

Jens-Peter Gregersen

Research and Development of Vaccines and Pharmaceuticals from Biotechnology

A Guide to Effective Project Management,
Patenting and Product Registration



VCH

Jens-Peter Gregersen

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Distribution:

VCH, P. O. Box 101161, D-69451 Weinheim, Federal Republic of Germany

Switzerland: VCH, P. O. Box, CH-4020 Basel, Switzerland

United Kingdom and Ireland: VCH, 8 Wellington Court, Cambridge CB1 1HZ, United Kingdom

USA and Canada: VCH, 220 East 23rd Street, New York, NY 10010-4606, USA

Japan: VCH, Eikow Building, 10-9 Hongo 1-chome, Bunkyo-ku, Tokyo 113, Japan

ISBN 3-527-30059-7

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Weinheim · New York
Basel · Cambridge · Tokyo

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Published jointly by
VCH Verlagsgesellschaft mbH, Weinheim (Federal Republic of Germany)
VCH Publishers Inc., New York, NY (USA)

Editorial Director: Dr. Hans-Joachim Kraus
Production Manager: Dipl.-Wirt.-Ing. (FH) H.-J. Schmitt

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data:
A catalogue record for this book
is available from the British Library

Die Deutsche Bibliothek – CIP-Einheitsaufnahme:
Gregersen, Jens-Peter:
Research and development of vaccines and pharmaceuticals
from biotechnology : a guide to effective project management,
patenting and product registration / Jens-Peter Gregersen. – Weinheim ;
New York ; Basel ; Cambridge ; Tokyo : VCH, 1994
ISBN 3-527-30059-7

© VCH Verlagsgesellschaft mbH, D-69451 Weinheim (Federal Republic of Germany), 1994

Printed on acid-free and chlorine-free (TCF) paper

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Printing: Strauss Offsetdruck, D-69509 Mörlenbach
Bookbinding: Großbuchbinderei J. Schäffer, D-67269 Grünstadt
Printed in the Federal Republic of Germany.

Preface

This book has been written for researchers in academic laboratories and industry, who are currently experiencing exciting scientific changes in the traditionally empiric life sciences, which coincide with a growing economic awareness in these areas. The biomedicinal sciences are particularly affected by an increasing dico-tomy between highly innovative research and – due to regulatory limitations – very conservative development of pharmaceutical products. Scientists who are engaged in applied research or development, spanning the widening gap between fundamental research and its application, have to cope with increasing scientific and regulatory demands. Rising concerns about the cost of research and development, time performance and competitiveness cause additional distress.

Conventional biological products were mostly developed by very small, highly interactive groups. The basic methodological repertoire was limited and most of it was shared by researchers, developers and manufacturers. This situation is near optimal for the development of new products. It is fast and effective and is afford-able for small companies which operate on a national basis, but it no longer applies to modern biotechnological products.

Biological products and particularly vaccines always had a special position among medicinal products and enjoyed several regulatory privileges. Modern biological products deviate from the traditional ones by more defined active ingre-dients, more complex formulations and by their manufacturing and analytical methods. Vaccines of the future will be applied for purposes other than the prevention of infections and will probably even differ by their mode of action, e.g. by the direct application of DNA. These new products have more and more in common with chemical pharmaceutical products. Thus pharmacokinetic, pharmaco-dynamic, safety and analytical investigations rank much higher and many more specialists are required to develop these products.

As a consequence, modern biological pharmaceuticals are no longer developed on the fast track. Their development times are much longer, the costs will be similar to those of drugs and they will have to recoup the investment into research and development on larger, international markets. The technical, regulatory and com-mercial basis for biomedicinal products has changed and with it the underlying research activities. Scientists in biomedicinal research should be aware of the changed situation and its impact on their activities.

This book is an attempt to summarize information on the fundamentals of pharmaceutical product development for modern biomedicinal products and to combine these with specific recommendations for effective planning and management of applied research and development projects. A reasonable selection of information was necessary to avoid confusions by too many details. This inevitably leads to omissions and simplifications, particularly on patent and registration issues. The reader should bear in mind that these sections are primarily intended to

explain the fundamental rules. For specific advice and interpretation of special cases the original and official documents should be consulted.

Acknowledgements

I gratefully acknowledge the efforts of several colleagues at Biotech Australia Pty. Ltd. and Hoechst AG who contributed greatly to this work. Gary Cobon critically reviewed the manuscript and made many important suggestions for its improvement. Richard Brown, Gerard Henry, Katrine Hill, Jim Hungerford, Rosalind Kaldor, Peter Kennedy, Jürgen Lindner and Werner Schmidt corrected and improved several major sections. Catherine Nelson-Smith and Sheila Yong provided valuable ongoing library and information support, Stephen Harston generously provided information material on regulatory aspects and Beverly Smallbone and Anne Marshall helped in typing the manuscript.

I also wish to thank all those colleagues at Behringwerke AG, Hoechst AG and subsidiaries and Biotech Australia Pty. Ltd. who contributed directly or indirectly, voluntarily or unwittingly to this book by providing competent advice and by setting countless good examples of achievements by cooperation and putting effective management into practice, without neglecting human interrelationships. The views expressed in this book are those of the author and are not necessarily those of the persons and companies mentioned in the acknowledgements.

Frankfurt, March 1994

Jens-Peter Gregersen

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'Would you tell me, please, which way I ought to go from here?'

'That depends a good deal on where you want to get to.'

'I don't much care where.'

'Then it doesn't matter which way you go.'

(Lewis Carrol: Alice's adventures in wonderland)

Biotechnology in Pharmaceutical Research

Recombinant DNA techniques have opened up almost unlimited possibilities to generate biological molecules for vaccines and therapeutics for the prevention, diagnosis and therapy of diseases in man and animals. Twice in history similar breakthroughs were achieved: The introduction of pure bacterial cultures and of cell culture techniques to produce viruses were technical innovations, which each resulted in a series of new and extremely beneficial vaccines. Compared to recombinant DNA techniques, those historical achievements may only be minor steps forward in a limited area. We now hold a universal key to all proteins and antigens in our hands and with it the possibilities to develop not only new vaccines but also a variety of new therapeutics.

The ability to make defined peptides, proteins and antigens is only one aspect of the new technology. Other, more basic aspects may be even more exciting. The new tools and methods have stimulated basic research across all life sciences and the knowledge about basic physiological and biological processes has increased tremendously. Traditional applied sciences, such as immunology, virology, bacteriology and parasitology, have gained access to knowledge and methods to study the fundamental mechanisms which control the subject of these sciences and have moved into new and exciting basic research areas. With every newly discovered molecule and mechanism, new possibilities have arisen to apply the discoveries for medicinal purposes. Research funds and investment soared - and with these the revenue expectations.

The technology to apply the new knowledge was unable to keep pace with the speed of this scientific progress, which resulted in a widening gap between basic research and applied research. The legal and regulatory authorities which control the applications were even less prepared and are still struggling to cope with the new situation.

