overwrite Monday-to-Thursday tapes with current data
Friday — use a new tape called Friday 2
Week 3
Overwrite Monday-to-Thursday tapes with current data
Friday — use a new tape called Friday 3
Week 4
Overwrite Monday-to-Thursday tapes with current data
Friday — use a new tape called Friday 4
Week 5
Overwrite Monday-to-Thursday tapes with current data
Friday — use a new tape called Friday 5

Depending on the number of Fridays in a month, the last Friday's tape will be archived. All other tapes will be recycled for the following month, and the archived tape will be replaced with a new one. All current backup tapes should be stored in a fire-resistant safe for further security. The philosophy here is that the whole system can be resurrected after 1 d, 2 d, 3 d, 4 d, 5 d, 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, etc., thus providing you with the best possible coverage.

Some systems rely on using incremental backups, which is a lot faster, but it has been my experience that they can cause more problems when trying to restore the data in the event of a total loss. If the time frame window to take the backup is not very limited (normally open files such as databases are not copied during backup), I suggest that you go for the complete backup option at all times.

As mentioned previously, there can also be the problem of inability to access the tape media because of hardware or software obsolescence. Try to ensure that new versions of hardware and software are backwards compatible, which will ameliorate the situation to some extent. Obviously, there will come a point at which evolutionary change is superseded by revolutionary change, and, within computing, this is a real problem for archivists and company management because this can be a very short time scale. Maintaining copies of old retired software is one shrewd solution but in 10 or 20 yr time, will it run on the new hardware?

All we can do is do our best under these circumstances.

E-Mail in the Regulated Environment

E-mail communication between the CRO and sponsor is now the mainstay of operations between the two parties. Because we tend to send more and more electronic information between sponsors and the CRO, these must be considered part of the complete study record. In fact, some e-mails may contain critical study information and should be printed out and filed within the study archives (as discussed in the preceding text). But this is not the whole story. Hence, there is a need to again opt for a belt-and-braces approach of keeping the electronic data along with its meta data, which is essential for confirmation of origins, etc. (If you want to have a look at this information and are using Microsoft Windows®, right clicking on a message and selecting properties will show you most of the meta data.)

Special consideration should be paid to the contents of sponsor–CRO communications for two reasons, legal and moral. One of the main regulatory considerations is to ensure the communication is in writing but you should question this — is this true of printed e-mail?

Let us consider the following possible problems: they can contain illegal material, the issue of "blind carbon copies" and "carbon copies," work instructions, and authorizations. The latter two, work instructions and authorizations, are ones that should concern us in that we must be absolutely sure who sent them. It must be remembered that a printout of such mail does not prove who was responsible for sending the instruction/authorization. This information may only be held in the file meta data that indicates its physical origins and route through the Internet. Unfortunately, this information is lost when we print out the e-mail and delete the original message. Also, the information held in these meta tags may be spoofed (see the following text) and therefore incorrect, but that is another issue, e.g., some spam e-mails purporting to be from someone you know. Finally, we do not have a valid e-signature with a basic message.

This lack of meta data and signature within the printed copy may cause a problem in certain circumstances because we need to be sure of the message's origin and security. In the increasingly litigious society that we now live in, keeping electronic copies of all e-mails makes good legal sense for any organization. In a situation in which an employee makes a complaint regarding harassment or an external complaint arises about harassment or libelous remarks, etc., the evidence trail is preserved.

When carrying out server backups, it should be noted that it does make good practice to archive all e-mails at the same time so that historical and legal aspects are covered. If your e-mail system is on the same server as your data then they will most probably be included in your backup system already. However, if e-mail is on a separate server, then another set of similar backups to the ones outlined previously should be considered. Depending on the server activity, it may be necessary to carry out archiving sessions much more frequently than once a month (once weekly, perhaps).

E-Mail Security

When sending confidential information by e-mail, we must consider the fact that it is akin to writing the information on a postcard and sending it by conventional mail. Therefore, some form of security must be implemented if such a medium is going to be used to transmit confidential data. Another consideration we should make at the same time is one of authenticity of the sender. The practice of spoofing (the practice of forging "from" addresses to make it seem like the bogus e-mails come from a trusted source) is rife on the Internet. Such practices may well be within your own personal experience, such as where friends and colleagues have been unwitting victims of virus infections and hacker attacks, and you ended up receiving e-mail purported to have come from them because their address books were compromised. One solution to the privacy and authentication problem is to use encryption of your messages and sign them with a digital signature. In this way, you can be sure that your message does come from who it purports to come from and you are also sure that no one else could have eavesdropped on the contents or modified them. Such security systems are widely available (e.g., Verisign®, PGP®, etc.). I am sure you can find something that will accommodate yourselves and your sponsors.

However, whichever proprietary system you select for individual and organizational use, you must realize that no system is 100% secure. The best we can do is to tilt the balance in our favor. Such encryption systems do require that both users have digital certificates and that they are available for the computing platforms in the originating and recipient organizations. For Microsoft Windows®-based machines, there is no problem with this but with the Apple Macintosh® community (10 to 20% market share), it should be noted that only the most recent hardware and operating system (OSX® 10.3.x) has the ability to use digital certificates. You will have to research such privacy products yourselves and their applicability to your particular situation. Advice on such activities are outside the scope of this book. My purpose in mentioning this is to make you aware of the possible regulatory problems with e-mail.

If you do use e-mail, it makes sense from a regulatory point of view to ensure that electronic copies of all e-mails are maintained. These could be maintained in the server backups, but trying to find any individual message may be like looking for a needle in a haystack. It can make sense to include all such data in an electronic data management system; such a system, however, may be beyond the scope of the smaller organizations so that proper, structured storage and documentation of the server disk store will have to suffice. Another answer given by some organizations would be to define e-mails as transitory or business records (the legality of such a position in your country should be confirmed before taking the action described). Such records should be destroyed as soon as possible and a company policy should be implemented to ensure this is rigidly adhered to. (This view was put forward by one organization but I find it hard to reconcile this with the

fact that we tend to use e-mail to send documents rather than just for communications). To obtain such a transitory environment, you would use e-mails sparingly and only when appropriate. To avoid any legal or moral issues, the policy should also ensure that the contents of e-mails are kept factual and to the point. You should still use older methods such as writing, fax, etc., where this can affect study interpretation or compliance. This tricky situation may clarify itself in time as technology improves; for the present, you will have to define your own policy on how to deal with such perceived problems as those outlined in the preceding text.

Another problem with the use of e-mail storage systems is that they must be compliant with the Data Protection and the Freedom of Information Acts (if relevant). Should any legal action be taken against one of the staff either internally or externally, it is important that no personal information be stored in any e-mails such that the Data Protection Act may be breached inadvertently. It must be remembered that to comply with the Act you must be able to supply all personal data pertaining to the individual who requests it. Should such information be deposited at random in some stored e-mails, it would be nearly impossible to retrieve all such information and be sure that you have not forgotten any. If it is later discovered that you have not disclosed some personal information about an individual, you may be liable for prosecution, at least under UK law. Due to the immediate nature of e-mail and the ways in which we tend to deal with it, especially in a clinical organization, there is the possibility that similar organizations will communicate such data to prevent the "professional" volunteers taking part in too many trials. It would appear prudent that there should be an organizational policy statement that no personal data should ever be the subject or content of any e-mail communication. All such personal communications should be conducted by some other method and be carefully tailored such that possible breaches of the Act should not happen.

E-Transfer of Documents and Signatures

Although e-mail is used in the same way as telephone conversations, faxes, or letters, it is also used as a courier service to transmit the original documents to the recipient via attachment. This is the normal way nowadays, so as to ensure rapid receipt of documents between internal and external sites. Of course, with documents such as protocols that must have multiple signatures appended from multiple parties, the rapid transfer of the document to all parties is of great importance. The same considerations regarding authenticity should be observed. As stated previously, both parts must be treated as one unit during the transmission/reception stages. Passing documents electronically in this manner does cause us problems due to the fact that there are no wet-ink signatures.

We could accomplish this by appending signatures that were collected from samples of signatures from all staff and scanning them in as bitmaps, saving each one in a file, and then inserting this into the document. This

sounds like an excellent idea until you look a little closer. The immediate QA questions in this scenario are: How are these signatures controlled? Who has access? Are they available outside my organization? There are a myriad of questions you could ask about such a system, and if any one answer is not to your satisfaction, you should reject such proposals. You should ask yourself if you would trust anyone else, using such mechanisms, if they were able to withdraw money from your bank account. Of course not! We must find another solution to allow multiple persons to sign the electronic document.

Another aspect of this topic to consider must be the type of documents being sent. Is it a word processor file or a spreadsheet, i.e., a native-application file type. These can be easily modified en route, and the recipient would be none the wiser. In fact, the recipients could modify to suit their own purposes. (Note: Always keep a printed or read-only electronic copy as a reference document.) Some of these files can contain embedded applications such as automatically executing macros. These are a possible route of virus infection and other malware transmissions, especially when the documents are created in popular office suites. These can be inadvertently sent to recipients, and such expected mails tend to be mistakenly trusted. This can have serious unexpected consequences for the recipient.

How do we combat such possibilities? One possible way is to discourage the practice of sending native application files to recipients, instead you can use rich text format (RTF) or create Adobe Acrobat® files (portable document format, PDF). These file types also permit the opening of the document on different platforms. You should also remember that not everyone uses a Microsoft Windows®-based personal computer or Microsoft Office® applications. Such a nondenominational solution is safer and is much more politically correct. An added advantage when using PDF files is the ability to insert digital signatures. The disadvantage to using proprietary formats such as Adobe PDF® is that the format can change rapidly over time, and it may not be possible to access electronic documents in say 10 yr, let alone the 15-yr minimum archive time frame. As far as archiving electronic data is concerned, it is preferable to try and ensure your e-records are written in a nonproprietary, public format, such as ASCII or HTML, so that archival permanence can be almost guaranteed.

It should also be remembered that records, whether paper or electronic, are the assets of an organization and must be managed throughout the period of their existence.

Digital Signatures in Documents

What we need from a digital signature (graphical representation) is that when it is appended to an electronic document and that document is in anyway modified, the signature clearly becomes defaced and obviously invalid. One possible solution is to use CyberSIGN® in conjunction with Acrobat®, so that not just a graphical picture is used but a biometric representation of a hand-written signature embedded within the e-document. This

does exactly what we want and require — a simple, secure way to sign electronic documents. No doubt, there are other solutions out there but it is the principle that I am trying to get across here, not the advocating of any particular technology or product.

Recently, there has been an initiative called Secure Access For Everyone (SAFE). This, I hope, will start to bear fruit relatively soon. This is an across-the-board e-signature-acceptance project that has been eagerly adopted by the pharmaceutical industry. This project consists of a consortium of twelve major pharmaceutical companies who have agreed on a system of secure access and mutual acceptance of data interchange.

Their eventual goal is to gain global approval of electronic verification systems that can allow the pharmaceutical companies to conduct validated, paperless transactions with external partners. In essence, this system is based on a Public Key Infrastructure (PKI), by using a personal encrypted smart card. This can be swiped through a card reader to digitally sign the document you want to transmit. At present, such practices require the use of different tools used in different organizations. Through the SAFE initiative this is expected to be reduced to one universal card, a Visa® card if you like. This should not be considered as a computer system enhancement as much as it should be considered as a business facilitation tool. Hopefully, such a system will be welcomed by the CRO industry as a means of producing better business partnerships, with faster validated transactions, which will, of course, benefit both parties.

With such technologies, I am beginning to think that the concept of the paperless office may now be closer than we think. By reiterating what I said at the beginning of this chapter, it has come upon us by stealth and evolution rather than the revolution originally envisaged in the late 1970s. This will, therefore, have the consequence of changing QA techniques from paper-based error and fraud detection to the electronic arena. E-auditing requires new tools and skills that we must develop and hone to get the most out of these newly emerging technologies. This is a great opportunity for QA to become much more versatile and enhance their professional skills. I suppose you could consider it a case of adapt or be left outside.

QA and User Authentication to Computer Systems

Within the Phase-I clinical environment, we are quite often called on to conduct a pharmacokinetic study, in which there are, perhaps, 12 subjects and 15-min samples/measurements to be taken. This will involve several people putting information into the data collection system and using only 2 or 3 notebook computers. Requiring staff to log in and log out, along with log-in script processing and application loading takes too long and may well spoil the workflow. Such a situation can easily lead to missed data captures. If we could use one account and assign the data entry to an individual, the same as recording and signing for data within a CRF, this would provide us with the ideal we are seeking.

Biometrics can be a solution here, where the individual making the entry provides the token that uniquely identifies him or her. Several options are available for people to use — retinal scans, fingerprints, etc., all of which are secure methods of authentication. If we go back to our original scenario of timing in our pharmacokinetic study, these methods are not much better and, in some cases, of no practical use. The retinal scan requires staring at a sensor to capture the image required — reasonable, but the scanner is quite large and awkward to move around. Using the fingerprints method can be impossible if the staff is wearing gloves for protection. As suggested in the previous section, handwriting authentication is probably the least intrusive way of modifying an existing workflow pattern. You have probably realized by now that I personally prefer the biometric approach. I sincerely believe that these systems will form the basis of identification of people in the future. We must also remember here that we are QA and that we have got to authorize the use of such a biometric-based authentication system. How can we audit such a system?

This is a two-fold problem for QA; you will have to:

1. Audit the validation system for authentication.
2. Audit the e-records for proper assignment and accuracy.

Problem 1

To start with, it is useful to understand some definitions to appreciate what is being proposed.

Definitions of Biometrics

Biometric authentication can be ascribed in two types:

Identification or Verification

Identification: Tends to be once only, e.g., log in to the system. The user makes no claim on their identity.

Verification: Makes a positive claim requiring comparison to a submitted sample previously enrolled.

When auditing the validation plan and/or report, the following points must be addressed.

Biometric Testing (a Selection, Tables 4.1 and 4.1a)

- Verification is the best method of authentication.
- Requires testing using genuine and impostor transactions.
- Testing of enrolment into the biometric token database.

Table 4.1 Sample Test Program for Authentication and System Access

Component	Test Details	Criteria for Pass/Fail
Biometric authentication	Pre-enroll test signatures (5)	No failure permitted.
	Five persons' signatures	>3 log-in attempts indicate failure.
	Forgery of signatures (5) From 2 of 5	Any false positive will cause failure.
	Non-enrolled impostor	Any acceptance is a failure.
	Failure to acquire	No enrolment of any signature is a failure.
	Simultaneous signing (2)	No failure acceptable.

Table 4.1a Sample Test Program for Authentication and System Access

Component	Test Details	Criteria for Pass/Fail
Server access	Authentication confirmed.	No failure permitted.
	Proper rights assigned to individual, Create rights only, no modify or delete, etc.	No failure permitted.
	Individual can access the database file.	No failure permitted.
	Server security, no individual other than administrator can access data at the server console.	No failure permitted.
	Database security backup plans and archiving.	Documentation in place and can be done.
	Biometric profile security.	No failure permitted.
	Backup and storage.	

- Check for compromise by failure to enroll and failure to acquire proper biometric profile.
- Authentication to profile must have acceptable threshold levels set before testing.
- The biometric should not be sent over the network. The client should produce a HASH, which is sent to be authenticated against the same HASH generated on the server.

Source: Best Practice in Testing Biometric Devices, Biometric Working Group, 12/01/00.

Biometrics

> Biometrics work great only if the verifier can verify two things: one, that the biometric came from the person at the time of verification, and two, that the biometric matches the master biometric on file. If the system cannot do both, it is insecure.
>
> **Bruce Schneier, in *Secrets & Lies***

Table 4.2 Sample Tests for E-Record Storage

Component	Test Details	Criteria for Pass/Fail
Data files	File exits and identifiable as a project.	No failure permitted.
	File data proper assignment of data to the individual.	No failure permitted.
	File data assigned correct time point.	No failure permitted.
	Edit some of the captured data by deletion and change.	No failure permitted.
	Audit file contains all details previous values, new values and who, when, etc.	No failure permitted.
	Data file/audit file backup and security.	Can be done and recovered with documentation.
	Additions to file by enrolled volunteers records maintained in audit file.	No failures permitted.

Problem 2

This type of audit has to be one of system validation and trust. Once tried and tested, it should not be necessary to audit again unless there are system changes. Because we are dealing with data capture systems in the main here, provided everything remains constant, the risk of error is minimal. We must examine any such system carefully in the first instance by doing inspections to ensure that the captured data is consistent with that observed (Table 4.2). This is a task that QA should carry out, and the use of a checklist similar to that given in the following text is most useful to ensure that all major concerns are addressed.

QA Actions: Acceptance Testing

- Primary:
  - System validation has been done.
  - Determine who did what and when?
  - Parallel testing — paper vs. electronic.
  - (QC check on input data and output 100%)
  - Check electronic reports for valid signatures.
  - Check on CD-R archiving.
- QA Actions: secondary.
- Ensure documentation exists for all software.
- Ensure change control is in operation.
- Check protocols against e-CRF.
- Ensure appropriate training is provided.
- Audit all of these steps.

IT Security Considerations

Most security threats to an organization's network and IT infrastructure are perceived as coming from external sources such as viruses, Trojans, and hackers. In fact, this is not so; statistics indicate that you are more likely to be attacked from inside your organization than from outside. This includes the inadvertent failure of staff to implement system updates to patch vulnerabilities, and thus leaving a system open for any malicious acts. In fact, the only safe system is one that is not connected to anything else and has no users; consequently, this means that every system is vulnerable.

This sort of problem is traditionally an IT one but as it can affect the quality and compliance of a study, QA are becoming more and more involved in such issues.

Because most attacks come from within an organization, you must look towards having a secure system (I doubt if this is a problem with very small organizations). A personal computer connected to a company intranet with a user logged in and away for coffee is a security problem, as anyone could come in and cause havoc in and around the network areas that the logged-in user has access. Such behavior could, of course, just be limited to changing some data in a file, which would not be immediately obvious but may have a significant quality impact. These latter aspects are the most worrying from the QA perspective. Furthermore, it is the logged-in user who will be responsible for the damage as it was their account that was used.

Therefore, let us consider some questions: How do we secure internal systems? How do we secure our systems from external attack? The simple answer is that we cannot. All we can do is minimize the risk of any attack, and if an attack is successful, place limits on the potential damage.

Internal Security

- Ensure that there is a rigid policy for regular password changes, password length, and password type.
- Ensure that there are no communal passwords/user accounts (except when absolutely necessary).
- IT security breaches of policy must be considered a disciplinary offence.
- Ensure users log out immediately when they leave a terminal, or have some automatic system.
- Ensure that there is a system to implement security patches and update antivirus signatures.
- Consider physical barriers where systems must be kept open — locked keyboards, locked rooms, etc.

External Security

- Ensure that external connections are kept to the minimum necessary.
- Ensure that there is a hardware firewall in operation and that it is working.

- Wireless networks should be encrypted and not left on default settings.
- Internal wireless networks should not be connected directly to the Internet.
- Separate servers used for external and internal functions, if possible.

Considering the external systems first, most of these solutions are "fit-and-forget" as far as IT are concerned. QA should be checking the network schematic for Internet connections and internal network connections that may cause problems (e.g., wireless). All hardware firewalls create logs of activity. Inspection of these should be made part of QA's facility audits to ensure that they are being maintained and working correctly. I also suggest that such records be maintained in the archive of your organization.

Looking at the internal systems, the major problem is with people logging into a system and not logging out when finished. Such actions are perhaps not so much a problem caused by users as the operating system designers. It is the multitasking nature of current systems and applications that cause some of the problem. When IT systems were simple and expensive in the early days of single tasking, you logged in to carry out a single task then logged out when finished. This is not the case nowadays; network operating systems have a central database such as Microsoft Active Directory® and Novell e-Directory® which offers a single point of access for all applications, data, and resources, so that you can be working on project material and non–project material at the same time. Human nature being what it is means that with the best will in the world people will forget they are logged into the network. If they leave their workstations unattended then the "secure" resources are available to anyone who chooses to use the workstation and cause mischief.

How can we unobtrusively minimize such risks ? What we want is to have users log out before they leave the workstation. I have seen several mechanistic systems that appear to fit the bill, such as fingerprint readers on the mouse or keyboard to authenticate the user constantly or, more usually, at specific time intervals. Of course, this may not be possible due to the wearing of protective gloves; also, the time-out periods, if inappropriately set, may allow a large window of risk. A simple system, which I have seen and consider best of the breed, is one in which the user wears an ID badge with a radio transmitter embedded that is tied to a receiver in the workstation. The badge emits a radio signal that allows the computer to process information from that user. If the specific user moves out of range (a few meters), the PC will not accept any input until the user comes back into range. The beauty of such a system is its ability to match human activity and forgetfulness. I have no direct experience in using such a system myself, but reviews have indicated measured success. As with most such technology, it is constantly evolving and improving; hence, market investigation is encouraged in this sphere.

chapter 5

QA Activity

So far I have put forward a whole series of possible problems and general solutions. It is QA's job, however, to implement a solution that encompasses all aspects of an organization's business, whether it adheres to the U.S. Food and Drug Administration's (FDA's) Good Practices standard (GxP) or some other standard. In order to give you a sense of the types of items we look for in our organization and to put you on the right track regarding inspections and audits, I will provide you with some checklists that you can use to set up, or perhaps even improve, your existing quality system. Such lists are not exhaustive and only cover the main points that QA thinks are the critical areas (Table 5.1). As with any checklist, the inspector or auditor must feel free to curtail or expand any inspection or audit.

It is always nice to take your completed checklists, thoughts, and notes and compile your report at your desk, then have it circulated to those it affects and who can action any suggested change. However, there are times when such a process is inappropriate, and some form of immediate notification and affirmative action is required, e.g., for a protocol noncompliance observed during an inspection. QA must have a short-circuiting mechanism that can record the problem and get an immediate fix, which can be documented as well.

When we have such a problem, a corrective action request (CAR) is completed and issued to the offending party (example form presented later). They must immediately stop the process, fix the problem before continuing, record the fact that they have repaired the defect on the CAR, and return this to QA, who should carry out a further inspection to confirm the correction.

When do You Carry Out an Inspection?

You will have to determine from the study schedule what activities are being carried out at what times and what the critical phases are for your particular circumstances (these can be determined in advance by referring to the protocol). I can, however, provide a few suggestions here, such as collecting informed consent, appropriate dose preparation, the dosing, pharmacokinetic blood sampling, and pharmacodynamic evaluations.

Table 5.1 Checklists for QA Activity

Checklist	Definition
Laboratory facility inspection	The main non-project-specific areas, CVs, training, maintenance records, etc.
Ward area inspection	The main non-project-specific areas of the clinic as above and calibration
Laboratory project inspection	Looking at project-related data recording, QC, etc.
Clinical project inspection	As above, together with subject parameters
Corrective action request	Document used to notify line managers of a problem that requires immediate fixing

You could also consider scheduling random standard operating procedure (SOP) compliance inspections. These can show up differences between the SOP instructions and the procedure as it is actually carried out. These inspections can provide very revealing results, which are difficult to find by any other means, and they certainly are not apparent during a report audit.

Inspection of support facilities such as laboratory analysis should be carried out during the in-life phase of the clinical trial, if at all possible. In some cases such as pharmacokinetic sample analysis, this may be done some time after the clinical phase has ended and thus precludes such actions. Of course, if this is an in-house laboratory support procedure for biochemistry or hematology, then an inspection is possible and desirable, so that the status of operations may be determined for that particular study.

If, however, these laboratory tests are subcontracted to a third party, then such activity may not be possible, and you will have to rely on their own internal QA if they have one. If this is a problem you are always going to have, then setting up a rolling program of inspection for data acceptance will be required.

How Often do You Inspect?

The frequency of inspections and inspection types is dependent on your levels of activity as far as operational items are concerned. I am of the opinion that an inspection is critical during the first dosage phase as the potential for errors is maximum. However, I also feel that it is imperative to ensure that every study is inspected at least once during its active phases. If the study is the first in man and perhaps involves dose escalation, I would seriously try to inspect it during each and every dosing period.

Where there is ongoing data collection from pharmacodynamic evaluations, incidental inspection can be used to ensure compliance with protocol and SOPs.

The other types of inspection such as facility review will require that you set up a rolling program in which you will inspect all non-study-specific aspects of your organization. For instance, checking training records, emergency drugs, and validation and calibration records (examples are provided in the facility

checklist). Such activities could quite easily be carried out on a monthly or quarterly basis, again depending on an organization's levels of activity.

What Records Should QA Keep?