The development of technological innovations is following scientific progress with some delay and at a much slower pace. The time that it takes to develop new products is almost invariably underrated. On average it took about 20 years from conception to realization of major innovations (Batelle, 1973; Rosen, 1976). This average figure was deduced from the development periods of a whole range of innovative products, including for example antibiotics (30 years), instant coffee (22 years), liquid shampoo (8 years) and the zipper (30 years).

Can we expect that biomedicinal product concepts will be developed much faster?

Biotechnology in the 1990's

After more than a decade of modern molecular biology research, it appears appropriate to take stock of the assets and deficiencies of the new technology and to adjust the future direction if necessary. An evaluation such as this must concentrate on the situation in the USA, which has been at the forefront of development.

On average, each of the 550 pure biotechnology firms in the USA went into the 1990's with a turnover of \$ 11 million and a research and development budget of \$ 4.6 million (North Carolina Biotechnology Center companies database; see also Dibner, 1989). Only 30% of the income of these companies was derived from product sales (Stone, 1993). Most of this income was generated by only a few of the 550 firms, the vast majority had no significant sales at all. In these companies research and development activities account for considerable losses, which cannot be maintained over a very long period of time. One would expect a whole flood of new, profitable products from these companies within the following few years. But if we look for products from biotechnology on the current market, there is still only a handful of pharmaceutical products and some diagnostic tests. The list of products in the advanced clinical development is also not very impressive. Most product candidates in clinical development are still in Phase I clinical trials (see for example Pharmaceutical Manufacturers Association survey reports and Vitetta et al., 1993). Experience tells us that many of these developments will be abandoned. Successful products in Phase I usually still need about 3 years or more to get onto the market. Quite obviously most of the expected biomedicinal development products have not advanced as expected.

An evaluation of the situation of US biotechnology by an insider (Dibner, 1989) may be helpful to explain the reasons. According to his assessment, successful basic research and favourable environmental factors, such as a strong pharmaceutical industry, entrepreneurial spirit and a culture which supports innovation and risk taking characterize the strengths of US biotechnology. Contrary to these advantages, Dibner noticed several significant weaknesses which may be summarized under three headings:

- Technical weaknesses, e.g. in fermentation and bioprocess engineering;
- Structural weaknesses, e.g. in applied research and training programs, lack of collaboration and targeted programs, short-term funding, small firms;
- Regulatory uncertainties concerning patenting, medicines registration and other legal aspects.

Uncertainties about regulations for a new technology are not unusual. Regulatory systems are established in parallel with the applications of new technologies. The details cannot be determined before the subject of these regulations is defined. Thus, patenting and registration policies for products from biotechnology are still developing and will continue to do so for several more years. Two separate chapters below will deal with these aspects in detail.

The noted technical weaknesses are certainly not due to the total neglect of such issues and are probably not unexpected. It simply takes considerable time and effort to develop the technology to exploit the new techniques. Those who started early, developing the techniques to a level where these can be sufficiently controlled for an industrial application, are more likely to win the race to the market place. In the case of medicinal products from biotechnology, fermentation technology is an essential element of the technical development. In Japan this has been recognized very early and Japan's breweries have put considerable money into fermentation research.

In principle, the technical problems can be solved if sufficient time and money is available. But the results will not always be as desired, and it will initially be necessary to accept many compromises in terms of scale, yields, reproducibility and cost of production. Given the technical feasibility, the impact of time, money and lower than expected performance tend to be neglected. In the end they may be critical success factors!

Structural problems can have significant inhibitory effects and are probably the most difficult ones to change. A central problem lies in the observation that target orientation and collaboration is lacking. In the context of biomedicinal research and development, insufficient information about the magnitude of the task and overrated capabilities are partly responsible for these shortcomings, but the true reasons lie deep in our research system and warrant further consideration.

Research Structures

If one considers the structures of biomedicinal research, its purpose must be defined first. Medicinal research is done (and funded by governments) to generate new knowledge and in order to promote public and economic welfare. Research must not stop after the knowledge has been published. Science fulfils its purpose only, if it enables the public to apply the knowledge and to benefit from it. Medicinal research must lead to applications of scientific discoveries for the prevention and therapy of diseases.

Our current publication-driven research system motivates those who discover and publish. Those who build on these foundations, find all the missing parts, set

up a static framework and finally create a useful construction, are less favoured. Their work requires a high degree of creativity to fill the gaps in the original outline and much perseverance to overcome the numerous, unexpected difficulties. This kind of research progresses in small steps. After several years of creative and constructive work in applied research, scientists may have lost major career chances, because the number of publications in the required type of journals is not sufficient. Measuring a researcher's expertise by counting publications and by giving extra marks for papers in journals, which publish basic research, may be justified for fundamental research; It certainly does not recognize, reward and motivate applied research. In this situation "the only lasting remedy is that the link between publication records and reputations should somehow be broken" (Maddox, 1993).

The disregard for applied research is rarely uttered openly. It is reflected, for example, by the simple equation which is hidden in the following sentence, quoted from an article which claims to speak for the entire scientific community: "Enactment of policies that favour practical applications over basic research or narrowly defined objectives over scientific excellence is likely to come at the expense of traditional, broadly conceived explorations of biology." (Science 259; p.445, 1993). This sentence claims "scientific excellence" for basic research; applied research is viewed as being guided by narrow concepts.

It is hardly surprising that under these circumstances applied research is neglected or quietly delegated to others, for example the industry.

This leaves a wide gap between those who do fundamental research and the industry which builds on applied research to develop innovative products. The industry, particularly if it consists of small firms, is only to a very limited extent in a position to bridge this gap by internal research activities and by funding external research.

The weaknesses in applied research have been recognized, and after more than a decade with emphasis on fundamental research in biomedicinal research, the priorities have changed. These changes are neither unique for biotechnology nor are they new. They were and will be noticed in every new scientific area. In the initial phase of any new subject or technology, basic science will have priority. Unless the research budget increases exponentially, there will soon be more identified potential applications than funds to develop these. In that phase more funds will be directed towards applied research. Scientists in basic research will either have to reduce their research or change their orientation and style. Unfortunately our publication-driven research system does not provide any motivation to accommodate such changes.

Researchers in the USA and in Europe are currently experiencing this shift from basic towards applied research. Of the \$ 2 billion per year research budget

of the central EC organizations in Brussels, only \$ 100 million is allocated to biologically relevant basic research (Philipson, 1992). The EC budget is only a small part of the overall public research budget of the member states, but the general policy in the member states is similar.

In the USA the number of scientists has almost doubled between 1968 and 1989, whereas the amount of federal funding grew by only 20% (inflation adjusted) in the same amount of time (Lederman, 1991). Research funds from industry became increasingly important. Whereas in the 80's industries and their investors funded more basic research, they will now have to tighten their budgets considerably, because the expected products and revenues have not come as early as expected.

In biomedicinal research public and industrial funding will be more and more tied to applied research and specific goals. It will be a long and frustrating process for both researchers and those who provide funds, if these changes are introduced only by cutting funds from one end and adding them to the other end. But proposals for better structures are rare and it seems as if changes will be forced upon the scientific community.

An almost desperate idea to change current research structures and attitudes was recently discussed in the British government. It considered teaching graduate students management and industrial economics (Anon., 1993). Although the proposal seems inadequate, it clearly illustrates the underlying dissatisfaction about science which sees its only task in creating knowledge and publications rather than applications.

Looking back at ten years of massive effort to develop a vaccine against AIDS, Hillemann (1992) also concluded that "the greatest deficiency ... may lie squarely in the research and development organizational structure which is supported, in the main, by governmental initiative". Based upon his extensive experience in the development of traditional and recombinant vaccines, Hillemann proposes "collective committees" which assemble a critical mass of the required disciplines with a sole intent and under a single roof. These would facilitate more targeted, coordinated and dedicated research programs and overcome the current research structure in which the individual as well as organizations are driven by success in fundamental research and early publications.

As long as these programs are not defined too narrowly, there is no reason why a resource and effort converging management system, which is so vital for industrial development projects, should not work in applied research as well. These organizations would probably also provide a better basis to judge scientific merits which are not easily measured by the number of publications and provide chances for promotion also in applied research.

Basic or Applied Research or Where Do You Want To Get To?

The boundaries between basic investigative and applied research are not distinct and cannot be defined by the subject. One can cross the line between the two at any stage and in both directions. It is simply a matter of a decision for the target and future direction of one's work. However, the decision is not an easy one: The funding organizations require effort focussing on applications whereas the scientific community demands high-profile publications in rapid succession. In this situation scientists often "decide" to go both ways and avoid the decision altogether.

Why is it necessary to make a choice? The answer is quite simple: Concentrating the limited resources on one goal improves the chances of success and ensures that one remains competitive - no matter whether in basic or in applied research. The question is where one wants to be successful and how serious one is about it. Avoiding the decision and lingering in both fields could mean lowering oneself into irrelevance.

Those who feel capable to follow both routes and have adequate resources to do so, should at least split the two into separate projects, each with its own final aim and different short-term objectives. The two can move forward without dragging the other behind. The applied project could for example work in animal models to study combined, biological effects and their useful applications - most likely without fully understanding or bothering about the underlying mechanisms. The detailed investigation of these mechanisms could be transferred to the fundamental project where it may be taken up if it appears attractive enough and fits into the program. These separate projects will probably not only use different models and systems but also different collaborators and funds. The effects on the project plans will be considerable. But most importantly the separation makes sure that one does not lose sight of the different aims.

Those who choose the applied research route for a particular project or for themselves (e.g. by taking up employment in applied research organizations or in the industry), have to remind themselves occasionally what their decision implies. Applied research aims at useful applications and probably patentable inventions rather than at discoveries and rapid publications. In contrast to fundamental research which concentrates on a very specific topic, applied research embraces several disciplines and focusses them towards one common goal. Thus, efficient collaboration is essential. The success of the project is at stake, if an individual scientist prefers to work in isolation.

Applied research requires effort to be focussed on a clearly defined target which often results in unanswered questions and loose ends. These scientifically interesting side-aspects are a common trap, because there are always scientific arguments as to why it could be useful for the project to solve these little

problems "en passant". In the end there will be more interesting side-aspects than expected and these are usually not solved by just a few experiments.

The Aim of a Project

Defining the Aim

Numerous scientific papers and contributions to conferences in the field of biological sciences finish with a statement on the usefulness of the presented work for a commercial product. In most cases the idea can be considered as a starting point for an applied research project - rather than the end of it.

How does an applied research project start? Since any project is a unique event with a specified end result, the end point (the aim) needs to be defined first.

Let's assume, the aim is defined as "proven efficacy of the discovered active principle, reproducible under various conditions, and laid down in a patent application".

Is this definition sufficient to critically assess the required resources and the spectrum of methods and skills needed to start planning a project? The most likely answer at this stage is that there is not sufficient knowledge on several aspects for a reasonable judgement. A more exact definition of the aim or splitting it into its different elements may help to define what is required.

What, for example, should be the "active principle"? A vaccine may be used to prevent infections or only to avoid the appearance of clinical symptoms and to inhibit the spread of the microorganism. A new molecule may affect several physiological mechanisms and could be useful for several indications or applications. A veterinary product could be useful in several species and for different purposes. Different approaches, methods, models and most likely also collaborating specialists may be required to address these options.

What does "proven efficacy" mean? Which is the best system or model to test and prove the efficacy and what degree of efficacy is required to call it a successful result? It is essential to define the degree of efficacy in a measurable category to make it a useful goal. If directly measurable parameters do not exist, it may be useful to find a definition which relates to existing products or therapies.

Another point which should be considered at this stage relates to the chances of getting meaningful patent protection. Publishing a second paper on a very similar topic is possible and occurs frequently. Filing a patent with claims on what has already been published or described in other patent application is useless and a waste of much time and money. Those who aim for a patent should perform a patent and literature search during this project definition stage. Without this one cannot seriously consider a patent as the aim of the project.

If the aim leads to a rather specific product, it seems adequate to collect some information on the basic requirements for such a product in terms of efficacy, safety and quality. Without this information one might invest years of research

into a project only to learn at the end that the entire effort was useless or that essential parts have to be repeated.

For example, the chosen expression system for the active component or the crucial adjuvant component of a vaccine could be unacceptable for registration authorities. This would require the development of another system and the repetition of all critical experiments. One might also find out that the efficacy of the product in mind cannot compete with already existing therapies.

Instead of conducting a project which is unlikely to lead to success, other strategies and options should be considered. In the project definition phase changes are easy, later on they will be costly. Scientific success and advantages over scientific or commercial competitors can depend on this initial assessment.

These few questions and examples might explain that the time and effort used to define the aim of a project as precisely as possible is probably the best of all investments and warrants a more systematic approach. This does not require major effort nor is it very time consuming. Once the questions are known, most of the information can be collected quite easily.

Creative Market Research and Other Valuable Background Information

According to a study "Management of New Products" by Booz, Allen and Hamilton in 1968, on average about 70-90% of the money spent in research and development of new products is used for products which are failures. No industrial organization would commit itself to research or development without investigating the general and market situation to reduce this failure rate. There is no reason why publicly funded research projects should not do the same. Starting a project without such an assessment means being more concerned about doing the project right than doing the right project.

Researchers (in academic institutes as well as in industry) tend to view market research in a very narrow sense. They do not perceive the potential of the approach, thus missing innovative ideas. Market research may, in fact, bring research ideas back to the earth and help avoid major mistakes. If used with a wider perspective and by a creative mind, it can also help identify interesting options.

Market research should add information and use it for a better assessment of chances, risks and options. It should not be used to reduce the project idea to a few simple figures. The usefulness of market research depends a good deal on intensive interaction between research and marketing and information exchange in both directions.

A basic assessment of important market and other environmental factors does not necessarily require marketing experts. But if their advice is sought, it should be by an interactive process, not by presenting the idea for a verdict. During this process the marketing expert will probably identify the weak spots of the researcher's proposal. With reasonable background information the researcher (who else?) should also be able to recognize and understand the subjective assumptions (i.e. weaknesses) of the marketing expert's assessment and to challenge them where adequate.