QA should maintain a master schedule of all studies, listing the sponsor, project identification, protocol and study plans, and ethics permissions. Summary information may also be usefully held as a computer record within a QA database. The following records should be maintained:

- For each study, a project file, including ethics submissions, copies of all QA reports and responses, (protocols and study plans may be kept with the generated project data, provided QA has free access to these documents), and any other information required for accurate execution of the QA program.
- Records of in-process inspections (Forms 5.5–5.9) and corrective action requests (Form 5.10).
- Records of facilities inspections (Forms 5.5–5.9) will normally be filed under the appropriate project identification. If an inspection is not project specific, the record should be filed separately, in a general inspection file.
- Records of other QA procedures (e.g., inspection of external suppliers or contractors) are not included in the preceding items. They should also be filed in the general inspection file.
- At the completion of a final report audit, the QA file label status (see the following text) should be changed to "archived" in the QA project file, and if the records of inspections are also in a computer database, the status field should be changed from "current" to "archive."

The project file is conveniently created using a punched poly-pocket folder with a self-adhesive label attached to the front, stating sponsor, project number, date started, and current project status. These can all be held in a lever arch file.

Checklist of Various Items in a Clinical Inspection

- Acceptance procedures for subjects in a study
- Grouping and randomization of subjects in a study
- Dosage forms, stability, and accountability
- Observation procedures and adverse event recording
- Volunteer contracts and consent forms
- Ethics committee approval
- Regulatory approval
- Sample collection procedures, including proper documentation and identification of subjects
- Pre-, post-, and intra-study hematology and biochemistry

Form 5.1 Laboratory Facility Checklist

Current project no.(s)_____ Date_____

Primary or secondary inspection?	Y	N
Facilities, are areas designated and decommissioned as required?	Y	N

COMMENTS

Personnel (training records up-to-date, including CVs, etc.)	Y	N
Staff competence level, training program SOP being used	Y	N

COMMENTS

Specimen Handling

Is log of incoming samples up to date, as well as storage location (compare dates log with lab sample receipt log)?	Y	N

COMMENTS

If of external origin, details of condition on arrival, time in transit, and history of sample storage?	Y	N

COMMENTS

Has freezer log all the above information?	Y	N
Freezers checked at inspection (ID numbers)?	Y	N
Warning device on freezers working?	Y	N
Emergency contact available?	Y	N
Is there good compartmentalization of samples?	Y	N
Check temperature-monitoring log OK?	Y	N

Form 5.2 Laboratory Facility Checklist

Current project no.(s)_____ Date_____

Equipment

General condition of major pieces of equipment used in studies: satisfactory or unsatisfactory?	S	U
Is service or maintenance log updated?	Y	N
Problem minor equipment list types and serial numbers below		
Calibrations of pipettes, etc., within SOP and manufacturer's limits?	Y	N
pH meter calibration log up to date?	Y	N
COMMENTS		
SOPs available for preparation of reagents and standards?	Y	N
SOPs have current and controlled copies?	Y	N
Are they being used?	Y	N
Labels on reagent bottles expiry, preparation date, etc., filled in?	Y	N
Are balances performing to specification?	Y	N

Data Handling

Are all data recorded?	Y	N
Is lab book spiral bound?	Y	N
Are pages chronologically ordered?	Y	N
Are they signed daily by owner?	Y	N
Are all raw data available in the files?	Y	N
Do all machine outputs bear operator's name?	Y	N
Do machine output labels have a lab book reference?	Y	N
Is the lab book data confirmed by lab director?	Y	N
Are process SOPs being applied (QC acceptance, data interpretation)?	Y	N
COMMENTS		
Are there explanations for any lack of signatures or dates?	Y	N
REASONS		

Form 5.3 Laboratory Facility Checklist

Current project no.(s)_____ Date_____

Any members of staff verbally told about problems requiring immediate attention? Y N
If so, names below

Comment made?

To whom?

_____

Other Comments

_____

Clinical Inspection Procedure

It is impossible to lay down procedures for the inspection of any facet of a project protocol. The following guidelines should be followed as far as is practicable:

- In general, inspections should be unannounced, but when timing is critical (e.g., pharmacokinetic studies) the inspector should ascertain the most appropriate time in advance.
- On entering the place of inspection, determine the work in hand and the personnel performing this.
- Check that the current versions of appropriate SOPs are available in the area.
- Observe the operations being performed in the area and ensure that they are being performed within the spirit and letter of the appropriate SOPs.
- Check that the records in the area are those specified in the project protocol and ensure that they are being properly maintained for the operations carried out in the area.
- Identify any apparent discrepancies in the records. If deemed necessary and practicable, request a repetition of any measurements that appear to be potentially aberrant. Discuss any dubious findings with the staff member or project leader before making a written report.
- Check with the personnel involved to ensure they are adequately briefed on their work and the project requirements.
- Check instrumentation maintenance and calibration records.
- Check the safety systems and general environment within the area.

Form 5.4 Ward Area Inspection Checklist (Non-Study-Specific)

Project No. _____ Area _____ Date _____

Are freezers kept well (samples, defrosting, etc.)?	Y	N
Are calibration logs kept up to date for:		
BP	Y	N
Infusion pumps	Y	N
Balances	Y	N
Maintenance log	Y	N
Sample logs and sample transfers	Y	N
SOP index	Y	N
Controlled copies only	Y	N
Problem areas	Y	N
Nurses Training Records		
Recent entries	Y	N
Venesection records	Y	N
PIN number update	Y	N
SOP coverage complete	Y	N
Condensed CVs available	Y	N
Current Project		
Study-specific signature register up to date?	Y	N
Does this include external personnel?	Y	N
Crash trolley inspection check (expired reagents)?	Y	N
Checking of data (internal QC) ?	Y	N
For Relevant Studies		
Online data collection?	Y	N
Are there calibration records?	Y	N
Are data appropriately labeled?	Y	N
Are data properly maintained (lost clusters, etc.)?	Y	N
Records of computer file existence OK?	Y	N

Inspection by _____ Date _____

Form 5.5 Laboratory Project Inspection Checklist

Project No. _____ Date _____

ASSAY OF XENOBIOTIC _____

General

Is the assay specific?	Y	N
Published method?	Y	N
Validation SOP complied with?	Y	N
Are QC samples within SOP limits?	Y	N
Trends?	Y	N
Has the stability of test samples been determined?	Y	N

COMMENTS

Sample Analysis

Were samples randomized before analysis?	Y	N
Coded samples (blind sample assays)?	Y	N
Was code broken before analysis?	Y	N
Were standards used with each run as defined in SOP?	Y	N

If NO, what evidence of quantitation can be shown?

Notes

Were standard curves obtained for each run?	Y	N

If NO, what method was used for quantitation?

COMMENTS

Form 5.6 Laboratory Project Inspection Checklist

Project No. _____ Date _____

QC samples within assays checked by (name)		
Prepared by (name)		
Are QCs analyzed as unknowns?	Y	N
Volunteer biological fluid	Y	N
Are double blanks included?	Y	N
Drug standard sample approved?	Y	N
Final analytical method in book?	Y	N
Chromatograms ?	Y	N
Repeat assays: Are QCs included?	Y	N
If repeat was new, standard curve prepared?	Y	N
Reasons for repeats documented?	Y	N
Count repeats (at end of study only)?		
SOPs available for preparation of reagents and standards?	Y	N
Are they being used?	Y	N
Labeling of bottles: all information given?	Y	N
Expiration dates adhered to (check batch number log)?	Y	N
Controlled SOPs used only?	Y	N

Data Handling and Storage

Are all data recorded?	Y	N
Is lab book spiral bound?	Y	N
Are pages chronologically ordered?	Y	N
Are they signed daily by owner?	Y	N
Are all raw data available?	Y	N
Do all machine outputs have operator's name?	Y	N
Do all outputs have lab book reference?	Y	N
Is lab book confirmed by study director?	Y	N

COMMENTS ON MAINTENANCE OF DATA:

Form 5.7 Laboratory Project Inspection Checklist

Project No. _____ Date _____

Are there explanations for lack of signatures or dates? Y N

If NO, state reason below:

Personnel informed of deficiencies (names of persons directly spoken to)?
Comments in general:

Inspection carried out by _____ Date _____

Form 5.8 Clinical Project Inspection Checklist

Sponsor: _____ Project No. _____ Date: _____

Time _____ Location_____

Are doses administered according to the protocol?	Y	N
Formulation/batch number for this phase?		
Number of subjects observed in unit?		
Number there should be according to protocol?		
If a discrepancy, state reasons below:		
Multiphase trial?	Y	N
Filling-in subject gaps in study (how many?)	Y	N
Predose compliance recorded?	Y	N
Problems:		
Inclusion criteria met re screening drugs?	Y	N
Volunteer weight ranges protocol compliance?	Y	N
Dosing records OK?	Y	N
Sponsor's records with flags?	Y	N
Contracts/informed consent, etc. (first visit) match above nos.?	Y	N
Biochemistry /hematology data transcribed?	Y	N
COMMENTS:		
Are the blood sampling times entered in real time?	Y	N
Labeling of sample containers, subject, phase, date, test?	Y	N
Is this with a standard label?	Y	N
Supplier?		
Protocol in study file?	Y	N
Protocol signed?	Y	N

Form 5.9 Clinical Project Inspection Checklist

Project No. _____ Date _____

Sample Collection and Preparation Procedures for Biological Samples

Appropriate containers for routine internal assay?	Y	N
Urine analysis records signed?	Y	N
Urine collection sheets?	Y	N
Calculations OK?	Y	N
Transcription of above OK	Y	N
Fluid/food intake in compliance?	Y	N
Is the centrifuge kept clean?	Y	N
Any deviations from SOPs?	Y	N

SOP for biological specimen handling being followed? Y N

COMMENTS:

Machine-Generated Data

Are all ECG outputs labeled and signed?	Y	N
Is the ECG output reviewed?	Y	N
ECG transcription checked?	Y	N
Are all other devices (CI and Vital, etc.) calibrated properly?	Y	N
Are all outputs labeled and signed, including study no.?	Y	N
Blood pressure recording OK?	Y	N
Witnessed for check on correct transcription of above?	Y	N

Clinical Signs

Adverse effects: are these recorded satisfactorily?	Y	N
Management recorded?	Y	N
Comments sheets detail main information below?	Y	N

COMMENTS:

CAR issued?	Y	N
Reply required?	Y	N

Inspection carried out by _____ Date _____

Form 5.10 Corrective Action Request

Sponsor: _____ Project No. _____ Date: _____

Location

QAU Comment

Deviation from protocol? Y or N

Deviation from SOPs? Y or N

Written response to comments required? Y or N

The item above is now subject to a second inspection for compliance.

Signed _____ Date _____

Quality Assurance

Long-Term Projects: Data Review Procedures

For major long-term projects it is important that data be independently reviewed at regular intervals rather than at the end of the project, so that any errors can be detected at an earlier juncture. This allows you to ensure that complete data exists in a well-regulated fashion in accordance with the protocol requirements.

- Obtain from the project leader the project folders containing all the data pertaining to the given project.
- Ensure that the folders are in a properly maintained state with the original data recorded, dated, and signed in an acceptable manner.
- Using the case record form and the protocol as central references, ensure that data of the various appropriate types exist for each subject over the period of the project.
- Check for any inconsistencies in data records. For example, check for agreement between the number of subjects and subject numbers on each set of data records.
- Check for inconsistencies in data showing unexpected trends, scatter, and individual aberrant points or deviations.
- Record the observations of the data audit in an inspection report, and date and sign the record (Form 5.10).

Archive Inspection

One important aspect of QA's role is to ensure that project records are maintained properly and are in good condition. To this end, I have produced a checklist of items I look for when carrying out an inspection of our local GLP archive:

- Produce a list of studies archived from QA records of inspections and select several projects that cover the widest possible time frame from the earliest to the latest.
- Check to ensure that the project is entered into the archive lodgment index along with number of files and contents, etc.
- Check that the project records are actually in residence.
- Check the archive access record to ensure that minimal access has been achieved and that any that have occurred have been authorized.
- Check the record keeping for regular maximum and minimum temperature and humidity measurements.
- Check fire and smoke detectors for proper operation and routine testing.
- Check that older projects are reviewed from time to time for readability of contents, e.g., thermal paper printouts.
- Check compliance with archiving SOPs.

- Check archive lodgment records with QA project records to ensure a match is made.
- Check that removals have been authorized and are returned within the time frames requested.
- Confirm that electronic data are being maintained as expected, i.e., regular deposits of archive tapes, disks, etc.
- Check that proper records are maintained of nonproject material such as SOPs, logs, and registers, etc.
- Confirm residence of the aforementioned material

Personal Research Projects (Non-GxP)

This type of project is quite common in the academic field, so that the better facilities can be used and are therefore sometimes employed in the regulated environment. The problem that can occur here is one of dual standards. Under the applicable GxP regulations, this is not allowed. If any work is to be carried out in the regulated environment, it must be carried out according to the GxP code. The only difference should be that the data or final report is not audited and no certification of compliance is required. The work will still be monitored by the QA unit during its normal operations to ensure GxP compliance. Any such inspections must still be reported to management for information purposes and to provide a complete history of all projects carried out. The data generated under such a project is not required to be archived, but it may be prudent to do so. If you do archive such material, you should also note in the archive lodgments register that it does not have to be held for the same period as your GxP material. This type of flag is very useful when you wish to clear space from your archive, and you can quickly identify and easily remove such material.

CVs and Training Records

A full CV of every person employed in the unit should be maintained and regularly updated. In my organization, this is at least annually, and they must sign and date the document to ensure personal approval. For sponsors who request a copy of a CV from all project staff, this is facilitated by producing a single A4-page summary CV and not the full CV, which in some cases (academic CVs) can run to several dozen pages.

One procedure we try to follow is to separate the training from the CV in such a way that the training record may be considered as an appendix to the full CV. The way I approached this was to provide each member of staff with a simple word-processed document that was a two-column table in which the first column contained the year and the other, details of the training attended or received. This, then, provided a simple list that could be updated at every change and then printed or merged with the CV update. Such a record can be printed manually, signed, dated, and kept in a person's

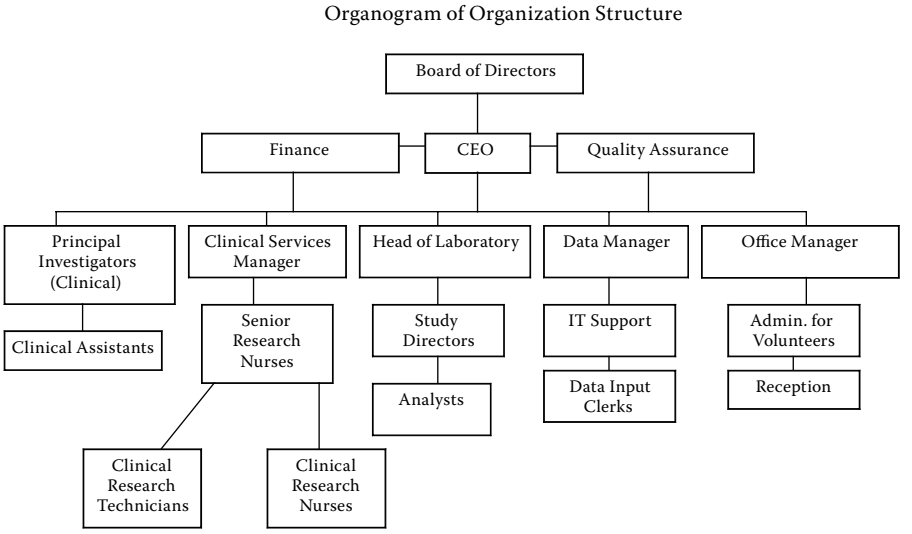

Figure 5.1 Organogram of organization structure.

individual training record. If staff appraisal is in operation, such records are usefully passed over to the staff member in order to assist in the appraisal process. This is an added incentive for staff to ensure their training records are as up to date as possible. (Training is covered in more detail in Chapter 3.)

This type of list, however, should not be considered the definitive training record but a summary. In most cases it is prudent to ensure that any copies of certificates are on file as well. We have a system of "core" training units such as "Health and Safety," which is implemented across the whole organization. This consists of tasks based on SOPs that are regarded as absolutely necessary for each member of staff. Such training is also dependent on job description and, additionally, the training records may contain the classifications of training such as "competent," "competent to train," etc. All training records are signed by the trainee and the trainer to provide proof of training and acceptance of that training by the trainee.

Job Descriptions

These are very important documents from the external auditors' point of view (as well as to the individual jobholder), allowing them to see what each individual's spheres of influence was within a given project. It also allows them to fill in the gaps left when looking at the reporting structure organogram (Figure 5.1) of the organization, which is necessarily vague owing to the limited space in such diagrams. All job descriptions should be signed by the individual and by management; such acts indicate that the employees accept the tasks assigned by management to them. If the job descriptions are not signed and therefore not authorized by management, there is no documentary evidence that these tasks have been assigned to any individual.

A useful point to make here is the use of titles in organograms, SOPs, and job descriptions, rather than people's names. People tend to be given different responsibilities or leave employment; therefore, any documentation can quickly become out of date and patently incorrect. You can eliminate the task of sifting through documentation for individuals' names by using titles instead. Although this does not make it easy to determine who does what job, so it is advisable to produce a staff list of names and job titles. This document can be regularly and easily updated, say, monthly or immediately, if required, without a large administrative burden.

Carrying Out External Audits

When looking at subcontractors providing support services for your clinical operations, you have an obligation to inspect and audit your suppliers (as your sponsors also have to audit you). This is your turn to "get your own back" on someone else. I suggest, from our experience of being inspected by our sponsors, that once every 2 yr would be an appropriate frequency. This will provide you and your sponsors with the evidence that you have ensured the quality of your "raw materials."

Prescriptive points for audit will, of course, depend on the services being provided, but you must be consistent. We have had cases of facility compliance audits that were based on the other organization's operational SOPs (not external audit SOPs), study-specific items, and ICH GCP, all in one audit. To top it all, the exit meeting was constructed such that no responses to comments were accommodated and no audit report would be supplied! This situation is not to be recommended for any audit you carry out. It leads to incorrect findings, anger, and animosity against the sponsor by the staff involved and, of course, there is no chance to explain the errors in findings.

You are required to have an audit plan of what you will want to see and do, and this can be based on your own checklists with specific items added, for example, checking for QC participation in national schemes in clinical chemistry labs. What is important here is that you tell the auditee what type of audit you will be carrying out and what standard you are going to use, and stick to it. To assist this activity, I have included a series of criteria below that you may find useful as the basis for a rolling program of subcontractor facility audits:

- It will normally be necessary to inform the subcontractor in advance of a QA visit. Such activities are facilitated by the use of questionnaires that probe the contractor about their operational systems prior to a QA visit. This allows you time to formulate a more targeted inspection plan. QA must maintain records of all such inspections and audits.
- Ensure that the subcontractors appreciate what is expected of them in the protocol, study plan, or technical agreement, and with reference to the GxP regulations.
- Ensure that there is a quality system in operation.

- Ensure that subcontractors carry the correct level of liability coverage.
- Do a financial check when a private sector contractor is being used.
- Archiving procedures (responsibilities).
- An inspection plan should be drawn up by QA that reflects the services being offered and which will be measured against applicable regulatory requirements, ISO standards, and your own SOPs. Where no formal SOPs are available within the facility, working-practice documents may be used as the reference documents.

Approval Process

- After the inspection of the subcontractor, QA should produce a written report of the findings and either recommend or reject the acceptance of the contractor's carrying out project-related work. The final decision on acceptance or rejection lies with management.
- The subcontractor will be approved by management, following a written recommendation from QA after the aforementioned visit. This approval may be formally indicated by a signature of a senior manager on the QA approval report. Only then may the contract be awarded.
- During the execution of the subcontracted work, QA staff may, at their discretion, visit the subcontractor to inspect and audit any work in progress.
- In the case of subcontracted work of a continuing nature, approval of subcontractors should still be valid while it can be demonstrated that ongoing internal and external quality control and monitoring of the facility still exists.
- It should be a policy of your organization to ensure that regular subcontractors are visited at least once every 2 yr by the QA to confirm continued compliance. In some cases, just sending out a questionnaire may be enough to continue the relationship.

Smooth QA Operations

In order to facilitate QA operations and to remove a lot of tedious record searching, extensive use of computer databases and reporting capabilities are employed in my organization. QA in our organization are involved with the following general operations:

Control and issue of SOPs, MOPs, validation documents
Archive deposits
Inspection details
Audit details

When QA was first started within the company, it was a part-time job within a full-time job for me, and anything that allowed a slicker approach to record keeping and reporting was seen as a necessity. As I was very keen on computing and databases, in general, it seemed like a good idea to use electronic record systems. In these early days we used a flat file database system; today, we use a relational database management system. This electronic record system has saved innumerable hours when producing QA reports and summarizing information. There is one proviso, though, that must be kept in mind when using computer-based databases; if you put junk in, you get junk out. The databases do require maintenance from time to time to ensure that the data are correct and no errors have crept in and, more usually, that no data are missing.

What I needed was a system that contained dates and summary details that could be interrogated to provide reports of inspections, audits, lists of SOPs requiring review, and outstanding QA reports. Although all the data during an inspection or audit is still kept on paper (e.g., the preceding checklists), a summary of this information is typed into the database, and it is normally the electronic record that is the first port of call.

Quality Metrics

Details of audits are maintained in a separate table within the QA database but are still related to the project number and ID, so that quality metrics can be recorded and summary reports produced. The metrics maintained within the database have relatively simple classifications:

Type 1: Minor errors such as typos, page numbers, etc.
Type 2: Moderate errors, if left may compromise the study
Type 3: Major errors, which would certainly compromise the study

The allocation of type is purely subjective on the part of QA, who records the metrics; as this is normally done by one person, any bias is hopefully minimized. How you classify the problems observed and what metric to use is up to you. You can make it as complex or as simple as I have done. In Chapter 6, I will describe the methods I use to break down the three error types defined here into physical problem areas.

Larger organizations can afford the luxury of analyzing specific topics monthly and obtaining regular reports, but in a small organization the information returned in a short time frame is statistically meaningless. It has been my experience that in the smaller organization quarterly reports can provide enough metrics such that some statistical analysis and interpretations can be made. However, reporting on an annual basis is still preferred, but if any trends are noted, this can mean that it is a long time before any action can be taken. In saying that, it must be remembered that it may take a long time to get enough data in order to see a trend in the first place.

Table 5.2 Contents of a QA Activity Report

Summary of QA activity in period	Number of inspections, projects, SOPs issued, archive inspections, protocol audits, report audits, study plan audits, CRF audits, data management plans, etc.
Analysis of audit and inspection reports	Histograms of error analysis
Analysis of errors found in QA reports	Histograms of errors found in reports
General statistics across the company	Metrics from the four quarterly reports, number of audits per project, time to reply, and number of report audits tabulated against months and years
Clinical inspections	Number of inspections carried out
Laboratory inspections	Number of inspections carried out
SOPs issued or reviewed	Number of SOPs and titles issued in past year
Corrective action requests	Summary details of each request (+ totals)
Ward inspections	List of ward area inspections (+ totals)
Audit summary	List of all audits (+ totals)

The collection of such metric data does allow the QA unit to produce an annual summary of operations and illustrate year-on-year performance differences and quality improvement, if any. I have found these reports to be a powerful motivator of section management who like to compete for the best improvements and least errors. Our annual report of company performance contains the information shown in Table 5.2.

We must take cognizance of the fact that because we have a comprehensive QC system in place and QA only audits reports after they have been through the QC process, the errors found will tend to be mainly Type 1. It is important, therefore, that each department keep all of its QC findings as well, otherwise a "nice" but highly biased picture will emerge. As we introduced a robust QC system, this is exactly what we saw in our organization (illustrating clearly that you must be careful where your quality metrics come from). We have found that QA can usefully coordinate these QC metrics from the other section leaders and present the quarterly findings at one of our regular monthly quality meetings. This can then show the true picture, warts and all, of the organization's quality system.

Preparing graphs of metrics for inclusion in your reports is easily facilitated by using a spreadsheet such as Microsoft Excel®. By installing the data analysis pack add-in (not installed by default), you can obtain histograms (for frequency analysis) and summary statistics; the data can be easily manipulated into the required format. It is also reasonably simple to output your quality metrics from your database directly into a spreadsheet for analysis. The integration of the Microsoft Office® suite and Microsoft Windows® can be used to your advantage here (the Microsoft Office suite for Apple Macintosh® unfortunately does not have the Access® database).

Production of such summary documents encourages you to take a step back and look at the big picture rather than being concerned with minutiae.