The problem is that the additional information usually requires changes of the direction or the priorities of the project. Unless there are very convincing arguments, a researcher who is convinced of an idea is unlikely to consider such changes.

The most convincing arguments are those which are developed from one's own considerations. Thus researchers should do their own market assessment to develop an opinion about the chances, risks and best applications of their approach. (If they don't like the term market assessment, they may call it "SPA" for "strategic project assessment" if this sounds more reputable.) One needs no special skills to identify the major threats to and opportunities for a project. These are usually rather obvious, if some basic information is available and is considered critically.

At the beginning it must be kept in mind that it is very easy to define an "ideal product". But this ideal product is probably the most difficult one to develop or may be an unrealistic development target. Sooner or later it pays off to have identified all options, including the lesser ones with a higher probability of success. Of course, the optimal product may be chosen as the aim of the project, but minor options should be included in the planning as a fall back position.

The more detailed the collected information is, the better it serves its purpose. Acquitting oneself of the task by only quoting a figure about the (ill-defined) "market potential" of a product (usually followed by a sum of some hundred millions or even some billions) obscures the matter rather than illuminating it. In many cases this figure is so meaningless that it would not result in any consequences for the project, if somebody simply changes the currency unit from British Pounds to Italian Lira.

Creative market research should initially collect a few basic figures on the occurrence of the disease or condition to be treated. Scientific review articles and epidemiological investigations as well as disease statistics may serve to provide these. As a next step information should be collected about current methods to diagnose and treat the disease or condition. This includes the products or compounds used, the frequency of their application, cost of the products used and the overall cost of the treatment. Most of this information can

be obtained by a specific literature search in the medicinal field or from physicians and clinicians. Clinicians should also be asked for deficiencies in the current products or treatment schemes, such as side-reactions, lack of efficacy (in general or under certain conditions) and for other medicinal treatments (e.g. prevention or surgical techniques) which have an impact on pharmaceutical products in this area.

This background information should be used to identify the needs of the "market", i.e. of patients and physicians, of veterinarians and their clients or of diagnostic laboratories. It also serves the purpose of checking whether the project in mind has the required potential to improve the existing situation.

A simple assessment of the likely cost of the new or improved product, compared to the benefits that it provides, can be very illuminating, even if the figures are only rough estimates. Acceptable costs for the new product may be deduced from prices of comparable product classes or from specific products which are currently used to treat the disease in question. These prices are likely to give a reasonable estimate. Depending upon the estimated value of additional benefits of the new product, a premium can be added to the basic figure. This sort of simple calculation and estimate is particularly warranted for veterinary medicinal products and for products which will compete with already existing and established products. If the existing products or prophylactic treatment schemes cost only a few dollars, the active ingredient is only worth a few cents. To get a rough idea about the upper limit for the cost of the active component in these cases, the market price of the existing product may be split up by the following "rule of thumb calculation": about 40-50% for cost of sales and a profit margin (before tax), 20-30% for quality control, packaging and labelling and 10% for formulation. For lower priced products in a competitive environment the active ingredient may account for only about 10-30% of the market price.

If it is believed that the proposed new product can compete in terms of cost of manufacturing despite a more demanding process or that the product offers significant advantages which justify a higher price, it will be necessary to present evidence for a high-yield system or to focus on a proof of the claimed advantages.

Live and vector vaccine approaches should take into account the epidemiological situation and health care schemes in the target countries. The efficacy of live vaccines and vectors may be affected by a pre-existing immunity in the population. Live vaccines can also interfere with screening tests, e.g. for salmonellosis in people who handle food or for bovine leukosis in eradication schemes.

Diagnostic tests may be rather useless, if the test result does not lead to any consequences, for example when no effective treatment is available or because the test procedure takes too long to influence the choice of therapeutic options.

In the latter case a much faster and simpler "bed-side test" (or cow-side test for veterinarians) may be the better solution.

The use of medicinal products and therapies in man is more driven by ethical and much less by economic considerations. Direct commercial aspects such as cost of the product may be less critical. Instead, the assessment should concentrate more on safety and quality aspects and their scientific and economic ramifications.

Which safety standards must be met by the product? Does it contain components with an unknown safety profile or a poor tolerance at the application site? What are the chances of replacing these and getting access to better components? Are adequate safety tests for attenuated or genetically modified microorganisms available or must/can these be established and will these tests give sufficient confidence in the safety of the product to justify later trials in human beings? Who would be interested and could contribute to address the safety issues, e.g. by characterization of the strain of microorganism used, by developing adequate models and tests? How early should these activities start or how long should the project proceed without addressing these very critical issues?

Not only live vaccines, but also therapeutic polypeptides and subunit vaccines, have to meet very demanding safety requirements before they can be tested in humans. As soon as a protein with potential as a vaccine component or a therapeutic drug has been identified, the questions arise of which systems and methods should be used to produce the active component, how to separate it from potentially harmful components and how to purify it to the required degree. Assuming that a purity of at least 95% and only a very limited number of known and defined impurities will be allowed for a human medicinal product, the expression and purification systems and yields warrant some careful considerations at a very early stage. The wrong choice or taking what is readily available, instead of using the best option, can result in a loss of time, impractical patent applications and a loss of the competitive edge of one's research.

A list of aspects to be examined as part of a creative market research and far-sighted project planning is given in Table 1. Depending on the maturity of the project, it may not be necessary or possible to cover all aspects. However, the assessment should be guided by the attitude that it is better to gather as much information as possible and then decide whether a specific piece of information is useful. Information never comes too early, but frequently too late!

Table 1: Points to Consider in Strategic and Market Oriented Planning of Research and Development for Biological Medicinal Products**General aspects**

Occurrence of the disease or condition: geographic distribution and frequency.
Current diagnostic and therapeutic measures.
Deficiencies of current treatment: efficacy, side-effects, cost, practicability.
Potential improvements of existing methods.
Acceptance of potential improvements: safety, cost, practicability.
Interaction with health care and eradication schemes.

Efficacy aspects

Potential indications, scientific feasibility and risks.
Degree of efficacy required.
Systems and models to demonstrate efficacy.

Safety aspects

Potentially harmful effects of the proposed product.
Safety requirements: similar or better than existing products.
Systems and models to assess safety.

Commercial aspects

Product prices and cost of current treatment.
Frequency of application of existing products.
Likely cost of the proposed new product and treatment.
Cost/benefit relationship.

Patent aspects

Existing patents and applications in the field.
Gaps and chances for an own patent application.
Availability and costs of patent support.
Cost/benefit of patenting.

Project-related aspects

Other research and development projects in this area: scientific competitiveness of the own project.
Specific skills and methods required.
Collaborators for specific problems or to extend the scope of the project.
Who would be interested in the project/product and provide practical or financial support?
Funding organizations to be approached: interest and user groups, industry, government and special research funds, supranational funding organizations.

Project Planning

Developing a researcher's idea into a pharmaceutical product requires resources and clear objectives. These objectives will remain a dream if there is no plan which outlines the way to achieve them and if the commitment to meet these objectives is missing.