It is very revealing in most cases because you can see trends that are not visible by any other means. Individual errors are easily fixed, but recurrent problems may be difficult to identify because their natures are different, although their root cause is the same. These are the ones we must tackle if we are to improve quality and compliance. One other very useful tool is to set QA annual targets based on your metrics, for example, to reduce the number of Type-1 errors by 30% and Type-2 and Type-3 errors by 50%. Of course, these must be realizable by QA or someone else who suggests some changes to operating procedures that would allow this to happen. These targets can easily be published in the QA annual report to management and also provide a vehicle to publish the progress in meeting those set targets. In most cases, achieving QA targets is out of QA control, so there has to be heavy reliance on others within the organization. There is also a requirement that management back these initiatives to the hilt so that maximum effort is forthcoming. Of course, with any such initiative there may be resource implications in that what you are trying to aim for will require the investment of money in new equipment or software, etc. In some cases, these may be very expensive in relation to what you are trying to achieve and, therefore, will not be cost-effective. In such cases, it is up to management to decide what the limiting quality standard will be.

QA Reporting

When QA finds a problem that is general and not a random occurrence and reports this to management and the project leader, some mechanism must be put in place so that the underlying template documents are updated and the same problem does not recur. We indicate this by placing a "**T**" after the action point noted in the last item in the example the QA report supplied.

When such template errors are noted, someone must be assigned the correct permissions and given the responsibility to amend the original template with the correction. If access to such documents is not controlled, then chaos can reign supreme. Such a refinement within your quality system is of paramount importance in closing your quality "loop" of improvement. It is the duty of the project leader to inform the template modifier of the changes required and to ensure that these are implemented (Form 5.11).

Form 5.11 (Example Template Modification Suggestion)

Quality Assurance Report

Audit Date: Study no.: Sponsor:

Report on the Audit of Tables of Data

QA Comments	Action	Responder's Comments	Initial/Date
1. Table 16.2.9.5. Urinalysis. Sub 26. Screening. A repeat sample was taken and tested on 17/3/03. Shouldn't the details be entered into the first table?	X		
2. Table 16.2.9.8. Concomitant medication. During study. Where medication is administered in both March and April the entries are in reverse chronological order, i.e., 7/4 precedes 31/3.	X		
3. Table 16.2.9.13. Headings should be in bold and centered.	**XT**		

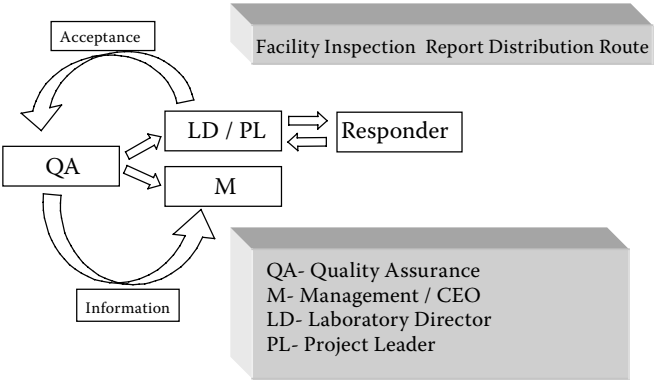

Figure 5.2 Facility inspection report distribution.

Getting the QA reports to staff means that multiple copies of QA reports to interested parties; this may cause confusion over who has to fill in the response and return it to QA. We eventually came up with a solution: the copy to be completed was printed on yellow paper, and the others on standard white. This had the added advantage that it is easier to spot on a desk or tray filled with paper (Figure 5.2). All reports of QA inspections are sent directly to the appropriate study director or project leader for action, if required. A copy of any report is also sent to the management for their information. Comments that will appear in the report are also quoted verbally to the immediate members of staff involved with the study so that changes may be incorporated into processes immediately if this is appropriate.

Report Audit Procedures

The main aims of any report audit are defined as:

- To confirm that a study was performed in accordance with the agreed protocol or study plan
- To ensure that the study is accurately and completely reported
- To check that the minimum required contents are present
- To check that the report is internally consistent

In our organization, audits of reports are carried out at the draft-report stage, rather than at the final-report stage, to allow the incorporation of any sponsor comments. If, for any reason, no draft report is to be issued, the project leader should individually arrange the final report audit with QA.

The following list provides examples of items that might be covered in a typical audit. They should not be regarded as comprehensive or obligatory. It is my contention that auditors must be allowed the freedom to extend or even curtail an audit if they feel it is appropriate.

1. Check that the start and completion dates in the original data and the report agree.
2. Select each type of data in turn, e.g., hematology, dosage records; check that the data in the report are correctly identified and that they were collected at the times required by the protocol.
3. Check that the original data correspond to the data in the report. This should be done on a sampling basis.
4. For summarized or reduced data, it would normally be necessary to follow through data reductions or calculations. This may be deemed unnecessary if calculations are made from a database using a validated computer program, with a hard copy of the input available. In such cases only the input data and final reported results need to be checked.
5. Check the text of the report to ensure that the project and its execution are accurately described and that its execution complied with the protocol and appropriate SOPs. You should also be confirming the dates, times and time periods, the preparation, administration and control of test substances, and the acceptance criteria for volunteers.
6. Check that any divergence from the protocol or SOPs has been fully authorized and documented.
7. Check that there is appropriate commentary on any unforeseen or untoward occurrences during the project, e.g., adverse reaction sheets and comments sheets, etc.
8. Check the data and the text of the report for consistency and for mutual compatibility and self-compatibility. This includes checking on adverse events in clinical studies and the subsequent record keeping.
9. Check clinical reports for adherence to the International Conference on Harmonisation (ICH) listings of tables.
10. Finally, use should be made of QA inspections carried out during the study to check for appropriate action being taken to correct your observed deviations or any noncompliance issues.

Assuming that the Audit is Satisfactory

Prepare a list of inspections for inclusion in the final report, giving the dates and details of inspections and reports to management. This is easily accomplished by using the QA database, in which all such information is stored for just this purpose.

If for any reason audit is carried out after issue of the draft report or summary data to the client, the fact that the report or data are still subject to audit must be notified to the sponsor along with the data. (This is quite a common occurrence when the sponsor wants the data sent as soon as it becomes available.)

Assuming that the Audit is Unsatisfactory

Audits may be truncated if certain criteria are met and the report returned to the originator for revision. For this, the report should have more than two critical errors, three moderate errors, or five minor errors. You should, of course, develop your own criteria in light of your own experience. A report detailing the reasons will be issued to management. When the report is returned to QA after reworking, it will require a complete reaudit.

- *Critical errors* are defined as errors that would affect the interpretation or compliance with protocol or GxP (e.g., incorrect title, table headers, protocol deviations not reported, incorrect adverse event recording, or major problems with data).
- *Moderate errors* are defined as those that could affect interpretation or compliance with GxP (e.g., missing definitions, SOP deviations, minor data problems).
- *Minor errors* are defined as those that do not affect compliance or interpretation of the report (e.g., typographic errors).

Such draconian measures to reject a report can only really be justified when a robust QC system is in place and is working satisfactorily. But such measures are useful tools to get across the message that you are not there to error-check their work and that you have better things to do.

QA Record Keeping

Following an audit, you should prepare a report that indicates the page, appendix, or portion of the report audited, the data checked, and the errors found. It should also include a description of any other data errors and other comments as necessary. The report should be signed and dated by the auditor.

The audit report (on yellow paper) should be sent to the principal investigator or study director for comment or action (Figure 5.3). A second copy (on copy paper) is sent to management for information only. The front page should contain a circulation list for the completed report; this can be neatly accommodated as a document footer.

The audit report with the appended responses is held within the QA. It is at this point that the assignment of error types is made in the database. The reason for the delay in assigning these metrics is simply that QA may have made an incorrect observation. This helps us to ensure that incorrect metrics are not included in our summary statistics.

Following a report audit, further checking may be required if the sponsor or CRO want to incorporate last-minute changes or corrections. The extent of such rechecking by QA would be dependent on the extent and type of changes made to the report.

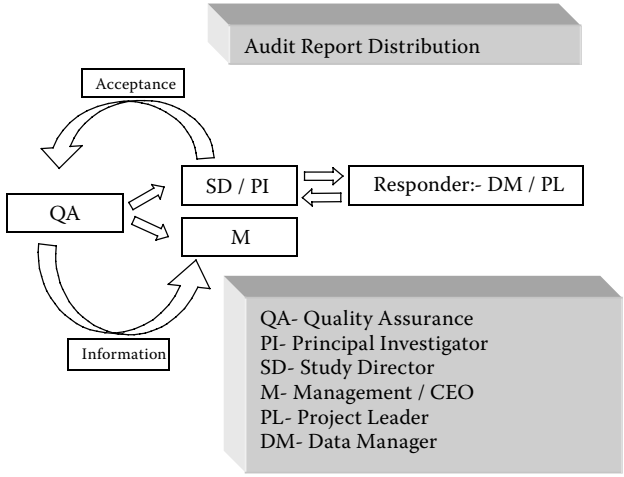

Figure 5.3 Audit report distribution.

Finally, when you deem the report satisfactory, you are then in a position to sign a QA authentication page to be included in the final version of the report. No further alterations to the report after this are permitted. Any further changes should be dealt with as a report amendment document.

chapter 6

Beyond Compliance

Other Quality Systems: A Brief History

There are many quality standards available that organizations can use to improve. These are in addition to those necessary for legal compliance, such as the U.S. Food and Drug Administration's (FDA's) Good Practices guidelines (GxPs). When I first started in the good laboratory practices (GLP) area and wanted to know more about the basics of quality principles, my first point of contact was with British Standard (BS) 5750, later known as ISO 5750. (I suppose the rest of the developed world could see a good system and decided to adopt the British system *in toto* as no major changes were made to the text.) These were general documents in much the same way as the U.K. GLP *Blue Book*; they provided outlines of what was required but no real details or interpretation. I knew by meeting people within the British Association for Research Quality Assurance (BARQA) that such networking was especially useful in interpreting guidelines. You could interpret the rules yourself, but what would be more useful would be some information from people who had interpreted the guidelines and been approved by some international third party such as Lloyd's Register Quality Assurance® or SGS®, etc. The problem here for me was getting this information. Another area that concerned me was that I did not have any tools or basic understanding of what the foundations of quality systems were. I found that one avenue open was membership in the Institute of Quality Assurance. This provided the framework to build and advance my knowledge. My previous experience and qualifications allowed me initially to obtain the Licentiate grade of membership. This gave me access to the publications of the institute which, in itself, was worth the membership fee. By studying for the institute's A3 examination in quality management, the foundations of all these quality ideas were revealed to me. Passing this examination gave me the advantage of the professional designation of membership in the Institute of Quality Assurance (MIQA). The major drawback with this approach was that the institute and the examples were engineering or manufacturing oriented, which was not really appropriate for the science-based, service-area requirements I had in mind.

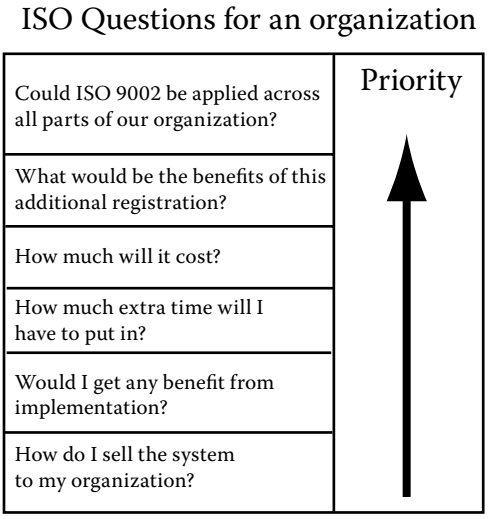

Figure 6.1 ISO questions for an organization.

Although not entirely relevant, it was clear to me that the basic principles were independent of the field. It took just a little work to convert these to my GxP requirements. I could now begin to see outside the regulatory compliance framework and into the world of business improvement.

My being "outside the box" brought up several questions (Figure 6.1). Let me look at each of the questions in turn and explain the reasoning for adopting the system in my organization:

1. *Could ISO 9002 be applied across all parts of our organization?*
Yes, this was the big attraction for management and me. Our current systems of good clinical practice (GCP) and good clinical laboratory practice (GCLP) did not cover some important areas of our organization. The main areas that we would prefer to have included in our extended quality system were financial (purchasing and invoicing, etc.) and general administration.

2. *What would be the benefits to us of additional registration?*
It would give us total coverage of all aspects of the company's operations. To sponsors, this probably was not very significant. All the sponsors wanted from us was GLP compliance. We also had Association of Independent Clinical Research Contractors (AICRC) accreditation which, at that time, provided a third-party assurance of our compliance with ICH (International Conference on Harmonisation)-GCP guidelines.

3. *How much will it cost?*
Not much for an organization such as ours, but it does depend on who you get to approve your systems, and how much work they have to put in, e.g.,

production of the documentation such as the quality manual. It is normally still much less than the annual fees for a U.K. GxP registration.

4. *How much extra time will I need to put in?*
Again, not much, as most of the audits and inspections are already being carried out and do not have to be done again. Some extra inspections and audits are required for the new areas being covered, but the increase in workload was not too significant. You may have some extra work initially owing to the obligatory documentation required, such as production of a quality manual or editing one produced for you by a consultant.

5. *Would I get any benefit from implementation?*
QA can benefit from such registration by being able to account for all business activities, not just the regulated ones. This is especially true when you start preparing your quality manual. Auditing and inspecting areas outside the normal remit allows you to see the whole picture and from a different perspective. Our first thoughts when audits were carried out were to spot areas of inefficiency, and we were able to suggest improvements.

6. *How do I sell the system to the organization?*
As can be seen from the above arguments, it is not a simple matter to convince your management that it is worthwhile spending more money on something they perceive they "already have." It is normally seen as an extra layer of bureaucracy that is expensive and unnecessary. It is the value-added service of being outside the regulations looking at nonregulated activities that results in the most benefits, e.g., standardized templates for documents.

Once you have achieved registration and started carrying out the tasks required, you will begin to see the standards' weaknesses in some areas within your specific boundaries. The lack of science-based criteria and lack of required detail are some of the main problematic areas. As you are already working to the GxP standards, these gaps can be more than adequately covered.

Since its inception, ISO 5750 and its various parts have evolved through various stages to ISO 9002, ISO 9001, and now to the coherent standard of ISO 9001:2000, the current standard. The main change among the different incarnations is the move towards identifying processes rather than individual procedures and the inclusion of design aspects. This design element was always separate within the original standards and was optional; a considerable number of companies ignored this section as it was considered the most difficult, although possibly vital in their actual operations.

This component is now considered absolutely necessary, and there is no avoiding it as it is a fundamental part of the standard and not an optional extra. The manufacturing industry managed to avoid such registration in the past by not being certified to ISO 9001:1994 by selectively picking the parts they found easiest and only registering for that subsection. I must

admit, though, that the new standard makes interpretation and compliance with it much simpler. The whole quality standard is now integrated, and for our purposes of scientific data quality, it allows us to encompass the production and design of studies, study plans, and protocols, etc.

A possible downside is that we have moved to a process-based procedure, and each process may encompass several standard operating procedures (SOPs). This does seem to be at variance with the GxPs, which still require individual procedures, but so far it has not caused us any problems with external audits, sponsors, or regulatory bodies; perhaps it is still too early to tell.

This current standard focuses much more on management control and review of the processes, and is much better suited to meeting the objective of continual improvement. In this sense, it is a little easier to sell the idea of registration to management as the system is in agreement with taught, general management principles.

Some sample process diagrams from our quality and procedures manual are provided in Figure 6.2 to Figure 6.4. These examples clearly show that multiple SOPs are involved in each process. Such diagrams also allow you to see clearly the relationships between each SOP and how it evolves to produce the end results. From a QA perspective, it provides you with the ability to see interactions that you perhaps never imagined existed.

A list of flowcharts (processes) are contained within our quality manual:

- Control of documents
- Control of quality records
- Control of monitoring and measuring devices
- Control of nonconforming product
- Corrective action
- Preventive action
- Process flowcharts

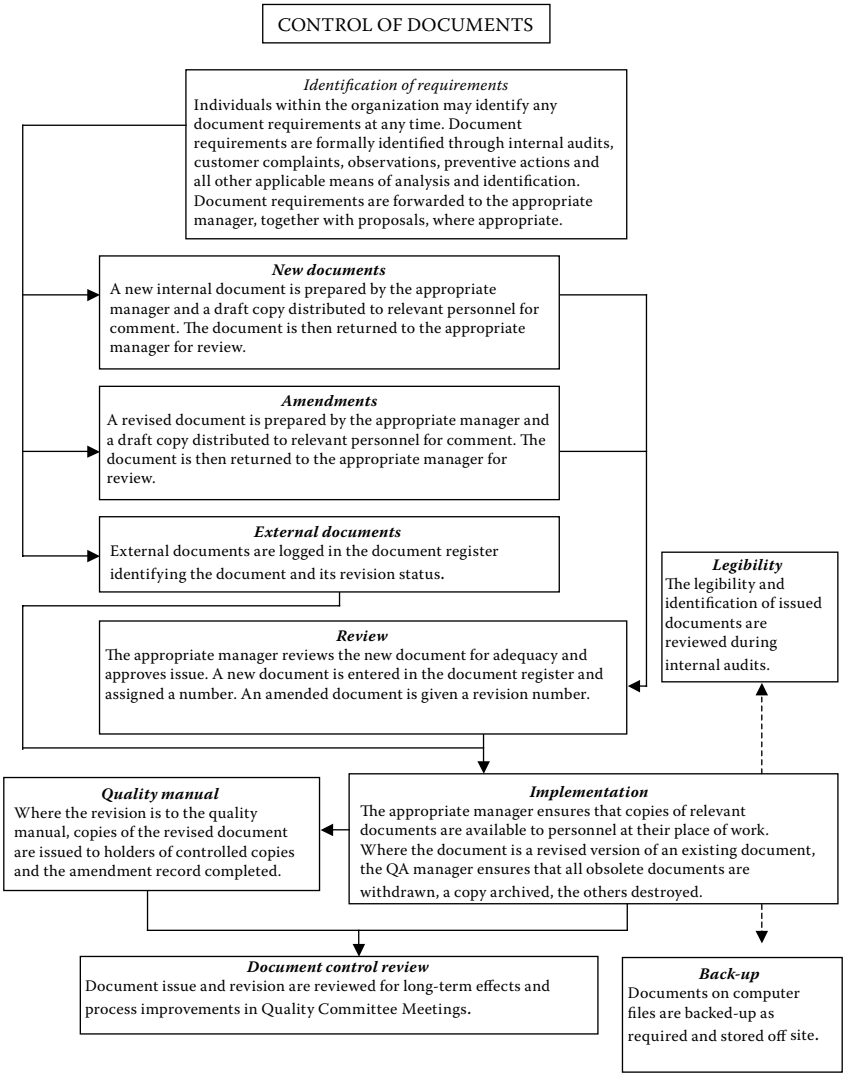

Figure 6.2 Control of documents process diagram.

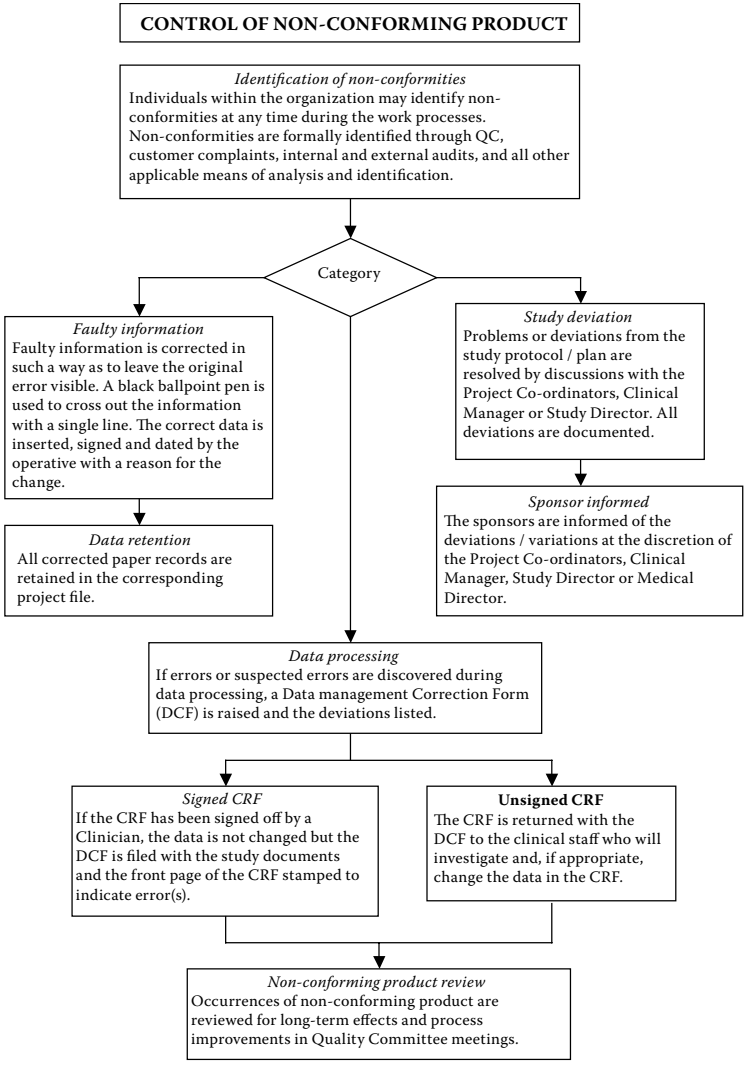

Figure 6.3 Control of nonconforming product process diagram.

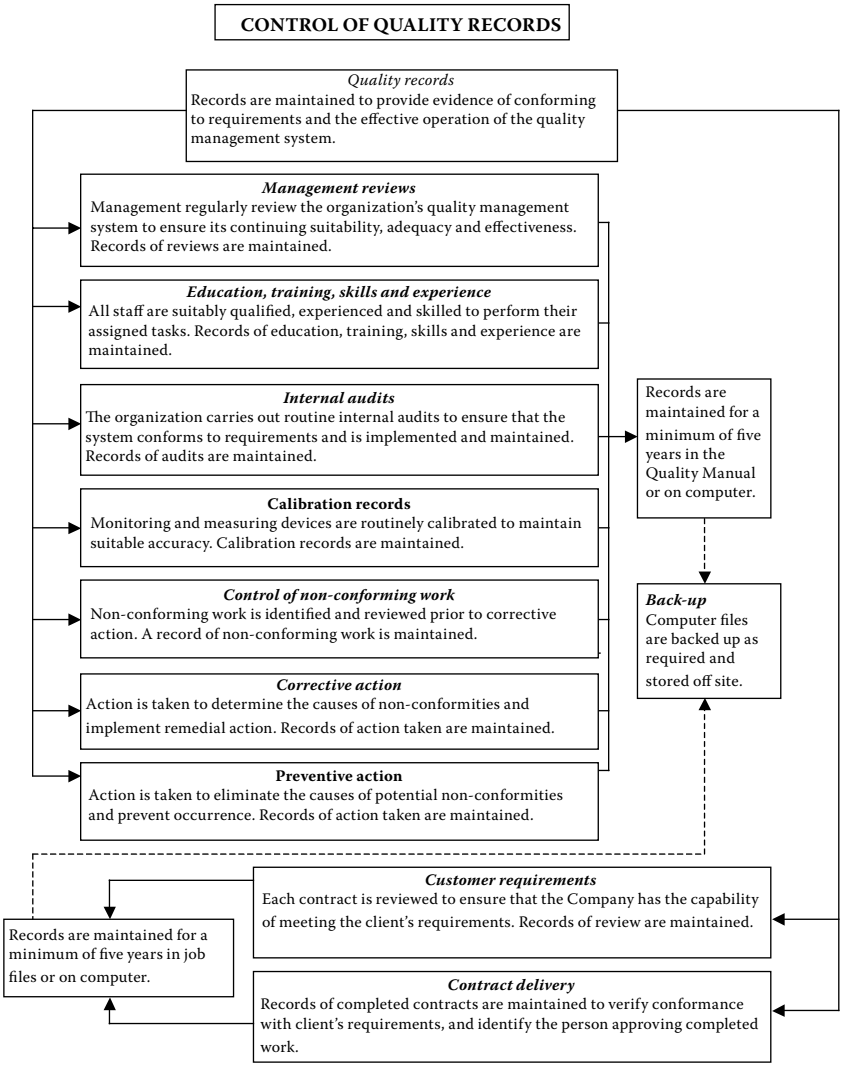

Figure 6.4 Control of quality records process diagram.

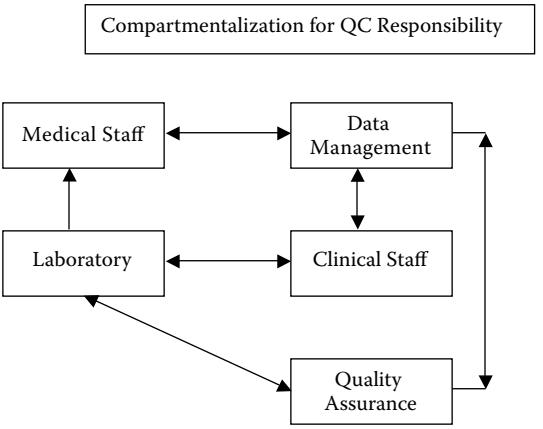

Figure 6.5 Compartmentalization for QC responsibility.

Quality Control vs. Quality Assurance

How do you start a QC system? In the laboratory, it is a matter of preparing a large batch of spiked standards across the expected analytical concentration range or else purchasing them from a reputable source. You can then intersperse these QC samples within your batch of unknowns and analyze them. Your SOP on QC samples will define your acceptance and rejection criteria. Seems simple, but what do you do with data listings, report text, and tables? Not so easy.

As you have probably realized by now, I consider this not to be a QA function, but a "producer" function. The QA function is to suggest ways of doing things and confirming that they have been done correctly. If a problem is detected, then QA should consider ways in which to change the system or process such that the problem does not reoccur.

First and foremost, we must try to eliminate the problem of delegating checking to staff outside the producers' area. This appears to be a problem that correlates well with qualifications and status within an organization. The higher the status or qualification, the more likely the perception is that they are "too important" to waste time checking over items they consider to be perfect anyway. We need to establish compartmentalization of producers such that they themselves are responsible for the quality of their own output. We used the natural divisions within our organization to provide the compartmentalization required (Figure 6.5).

The double-headed arrows indicate that a QC document must be produced within the originating section, completed, and passed on to the next section. Acceptance between compartments is described in the following text. The details of how this can be implemented are provided by extracts from our own documentation.

Definitions

Report QC can be split into five divisions, each with its own QC requirements:

1. The report must be compliant with the protocol requirements.
2. The report must be backed up by audit-trailed raw data.
3. The results, summary, and conclusions must be backed up with accurate statistics.
4. The text, tables, and figures must be consistent with the data reported.
5. No typographical errors exist.

Protocol and Study Plan Compliance Checks

Check that all requirements have been met:

Number of subjects or samples reported consistent with that expected.
Study number agrees with protocol and study plan.
Agreement with PI or SD matched by signatures and dates on protocol.
Study report title agrees with protocol and study plan title.
Check that each specific requirement has been carried out and reported, e.g., number of samples, requests for biochemistry and hematology, correct tests carried out.

Tables to Raw-Data Check

Ensure that each datum reported has source-data verification.
Ensure that all QC values are reported.
Ensure that QC acceptance criteria have been met.
Check summary statistics of all tables of QC data.

Summary Check

Ensure that summary statistics in text match those in tabulated data.
Check precision of reporting values, e.g., decimal places, significant digits, and rounding.
Check that the overall results support the conclusions of the report.
Check that conclusions match statistical probability values.

Consistency Checks

Check table titles for accuracy.
Check units used in tables, especially when two different parameters are measured.
Check that footnotes are consistent with contractions used in report.

Check that any contractions used are either tabulated or defined on first occurrence in the text.
Check figures are consistent with the project ID, title, and expectations.
Check figure axis for correct units.
Check all tables and figures for links to report with page numbers, etc.
Check table of contents is complete and supports the actual contents of the report.
Check that all externally supplied documentation is consistent with the study, e.g., certificate of analysis, batch numbers, expiration dates, etc.

Typographic Errors

Read text to check for any spelling, punctuation, standard unit definition errors.
Check to see page numbering is consecutive and no blank pages exist.
Check all running headers and footers for consistency.
Check total number of pages in the report.
Check sponsors reference number and cross-reference with the protocol.
Verify that the unique report identification number, which is incremented with each revision of the draft report, is in place.
Check that all units used are correct and in the correct format required by the sponsor.

Organizational Units and Report QC

These are compartmental divisions within the organization as defined by your work area, e.g., medical, data management, clinical, laboratory, etc.

A report or portion will not leave an OU before QC checking, and this fact must be documented. It is not permissible for one unit to use another unit for specific QC. The responsibility for errors lies with that organizational unit (OU) and cannot be transferred.

If a report or portion that is QC checked and passed to another OU is subsequently found to contain errors by the receiving OU, this will be returned to the issuing OU for correction.

OUs will produce their own specific QC checklists, which will be based on the preceding items. These checklists will be evolutionary, depending on types of errors found in that OU and their frequency of occurrence.

Example Rejection Criteria to Be Used by a Subsequent OU

If more than five typographic or minor errors are found.
If any one major error is found, e.g., study number, inconsistent dates.
If any errors are noted that are signed off as QC checked on their QC checklist.

On rejection, the reasons for the rejection will be itemized on the QC checklist and signed by the person making the rejection. QA will be informed of any such action by means of a copy of the amended QC sign-off from above.

Final QA Audit

The report or section is passed to QA for audit along with the appropriate QC sign-offs. If during this audit errors are noted, the report will be returned to the study director or project coordinator for any corrective action.

The returned report with QA comments on errors and omissions must not be considered in isolation. If QA finds errors at this stage, it is to be expected that there will be others, and the whole report must be subject to a 100% check for errors of the same type, before resubmission to QA.

Such QC systems have made QA's job much more satisfying, and have also reduced the number of QC activities we had to undertake. By defining who had ownership of the problem and having management buy in to the idea, we were most of the way there.

A common question asked of QA is how long the report audit will take.

This tends to be received negatively when the report arrives for audit several days late (this should strike a chord with other auditors!), but the delivery date must not slip! This occurs often because, traditionally, all the auditing is done at the draft report stage rather than during the data collection process. QA needs to verify the data long before it gets to the draft report stage if these time constraints are to be met without compromising the audit. No matter when a report arrives, you should allow yourself plenty of time to carry out your checks and, within this small window, ensure that you include plenty of breaks to prevent yourselves from becoming stale and missing vital problems. These breaks can be changes in tasks, such as inspecting a process; the task does not matter, so long as you are not concentrating on the same process hour after hour. You will become a much more efficient auditor as a result.

Sampling for Quality

We are never likely to ever find the error-free report, but we must ensure that whatever we do is acceptable to our sponsors and ourselves. There are standards out there for doing sampling such as Mil-S-105E and BS6001, but these tend to be sampling by attributes for "widgets." However, there are some benefits in exploring such tools in the service provision area as well, especially when dealing with large tables of data. Such plans can be very useful in providing a statistical basis for your sampling and acceptance or rejection criteria. These sampling plans require that, for a given lot size and sample size, if a certain number of defects are found, then the batch should be rejected, i.e., the whole table or report returned to the author for reworking, rechecking, and reaudit. If this happens often, then the author is soon convinced

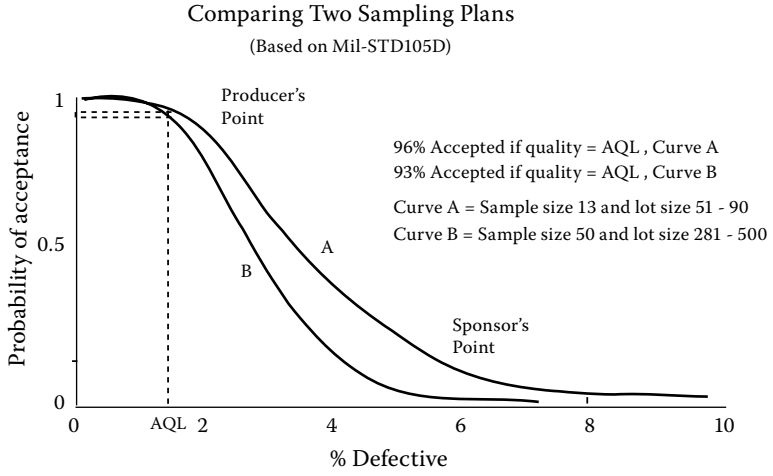

Figure 6.6 Comparing two sampling plans (producer's risk).

that they should get it right the first time. However, we must also consider our fixed time frame to send the report to the sponsor; this probably will get in the way of such ideal actions.

Figure 6.6 shows two operating characteristics curves for an acceptable quality limit (AQL) of 1.5%. Curve A is for a lot size of 51 to 90 with a sample size of 13. This provides the criterion of "accept zero errors, reject on one." Curve B illustrates a lot size of 281 to 500 with a sample size of 50. This provides us with the criterion of "accept two errors and reject at three errors." It is clear that both sample sizes are good at accepting lots better than the AQL, but they differ in their ability to throw out lots, which are worse than the AQL.

It should be borne in mind that these plans are to provide a safeguard against your risk of rejecting good batches, which is not quite what we need in the data market or even in widget production; we need to protect our sponsor (and our reputation). Although sampling plans are often used to protect the receiver, acceptable-quality-level-related plans are not well adapted for that purpose. The reason for this is simply that these plans focus on average quality over a succession of batches. It would be a real problem if the report or tables you sent to your sponsor were full of errors but passed your quality standards! This could happen if you are not careful about the application of principles.

A better system, such as those described in Mil-S-19500 and Mil-M-38510 that safeguard the sponsor, is required for our purposes and, fortunately, we can use Figure 6.6 to illustrate this point; the other ends of the curve provide us with limiting quality sampling values. Lot Tolerance Percent Defective (LTPD) is the sponsor's point where we are trying to protect them from any defects. Using the graph from Figure 6.6, we can clearly show the effects of differing sampling plans.

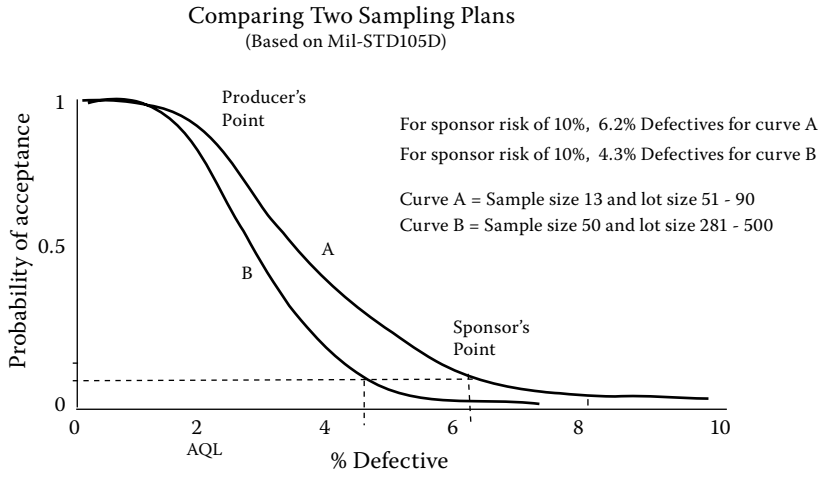

Figure 6.7 Comparing two sampling plans (sponsor's risk).

Figure 6.7 is a graph showing the operating characteristics for our two particular sampling plans, i.e., for a given sample size and acceptance number. For a sponsor risk of 10%, curve A would provide a risk of 6.2% defects and curve B, a risk of 4.3% defects.

This type of model is much more appropriate for our line of work, but it still leaves much to be desired. It should also be remembered that this type of sampling should be carried out by production staff and not by QA. However, QA can also use such plans as the fundamental basis for their sampling SOP if required. It is my opinion that QA should be more concerned with the output after such QC has taken place and question whether or not the production data sampling is sufficient to ensure that errors are caught.

Do you feel that such an error rate in data listings, etc., is acceptable? I feel rather uncomfortable with accepting errors that I know about. However, we must also consider the amount of time involved in decreasing the errors to as close to zero as possible. Such ideals are probably not achievable, but an error rate of 10% in a sponsor's data is clearly not acceptable. We need to change the process that produces the data, not correct the errors; we can be in danger of "inspecting in" quality. More delicate sampling plans are needed here, and it is my contention that QA must assist production staff in modifying their procedures in order to minimize error. I will add at this juncture that I think that QA should be the first port of call for advice by all departments introducing QC, so you should at least be familiar with sampling and acceptance criteria.

Statistical sampling plans can offer benefits to both production staff and to QA. For QA, they can provide a framework and structure for auditing, and they are relatively easy to use.

Sampling for QA

After reports or listings of data have been through the QC systems at each stage, QA should be provided with the material and the completed QC checklists. These completed checklists are the evidence that the data presented to QA has passed all known checks. It is now QA's job to ensure that the QC system is covering all the bases, and only by checking this data again can we be sure this is the case.

If we concentrate on data listings and tables, we can make the assumption that the data is 100% correct and that any errors we find are due to QC failure of some sort. I tend to start with a random selection of subjects, say, a ratio 3:12. These subjects' data are then checked at source (Source-data Verification [SDV]) and then worked through for any derivations reported. Each subjects' complete data (all parameters, all phases — biochemistry, hematology, pharmacokinetics, BPs, temperature, etc. — in effect all measured parameters) are verified through each stage of reporting. If no errors are found, then the data for the whole trial is accepted. If errors are found, then these must be corrected, and the existence of others in the nonsampled data is assumed. QA must now analyze these errors to ascertain how or why they came about and suggest changes to the procedures involved so that they do not recur. In other circumstances, it may be that the QC did not look at that parameter and, therefore, the QC system requires modification so that the faulty parameter is checked in the future.

The QC system must be seen as a cyclical process that is continually being improved and, as a consequence, ever evolving.

Should major errors be uncovered with our ratio of 3:12, then it may be pertinent to look at another subject's data, thus changing the ratio to 4:12 or 5:12. This will, of course, increase QA's time to audit between 25 to 60% if all the data are checked. This time may well be significant, and the task impossible to do within the time frame allowed to get the report to the sponsor. It may well be necessary just to check the data for the problem parameter rather than all the subjects' data.

What we are aiming to do here is to reduce the ratio from 3:12 to 2:12, but in order to do this we must be absolutely sure that we are convinced our QC and production systems are robust. This is an area in which simple statistical analysis (e.g., frequency analysis of error types) of the quality metrics or QA reports can identify areas of weakness that require remedial action. If, for instance, it was found that continual errors were found in the reporting of adverse events, methods for improving the reporting functions can be investigated and solutions put in place.

Summary Statistics in Tables

Normally, some summary statistics are included in our tables for corroboration and to make it easier for the client to see the basis of the conclusions.

Such statistical analyses tend to be done using standard techniques and algorithms, and are usually not a source of error. Routinely, errors are evidenced in such reported statistics by the number of decimal places quoted, which far exceeds the original precision of the source data. This indicates a degree of precision in the answer that was never available with the original measurement. Such overstatement of facts should be discouraged and standardized methods documented for dealing with such data (e.g., one decimal place more than the individual data values). Other types of error noted tend to come from the way missing values are handled; again, a documented procedure is required to define that what is done is necessary to prevent false errors from being recorded. This is especially true when it comes to pharmacokinetic measurements, and you are dealing measurements below the level of quantification (BLQ).

If the software or algorithms are modified or changed, then the system validation is no longer integral, so there is a possibility that the statistics produced may become erroneous. In that case, some sampling of summary data should be carried out to ensure such errors are caught. Of course, there must be a software-change-control policy in operation or else how would QA ever know that something had changed and subsequently check it?

Our sampling rate for such summary data would be something like 1:10 or 1:20, depending on the number of tables and when all statistics for one table are measured. Such a system has always provided us with a good return for the effort; the power of detection of errors is high owing to the systematic use of the validated software used to determine the statistics. It should be pointed out here that QA does not use the same software to determine these statistics as the production staff but uses a calculator or a spreadsheet (all of which have been exhaustively tested).

Summary tables, which are extracted from presented main tables, tend to be carried out manually in the smaller facility. This is normally due to the lack of software or specific coding in order to extract such first-level summary data, and the perception is that a person can do it just as easily. As with any manual process there is a strong possibility for errors to be introduced. It has been my experience that when such summaries involve details of adverse drug reactions the incidence of errors increases exponentially. Perhaps it is due to the complexity of such data that is the problem. One simple way that QA can check such data, (and also provide a solution for its extraction in the first instance) is to use the pivot table function in MS Excel®. If you have never used this tool before, now is the time to get your hands dirty and play around. For table analysis it should be viewed as QA's best and most important tool. If we take, for example, a table of adverse reactions (Table 6.1) recorded for a given trial, we can quickly summarize the data by selecting the categories we wish to analyze, e.g., groups vs. class of event, groups vs. drug relationship, or group vs. severity (Table 6.2).

The pivot table tool is 'wizard' based and is therefore relatively easy to use. By selecting your table of data and its column headings you can produce

Table 6.1 Adverse Reactions Observed

Group	Sub	Dose	Event	Severity	Related	Class
3	18	150 mg(md)	Mouth ulcer	Mild	Unlikely	GI disorders
3	22	150 mg(md)	Mouth ulcer	Mild	Unlikely	GI disorders
3	17	150 mg(md)	Raised AST	Mild	Possibly	Investigations
3	17	150 mg(md)	Raised ALT	Mild	Possibly	Investigations
3	20	150 mg(md)	Raised GGT	Mild	Possibly	Investigations
3	17	150 mg(md)	Headache	Moderate	Unlikely	Nervous
3	17	150 mg(md)	Headache	Moderate	Not related	Nervous
3	17	150 mg(md)	Headache	Moderate	Not related	Nervous
3	22	150 mg(md)	Headache	Mild	Not related	Nervous
1B	2	150 mg(fast)	Cough	Mild	Not related	Respiratory
1B	5	150 mg(fast)	Viral URTI	Moderate	Not related	Respiratory
3	22	150 mg(md)	Epistaxis	Mild	Not related	Respiratory
3	22	150 mg(md)	Epistaxis	Mild	Not related	Respiratory
1B	8	150 mg(fast)	Contusion left wrist cannula site	Mild	Not related	Skin
3	17	150 mg(md)	Erythema at electrode sites	Mild	Not related	Skin
3	22	150 mg(md)	Bruising left upper thigh	Mild	Not related	Skin
1A	8	25 mg	Paraesthesia over left wrist	Mild	Not related	Nervous
1A	2	25 mg	Nasal congestion	Moderate	Not related	Respiratory
1A	5	25 mg	Cough	Mild	Not related	Respiratory
1A	5	25 mg	Cough	Mild	Not related	Respiratory
1A	5	25 mg	Cough	Mild	Not related	Respiratory
4	27	300 mg	Slight edema around cannula site	Mild	Not related	Injury
4	29	300 mg	Raised ALT	Mild	Possibly	Investigations
4	28	300 mg	Drowsiness	Mild	Unlikely	Nervous
4	28	300 mg	Headache	Mild	Unlikely	Nervous
4	27	300 mg	Viral URTI	Mild	Unlikely	Respiratory
4	28	300 mg	Nasal congestion	Mild	Unlikely	Respiratory
4	31	300 mg	Viral URTI	Mild	Unlikely	Respiratory
4	32	300 mg	Viral URTI	Mild	Unlikely	Respiratory
4	27	300 mg	Redness at electrode site	Mild	Not related	Skin

a summary table like those above with any combination of group, subject, treatment, etc. It is difficult for me to describe the use of this tool, I feel it's up to yourselves to experiment with it and to apply its versatility in your workaday life, it can save you hours of painstaking manual work.

Table 6.2 Pivot Table Analysis

Count of Event	Group				
Class	3	4	1A	1B	Total
GI disorders	2				2
Injury		1			1
Investigations	3	1			4
Nervous	4	2	1		7
Respiratory	2	4	4	2	12
Skin	2	1		1	4
Grand total	13	9	5	3	30
Count of Event	Group				
Related	3	4	1A	1B	Total
Not related	7	2	5	3	17
Possibly	3	1			4
Unlikely	3	6			9
Grand Total	13	9	5	3	30
Count of Event	Group				
Severity	3	4	1A	1B	Total
Mild	10	9	4	2	25
Moderate	3		1	1	5
Grand Total	13	9	5	3	30

Sampling Pharmacokinetic Parameters

No specific examples here except to use the type of ratios already stated previously. Where QA is checking these parameters by carrying out their own calculations, care should be taken when extracting the data from the presented tabulated data as differences may well be seen due to rounding errors. In general, the calculations presented by the report author will be carried out using the raw data and therefore are not subject to the vagaries of tabulated precision rounding. In saying this, there should not be any really significant differences. It is my contention that sponsors are going to do what you are doing because that is the only data they have access to, so any differences must be seen as explainable and minimal.

The main areas of difference found by QA, in my experience, is when different sets of data are used to calculate half-life, and missing values or Below Limit of Quantitation (BLQs) are used or not used in the calculation of area under the curve. This appears to be a case of SOP noncompliance, if this is the problem, but it may not be so as some sponsors want interpolation or BLQs treated as zeros included. Such problems can be avoided if the protocol defines these items in advance but normally this is not the case as

the protocol may not go into such small and critical details. I think the problem arises due to two competing SOPs, one at the CRO, the other at the sponsor, but no one tells the CRO which to apply! (This is a general problem in the clinical arena where sponsors want their SOPs applied but in some cases don't tell you.)

Process Identification and Inspection

By using the process flow maps from the ISO 9001:2000, the main systems can be identified, and it is now your task to identify the areas of risk. This can be achieved by analysis of your QA reports as illustrated previously and also by considering the internal QC failures. Targeting inspection for maximum impact is trickier, and I have found a very useful technique borrowed from the quality toolbox. "Fish bone" diagrams (Ishikawa analysis) are very useful for brainstorming, and identifying key areas and milestones within the processes. These areas are the ones that QA can look at systematically after you take into account your report analysis. This is a slight variation on the original idea. Rather than just identifying failure points, it is also a useful tool to identify the components within a total process. I have illustrated the paths from protocol to final report for a clinical study (Figure 6.8) and a laboratory study (Figure 6.9). The two diagrams illustrate what I felt were the main components in the study process. These "bones" can be further expanded into "fish bones" of their own (Figure 6.10).

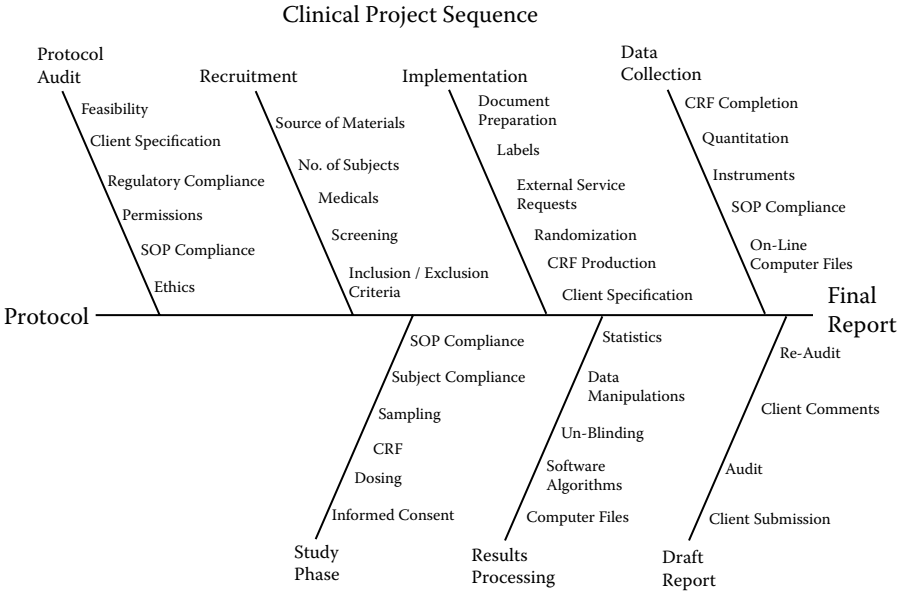

Figure 6.8 Clinical project sequence.

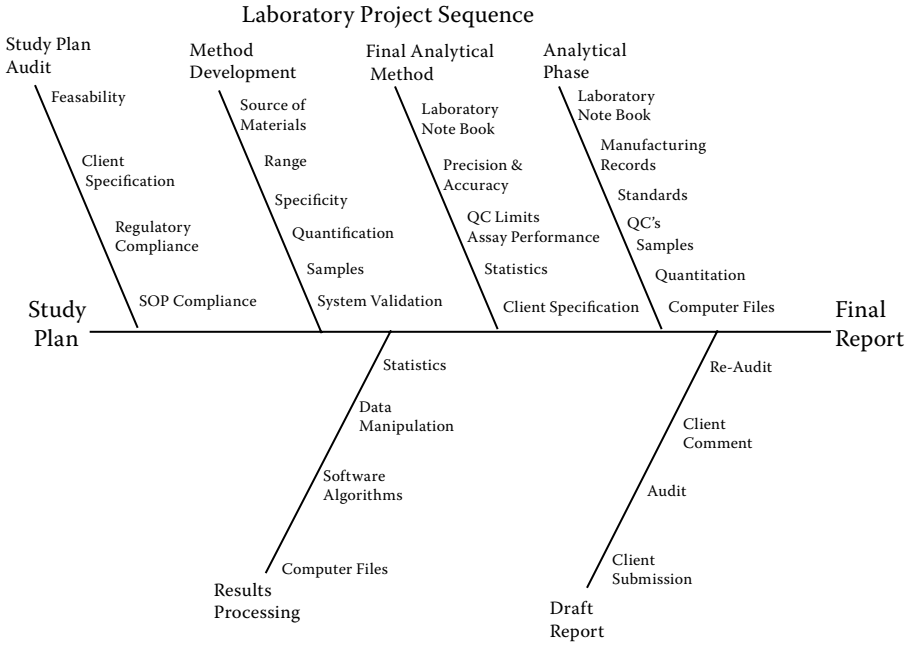

Figure 6.9 Laboratory project sequence.