Most plans suffer from three main deficiencies:

1. The aims and objectives are not sufficiently defined so that their completion remains uncertain.
2. Major risks and foreseeable difficulties are not identified and taken into consideration which renders the plan untrustworthy.
3. Plans are not comprehensive with only vague descriptions of the activities and/or missing key resources and key activities.

One obvious reason for these deficiencies lies in the fact that research results are not predictable, whereas any plan is based on predictions. This seems to be a basic dilemma of all research planning. But there are solutions or at least acceptable compromises.

Researchers are used to planning experiments. Their project plans are often presented as a sequence of experiments, each of those addressing another critical aspect of the subject. Since the results of the first experiment are not exactly predictable, all subsequent experiments which build upon these results bear many uncertainties. Any attempt to take the possible variations in results into account will result in a massive complexity of the plan to cover the ramifications from each experiment. At this stage many efforts to establish a reliable plan are given up, simply because the plan becomes too complex to be of any use. As a solution other plans are designed which assume only the desired result at the end of each experiment. Inevitably such plans have to be modified frequently, since they are over-optimistic.

The planning process as outlined below and in the example in Figures 1 and 2 represents a more strategic and goal oriented approach than the "experiment-after-experiment planning" method. It initially concentrates on the "what" (what is intended, what must be achieved) before the questions "how", "when" and "who" are addressed. As a consequence, the project is planned with a much wider perspective and tends to be less compromised by the many limitations that every researcher experiences during the daily work. The aim of one's research may be set wider or more ambitiously. Ambitious does not necessarily mean more risky, if potential collaborators are included in the considerations.

Clear and quantifiable statements of objectives are essential for any plan to succeed. If defined in measurable categories, objectives avoid confusion and misunderstanding about the goals of the work and increase the reliability and exactness of the plan. An agreement among the project team on the aim and objectives creates responsibilities and delegates these to the individual project team members. Feelings of responsibility for achieving the objectives completely and within time can be a tremendous driving force and is crucial for success.

The Backwards Approach to Establish a Plan

To avoid getting stuck in unsolvable details, planning should concentrate on the objectives and tasks rather than on individual experiments. This is best achieved by designing a plan backwards, starting with the ultimate aim. Figure 1 exemplifies this approach and is meant as a purely hypothetical project. I have chosen a fairly basic but practical research project which involves several disciplines for this example, to show that clear objectives are also very useful for research projects and are not restricted to strongly market oriented development projects.

The first and very important part of any plan is the exact definition of the aim, as explained in the previous chapter. This is followed by a list or sequence of major tasks or sections which each must be accomplished in order to achieve the aim. Since these major sections each define critical steps of the project, success criteria or objectives for each of these must be described and agreed. These objectives should specifically address known or potential difficulties (in our example: the purity of antigen that is needed, the required test systems, etc.) and should be defined as exactly as possible at this stage and updated when necessary. The definition of objectives requires a reasonable knowledge of the subject and should thus be discussed and agreed with the specialists in these fields and with those who have to meet these objectives.

Once the main objectives are defined, more specific project tasks can be described which are necessary to address and achieve the objectives (e.g.: the improvement of the expression system, development of specific tests, models, etc.). It becomes apparent where the risks and problems of the intended project will arise and which specific skills are required to solve the problems in due time. Collaborators may be

contacted for help in these areas. However, some aspects will still appear rather risky and may bring the project to an early end, if no solution is found: What if the yields in the chosen expression system are not high enough to purify sufficient amounts of antigen? What will happen if Antigen X is not sufficiently immunogenic in laboratory animals? Should one compromise the entire program and try the ultimate challenge test with what is available - despite the low chances of success?

To address these issues, alternative approaches to solve the main problems should be evaluated and added to the plan where reasonable. In the project example in Figure 1 the risk of low antigen yields and of insufficient immune responses seems very high and the plan includes tasks to address these problems (for example the improvement of yields, the optimization of the formulation). Since a failure of these parts would halt the entire project and these measures may not succeed, further contingency measures seem adequate. As a consequence, the investigation of other expression systems to improve yields and probably also to improve the conformation of the antigen as well as methods to refold the antigen, are added to the plan as contingencies in case of failure.

The project idea has meanwhile gained some shape and it is now the time to add the next dimension to the emerging plan before it becomes too complex. First (conservative) time estimates for the individual tasks can be made. The smallest reasonable time unit for research projects of this magnitude should be a month, less would be unrealistic. Sections and tasks can now be arranged parallel, overlapping or consecutively, according to the time requirements and dependencies.