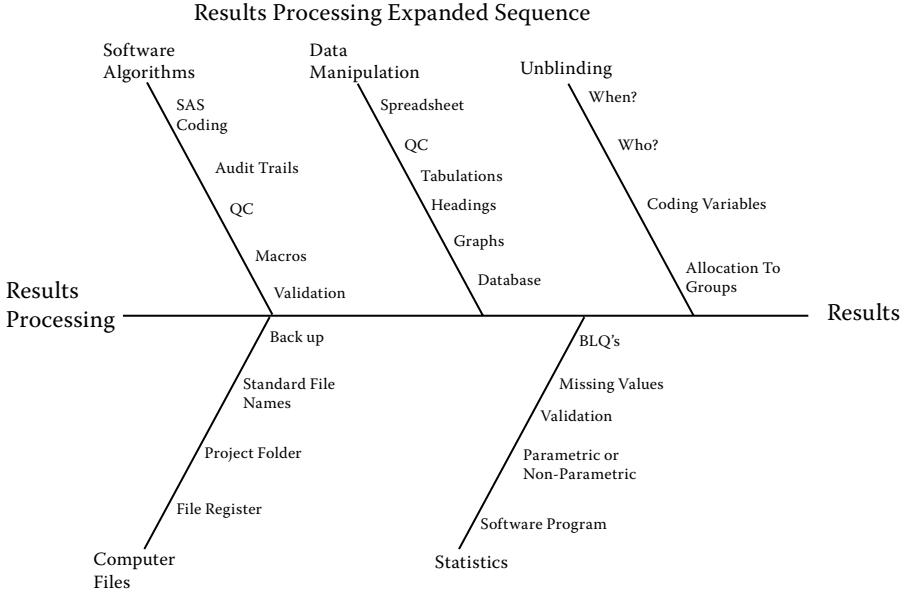

Figure 6.10 Results processing expanded sequence.

As you can see by the above example (Figure 6.9), we are probably now down to individual SOPs rather than processes. We can inspect each of the identified components, and by using the information from the QC analysis as well, we can identify the procedures and where the problems lie, and try to work out the root cause so that we can suggest a fix to management.

Probably more useful to QA is the ability to predict where the greatest risks to quality are. This can be done by using your knowledge of where errors have arisen in the past and identify similar areas (e.g., use of spreadsheets and macros). As we have determined that this is an area of high risk, you can routinely inspect the systems in order to try to determine the least risky way of carrying out the procedure. It has been my experience that such techniques do work and can improve work flow and reduce error. Exactly the product we want to achieve. Improvement in business efficiency and, normally, a move closer to compliance also follows.

chapter 7

Business Improvement

Managing Quality

From the suggestions and ideas presented in the previous chapters, it should now be very clear that quality does not just happen. It has to be built into your processes. It also has to be managed in the same way as any other system or process. Quality managers must look beyond the inspections and individual standard operating procedures (SOPs) and devise a plan that integrates the entire workflow process. The process-based approach of ISO 9001:2000 provides a good starting point and preparing the flowcharts will allow you to see the entire process and identify areas in which the risk of quality defects is the greatest.

This latest version of the standard describes the requirements for a quality management system rather than a simple quality system such as ISO 9001:1994. It is much more orientated toward management, process control, and competencies. This is exactly the type of evolution that business managers require, a move from the abstract to the practical and, as such, we can use this model to advance our quality ideals.

In the past, the main function of quality assurance (QA) has been to provide inspection so that any procedural errors can be spotted as early as possible (e.g., in-process inspections). Any error can then be dealt with immediately, corrected, and the process allowed to continue with little chance of the error appearing in the final report. (This includes SOP noncompliances and protocol deviations). This is still the most important aspect of QA's function and as many inspections of live processes as possible should be carried out. Traditionally, most of the effort of QA has been focused at the end of the project, carrying out audits on the draft report and listings and then issuing QA reports on the defects found.

I suggest that this end-of-project audit is inappropriate for several reasons:

- It delays release of the final report.
- QA time frames get tighter, and auditing is less likely to reveal problems.

- Errors are difficult and more expensive to repair.
- Production staff does not like work being returned a long time after they considered it finished.

I am not advocating stopping these traditional processes of QA activity, but just modifying them so that the focus is on targeting specific risk areas rather that completely auditing the report. My reasoning here is that by the time a systematic error has been found in a report, it would have become very expensive and disruptive to repair. It is obviously better to catch errors much earlier in the process.

I will suggest solutions and tools to assist in identifying these risk areas as I progress in this chapter.

Responsibilities: QA and Management

Regular reports of the quality system (QS) output, such as audit reports, corrective action reports, quality control (QC) failures, and customer complaints can all be summarized by the heads of each unit and fed back to the QA manager for analysis and tabulation. QA can then provide an overview and statistical summary of the types of defects or improvements observed within the last measurement period. QA can use some form of subjective assessment on the problems found by placing them into various categories (e.g., Table 7.1). We present such information to our monthly quality committee (comprising the chairman, CEO, and senior personnel from each organizational unit [OU]) meetings as a standard item on the agenda. Any particular issues are discussed, and "fixes" are proposed and allocated to personnel to carry out.

The problem in using only QA audit reports to establish the real problem areas requiring attention is that if you have a comprehensive QC system in place, QA only audits the sanitized report or data. Such reports tend to indicate that reports only contain trivial errors and will therefore skew the inference. Inspection reports, however, provide a real, unsanitized picture that can provide very revealing information on processes. (Inspection reports are based on QA's checking that the SOPs are being complied with, to the

Table 7.1 QA Report Analysis

Report Type	Problem ID	Key
Adverse drug reactions	6 incorrect timings	Timings — wrong or no sense
x3	15 incorrect assignment to dose	ADR assigned to wrong dose WRT date
	2 typos	Spelling errors, etc.
	4 format errors	Standard format not met
Facility inspection	5 record-keeping problems	Failure to keep records properly or up to date

Table 7.1 QA Report Analysis (continued)

Report Type	Problem ID	Key
x7	6 staff task error	Staff assignment not carried out
	5 facilities problems	Fabric problems observed
Tables	4 label errors	Standard format not met
X160	6 format errors	Standard format not met
	3 set missing values	Reference to dose or subject incorrect
	1 rounding errors	Rounding errors
	3 typos	Spelling errors, etc.
	1 units problem	Incorrect unit used
	4 wrong values	Incorrect data reported
	1 QC failure	No evidence of corrected QC findings
Statistical analysis plans		
X0		
Methodology and conclusions	54 typos	Spelling errors, etc.
x46	9 procedural problems	Possible compliance issue
	12 missing information	Information that enhances report
	14 format errors	Standard format not met
	2 timing problems	Inconsistency with time recoding
	2 incorrect data reported	Misassigned data or missing data
	1 SOP noncompliance	Specific SOP problem
Protocols	2 compliance issues	GxP compliance
x5	13 typos	Spelling errors, etc.
	8 formatting errors	Standard format not met
	1 reference problem	No bibliography for reference
Data Management Plans	9 spelling errors	Spelling errors, etc.
x2	1 incorrect interpretation	Protocol specification not met
Case record forms	6 typos	Spelling errors, etc.
x5	6 incorrect interpretations	Protocol specification not met
	8 format errors	Standard format not met
	2 inconsistencies	Inconsistency within document
	4 missing items	Protocol specification not met
Validation Study Plans	4 incorrect interpretations	Difficult to interpret
X4	1 typo	Spelling errors, etc.
	4 format errors	Standard format not met
	1 tense errors	Incorrect use of future or past tense
	1 reference problem	No bibliography for reference

Table 7.2 Summary of QA Metrics

Summary Table	Total
Typos	91
Format errors	48
Date and time errors	29
Record keeping	11
SOP compliance issues	3
Wrong or missing data	26
Protocol compliance errors	15

letter and the spirit for the tasks being observed). It is therefore important that QA get the full QC summaries from heads of sections. Please note that QA can assist with this process, but it should be passed back to section heads to carry out, as they are the only people who really understand the activities within their own area (see also Chapter 5).

For example, reviewing the QA reports issued for documents submitted or inspections carried out within a given time frame (3 months) produced Table 7.1.

The numbers below the report type indicate the number of audits or inspections carried out. This is not necessarily the number of projects or individual items presented to QA; each time a document is reaudited, it is counted as a new audit.

This type of summary allows QA to separate the trivial many from the critical few and to target these to get quality improvement. Some of the items listed in this table have already been commented on in earlier sections, such as tense in reports or protocols, format errors, and SOP compliance issues. It is important to find these and determine their frequency of occurrence, and then establish the root cause of the problem and present a fix to management. These are the types of problems that continue to linger if the root cause is not eliminated. Also, in my experience, when such major problem types are eliminated, the speed of report production increases and not just by a reduction in QA audit time.

Taking the summary table (Table 7.2), we can clearly see the main critical error groups are the smallest in terms of totals, which is what we need. We do, however, require isolation of these critical groups as they are the ones that will cause the most problems with the sponsor or auditors, e.g., protocol issues, date and timings, SOP compliance, and wrong and missing data.

You now need to focus on each type individually, establish whether or not there is a pattern to the errors recorded so that they may be eliminated by changing procedures, and start some form of remedial training. We must also keep in mind that no matter what changes we make, all problems may not be fixed as they may be random in nature and consequently "unfixable." The law of diminishing returns rears its ugly head again. As QA, you will have to determine the point at which you will stop trying to fix the perceived problem so that the minimum amount of resource is used.

Some study personnel such as study directors and project leaders, especially in larger companies, may argue that it is not QA's job to comment on the grammar, spelling, etc., of text reports; they should stick to the compliance issues! This argument may or may not be valid, but for a small organization wishing to present a quality image, I see this as an essential and necessary part of the value-added process of QA. If a client gets a report from us that is peppered with typographical errors, it does not inspire confidence in the science and conclusions that they are paying for.

Repeat business may then be very difficult or even impossible as they may well feel that they will have to spend too much time finding and correcting your errors — so why not go to someone else? This is definitely not the way forward for business success. It seems very difficult to spot spelling errors and even more difficult to spot punctuation errors. Some people seem to have the knack of being able to spot the proverbial "needle in a haystack." Spelling and punctuation errors just seem to jump out at them. Why this should be so may be partially explained by the following lighthearted example:

> "I cdnuolt blveiee taht I cluod aulaclty uesdnatnrd waht I was rdgnieg. The phaonmneal pweor of the hmuan mnid. Aoccdrnig to rscheearch at Cmabrigde Uinervtisy, it deosn't mttaer inwaht oredr the ltteers in a wrod are, the olny iprmoatnt tihng is taht the frist and lsat ltteer be in the rghit pclae. The rset can be a taotl mses and you can sitll raed it wouthit a porbelm. Tihs is bcuseae the huamn mnid deos not raed ervey lteter by istlef, but the wrod as a wlohe. Amzanig huh? yaeh and I awlyas thought slpeling was ipmorantt!"

Protocols, Contracts, and Quality

When meeting with prospective sponsors or discussing protocols for the first time, it is my contention that QA should be involved in these discussions. My reasons for this may not be immediately apparent to the management personnel who normally conduct such meetings. The reason is simply that if you are there, you can point out any possible quality problems that might surface by trying to implement the sponsor's wishes.

The management of contract research organizations (CROs) may tend to bend that a bit too far in order to secure a contract. This can sometimes even be at the limits of the organization's capability. Such actions may also leave you open to the misinterpretation of what the sponsors' requirements are and what they really want. It is better to get such possible problems discussed and compromises agreed upon before the protocol is written.

One major quality problem that QA-inclusive meetings can assist in solving is that of the sponsors' wishing their procedures to be used for common tasks such as BP measurements, dosing procedures, and recording

data in case record forms (CRFs). All of these tasks are subject to the organization's SOPs, so changing these procedures runs the risk of compliance problems through noncomplicance with your own SOPs. Such changes are permitted, provided all such deviations are documented and justified (as with GLP). This, I consider, is not the real problem; it is a fact that as you are not carrying out the procedure according to normal routine, there is a much greater chance of mistakes happening. In my experience, all these type of changes invariably do increase the number of mistakes. Any changes to the organization's SOPs also have the additional burden of retraining staff in the modified procedure, which, of course, takes additional time and resources. These new procedures are normally just outlined in the protocol, so constant reference to the protocol is required for staff rather than the detailed SOP information that is normally supplied. As most clinical protocols are quite substantial documents, it is sometimes difficult to extract the specific information they require.

I feel strongly that if sponsors want a quality product on time, they should not change the organization's procedures unless they have a substantive, valid, scientific, or clinical basis for doing so. Any compromises your management makes should be fully detailed in the protocol and documented in the contract, so that you are fully aware of your contractual obligations as well as the project obligations.

Total Quality Management

Quality should not be seen as an extra "bolt on." I therefore suggest that quality management must be built into an organization. One surefire way to integrate quality ideals and practice into the organization's thinking is to have a quality practitioner as part of the management team. They should then be able to communicate the quality ideas as an integral part of the strategic thinking and implementation of contracts and practices for the organization.

This topic of total quality management (TQM) seems to be out of current favor at present by the world's larger corporations, and they appear to be moving towards the Six Sigma® philosophy. All such concepts and ideas usually have courses presented by consultants and consulting companies, normally at high costs, and, to my mind, provide very little cost-to-benefit ratio to the small CRO. None of these titles and initiatives really matter; what we are trying to arrive at is a compliant, high-quality report, produced on time and with as great as profit as possible. I tend to take a holistic approach to quality management, look at the business operations in total, and identify the individual processes, improving their overall quality. You could study one or all of these techniques and philosophies and arrive at a definitive set of tools and ideas for your own situation. There is no "one size fits all" with any quality system — only the one that suits your operations.

System Inspection: A Change in Viewpoint

The theory is that if each component of a system is qualified as OK, then the whole system must also be OK. This may be a little simplistic, but it does state in essence what we are trying to achieve.

Once you have your system identified, the objective is to examine it by looking at QC failure reports and QA reports to see which individual components are causing most of the problems. Depending on the frequency of error type, define a priority for elimination of the problems. The higher the frequency found, the greater the risk of errors occurring.

One of my main quality tools used to identify areas of risk is the "fishbone" analysis that I illustrated in the previous chapter. Examination of the error type (your own subjective classification) will help you flesh out your "bones" with the procedures that are most at risk. At this stage you should also consider all the other procedures involved in the system, because even though they may not have shown problems in the past, they may do so in the future. This should save your going through the brainstorming operation of identifying components more than once for any given system.

When problems are found, identify the root cause, modify the procedure, retrain the staff if necessary, and modify the QC procedure to ensure that any reoccurrence is trapped. QA should monitor the changes by temporarily increasing the frequency and depth of inspections until convinced it is no longer a problem.

When we reach the point at which all the apparent problem areas have been repaired by modifying the procedure or training, etc., we can feel confident that we have arrived at a position of minimum risk. At this point, QA, in theory, should only have to look at the start and end of the process to be sure that it is OK. The amount of QA resource now required should be minimal, provided no changes (change control systems in place) are made to the process. If any part of the system or process is changed, then the risk of error due to the change will have to be assessed. Consequently, QA will have to monitor the system closely to ensure that the minimal risk position is still maintained; this can be simply achieved by selective sampling and analysis.

Physicians and Management

In my experience, having a clinician as an organization's CEO can cause some management problems. It is my contention that management should take a strategic view of company operations and be very much "hands off." This does seem to be a difficult balancing act for some clinicians. On the one hand, they want the business to do well and have the responsibility to "get out there," "knock on doors," and speak to the pharmaceutical companies directly at the medical level in order to get the contracts. On the other hand,

clinicians have this "affliction" of wanting to be hands-on as well, really coming to grips with the clinical trial day-to-day operations. This makes it difficult for the other clinicians to function properly or advance themselves if the boss is always appearing to be undermining their position as project leaders. It also has the knock-on effect that management has less time to commit to the more mundane but necessary tasks such as authorizing SOPs.

If the organization requires a clinician at its head, then I suggest that they be very much "hands off" of the day-to-day activities of the clinic and that they delegate this responsibility to other clinicians. This does appear to be very difficult for some as they seem to need access to the patient in order to keep up their clinical skills. I do not think this is a bad thing on a personal development level, but I suggest that it may not be in the best interests of the organization.

If, on the other hand, the organization has no such hard-and-fast rules about the qualifications of who is at the helm, I feel that someone with strong business acumen, experience, and enthusiasm is much more valuable in the CEO role (if, of course, this person happens to be a clinician, then that is even better). Such persons normally have a good grasp of quality principles to begin with, so the quality argument is won before it starts. Also, they do not want or need any contact with patients and are able to provide the strategic view that an organization requires if it is to expand and grow its profits.

IT to the Rescue?

In general, investment in IT infrastructure is seen as the most cost-effective way for an organization to expand and move forward. However, for the smaller organization this can be fraught with danger. Smaller organizations simply do not have the QA experience or the knowledge required to fully inspect and audit these systems. Quite simply, QA traditionally comes from either a chemistry or a life sciences background where computers are used as commodity items, similar to the way many who drive a car do not know anything about what goes on in the engine compartment. That in itself is fine, but the regulatory bodies require that QA does understand what is going on in the "engine," otherwise the job cannot be done properly. QA's job is to inform management of the state of play within the organization, but if they do not understand, they cannot advise. In most circumstances, the smaller organization with just one QA person either goes to courses to learn (difficult, if they are not really interested or motivated) or more simply just hires an expert to audit the systems in operation.

It has been my experience that a considerable number of CROs do not really get pushed by external QA inspectors in this area, generally because of its specialist nature. These auditors may have a science or life sciences background and not a computing one. Auditors will stick to the areas they know best, and that tends to be the good practices (GxPs) field; the supporting IT is usually left to the "techies," which is fine in large pharmaceutical

companies as they have specialist IT auditors in their own organizations. It can therefore be a bit of a shock to a smaller organization to be inspected by an expert IT auditor, as it normally shows up numerous problems for an organization and indicates that a considerable amount of remedial work is required.

Training your QA in what to look for in validated systems is one aspect, but it is only the tip of the iceberg. Much background knowledge about how software works, operating systems, programming languages, etc., will still be alien to scientific QA auditors. The only real experience they have is with the PC at home or on their desk in the office. Networks, security, firewalls, and permissions are probably still a mystery to them. The same would be true of asking an IT auditor to inspect a laboratory or clinically based project; the base knowledge is missing. A similar state of naïveté exists for those staff in an organization's IT section where, again, there may be only one or two persons. They well know from external training what is required for compliance and validation, etc., but if no one is pushing them hard (from QA), then the jobs tend to be skimmed over, and the QA audit will not notice that there are underlying problems. Only an expert in the field would be able to point out the deficiencies and suggest corrective action. The smaller organization should outsource these requirements. It would also be prudent for QA to shadow such auditors during their work so that they can become much more familiar with the techniques employed. This is an excellent learning opportunity for QA that should not be missed, and it may also save the cost of an external course to a small extent.

e-Archives

One of the biggest problems and recurrent costs comes from archiving large quantities of paper and from clinical trial CRFs, which can be large, voluminous, and numerous. If archiving is carried out in your own organization, secure storage space may be a problem, and with an external archive facility, costs are more of an issue. Nowadays, there is a great temptation to go for the electronic option; in previous years, this was normally a microfilm or microfiche method of archiving bulk paper materials. These older systems of optical storage have been tried and tested and allowed to be used as "original" data within the legal system. With newer electronic systems, legal precedents have not yet been set, so electronic imaging systems, though showing great promise, have not yet been allowed to supplant the older technology.

Electronic imaging systems are very attractive to management in that all they require is an initial investment in hardware and software; the running costs are negligible as the staff is already in place. Such systems usually consist of a automatic document scanner that can process several pages a second and also do this in color (which greatly improves the resolution of the document). Even if you do not want this investment, such operations can be subcontracted to the numerous companies that specialize in these

imaging services. This can be especially useful if you want to convert all your older material into such a medium. It should also be borne in mind that there may be issues that preclude subcontracting, such as confidentiality and recurrent costs, in which case your own single investment in the hardware may well be worthwhile. There is also a capital requirement for image storage and distribution of the scanned material, or else such a system would not earn its keep. The storage options such as large disk arrays or optical juke boxes attached to your network infrastructure are all the investment that is required.

Another big advantage is the new technologies' ability to optically recognize characters and automatically and intelligently create their own tables within a database management system so that queries can be carried out directly on the scanned material. There are tremendous advantages with such systems in that the archives truly become information resources and searching for given information is no longer a labor-intensive, time-consuming operation. It also means that with the benefit of networking everyone can have access to such an archive on their desk. It is highly secure, in that no one can modify any of the data, only observe it. As I said in earlier chapters, when you are dealing with sponsor-produced CRFs that are no carbon required (NCR), and the monitor goes off with the original data, normally you want a copy for yourself; so you end up delegating someone to photocopy the pages for your own use. The document-scanning procedure obviates this type of operation, and therefore speeds up the release of original CRFs back to the sponsor.

Before we go overboard here and get carried away with these new technologies, you must consider that there are a few disadvantages as well, i.e., the scanning systems do not like staples, bindings, and thin paper or multiple odd sizes of paper. In many cases, in the small CRO you do not have a choice. Hematology reports, clinical chemistry reports, etc., may be on nonstandard paper in whatever form they are supplied and have all the problems outlined before as well. If you are considering such a system, then you should look carefully at your specific requirements and ensure your system or contractor can cope.

So it appears that we have reached an ideal situation regarding the storage of paper records: we no longer need to do it, do we? Well, the answer to this question is not that simple. Any organization in the regulatory arena that has introduced such imaging systems has done so to create an information resource of archived materials that personnel can access at their desks. The caveat here is that they still hold on to all the paper records, as none of the regulatory authorities will definitively give an affirmative answer as to whether they can destroy them. It therefore still remains a very hot topic that may well become irrelevant in the future with the developments in direct electronic data capture and the subsequent electronic records and signatures. This, of course, leads to the other issues such as data security and audit trails as per 21 CFR Part 11.

The IT Infrastructure Option: The Works

What do we want from an electronic infrastructure system? Basically, push a protocol in at one end and get a report out at the other end. Far-fetched? Perhaps. However oversimplistic it may be, it is what we want to achieve in the end. How do we start to implement such a project?

Some of this may have been already done in your activities to identify any compliance problems with legacy systems under 21 CFR Part 11. You may have discovered when doing a gap analysis that you have a large number of devices that fall under the 21 CFR Part 11 regulations and trying to obtain compliance will be nearly impossible without replacing or modifying each piece of equipment. This still leaves you with the problem of indirect processing of data in computers using software such as Microsoft Excel® and SAS®, none of which provide the necessary controls, and what is more, the suppliers do not appear to want to do so.

What would be perfect here would be a system that encompasses both electronic data capture and document control. This would have the benefit of a "one-stop shop," which would reduce human error in transcription and, hopefully, also streamline business activities.

This is also good from QA's point of view as this means that you only have to validate one system, albeit a large one. Inspection of processes (the shift in perspective I suggested previously) becomes much more valuable as data in will exactly equal data out, and there is an inherent audit trail of who did what, when, and why, of all operations, at least in theory.

In summary, using an electronic system provides an organization with the following advantages:

- Less time checking data sets
- Raw data can be supplied to sponsor
- *Ad hoc* reports can be produced
- Checking is done earlier in process
- Faster report production
- Less transcription
- Less QC
- More accuracy
- Less archive space

Problems with Electronic Systems

The main problem with data capture systems such as laboratory information systems (LIMS) is that they can interface nicely to an instrument, but in any clinical trial there is much other information collected that involves no instrumentation. Examples include data collected during the screening period, demographic data, and recording adverse reaction information, as well as several other types of tasks. This could easily account for up to 70% of the

data collected in a trial, so some form of "front end" is required to collect such data and feed it into the main trial database. Some of the handiest examples use tablet computers or Pocket PCs® to collect handwritten data and convert them to typed text. There are several electronic data capture (EDC) products available for clinical trials in the marketplace, each with their own merits and demerits; it is up to you to determine which system fits your workflow best. To my mind, any system that involves handwriting and strong personal authentication is to be preferred, as the translation from paper to electronics is almost seamless and requires very little extra training.

Before we leave the issue of instrument interfacing, I would like to point out that most LIMS capture the output as if it were the final output device, normally a printer. This is fine for most applications, but there are some instruments that are computer controlled and still running an operating system based on a command line interface; some clinical chemistry analyzers show this problem. What this means in practice is that, although the output can be captured to your system, there are security gaps that allow the original data to be modified without any record of this being maintained. Such systems therefore require serious thought, as normally such systems can never be 21 CFR Part 11 compliant, no matter what "shell" you use. If such systems are integral to your clinical operations, then you must give considerable thought to the instrument you purchase to ensure it meets your electronic data capture (EDC) and regulatory requirements.

Electronic data capture is probably the most expensive item in terms of investment for any clinical CRO, but it holds the greatest promise for the future. This electronic route appears to be a step forward in assisting in the quest for pure electronic submissions, which are the preferred method of submission for the FDA and will probably become so for other world regulatory authorities.

Off-the-shelf EDC systems for clinical drug development are available from multiple vendors, but these tend to be aimed at the later phases of the drug development process (especially Part III and Part IV). All of the systems I have investigated have stated that FDA, 21 CFR Part 11 compliance is built in, and this is correct as far as it goes, but we need more, as I will explain below. Those EDC systems that have been successfully adapted to cope with the specific demands of the Phase-I process still have one basic attribute missing: instrument output capture. All these EDC systems can import data from a variety of instruments or computer systems but normally cannot capture that data directly. This fact alone indicates that we could be left with a huge regulatory compliance gap (21 CFR Part 11) if we just adopt their system.

Also, the infrastructure around some EDC systems can be a highly significant part of ongoing running costs. Some systems are very complex to operate and require specially trained staff to allow the system to evolve to meet the users' needs, for example, creation of a database based on a CRF. Success depends on how this is implemented in the software. Within the small clinical CRO, this is normally not an option, as such technical support

is very expensive, so a simple system that can be tailored to your requirements is probably high on managements' agenda. Of course, any system installed now, whether custom-built or "off the shelf," must comply with the predicate rules of 21 CFR Part 11 and any other regulatory requirements of the country you are based in.

When dealing with such a large investment in an IT system such as an EDC, we want to get everything compliant, but unfortunately this will not be so. Examination of the system in considerable detail is required, deciding exactly what we need in the way of electronic records and compliance.

The Phase-I industry requires a system more akin to the LIMS already in use in most commercial scientific organizations. Owing to the number of instruments, both laboratory and clinical, that produce data directly in support of the trial, these outputs must be captured by the EDC system, as well as those from all the other data collection processes. Luckily, the LIMS industry is well placed and experienced enough to interface their system to virtually any piece of equipment, whether laboratory or clinical, and so we can get our compliance issues sorted in one fell swoop; or do we?

If we go for the preceding system, we will end up with a compliant "raw-data" set — just what we required but not what we need! We still have to consider the manipulations required when we manipulate that data set, for instance, the use of spreadsheets, tabulation and statistical software, pharmacokinetic software, etc. All of these deal with the final reportable data and, therefore, still require control. How can we achieve compliance?

One possible answer to this question is also to use a scientific data management system (SDMS). This reflects the fact that LIMS are not just laboratory-only systems anymore, but have a much wider perspective. To simplify what I am trying to say here, a diagram will probably help (Figure 7.1). We require three systems: a LIMS to interface and capture our instruments

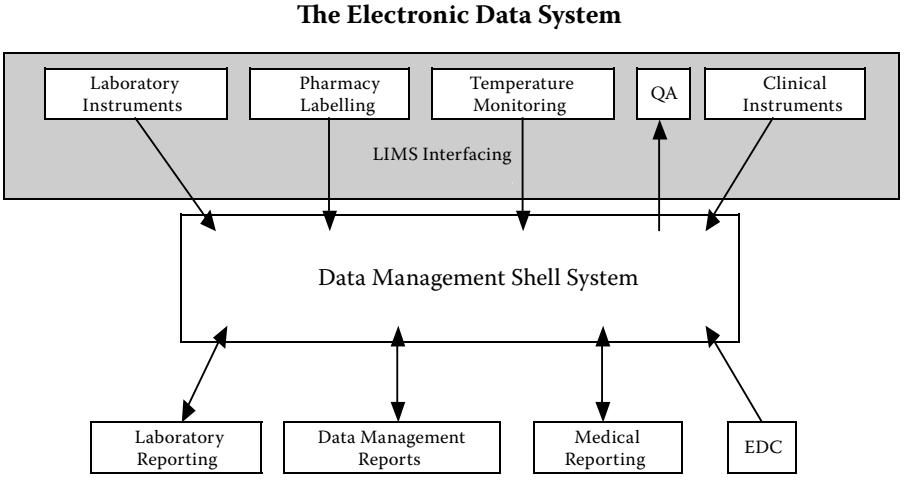

Figure 7.1 The electronic data system.

and data; EDC for clinical non-instrument-based data capture, and an SDMS that acts as a compliant shell for all data moving inside and outside the reporting process. The double-headed arrows indicate that information flows in and out. Single-headed arrows indicate one-way traffic.

One issue that I have mentioned previously, that of multiple people doing multiple jobs simultaneously, can happen several times during a pharmacokinetic study in which rapid sampling of blood and other pharmacodynamic tests are being carried out. Such activity is difficult but manageable when using paper records as it is only a question of entering a result in the CRF and initialing it. When such activities are recorded electronically and sometimes automatically, this is more problematic. As most systems require usernames and passwords to authenticate the operator, a time burden is placed on this process. Each user would have to log in, enter data, and log out, then the next person logs in, enters data, and logs out. Such a system does cause problems with the workflow and may, in fact, be unworkable. Some other solution to multiple-user data input and authentication must be found.

Multiple terminals and personal computers or handheld devices could be used, but this in itself may cause other problems. This would be a very investment-heavy approach and for the smaller organization, probably not sustainable, especially when you consider the useful life span of such equipment is measured at about 3 yr.

The main commercial solutions of clinical EDC in the marketplace, at the time of writing, only have authentication at the point of logging on, not at the point of data submission to the database. This, to my mind, is a failing of all such systems designed to replace paper. When our personnel record a result, they write it down and initial it; if they change it, they change it transparently and also initial it along with the reason. None of the systems I have examined really provide this level of security, and I suggest that they must if it is to be used in the regulatory field.

As far as I can see, the only practical solution to the problem is handwriting recognition and biometric authentication; this would be the natural progression from paper to the electronic media. So far, I have not found a system that is accurate 100% of the time, and all such systems are still in their infancy, but they do show the most promise for the future and the possibility of using these should be continually reviewed. In any case, it would be prudent to ensure that whatever system you decide on today has the capability of being easily modified in the future to allow some form of biometric authentication.

Such possible problem areas, outlined in the preceding text, must be closely considered during the validation and acceptance-testing phases of implementation, as these are prime candidates for failure of the system and nonacceptance of your system by your sponsors. This latter aspect is the most worrying, especially if you have made a considerable investment in your infrastructure. If your sponsors are not totally convinced by your system, its documentation, and your validation, then they are never going to

accept it and will insist on your using paper records, thus ensuring that you have expensive hardware and software in place that is not earning its keep!

Although such EDC and SDM systems are expensive to implement, there are considerable savings in time. The inherent quality of the data and the ability to supply the sponsor with raw data in real time is a substantial advantage in the development of a new drug, in which "stop" and "go" answers are required. In fact, with a Web-based system, the trial monitors or sponsors can see the results at their own desks and even query the data sets. The quicker the "stop" or "go" answer is received, the larger the savings can be, up to $7 million a day in lost revenue, based on the estimate of sales lost at end of the drug patent life. Thus, a rapid turnaround is vital for pharmaceutical companies and any CRO partners that they select. CROs will increasingly have to offer such a rapid results service. I would add here that any electronic system that you consider installing should also have a reasonable penetration into the pharmaceutical industry itself. If this is not the case, you may find that sponsors may again not approve of your system, and it may even prevent you from getting business. If there is one thing that the pharmaceutical industry does like, it is the idea of partnerships with CROs, and anything that fosters such a relationship is worth considering. Such partnerships will result in major repeat business, and a symbiotic relationship can be engendered. Whether or not you go down the EDC–LIMS–SDMS route, it does appear that such partnerships should be made part of your business model and encouraged at every opportunity.

Some QA issues to be considered when auditing or investigating e-systems:

- Security of data, if remotely accessed by the sponsor
- Security of the data (local)
- Authentication of the user (when and where?)
- Incorrect identifications of users
- Impostor acceptances
- Audit trails linked indelibly to e-records
- Complete audit trails

Asset Management: Staff

It must be remembered that the most important asset in a CRO is its personnel. These are highly skilled and regimented workers who provide the business driving force. These personnel can be used to generate more income for the organization by subcontracting them, especially useful during lean times. A prime example of this would be the supply of QA personnel to assist others in setting up their own QA unit, train staff in GxP, carry out audits on data, and carry out compliance inspections. This, of course, may mean that you must increase your QA staff complement to accommodate these extra activities, which will obviously have cost implications but will provide you with faster internal QA turnaround. It will also provide another revenue stream that can be used to offset the extra salary costs. Similar to

all business activities in the contract world, the latter depends on the work availability, but it does provide you with the possibility of more income flexibility.

One type of operation that can pay real dividends in your quality system is the temporary diversion of staff from other areas into QA. By co-opting, for example, nursing staff into the QAU, you can improve your staff QA complement. However, it must be remembered that this happens only at the expense of more supervision and training. The QA department will benefit from their specialist work experience from their original roles and what they know about the shortcuts they all use but are not in SOPs. Probably the most important benefit to be obtained from such a tactic is that you end up with personnel on the other side of QA who know, at first hand, the why and what of QA. You also produce allies within the work force.

If you introduce such a system, it must be made clear by management that coming into QA will not affect their service, their terms and conditions, or harm any promotion prospects. In fact, you should try to ensure that they gain something personally by volunteering and not just an extra section on their training record. In order for both parties to benefit from this temporary posting, it is suggested that the minimum term be somewhere between 3 and 6 months. This will allow the benefit of "on-the-job" training across the diverse areas that QA operates in. Any lesser period may well not be cost or ability efficient and is definitely not to be recommended. In most small organizations with limited staffing, one way around this time frame could be to take one person over a shorter period of, say, a few weeks, pass this person back to normal duties, then reassign for multiple sessions. This will work for about 90% of QA tasks, but there will always be those tasks that are outside the volunteers period of assignment, thus leaving some training gaps. Even so, such methods can create a more flexible workforce whose members are more knowledgeable about each other's jobs and organizational roles

Another area that can show promise as an additional revenue stream is undertaking the data management or QA consultancy for another organization. With the European requirement within educational research establishments to comply with GCP, such activities could reap considerable benefits. These types of activities can be sourced by the linking of your activities with that of QA consultants who can put your name forward as a potential partner. Such relationships can be symbiotic and should be encouraged. The external use of QA functions may be a problem here, but you will have to evaluate this for your own particular organization.

The QP: An Asset or Liability?

If you consider going the limited manufacturing route you will be required to employ a qualified person (QP) in order to obtain your manufacturing license. Such a step is expensive and must be considered with respect to either extra business or prevention of business loss. However, I suppose

having a QP on-site is always an advantage, but it will be costly as such personnel are in high demand in industry and are consequently paid premium salaries. The pertinent question is, how can I get better value for the money from my QP?

If all they are doing is approving the repackaging process, then I would consider the QP to be a liability. Of course, you will also have to consider the fact that sickness or other unforeseen circumstances may prevent the QP from carrying out the study requirements, and therefore you must have arrangements in place to provide an additional QP to cover this event. Some form of emergency cover contract is required if you are not going to have two QPs employed, which would aggravate the situation. If, however, you were to widen the scope of your "manufacturing" license, then there may well be an opportunity to get into a profitable situation. If, as I suspect, such repackaging from bulk supplies is going to become a more frequently requested task, then the case for more income generation may be self-fulfilling and the QP automatically becomes an asset to the organization. (This is one area where the pharmaceutical companies are not set up to do short runs such as those required for Phase-I clinical trials. They are set up to do very large continuous, single-product packaging. The smallness and flexibility of the small CRO are of great advantage here.) This, of course, assumes that the QPs are not employed by organizations for anything else. If they are part of the general QA team, then the QP portion of the job is only an added bonus. This, of course, indicates that the number of GCP-trained QPs must be large enough to feed demand, and it is my considered opinion that there will be very few people being sought by a large number of organizations. Therefore, QPs will command very high premium salaries. The number of QPs is expected to fall by 50% over the next 5 to 10 yr owing to retirement of the existing QP base; the race is now on to produce enough to cope with increasing demand. As far as the business case for having a QP is concerned, it is very much up to you to decide whether or not it makes economic sense for your organization.

Business Continuity

Thus far I have considered individual problems (e.g., data backups, security of paper archives) and how to check for solutions, but now it is time to take a step backward and consider worst-case scenarios: What if total disaster hits your organization, e.g., 9/11? How will you cope? Can you continue or does the business fail?

As with the whole theme of this book and quality management, we must consider the risk factors so that we can minimize them. In this exercise, after considering the risks, actions should be proposed in order to either eliminate or minimize the risk. The following section provides you with some sample areas that should be considered; of course, you will need to look at your own particular circumstances to see whether or not some other factors should be considered as well.

Possible Business Continuity Plan

Introduction

This document describes the risk assessment of various scenarios that may lead to a stop on all business operations. Each risk is identified as far as possible and contingency planning is also defined for each of the disaster scenarios.

Facility Risks of Fire, Explosion, and Flood

Fire

- Look at your fire prevention systems (sprinklers, fire doors, alarms, etc.).
- Consider the time for fire services to arrive (use false alarm times in your risk).
- Short time frame should keep damage localized.
- Water damage due to fire fighting (see flooding).
- Access to building (time frames).

Flood

- Electronic equipment (safety testing)
- Insurance loss adjuster access (time frame days?)
- Specific areas where loss is critical (main office, server room)

Contingency Planning

- Make use of inherent archive security for electronic media
- Use of a fire-resistant safe (for recent data tapes)
- Previous day's complete backup stored off-site
- Access to new server hardware (purchase/rent, time frames weeks?)
- Communication disruption (e-mail rerouting, telephone, etc.)

Loss or Failure of Tape Backup System

- Use of standard DAT and DLT drives that are in use in most organizations. In the event of loss and the requirement to restore lost data, it will be possible to borrow or rent a tape drive in order to carry out the operations required (test this works, time frame?).

Damaged and Wet Paper Records

- Wet paper records should be placed in a deep freeze.

- Contact an archivist or conservator for details.
- All current data kept in metal cabinets for security.

Consideration should be given to the type and nature of the documents, as recovery can be expensive and time consuming; determining an acceptable loss must be considered. If the loss is assessed as consisting of a complete study or studies, then any affected studies may have to be repeated. This latter case could cause financial penalties and loss of business owing to pressure on facility time and resources. The risk is therefore considered to be extreme.

Administration System (Financial)

- Failure or loss of the PC containing the financial records of the organization
- Replacement of hardware and software (off-the-shelf systems, time frame hours)
- Restoration of current data (daily backup, off-site storage)

Pharmacy Supplies

- Clinical trial materials (replacement time frame).
- Reschedule trials (delay for months?).
- Air conditioning (repair or replacement).
- Refrigeration (replacement or repair).
- Store all trial materials in secondary metal containers.
- No operations carried out in the pharmacy, which increases risk or loss.

Quality Assurance

- Records are maintained in the GLP archive.
- Multiple copies of responses distributed around the organization.
- Computer files centrally stored.

Clinical Offices

- Loss of paper records (protocol, ethics, CRF, lab data, etc.)

Data Processing

- Central repository for materials (CRFs, laboratory data reports, etc.).
- Store in metal cabinets to minimize incidental risks (water and floods).
- Electronic data (daily backup).

Service Disruption

Utilities

- Loss of power (fridges, freezers, computers, instruments).
- Consider increase in risk with time.
- Emergency backup power (load and capacity, testing frequency).

Disruption to Water Supply

- Laboratory instruments (external subcontractors)
- Supplies of deionized water (time frames for reserve usage)
- Toilet facilities (staff and volunteers)
- Catering facilities (volunteers)

Disruption to Main Gas Supply

- Cooking (volunteers, staff)
- Heating (volunteers, staff)

Disruption to Compressed Gas Supplies

- Disruption to delivery (stocks in reserve; time frame?)
- Disruption to pipeline (e.g., carbon dioxide backup to 70°C in freezers; time frame?)
- Identification of gas types most in use

Disruption to Freezers

- Access to spare capacity elsewhere
- Replacements (time frame?)

Disruption to Air Conditioning Plant

- Problem areas identified (pharmacy, freezer room, etc.)

Disruption of Telephone Network

- Dealing with the communication problems (mobile phones, radio systems)
- Computer network equipment e.g., routers switches, etc. (if relevant)

Disruption by Critical Suppliers

- Laboratory safety data providers (clinical chemistry, hematology)
- New laboratory normal ranges

- Consumables (needles, syringe, etc.; current stock levels)

Disruption to Supply of Volunteers

- Occurrence of epidemics (e.g., influenza), which could necessitate rescheduling.

Disruption within a Contracted Study

- Food-poisoning outbreak (contractual obligations, time frames?)

Disruption of Internet Access

- Loss of e-communications, but alternatives still in place: fax, telephone, snail mail, couriers (time frames?)

Denial of Access to Building or Organization

This may be due to any number of situations such as fire, floods, gas leak, etc.

- Plans for suitable replacement accommodation (time frame?)
- Equipment availability (rentals and replacements)
- Laboratory support (subcontractors)
- Data recovery (off-site backup, hardware availability; time frames?)
- Subcontracting projects (solutions in place)

Human Risks

As discussed in the section on asset management there must also be consideration of the effect of loss of staff due to unforeseen circumstances e.g., epidemics, accidents.

- Duplication of skills (finance, IT support, laboratory, clinical, etc.)
- Ability to pull in skilled staff (training in SOPs; time frames?)

Loss of Data to Human Error

- Company policy on data storage (network, individual PCs, restoration)

Loss of Data Due to Theft or Malicious Acts

- Data storage, backup and archiving procedures (recovery scenarios tested)
- Latent virus infection
- Procedures for recovery through restoration of last noninfected backup (extent of data loss, time frames?)
- Critical equipment

Mission-Critical Equipment with Significantly Impacting Loss Value

- Clinical chemistry analyzer
- Hematology
- Virology
- ECG
- File servers
- Lifts

Alternative Solutions in Place?

- Cessation of organization trading
- Data archives (contacting sponsors, recovering all stored materials)
- Agreements with third parties in the event of liquidation to handle data distribution

Cessation of Archive Partner's Trading

- Organization's plans to recover archived data (local records of lodgments, reallocation to new supplier, reindexing; time frames)?

Determining Risks

The extent of each identified risk should be determined and this exercise documented. It sometimes pays dividends to set up a disaster recovery team to brainstorm such ideas and solutions. In some cases there will always be a severe risk to business continuity, but what is required here is a documented procedure that describes how you are going to minimize that risk with an acceptable business continuity plan.

It should also be remembered that even in the research environment, where we are not dealing with a business *per se*, there is still the issue of grant awarders' requirements, contracts, and expected timelines to consider. As such, these should be considered in exactly the same light as if it was a business and your livelihood.

So You Think You Have a Good Quality System?

As with any quality system, there are always going to be gaps in processes and procedures. As I have said before, QA should always be trying to identify such gaps and instituting plans to fill them. External auditors will be useful here with their uncanny ability to pick up on your weakest areas, but use this discovery to your advantage in order to improve your system. However, there is another way to discover how good you are, and I am not speaking here about compliance inspections but your whole organization's quality system and ethos.

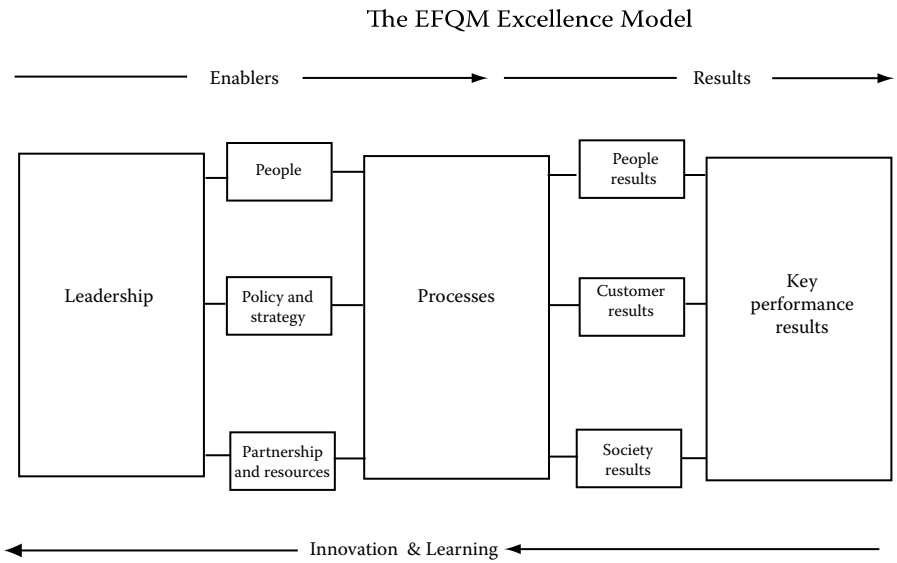

Figure 7.2 The EFQM excellence model.

There are awards for quality excellence, and these can be for small sections within a large organization as well as small- to medium-sized organizations, right up to the multinational corporations. If you think you have a robust quality system and culture within your organization, awards are certainly worth thinking about. Every country seems to have national awards for quality or business excellence, e.g., Canada, Singapore, Australia, the U.S., etc. A search on the Internet should provide you with all the information you require to get started. All such awards tend to be based on models of business excellence, and I will expand on two award systems to whet your appetite to seek more information for yourself.

The first award I will consider is that of the European Foundation for Quality Management (EFQM). This organization was founded in 1988 by 14 leading European businesses. They provided the driving force for sustainable excellence in European business activities. Since its inception, the organization has grown to encompass up to 800 organizations representing most European countries.

The organization provides the EFQM Excellence Model (Figure 7.2.) and manages the European Quality Award. This model provides the primary framework for assessing and improving organizations in order that they may achieve a sustainable business excellence advantage. It provides a framework of nine criteria that can be used to assess an organization's progress toward excellence. The fundamental concepts supporting this model are based on the TQM foundations of behavior and activities or initiatives. The terms *enablers* and *results* are used to describe two criteria; enabler criteria are concerned with how an organization carries out its key activities, whereas the results criteria are concerned with what results are being achieved.

Table 7.3 EFQM Categories

Leadership	Leaders develop the mission, vision, values, and ethics and are role models of a culture of excellence
Policy and strategy	Are based on the present and future needs and expectations of stakeholders
People	People resources are planned, managed, and improved
Partnerships and resources	External partnerships are managed. Information, knowledge, finance, and technology are managed
Processes	Processes are systematically designed, improved, and managed. Products and services are produced, delivered, and serviced
Customer results	Perception measures and performance indicators
People results	Perception measures and performance indicators
Society results	Perception measures and performance indicators
Key performance results	Key performance outcomes and key performance indicators

The labels of the nine criteria do require some explanation as to their specific meaning within the model, and without going into much detail here, I will present the concepts behind each as provided by direct quotation of the documentation publicly available from the EQFM.

Perhaps the last three items (Table 7.3) are the most problematic from the GxP perspective, as they move us outside our comfort zone into areas that did not earlier concern us much. Identifying and measuring results is a complex business. It can take management a long time to identify good metrics that can be used to estimate such abstract parameters. However, this effort is necessary if you are going to achieve a quality improvement culture and business excellence.

The process of applying for such an award is based on self-assessment, and as we have to work in a very regimented way in any case, it is perhaps even easier for us than for any other business operating outside the regulatory framework, for example, automobile manufacture. Such a system provides a medium for identifying and assessing an organization's strengths and weaknesses, along with an improvement program that will be regularly reviewed for effectiveness.

The award has three categories all of which are open to members and nonmembers of the foundation:

Level 1: European Quality Award (EQA)

This is the top award indicating that the organization has a world-class quality system in place. Smaller organizations or subsections of larger organizations are not precluded from this award; also, separate categories are available if required.