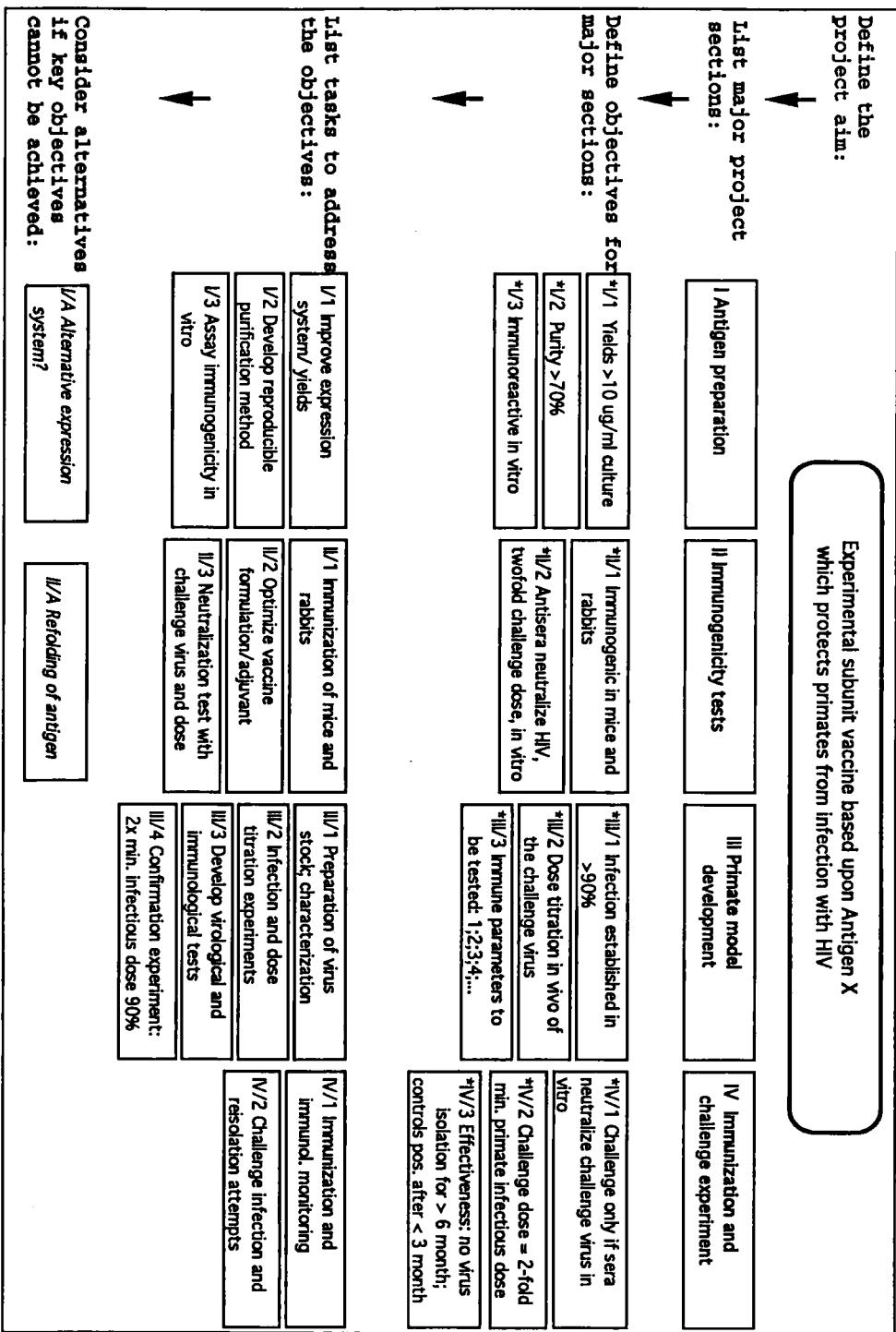


Figure 1: Establishment of a Project Plan

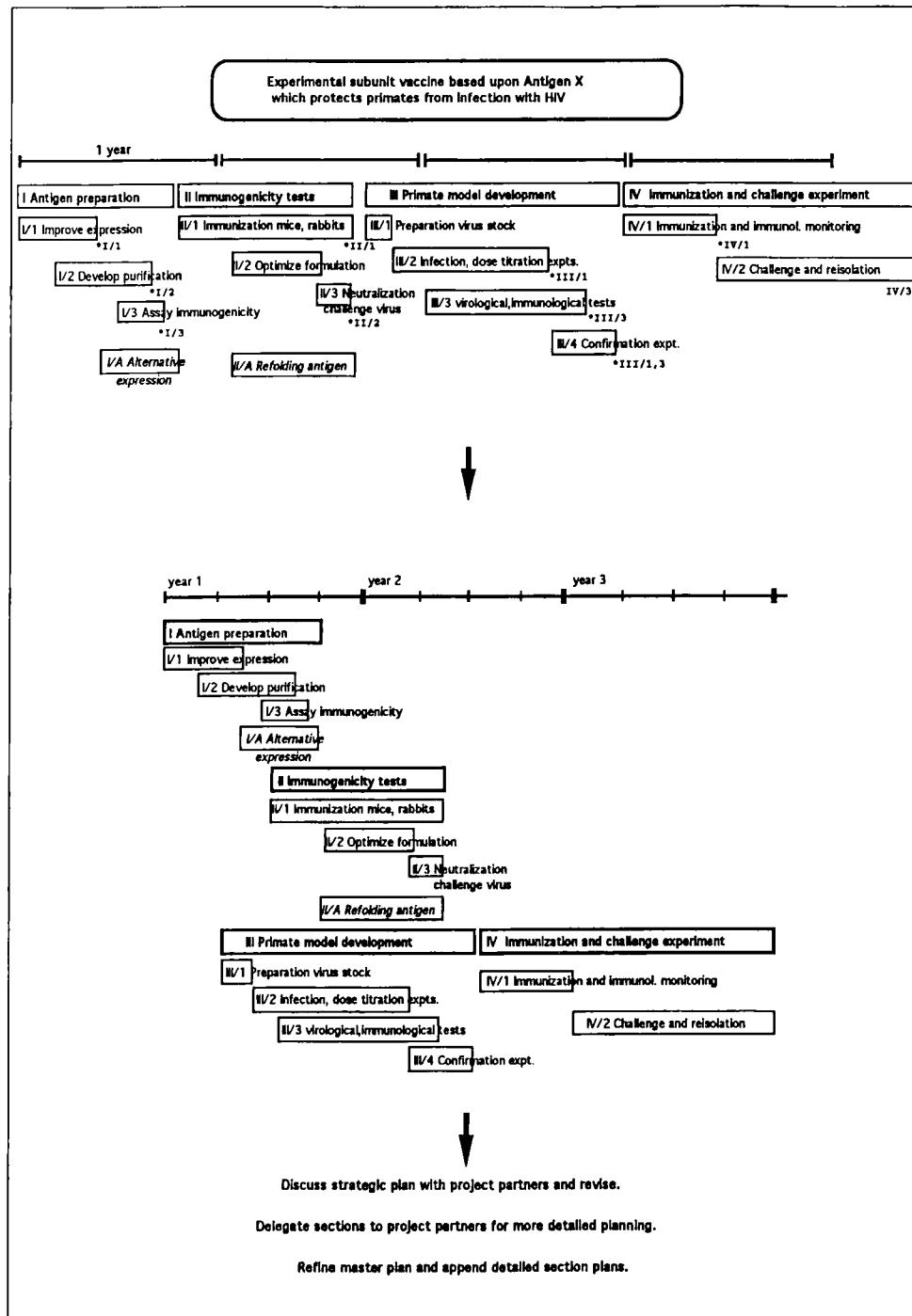
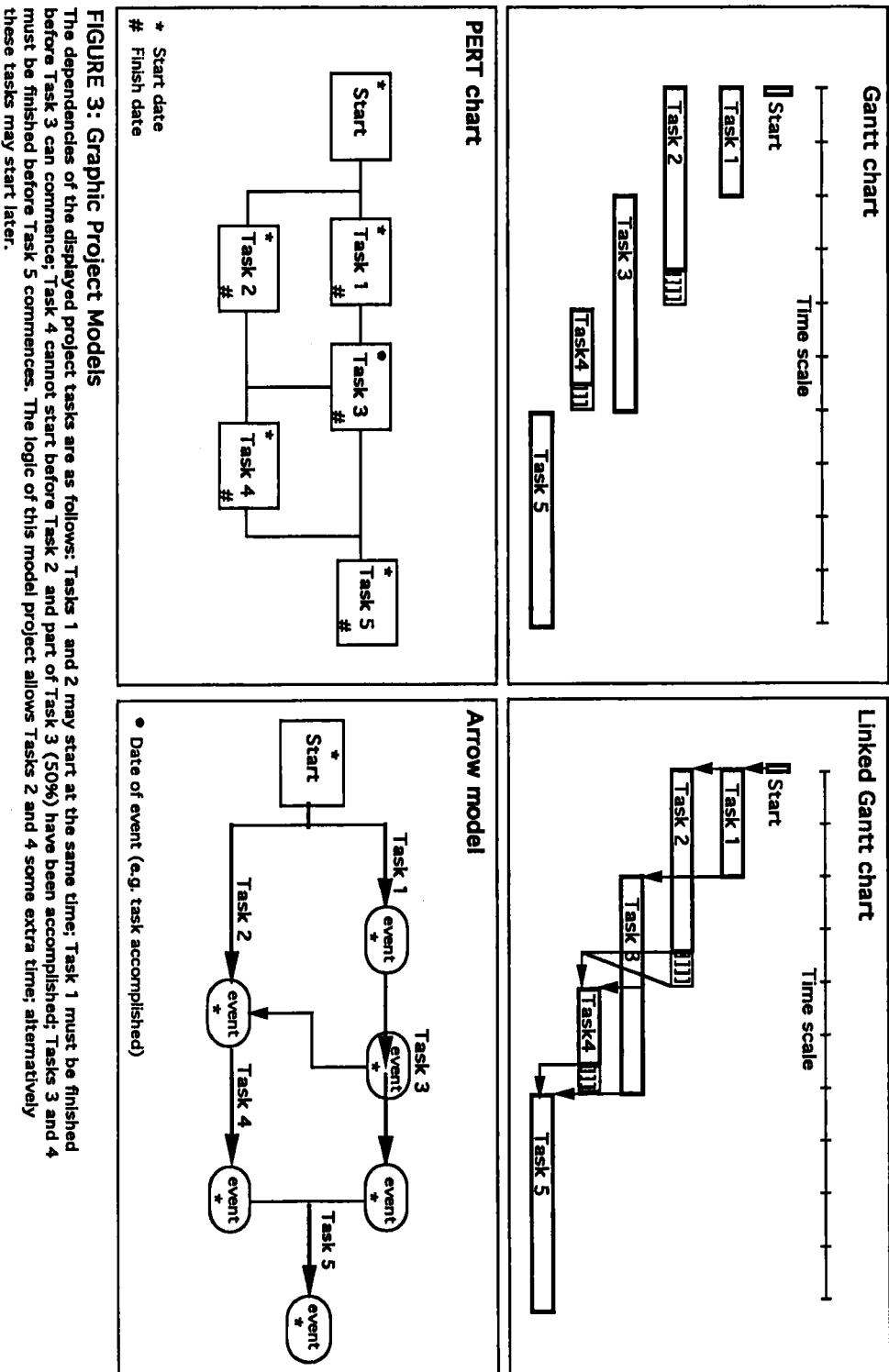