Level 2: Recognized for Excellence

Organizations that achieve this level are considered very well managed and have shown an excellent commitment to quality management.

Level 3: Committed to Excellence

This level is for those organizations that have shown commitment to the principles of quality management but are still at the start of their journey.

Even if unsuccessful in your first attempt at such an award, striving to attain your quality goal is still worth the work and effort. Whether or not you get an award, by developing a quality system based on the EFQM model, you will gain the following:

- Maximized effectiveness and efficiency in delivering your services
- A system of continuous improvement in performance of individuals
- A system of improving your capabilities
- Increased loyalty of your staff
- Increased competitiveness

Each of these benefits is worth its weight in gold to an organization, and provided you can also achieve compliance at the same time, you can expect to be either world-class or, more important, continuously strive to be world-class.

So far, I have only considered Europe, but the U.S. also has such a quality award system, the Baldridge Award, from the Baldridge National Quality Program. The U.S. Department of Commerce is responsible for the program and the award, and the National Institute of Standards and Technology (NIST) manages the Baldridge program. The American Society for Quality (ASQ) assists in the administration under contract to NIST.

The ideals and philosophy are similar in both awards. When applying for either award, it is an opportunity to examine your organization critically and identify strengths and opportunities to improve. It will be clearer if I present a list of the key benefits enjoyed by previous Baldridge Award winners:

- It allowed them to accelerate their improvement efforts.
- It energized their employees.
- It gave them an outside perspective on their organization's activities.
- It allowed them to learn from the feedback process.
- It kept them focused on their deliverable results.

However, you do not have to be an award winner to benefit; you only have to start using the prescribed model and principles in order to obtain progress. It is the quality system and processes we are considering, and even if you are just starting, there are significant benefits.

Table 7.4 Heath-Care Criteria for Performance Excellence

2005 Health-Care Criteria for Performance Excellence	
Category	Points
Leadership	120
Strategic planning	85
Focus on patients, other customers, and markets	85
Measurement, analysis, and knowledge management	90
Staff focus	85
Process management	85
Organizational performance results	450
TOTAL	1000

How Does the Baldridge System Work?

It is based on internal self-examination based on ten steps provided in the "Getting Started" document. This is then followed by external assessment of your systems by industry/sector assessors who provide feedback to the applicant and a score based on predefined categories, e.g., "Program for Health Care Criteria for Performance Excellence" (Table 7.4).

The model for the Baldridge system of quality management and business excellence is provided Figure 7.3. If you now compare the two models — EFQM (nine categories) and Baldridge (seven categories) — you can see the common themes between the two systems and their similar stances toward certain criteria, e.g., leadership, processes, people, etc.

Comparison of the two diagrams (Figure 7.2 and Figure 7.3) and categories identified indicates to me that EQFM may be a clearer model for us to follow because of its apparently better focus on measuring quality parameters. As I said in the preceding text, the measurement of customer results, people results, society results, and key performance results are best adapted to our type of quality metrics. These also have an impact on our estimation of the real cost of quality, which will be discussed as a topic later.

All quality award schemes should be seen as a means to an end. It is not the award, *per se*; it is the process of striving to obtain such an award, the systems analysis you have done, and your improvement along the way that are important. Any award should be considered the "icing on the cake." A good example would be: Would you be happier staying in a five-star hotel that is complacent or would you prefer to stay in a three- or four-star establishment that is striving to obtain the coveted five stars? What you need to take from both award scheme examples presented here is the fact that there is much information, examples, and help available, and it is up to you to decide which elements are best for you. The self- and external-assessment systems provided by these systems do allow you to take stock of your own organization's strengths and weaknesses. You now need to see how you can apply these ideas to your own circumstances in order to improve your business.

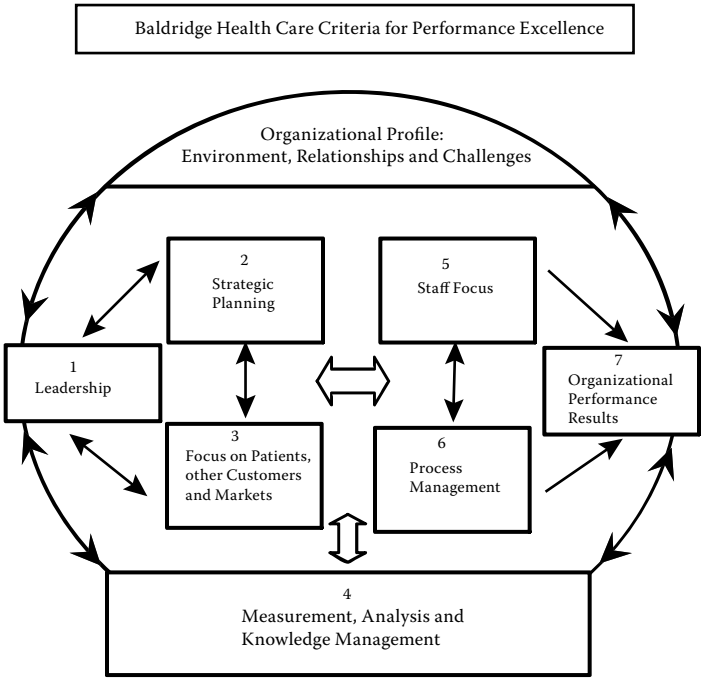

Figure 7.3 Baldridge health-care criteria for performance excellence.

Quality Costing

In most cases, management would not introduce a quality system unless it was a regulatory necessity. The establishment of the QA unit is seen as an overhead administration cost that is only necessary for compliance, but in this chapter we are going beyond compliance and trying to use quality principles to get us increased profit and quicker completion. A question still remains as to the value of a quality system in an organization, and nothing pricks up the ears of management and accountants better than evaluating things in monetary terms. ISO 9001:2000 indicates that you should use quality records to demonstrate the effective operation of the quality system. Costing quality can therefore assist this process.

In most organizations, costing of quality is either not done owing to perceived complexity, difficulties in collecting information, or the lack of specialist accounting software to accommodate such initiatives — even in environments in which you would expect a very high respect for such actions. For example, it has been determined that only 23% of the 1991 Baldridge Award finalists (22) actually measure the cost of quality. In any event, the typical accounting methods of allocating quality costs to overheads and administration, along with the separate cost of rework, really only determines the cost of scrap. What we need is a method that gets costs assigned to the tasks themselves, not the end product.

This subsection will provide you with some ideas on how you can cost your operations based on quality parameters. The cost of quality or, possibly more correctly, the cost of poor quality, can be summarized as a series of categories that when taken together account for an organization's quality costs:

Internal failures: Costs associated with problems found using your internal systems.
External failure costs: Costs involved in repairing problems after it is with the sponsor.
Appraisal costs: Costs incurred to provide QA/QC functions.
Prevention costs: Costs incurred to minimize problems and minimize appraisal.

Table 7.5 (quality measurement matrix) uses the four major factors of people, instruments, materials, and methods as the horizontal axis and value/cost, time, and quality of work as the vertical axis. The parameters have been specially adapted to the clinical trial process and should be easily assigned a reasonable monetary value.

Traditional accounting methods normally concern themselves with collecting the costs per project and the overheads associated with that project. In the main, with the type of operations we are considering here, the costs are nearly all time based, as the raw material costs are normally low. In this example, we will not consider the costs of purchasing the instrumentation that are necessary for carrying out trials; these can be treated as capital expenditure.

What we require is some method of costing the time spent on each activity (such as the activities indicated in Table 7.5), and not the time allocated to the project (which is what is normally done). Previous studies have indicated that low-volume services (such as clinical trials) can typically incur an overhead cost of between two to ten times that which was estimated. What we need, therefore, is a system whereby we can get better estimates of costs by looking at the time taken to carry out a given task. Activity-based costing (ABC) is a concept that is especially useful in our area of operations, in which we do not really have an end product, only information, interpretations, and conclusions.

What we are required to do is to institute a series of changes to the normal time sheet so that time is not allocated to a project but to a task, e.g., time taken to close out a corrective action request (CAR) or time taken to QC a set of results. The cooperation of the staff will be required in recording all the time spent on the different quality-related tasks. Of course, you will have to identify your own processes and also the appropriate components that you wish to track. The recording of such multivariate data on paper and then getting this information into a computer would be a very labor-intensive task; it would have its own overhead costs, which would discourage use of the ABC costings. However, because most organizations

Table 7.5 Quality Measurement Matrix

	People	Instruments	Materials	Methods
Value or cost (pounds)	Revenue per employee Training Shift allowances Sponsor audits	Maintenance Calibration Operating costs Replacement Added value	Volunteers Computer consumables Stationery Withdrawals Clinical consumables	Compliance Inspection/audit Activity-based costs Archiving cost/income
Time (min, h, d)	Time to close CARs Time to correct errors Time on regulatory tasks	Setup time Repair time Validation Acceptance testing Compliance	On-time reports Late reports Rework time Quality control Externally supplied data Protocols	Documentation Protocol review QC time Value-added time Risk analysis
Quality of results (good or bad)	Staff turnover Error rate Training hours per employee SOP review	Capability Down time Capacity Data security	Amendments Internal failure External failure Data security	Change control Number of CARs Errors per data set SOP updates

have some form of electronic time sheet systems in place or have access to spreadsheets, these can be set up with different categories to record the time data directly by the individual carrying out the activity. Accuracy and precision are not requirements here as the resulting costs can only be considered an estimate in any case. Worrying about recording times to the last minute introduces elements of precision that are not necessary or required, as we will be using the data to compare it against previously collected data and, therefore, it is not required to be absolutely accurate. What we do require, however, is that the recording of the time data be kept consistent and within the regulated environment. If SOP compliance is normally practiced, this should not be a problem.

The individual spreadsheets can be collected on a weekly or monthly basis and either imported into your ABC accounting package or a database package that can convert the individuals' times or mean hourly rate for the organization into costs and analyze the data in any form you wish, using your previously identified categories as variables.

By using the organization mean hourly rate, you can smooth out the differences between different grades of staff carrying out the same tasks. This will also allow you to have a consistent base for your comparisons over time periods.

Problems you will face:

- The cost of doing the ABC
- Reluctance of staff to complete detailed time sheets
- Reluctance to carry out more work for the same reward
- Worries about ABC itself

In essence, the buy-in here is exactly the same as with quality management. It has to come from the highest levels of management as a commitment. You may be in the lucky position of just starting on your quality journey, and if this is so, you could make a case for building such costings into your business model.

chapter 8

A Summary

In this chapter, I would like to summarize what I have presented in the earlier chapters and provide you with a distillation of all the ideas and concepts that go together to furnish you with the basics of a compliant GxP quality system and, if required, a business improvement model.

Defining Your QA Person

If you are required to appoint someone or have access to a QA (quality assurance) professional, there are some qualities that you should look for. Some of these are essential, some are very useful, and some, a generous bonus.

Essential Qualities

- A good communicator
- Gets along well with people
- Not intimidated by the organization hierarchy
- Has an analytical approach to problems
- Observant
- Organized
- Well qualified in physical, life, or medical science
- Has an excellent knowledge of regulatory requirements

Useful Qualities

- A good teacher
- Experienced in QA (your choice for "essential" or "useful")
- Computer system knowledge
- Understands and uses statistics

Bonus Qualities

- Cross-discipline knowledge and experience
- Knows computer system validation procedures
- Experience in pharmacology and pharmacokinetics
- Has worked for a competitor

The preceding example requirements can be used to select the most appropriate person for the position of QA person. Of course, you may want to move some criteria into the essential category or downgrade some, depending on your specific requirements. The difficulty arises during interview in establishing that you are asking the correct questions to ensure that your requirements are met.

Defining Your Quality System

- The fundamental basis of any quality system is that you understand what you are trying to achieve and that management fully support the quality initiative. It also follows from this that all staff are to be involved and encouraged to contribute to the benefit of the organization.
- Develop a mission statement that concisely defines what you are aiming for. This will provide the target and help develop staff motivation for success in your quest.
- Set up a QA unit with an experienced quality manager who will guide, assist and manage your quality efforts (see preceding text).
- Train all staff in the legal requirements of all of the relevant Good Practice regulations. Provide all members of staff with a set of the regulations that can be easily referred to.
- QA should prepare a set of SOPs for their operational requirements as outlined in earlier chapters.
- Production staff are to identify all your systems and processes, document these as lists, and then write the SOPs.
- Identify all your suppliers and subcontractors and establish what quality systems they use, if any (be wary if none exist). Also ensure that they know what your quality plans are and that you intend to approve to those standards. Management must ensure proper contracts are in place that define these standards.
- Control your "raw materials" volunteer base to select appropriate populations.
- Identify all computer-based systems (software and hardware).
- Validate all computer systems identified in the preceding text and ensure that change control is in operation. These records must be kept for the lifetime of the system, then archived.
- Identify each piece of equipment, record it, and keep a record of maintenance and calibration. These records are kept for the lifetime of the equipment, then archived.

- Management must define the organization's capability limits and adhere to them.
- Arrange for document and electronic data storage, security, and archiving.
- Ensure your staff are properly qualified and trained in their tasks. Document all training supplied, both in-house and external. Certificates of attendance, competence, registrations, etc., should also be copied and filed in a consistent manner.
- In the case of protocols and study plans, keep communication channels open between yourselves and the sponsor and include QA input.
- Prepare document templates for consistency, e.g., volunteer contracts, study reports, ethics submissions, etc.
- Prepare a site master file (dossier, see the following text)
- Identify areas of risk and places where quality control steps would be appropriate.
- Finally, it may be wise to get some external advice on your status before a regulatory inspection, perhaps from another friendly QA unit; or hire a consultant.

With these controls in place, you should have all the regulatory bases covered and the beginnings of a comprehensive quality system in place. You will then be in a position to request work, which will normally result in being inspected by the sponsor's QA department, prior to any work being placed. Of course, it goes without saying that should such an audit have critical findings you will not get the work! It is in your best interest to ensure you are fully prepared for such an audit, then the work you put in beforehand will pay dividends in the long run.

Academic Studies

If you are carrying out clinical trials or operating a laboratory supporting such trials, then there are a few points that I think you may like to consider.

In the U.K. university sector, a huge number of trials are carried out, and some highly research-orientated bioassays are being performed in support of these trials. For many years, such a situation has been conducive to industrial income generating research and has been fostered by academics and industry combined. Industry gets its research cheaper owing to the tax breaks and the lack of overheads, advantages they would not have if they were to do it themselves or hire a CRO. The academic route, in some cases, also had the added kudos of having an internationally known opinion leader to add weight to the trial results.

The situation in the U.K. and Europe changed forever with the introduction in the law of the European Clinical Trials Directive and the state-specific legislation making compliance with GCP a legal requirement. In the U.K. this act came into force on the May 1, 2004. Since then, it has been a struggle to keep within the legal framework for most researchers; here were a set of

requirements that were not budgeted for, in a monetary sense or a Good Practice sense. The only solution to the problem is compliance, but to do this within the academic framework is very difficult.

The issue of charity-led research initiatives, however, cause more uncertainty because this type of noncommercial research may appear to be exempt from the main GCP requirements. (EU Draft GCP Technical Directive (2004)). This causes confusion, to say the least, in that it appears that the EU are suggesting a two-tier GCP system. From my arguments throughout this book, it should be clear that I do not think this is a helpful situation and that quality principles should be adopted wholeheartedly and not implemented in some piecemeal fashion as that suggested in this directive. As this is still a draft at the time of writing, only time will tell if the correct quality path will be taken. The examples I have provided in this book are some practical solutions that can be used to move you along the compliance path, but the problem remains as to how to implement GCP and GCLP with the minimum of disruption and cost to the research process.

Under the European GCP Directive or the U.K. Statutory Instrument, there is no requirement to have a QA unit per se, but it is necessary to have someone who will look at your systems from an independent regulatory compliance perspective. How can we resolve the situation? The simple way is to employ someone, independent of the study, who can manage your quality requirements. This, of course, is the most expensive solution and is probably not an answer unless you are doing trials or supporting trials every day of your life. Another alternative is to buy in the expertise in the form of a consultant, as and when required. This, however, can be very expensive. Additionally, someone has to carry out regular inspections of your processes and documents, and consultants do not come cheaply.

One possible solution that could be considered is the centralized functional QA within a university faculty (e.g., medicine, therapeutics, and life sciences) that provides the QA services that you require. The costs of this unit can therefore be shared among all the faculty researchers, and this solution can become a much more manageable and affordable prospect. Such a unit could be funded, say, on a per-study basis or by annual subscription to the university. However such a proposed service is funded, it does provide tremendous advantages for the researcher. A potential added bonus with such a service, provided the unit is staffed by experienced QA people, is that they can also impart quality training to the academic staff on a very low cost-to-delegate basis.

The requirements on the part of support laboratories to have excellent QA monitoring mean that the QA resource required in that field may well indicate that they have to appoint an individual to look after such issues if they are to operate to the GLP standards required by the GCP monitoring authority. Again, this depends on the extent and quantity of regulatory work performed, and the faculty system may well be enough for compliance.

The challenge for the future is, therefore, to get all tertiary education centers (and grant-awarding bodies) up to speed on quality issues and how

they can benefit the research process rather than submit to the current thinking, at least among academics, that it impedes the process. I believe that if you are reading this book you will probably agree with me that once you have experience of the Good Practice way of doing things, you feel uncomfortable about going backward to work in the undisciplined environment. The Good Practice situation is the one we must strive for in all areas of science and medicine in order to benefit mankind and the world regulatory bodies, in particular.

Sponsor Audit Preparation

Sometimes, before an audit you may well be requested to complete a questionnaire on details of your quality system. You should have little problem by now in filling out such a document. I have included two lists of questions asked in a typical request at the end of this chapter, not so much for your answering as for your use in your own subcontractor audits. There is a general quality system questionnaire (Form 8.1) and a more specific archiving one (Form 8.2). It is this latter one, covering an area that is sometimes too easily skipped over during inspections, that really does require in-depth coverage. The sample only concerns itself with paper records, but you should also consider the archiving of electronic data as well.

Note that some of these questions may not be answered by all organizations as they may consider them to be "none of your business." For example, consider this question: Has your organization received any critical findings as a result of a regulatory inspection?

They may choose not to answer, in which case please accept that no answer is acceptable. In some cases, you may be lucky, and they will not have a problem with such questions. Whatever the results of the questionnaire, it is up to you as an auditor to check that your chosen supplier meets your quality needs by doing your own investigating, not having them do it for you. Any negative findings you observe should be classified as not significant unless you consider that they could have a direct effect on the service you are requesting.

Form 8.1 Questionnaire on Quality Systems

- Do you have an independent QA unit?
- Do you have any quality certifications, for example, ISO 9001:2000?
- Has your company been inspected by any regulatory agencies within the past 10 yr? Yes or no?

  If yes, please provide dates and time frames, what type of audit, what systems were audited, the key findings, and how these have been addressed.

- Has your organization received any critical findings as a result of a regulatory audit? Yes or no?

  If yes, describe the nature of the problem indicated.

- How do you ensure compliance to ICH GCP?
- Please provide, as an attachment, a list of SOP titles.
- How often are your SOPs updated?
- How often are you required to use a sponsor's SOPs or a modified version of your SOPs?
- How do you ensure that your CROs and suppliers adhere to new versions of guidelines and SOPs?
- What is the size and experience of the QA and audit function?
- Are inspections performed on work in progress? If yes, please describe.
- What type of audits and inspections are performed and with what frequency?
- Briefly describe the process for report audits, database audits (i.e., how are these audits performed?).
- How are audit findings reported? Are these made available to the sponsor?
- May we have access to your audit reports on your suppliers? (Yes/no). If "no," would your procedures allow coauditing by us?
- How are project-specific quality plans generated?
- What is your procedure for handling inspection notifications or requests?

Form 8.2 Questionnaire on Archiving of Documents

- Please provide information or procedures in response to the following items:
- Describe your archiving staff organization, experience, and workload.
- Storage of "in-life" documents prior to archive:
  a. Who is responsible?
  b. How are contents tracked?
  c. Access and security of facility?
  d. Adequate space and storage?
  e. Adequate environmental controls (fire, humidity, and flood)?
  f. Ease of retrieval?
- Permanent archiving of clinical trial files:
  a. Who is responsible?
  b. How are contents tracked?
  c. Access and security of facility?
  d. Adequate space and storage?
  e. Adequate environmental controls (fire, humidity, and flood)?
  f. Ease of retrieval?
- Describe your normal archive arrangements and data retention policy (return to sponsor, keep on-site, or external facility)?
- Do you have QC activities commensurate with data security and legibility?
- What procedures are in place should you be required to relocate the archive material?
- Do you use any document imaging system (availability, process, and validation)?
- Give details of any external organization used for archiving.

The Site Master File/Dossier

Every time you are faced with a compliance or facility audit you will be asked for specific documentation. It makes sense to have a dossier of these items prepared in advance (site master file). Luckily, a lot of the documents requested are common and do not change regularly, so copies can be kept on file, e.g., organization organogram, job descriptions, etc. Other items must be prepared just before the audit is planned, e.g., a list of current SOP titles and staff lists. The normally requested documents are listed in the following text:

- Organogram
- IT system organization plan
- List of validation document titles
- An overview of the organization's operations and facilities, e.g., laboratory service provision, manufacturing, and archive facilities.
- List of current staff with titles
- List of studies, titles, principal investigators, number of subjects, and trial status
- List of current SOP titles
- QA SOPs (in total)
- Contracts you have with external suppliers, e.g., lab services

- Certificates of insurance indemnity for trials
- Evidence of external QC schemes
- Sample training records
- Job descriptions (signed and dated by management and job holder)
- CVs (signed and dated by individual)
- Quality manual (if you have one)
- List of members of ethics committee
- Insurance certificates and policy details
- Accreditation certificates (ISO, GxP, etc.)
- GMP license (if appropriate)

It is also a good idea to provide your auditors with an agenda of what you think they would like to see and do. This provides a structure to the audit, especially for your organization's staff, whom you do not want tied up all the time during an audit. Of course, the timings must be mutually agreed upon, but in my experience, auditors are normally amenable to these actions. A sample facility audit agenda for a Phase 1 unit is presented at the end of the chapter (Form 8.3). Of course, the timescale for such an audit is dependent on the size of your organization.

Auditor/Inspector Interview

Depending on the size of your organization, it may be helpful for QA to play the role of external auditors and interview staff. This allows the staff who may be interviewed a chance to practice their interview technique, which may not have been exercised since their last job interview. It must be second nature for them not to be tempted into answering questions that may be on the periphery or outside their knowledge. To all such questions, they must refer the auditor to the relevant person and not even try to answer the questions. It is only natural, especially for younger members of staff, to be a bit overwhelmed when faced on a one-to-one basis with someone who can make or break your organization. They must be trained to recognize that they are not on trial here but only providers of the information that the inspector requires in order to get a clear understanding of the organization's operations.

Once you have been through several of these external interviews, you begin to have a second sense about the type of auditor you are dealing with. It is my experience that you can have several types of auditors: those who think they can only justify their actions if they can find faults, those who are so aloof that a proctologist would be required to get them to smile, and those who have a hidden agenda, or a combination of all three. The best auditors are those who can be "friendly" and coax you into disclosing information. However, this is not a malicious act on their part; it is only for their use, and they will make a balanced judgment on the effects this may have on studies. This latter approach gets the best out of all concerned. It would be in your interests to ensure that your training of inexperienced staff covers all types

Form 8.3 Example Facility Audit Agenda

Day 1	
10:15–10:30	Staff introductions, facility overview, etc.
10:30–12:00	**Tours and process overviews of clinic and supporting services** Bed, catering, lounge, administration, bathrooms • Sample collection and processing area • Laboratory • IMP storage and dispensing • Equipment, e.g., fridges and freezers, balances • Emergency procedures • Meeting rooms (CRA workspace, etc.) • Archive
12:00–12:30	**Quality management overview** • General processes • Regulatory inspection history • QA SOPs
12:30–13:30	**Trial conduct and project management overview** • Project management • Subject recruiting, intake, informed consent, screening, dosing, and observation • Ethics committee processes and procedures • Adverse event reporting process • Security
13:30–14:00	**Data management process overview** • CRF preparation • Database specification, design and testing • Data entry, queries, coding, and transfers
14:00–14:30	**Study operations** • Randomization • Data collection, testing, and controls • Data analysis processes
14:30–14:45	**Report-writing quality control processes**
14:45–16:30	**Document review** • Standard operating procedures • Training files, CVs, and job descriptions
Day 2	
09:00–10:30	**Computer systems validation process overview** • IT systems in use • Documentation
10:30–13:00	**Clinical support services** • Hematology • Biochemistry • Virology • Toxicology
13:30–16:00	**Lunch and document review and resolution of unclear issues** • Selective staff reinterview
16:00–16:30	**Close-out meeting and discussion of findings**

of auditors. Forewarned is forearmed with the required skills to deal with the "awkward" auditor.

Most experienced QA auditors also know that in order for QA to get movement on a particularly sticky quality issue by management, external pressure is a great expediter. The friendly QA auditor can be told of the problem, and this can be slipped into the audit report so that it appears to come from an external source; then this is used to reinforce your arguments and suggestions. Normally, management will bend over backward to get the issue resolved so that they do not lose the contract. Thus, the external auditors can become your allies, not adversaries, and everybody gets what they want, usually with the added bonus of better compliance.

U.K. GCP Regulatory Inspections

These are relatively new in the U.K., but previous experience of other regulatory inspections indicates that they follow a pattern. Normally, inspections are announced 3 months in advance; then at 2 months it is expected that the site dossier is sent. Then at 1 month prior to inspection, the suggested audit plan goes to the organization for approval. The advance sending of the dossier allows the monitoring authority to establish how things are done in your organization prior to the inspectors' arrival and allows them to optimize their time on-site. The agenda (set by them) and inspection will be very similar in activity to that outlined for facility audits but with the addition of an audit of some previously carried out study.

What is inspected:

- The quality system as a whole
- All contracts and agreements
- Project management
- Insurance cover (should meet Association of the British Pharmaceutical Industry guidelines [ABPI]).
- Computer systems
- Data transfers
- Record retention
- Protocol compliance
- Subject safety
- All facilities (including support laboratories)

The inspectors will consider your systems by looking at trial components in the report such as the clinical sample process in the laboratory. Another example would be examining what processes you have for dealing with the well-being and control of your volunteers. This can be illustrated in the following life-cycle diagrams (Figure 8.1 and Figure 8.2).

These regulatory inspections can be of great depth and are designed to probe both your weaknesses and strengths. The inspection process must be considered an independent inspection of your quality system that will discover

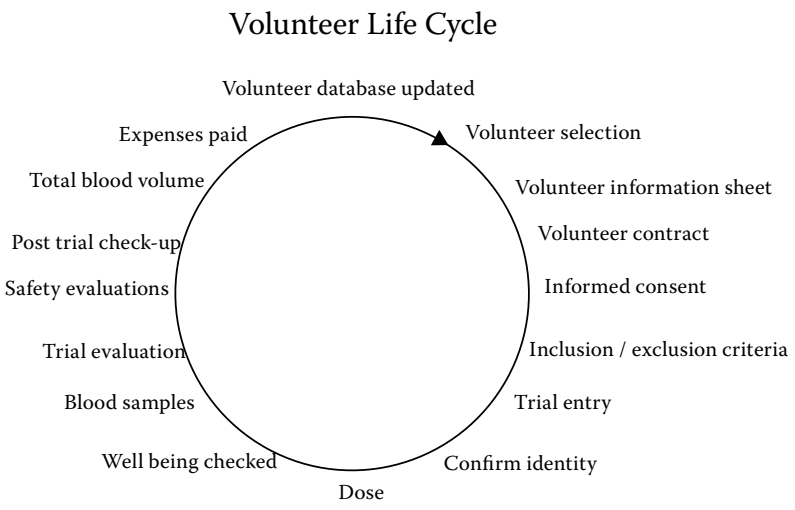

Figure 8.1 Volunteer life cycle.

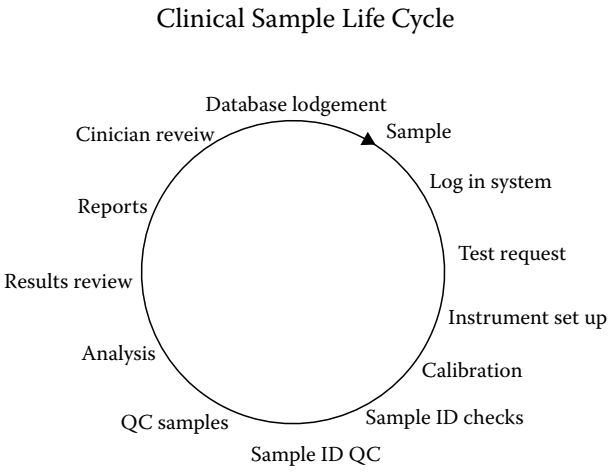

Figure 8.2 Clinical sample life cycle.

problems that you had not found yourself but that you can repair. It is difficult being on the receiving end, but you must remain positive throughout and after the inspection process.

It must be emphasized here, that it is only the compliance aspects that the inspector will be concerned with; any other organizational quality initiatives are not relevant to the inspection task. I should also add that compliance with other countries' specific requirements are similarly irrelevant to the U.K. inspectors, whose remit is enshrined in U.K. law.

Table 8.1 Example of MRHA Finding Categories

Category	Example
Critical	Safety, well-being of subjects, confidentiality of subjects compromised.
Major	Significant departure from the regulations.
	A series of "other" findings that, in combination, leads to a significant departure from the regulations.
Other	Any other inspection finding that is neither critical nor major.

After the inspection, there will be a formal exit meeting in which all the inspection findings are presented and discussed, and usually any anomalies or misunderstandings can be corrected. These findings will be categorized as "critical," "major," or "other." Examples of each type could be as in Table 8.1.

This will be followed by a written report (within 30 d) that will contain details of the inspection findings, positive and negative, and will follow exactly what was stated in the exit meeting. Any adverse findings must be corrected within a given time frame, and a formal written response to any findings will be required (within 28 d).

You should be aware that if the laboratory you are using is GLP accredited, it does not necessarily mean that it is GCP compliant. Laboratory staff should be instructed in the requirements of GCP as well as GLP and ensure that the relevant parts of the regulations are met in their operations.

Developing Your Systems

Now that you have your compliance status confirmed, it may be time now to look at some of the other aspects of quality management that have nothing to do with compliance but have everything to do with increasing profit and market share. These are the business improvement ideas.

Business Improvement

Several aspects have already been put forward, and it is now up to you to research the different schemes and ideas around and find the bits that can be adapted to your particular circumstances. There is a wealth of information freely available on the Internet, and simple searches will produce multiple hits. To get you started on your quest for information, you can try the addresses of the organizations detailed in the Appendix, Acronyms, and Information Resources.

Once you have found your ideal quality system and are happy with its performance, you may even consider going for a quality award such as EFQM or Baldridge. Again, check out the Web for local awards as well, as sometimes these can be offered by trade organizations and chambers of commerce. This type of smaller-scale award system may be more appropriate for the smaller organization. Whether or not you win such an award is not so important to your business as the processes you will go through in order to get your systems up to such a standard.

Costs of Quality

It should have become clear by now from my book that the purpose of QA to ensure compliance is no longer the primary function but has been relegated into the second place. Management has a tendency to get as much value out of the administrative departments as possible, as they can be perceived to be a drain on company resources. QA departments may cost the company money in the way of salaries and overhead, but there are innumerable case studies in the literature that indicate the savings made in "getting it right first time," which more than offset these outgoings. However, for individual QA units, it can be difficult to quantify such statements. (I feel that we are safe in the knowledge that if there is no QA unit, then there will be no work; staffing levels, however, are another issue!) One possible way, and perhaps the only way, to quantify such savings are to cost the time of correction and rework on a per-person basis. This may be still difficult to quantify, but with the help of the finance department, it should be possible to at least calculate an estimated saving. Identify the individuals involved with the error correction and rework, and then determine the amount of time they spend in making the corrections. Provide this information to QA for analysis. It must, however, be acknowledged that asking people to carry out "unnecessary" work is difficult at best, so I feel it is essential that management put its weight behind such initiatives.

One of QA's first tasks is to convince management that such extraneous tasks are good for the organization and will pay dividends in the end. It will provide management and financial controllers of an organization with the tools to fully understand the cost implications of not getting it right first time. Such activities will also, indirectly, provide more accurate costings for actual tasks and provide much more realistic time frames. These results are good for everyone concerned.

Estimation of the cost of quality should not be left to the accountants. If it is, then you can be sure that only the cost of QA time will be counted, and that will normally be on a cost-per-project basis. What you do not get is a breakdown of how much it really costs to fix an error or validate a process, etc. In order to do this, we must cost out the time to undertake a particular activity. This information, though difficult to obtain, will provide management and QA with the information to find out where the real costs are being used up and therefore allow them to take action to prevent the costs' getting out of control. There is now a great financial incentive for managers to root out the cause of the increasing costs and do something about them. QA is then not perceived as just a necessary administration cost but one that can save the organization money in the long run by investigating the root causes of problems and suggesting fixes. A system of ABC can assist management here by identifying the individual costs of activities. Management can thereby get a financial handle on the savings obtained by getting it right the first time.

End Note

It was never my intention to cover all aspects of regulatory compliance within this book, and you may have noticed that there are several areas that have either not been covered or have not been covered in any great detail. Also, there may well be some country-specific differences that you will have to take into consideration in conjunction with my suggestions.

What I intended was to provide the reader with some examples of how to carry out a QA function, present some possibly new ideas, and help readers avoid some of the pitfalls in setting up a quality system.

What you need to do now is analyze whether the ideas and examples presented will suit your existing operations or, more importantly, can be modified to fit within your own organization. I wish you best of luck as you progress in your journey on the path toward compliance and excellence.

Information Resources and Acronyms

ABC
Activity-Based Accounting
http://www.ucisa.ac.uk/events/2002/ conference/papers/5-cnl-ucisa.ppt
http://www.asq.org/topics/coq.html
http://www.asq.org/ed/conferences/aqc/public_proceedings/54_2000/14434.pdf
http://www.asq.org/ed/conferences/aqc/public_proceedings/57_2003/19384.pdf
http://www.prosci.com/abc1.htm

ABPI
The Association of the British Pharmaceutical Industry
12 Whitehall,
London
SW1A 2DY
U.K.
http://www.abpi.org.uk/

Adobe Acrobat
Software for creation and reading Acrobat Portable Document Format files
http://www.adobe.com

AGIT
(Arbeitsgruppe Informationstechnologie)
Guidelines for the Archiving of Electronic Raw Data
http://www.glp.admin.ch/legis/ArchElectRawData1_0.pdf

AICRC
Association of Independent Clinical Research Contractors (UK)
http://www.aicrc.org.uk/

Apple Corporation
1 Infinite Loop
Cupertino, CA 95014
U.S.
Macintosh OSX
http://www.apple.com/uk/macosx/

ASCII
American Standard Code on Information Interchange
http://www.webopedia.com/TERM/A/ASCII.html

ASQ
American Society for Quality
600 North Plankinton Avenue
Milwaukee, WI 53203
U.S.
http://www.asq.org

Baldrige National Quality Program
National Institute of Standards and Technology
Technology Administration
U.S. Department of Commerce
100 Bureau Drive, Stop 1020
Gaithersburg, MD 20899-1020
U.S.
http://www.baldridge.nist.gov

BARQA
British Association of Research Quality Assurance
3 Wherry Lane
Ipswitch
Suffolk
IP4 1LG
England, U.K.
http://www.barqa.com

Best Practices in Testing and Reporting Performance of Biometric Devices
http://www.cesg.gov.uk/site/iacs/itsec/media/protection-profiles/BBP.pdf
http://www.npl.co.uk/scientific_software/publications/biometrics/bestprac_v2_1.pdf
http://www.tech.purdue.edu/it/resources/biometrics/papers/elliott-ICARCV.pdf

BIRA (formerly, British Institute of Regulatory Affairs)
TOPRA, Ltd.
7 Heron Quays
Marsh Wall
London, E14 4JB
England, U.K.
http://www.bira.org.uk

BSI
British Standards Institute
389 Chiswick High Road
London, W4 4AL
England, U.K.
http://www.bsi-global.com/

CIPD
Chartered Institute of Personnel and Development
151 The Broadway,
London, SW19 1JQ
England, U.K.
http://www.cipd.co.uk/subjects/lrnanddev/

CPA
Clinical Pathology Accreditation U.K., Ltd.
45 Rutland Park
Botanical Gardens
Sheffield
S10 2PB
England, U.K.
http://www.cpa-uk.co.uk/

CR-CSV
Clinical Research — Computer Systems Validation Working Party
http://www.cr-csv.org/

1 CFR Part 11
A Website where people can access information on the rule and actively discuss issues and concerns with industry peers and government regulators.
http://www.21cfrpart11.com/
Lab issues with above
http://www.labcompliance.com/computer/fda-observations.htm

CyberSign
Cyber-SIGN Incorporated
180 Montgomery St. Suite 925
San Francisco, CA 94104
U.S.
http://www.cybersign.com

DoH
Department of Heath
Richmond House,
Whitehall,
London SW1
England, U.K.
http://www.doh.gov.uk/dhhome.htm

ECTD
European Union Clinical Trials Directive
(A UK perspective)
http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clintrialdir.htm
FAQs about the Clinical Trials Directive
http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clintrialdir_faq.htm

EDC
Electronic Data Capture
http://www.healthdec.com/
http://www.phaseforward.com/products_edc_inform.html
http://www.scian.com/electronicdata.html
http://www.clinicaltrialsoftware.com/

EFGCP
European Forum for Good Clinical Practice
http://www.efgcp.org/

EFQM
European Foundation for Quality Management
Brussels Representative Office
Avenue des Pléiades, 15
1200 Brussels, Belgium
http://www.efqm.org

e-SOP
Electronic Standard Operating Procedures
BARQA position paper
Authors: Barbra Kay-Farrow, Chris Montgomery, David Kill, Janice Birnie, Jean Samuel, Richard Winning and Tony Watts.
BARQA Publication, October 2003
ISBN 1-904610-03-X

EMEA
European Agency for the Evaluation of Medicinal Products
7 Westferry Circus
Canary Wharf
London, E14 4HB
England, U.K.
http://www.emea.eu.int/

ENMAW
The common Website for the Medicines Authorities of Europe
http://heads.medagencies.org/

EPA
Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460
U.S.
http://www.epa.gov

ESCROW
National Software Escrow, Inc.
8225 Brecksville Road,
Building Three,
Suite 105,
Brecksville, Ohio 44141
U.S.
http://www.nationalsoftwareescrow.com

FDA
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
U.S.
http://www.fda.gov

FDA
Independent Review Body Inspection Requirements
http://www.fda.gov/ora/cpgm/default.htm

FDA
Bioresearch Monitoring Program (BIMO)
Guidance for Industry, Computerized Systems used in Clinical Trials
http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm
http://www.fda.gov/ora/compliance_ref/bimo/default.htm
General Principles of Software Validation; Final Guidelines for Industry and FDA Staff.
http://www.fda.gov/cdrh/comp/guidance/938.html

FERQAS
Federation of European Quality Assurance Societies

GAMP 4 (2001)
Good Automated Manufacturing Practice
Guide for Validation of Automated Systems in Pharmaceutical Manufacture
3109 W. Dr. Martin Luther King, Jr. Blvd.,
Suite 250,
Tampa, FL 33607
U.S.
http://www.ispe.org/gamp/
http://www.ispe.org/Template.cfm?Section=gamp&Template=/publications/ISPE_Technical_Guides/GAMP4/gamp4.cfm
http://www.labcompliance.com/index.htm

GCLP
Good Clinical Laboratory Practice
A quality system for laboratories that undertake the analyses of samples from clinical trials.
Authors: Tim Stiles, Vanessa Grant and Nick Mawbey
BARQA Publication, March 2003
ISBN 1-904610-00-5

GCP Guidelines
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/e6_e.html
http://unpan1.un.org/intradoc/groups/ public/documents/APCITY/UNPAN009867.pdf
http://www.tera.org/pubs/comparisontable.pdf
www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB
www.cosa.org.au/documents/ICH_GCP_%20guidelines.pdf

GCP Technical Directive (draft)
Document title "directivegcp20040614.pdf"
http://pharmacos.eudra.org/F2/pharmacos/new.htm

GMC
General Medical Council
Regent's Place,
350 Euston Road,
London, NW1 3JN
England, U.K.
http://www.gmc-uk.org/

GMP (U.K.)
Good Manufacturing Practice
MHRA
1 Nine Elms Lane
Vauxhall
London, SW8 5NQ
England, U.K.
http://medicines.mhra.gov.uk/ourwork/ensurequalmed/gmpandgdp.htm

GMP (U.S.)
Good Manufacturing Practice
http://www.fda.gov/cdrh/devadvice/32.html
http://www.fda.gov/cdrh/comp/gmp.html

HNC
Higher National Certificate (vocational qualifications)
http://www.aimhigher.ac.uk/student_info/hnc.cfm

Home Office
Animal Procedures Committee
5th Floor
Allington Towers
19 Allington Street
London, SW1E 5EB
England, U.K.
http://www.apc.gov.uk/index.htm

HTML
Hyper Text Markup Language
http://www.webopedia.com/TERM/H/HTML.html

ICH
International Conference on Harmonization
Access to document stores via FDA site.
http://www.fda.gov/cber/ich/ichguid.htm

IQA
Institute of Quality Assurance
12 Grosvenor Crescent
London SW1X 7EE
England, U.K.
http://www.iqa.org

ISO
ISO Central Secretariat
International Organization for Standardization (ISO)
1, rue de Varembé, Case postale 56
CH-1211 Geneva 20
Switzerland
http://www.iso.ch/iso/en/ISOOnline.openerpage

JSQA
Japan Society for Quality Assurance
http://www.jsqa.com/en

Lab Compliance Website
Deals with current issues in compliance and good source of documentation such as SOPs, etc.
http://www.labcompliance.com/index.htm

LIMS
Laboratory Information Management Systems
http://www.labware.com/
http://www.limsource.com/home.html
http://labvantage.com/

Lloyd's Register Quality Assurance Management (LRQA)
http://www.lr.org/rules_and_standards/management_system_certification/

Lotus 1-2-3
IBM Corporation
1133 Westchester Avenue
White Plains, NY 10604
U.S.
http://www-306.ibm.com/software/lotus/sw-bycategory/subcategory/SW870.html

MCA
The Medicines Control Agency
U.K.
http://www.mca.gov.uk/

Microsoft Corporation
Windows operating system, Office Suite and other software.
http://www.microsoft.com

NAACLS
National Accrediting Agency for Clinical Laboratory Sciences
8410 W. Bryn Mawr Ave.
Suite 670
Chicago, IL 60631
U.S.
http://www.naacls.org

NATA
(National Quality Systems For Clinical Laboratories)
National Association of Testing Authorities Australia
Leeds Street,
Rhodes
NSW 2138
Australia
http://www.nata.asn.au

NCCLS
Clinical and Laboratory Standards Institute
940 West Valley Road, Suite 1400
Wayne, PA 19087-1898
U.S.
http://www.nccls.org

NEQAS
National External Quality Assessment Service (UK)
NEQAS Office,
PO Box 401,
Sheffield S5 7YZ
England, U.K.
http://www.ukneqas.org.uk/

Netware (Novell)
Novell House 1 Arlington Square
Downshire Way
Bracknell Berkshire, RG12 1WA
England, U.K.
http://www.novell.com

NIBSC
National Institute for Biological Standards and Control
Blanche Lane,
South Mimms,
Potters Bar,
Herts., EN6 3QG
England, U.K.
http://www.nibsc.ac.uk/

NIST
National Institute for Standards and Technology
Public Inquiries Unit
NIST, 100 Bureau Drive,
Stop 3460,
Gaithersburg, MD 20899-3460
U.S.
http://www.nist.gov

Oakland, John
Total Quality Management: The route to improving performance.
Second edition, 1993
Butterworth-Heinmann Ltd.
ISBN 0 7506 0993 1

OECD
Organisation for Economic Cooperation and Development
2, rue André Pascal
F-75775 Paris Cedex 16
France
http://www.oecd.org

PGP
Pretty Good Privacy
http://www.pgpi.org/

PICS
Pharmaceutical Inspection Cooperation Scheme
PIC/S Secretariat
P.O. Box 5695
CH - 1211 GENEVA 11
Switzerland
http://www.picscheme.org/

PKI
Public Key Infrastructure
http://www.pki-page.org/
http://csrc.nist.gov/pki/
http://www.pkilaw.com/
http://www.schneier.com/paper-pki.html

PRCSQA
Pacific Regional Chapter of the Society of Quality Assurance
c/o Mary Kay Erickson
MK Consulting
14385 Skyview Road
Madera, CA 93638
U.S.
http://www.prcsqa.org/intro.html

QP (qualified person)
http://www.rpsgb.org.uk/pdfs/QPbiblio.pdf
http://www.rpsgb.org.uk/pdfs/QPappguid.pdf

Regulatory comparison Websites.
http://www.thecre.com/quality/20021217_omb-watch.html
http://www.sendemissary.com/compass.nsf/key/ich.htm
www.tera.org/pubs/comparisontable.pdf
http://www.liquent.com/solutions/idrac-db-complete.asp

SAFE
Secure Access for Everyone
SAFE delivers unique electronic identity credentials for legally enforceable and regulatory compliant digital signatures across the global biopharmaceutical environment. SAFE is intended for business-to-business and business-to-regulator transactions.
http://www.safe-biopharma.org/

Sampling by attributes
Sungate Technologies Inc.
c/o ENGINEERINGREFERENCE.COM
3902 Cedarvale Drive
Eagan, MN 55122
U.S.
http://www.engineeringreference.com/Quality/sampling.htm

Sampling Plans
Excellent source of information on sampling plans and their use.
H & H Servicco Corp.
PO Box 9340
North St. Paul, MN 55109-0340
U.S.
http://www.samplingplans.com/

SAS
SAS Institute, Inc.
100 SAS Campus Drive
Cary, NC 27513-2414
U.S.
http://www.sas.com/

Schneier, Bruce
Secrets and Lies: Digital Security in a Networked World
John Wiley & Sons, 2000
ISBN 0-471-25311-1
http://www.schneier.com/

SDMS
Scientific Data Management Systems
http://nugenesis.com/pages/products/
http://www.waters.com/WatersDivision/ContentD.asp?watersit=JDRS-5WJQ3P

SGS (Société Générale de Surveillance)
SGS SA
1 place des Alpes
P.O. Box 2152
1211 Geneva 1
Switzerland
http://www.sgs.com

Six Sigma
http://www.isixsigma.com/

Statistical Quality Control On-line
A Website by Galit Shmueli
This application gives the single and double sampling plans for attributes, according to the Military Standard 105E tables, for a given lot size and AQL.
http://iew3.technion.ac.il/sqconline/milstd105.html

Qualified Person (QP)
Specific requirements for persons taking responsibility for release of pharmaceutical substances.
http://www.rsc.org/lap/educatio/registers/qpregist2.htm
http://www.rpsgb.org.uk/pdfs/QPsponsguid.pdf

Quattro (Borland)
Spreadsheet no longer available
Borland Software Corporation
100 Enterprise Way
Scotts Valley, CA 95066-3249
U.S.
http://www.borland.com/products/

Question Mark
Question Mark Computing Ltd
5th Floor, Hill House
Highgate Hill
London N19 5NA
England, U.K.
http://www.questionmark.com/uk/home.htm

RSC
Royal Society of Chemistry
Burlington House
Piccadilly
London W1J 0BA
England, U.K.
http://www.rsc.org

SAG
Scientific Archivists Group
c/o Qualogy Ltd
PO Box 6255
Thrapston
Northants NN14 4ZL
England, U.K.
http://www.sagroup.org.uk/

Site Master File
http://medicines.mhra.gov.uk/ inforesources/publications/gn30.pdf

SQA
Society for Quality Assurance
2365 Hunters Way
Charlottesville, VA 22911
U.S.
http://www.sqa.org

Structure & Content of Clinical Study Reports E3, 1995
http://www.fda.gov/cder/guidance/iche3.pdf
http://www.emea.eu.int/pdfs/human/ich/013795en.pdf

UKAS
United Kingdom Accreditation Service
21-47 High Street,
Feltham,
Middlesex TW13 4UN
England, U.K.
http://www.ukas.com

UKCC
United Kingdom Central Council for Nursing, Midwifery and Health Visiting
23 Portland Place
London W1B 1PZ
England, U.K.
http://www.nursingnetuk.com/registration/UKCC.html

Verisign
Delivers intelligent infrastructure services that make the Internet and telecommunications networks more reliable and secure
www.verisign.com

WHO (World Health Organisation)
Provides good publications for GLP training.
Communications Unit
Special Programme for Research & Training in Tropical Diseases (TDR)
World Health Organization
1211 Geneva 27
Switzerland
http://www.who.int/tdr/publications/publications/glp-handbook.htm
http://www.who.int/tdr/publications/publications/glp-trainer.htm
http://www.who.int/tdr/publications/publications/glp-trainee.htm

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