Figure 2: Establishment of a Project Plan: Sequencing of Project Sections and Tasks



Linking Project Tasks

Sequencing of project sections or tasks can be performed in different ways. The example in Figure 2 is displayed as a Gantt (proprietary name) chart which shows the duration of tasks as horizontal bars. Because of their clarity Gantt charts are a preferred means to present project plans.

PERT (Performance Evaluation and Review Technique) charts primarily show how the different tasks are connected by presenting these as a network of boxes (activities) linked with lines. Due to a lack of a common time scale, start and finish dates have to be added to each individual task box. Complex PERT charts are difficult to survey and are less suitable for presentation purposes of the entire project. However, they are commonly used during the establishment of a project plan and to illustrate dependencies within a selected part of the project, because they expose the logic of a project.

Linked Gantt charts visualize both key elements, task duration and dependency, by superimposing the task links as connecting lines on a Gantt chart. If complex dependencies exist, the plan loses its clarity or can become totally confused. This can be avoided by graphic means (line thickness, use of colours) or by indicating only those links which are critical and not obvious.

The Arrow model uses lines to represent tasks or activities. These activities are linked by junctions or nodes which represent events, e.g. the accomplishment of an objective or completion of a task. Arrow models concentrate very much on the achievements and less on activities. For the unexperienced, they are quite difficult to understand and to survey, which is probably the reason why these are rarely shown. Examples of these four models are shown in Figure 3.

Objectives and Milestones

Main project tasks should only be considered as completed when their objective has been achieved. As a control instrument, these objectives must be included in the project plan and must be defined in a measurable way. Figure 2 depicts these only as a symbol (*) followed by the reference number as given in Figure 1 to maintain the clarity of the example. Because of their importance, the main objectives may be accentuated and shown with their descriptions. They indicate the assumptions on which the rest of the plan is dependent. They also serve

as a milestone and decision point to approve, abandon or modify the subsequent plan.

In the example, the achievement of objectives *I/2 (70% purity) and *I/3 (immunoreactive in vitro) could be used as milestones which successfully conclude the antigen preparation phase. However, the definition "immunoreactivity in vitro" seems too inexact for use as a milestone. A better and adequate specification could be for example: "immunoreactive with monoclonal antibody Y", whereby antibody Y is directed against the most relevant epitope of Antigen X.

Phase II of the project example contains an objective describing the desired type and specificity of the B-cell response (*II/2) and it is specific enough in its definition (neutralization of the twofold challenge dose) to serve as a meaningful milestone - provided that the project team agrees on its usefulness at that place.

Time and Task Dependencies

As described above, the backbone of the plan is basically established starting at the end of the project, then working through to the beginning. To sequence the different task sections correctly it is necessary to check backwards and forward to see how the different tasks depend on each other.

The approach shown in Figure 2 consists of two steps. At first the tasks within each of the four project sections are timed and sequenced. Dividing the project into sections makes this step easier because less complex task links need to be considered.

Once the logic of the project sections is established, the draft plan is checked for remaining dependencies between the sections. In a second step, entire project sections are rearranged and overlapped where possible and necessary, according to the relatedness of tasks in different sections.

For very complex projects it is necessary to assign the dependency to each individual task already while each task is described in order not to overlook essential task links. This is best done using PERT charts or an arrow model.

Two major conflicts in terms of task dependencies between project sections remain in the example of Figure 2 (upper half) after a first arrangement of the different tasks within each of the four sections. In order to get an antigen which is immunogenic in mice and rabbits (see *II/1) at least some immunization experiments with Antigen X (task

II/1) must be successfully accomplished before Section I (preparation of antigen) can be concluded. Thus these experiments must be moved forward.

A more complex dependency concerns the challenge dose. The challenge dose is dependent on the minimum primate infectious dose and will not be known before task III/2 (the dose titration experiment) has been done. Because the achievement of objective or milestone *II/2 requires a successful neutralization of the twofold challenge dose, task II/3 must either be moved backwards or, as the better solution, the development of the primate model must start much earlier. Taking these dependencies into account, immunogenicity tests and primate model development could be performed in parallel, assuming that the work can be done at the same time since different people will work on these tasks.

Of course other aspects such as time requirements, time constraints, risk factors and resources should also be considered from this stage onwards to arrange project sections and tasks in an appropriate order.

Project Team Approval and Refinement of the Plan

The plan is now ready to be discussed in all details among the members of the project team or with potential collaborators (if that has not already been done). The strategic plan, as it is now, contains sufficient detail to seriously consider the basic rationale of the approach. Changes to the aim, objectives and some general aspects of the plan will most likely occur at this stage.

The collaborator who is responsible for the primate model could, for example, ask for proof that Antigen X is immunogenic before the primate model work starts. Thus section II needs to be readjusted and objective *I/3 requires an adequate definition (as proposed above) to fulfil its purpose as a milestone. The implications of these changes (e.g. the extended duration of the entire project, changed funding periods for the different groups involved) will be directly visible in the plan. Thus graphic plans are a useful tool to investigate various scenarios.

Once a general agreement on the aim and strategy has been achieved, the detailed planning of the sections of the strategic plan can be delegated to the individual working groups. The agreed objectives and first time estimates serve as a framework for their planning. They will be the most competent people to describe the individual tasks and to

estimate their duration, to decide where time buffers for contingencies are required and to define the required resources.

Finally, the individual elements of the plan are put together and the strategic plan is readjusted to a more exact time schedule. The revised strategic plan which summarizes the major project parts can now serve as a useful master plan and project overview to present and justify the project in general. Reference to the sub-plans should be made to allocate the resources and for progress monitoring purposes.

Allocation of Resources and Budget Planning

Resources comprise everything that is needed to carry out a project. Three separate categories are usually recorded and used to calculate a project budget:

1. **Manpower:** All staff involved in a project along with the time these persons spend on the project (e.g. 0.25 man/year equals one person working on the project for three months of the year or 25% of the working time for the entire year).
2. **Consumables:** all materials used, including equipment of minor value below the depreciation threshold.
3. **Capital Goods:** equipment and facilities above a certain value which are subject to depreciation.

With only very few exceptions personnel is by far the most expensive resource. Incorrect project cost estimates are most likely due to an inexact estimate of the manpower required. Most errors (mostly underestimates) occur due to deficiencies of the project plan which directly and considerably influence the manpower estimates. First of all, the time to accomplish project tasks is usually underestimated. Second, the project plan is not detailed enough for reliable manpower estimates, and third, the contribution of other than research personnel (management, administration, animal attendants, dishwashers and other services) is not taken into consideration.

Compared with personnel cost, all other costs are usually of lower importance. Despite this, many research fund applications require and contain more details and justifications of consumables and capital goods than for personnel. I have seen many researchers, urged to write extensive lists of types and numbers of consumables needed to run a project and spending hours or days to trace the cost of substances,

pipettes, culture vessels and so on. This exercise is a waste of time, except in very rare cases where larger quantities of very special and extremely expensive material is used.

Capital equipment cost should be justified and assessed on the degree of utilization, manpower savings or improvements of the quality of the work. Those who want to buy new equipment should be asked how often they will use it. The more regular the intended use of a certain piece of equipment the more likely it is a good investment. If it is only to be used for a few times or during a short period, one should look for somebody else who has the required equipment and skills to use it properly.

In almost all research units the ratio of personnel to other costs are fairly similar and constant. In countries with a high income level about 65-75% of the project cost are personnel costs and 25%-35% are other costs (consumables, administration, depreciation etc.). In a university institute where cost of buildings and administration are usually not included in the institute's budget, personnel cost may account for an even higher percentage of the entire budget.

With this in mind one should ask the administration for the following key figures which can be used to estimate project budgets within only a few minutes. Under normal accounting practices these key figures are readily extracted from the annual budgets.

1. The average annual budget per person (total annual budget divided by the total number of staff) or
2. The average annual cost of labour per person (overall personnel cost divided by the total number of staff) plus
3. The ratio of personnel cost to other costs that need to be assessed separately, e.g. cost of consumables or depreciation for capital goods.

Updates will be required for each fiscal year, if the total number of staff changes or in the case of other, major changes, such as new buildings or different organizational structures.

For an initial budget estimate, the first of the above figures (the average annual budget per person) multiplied by the man/year on a project gives a fairly exact idea of the cost of the project per year. If a further breakdown of the budget is required, the cost of labour can be assessed separately, using the average cost of labour per person and other costs, such as consumables, calculated as a percentage of these.

In most instances people of different income levels are involved in different projects at a rather constant rate. Thus, it does not effect the exactness of a budget estimate too much using the budget per person (or cost of labour) averaged across all income levels. Minor adjustments may be made, if the particular project deviates considerably from the normal work distribution.

A higher degree of confidence in the budget estimates may be achieved by grouping the staff involved in a project into different income levels and using the group average cost per person as a multiplier. In most instances, this mode of calculation will not improve the overall exactness of the budget forecast. Other variables such as potential changes of priorities or manning on the project usually have a much stronger influence on the budget.

It may be useful to calculate a model project using simple average figures and compare the result with more exact cost assessment methods in order to find the best and simplest way to calculate future budgets with a sufficient degree of exactness and confidence.

It must be kept in mind that all budget figures are only estimates. Their degree of exactness corresponds to, but cannot exceed the predictability of the work to be done. In other words: a project budget is only as good as the underlying project plan.

Changes to the Plan

No plan is perfect and minor changes, mainly additions, have to be made frequently during the project. These changes will first occur within the subplans. In order not to affect the project as a whole, every attempt should be made to contain these changes within the subplans. Everyone should try to achieve the objective of the individual task or section in due time, for example by putting a higher priority or more effort on the solution of critical tasks without affecting others.

The alternative approaches to solve critical tasks in a project should be initiated, as soon as serious problems are foreseeable. If a problem cannot be solved within a section and within the allowed time, the master plan will need to be revised and the collaborating partners will have to be contacted to reschedule their activities accordingly.

Changes to the master plan should not affect the general aim of the project and, if possible, not affect or delay the overall time frame. Tasks or sections could be performed more in parallel where this appears justified and not too risky. Time buffers may be shortened or if

there are no more such time buffers, because the plan was too optimistic, the manpower must be increased temporarily or outside help recruited. Unfortunately most organizations are rather inflexible to implement such cures. However, extending the entire program by several months or years is certainly the more costly alternative!

Changing the aim of a project should occur only if there are good scientific reasons to do so - not due to technical difficulties which can be solved.

Implementing a Project Plan

Every project needs a certain amount of coordination. To a great extent, coordination means communication. A project leader should optimally be appointed during the early planning stages and should play a major role in the entire planning process. This person must take responsibility for the overall project and drafts and controls the master project plan. The more complex the project is and the more dispersed the cooperating groups, the more important the project leader's role becomes. Coordinating the work of less than ten scientists can already be a real full-time job, if the project is to be conducted in a cost and time efficient way.

The best coordination of a project is achieved by a good project plan. The plan delegates the project tasks and links the activities and project team members. It allocates all resources including money and contains all necessary elements to measure and control time, cost and success. Finally, a project plan is a very effective means of communication: On the one hand it serves to explain the project to those who pay for it. (After that stage many project plans unfortunately tend to disappear and are forgotten.) More importantly, the project plan tells and continually reminds the members of the project team of the purpose of the whole project, what their roles and tasks are and what exactly they have to provide at what time in order to make the project a success.

A project plan which is not sufficiently discussed, agreed and communicated among the project participants is useless. The best means to ensure that everybody agrees with a project plan and is committed to it is to ask them to sign the plan. But don't be surprised if the request for a signature is met with reluctance and results in a further round of revisions of the plan! This should be seen as a positive signal which indicates that people have thought about their contribution thoroughly and recognize their responsibility. However, to avoid a

repetition of fundamental discussions it is best to announce the intention of having the plan signed, before the individual sections are planned.

Meetings of the project team should occur at regular intervals. It is a good idea to start these meetings with a presentation of the project plan and to point out the expected status. During these meetings the progress over time is assessed, existing and potential problem areas are identified and discussed with a view to their implications of the entire project. Project tasks on the critical path need special attention, because any delay in these activities will delay the overall project. Plans and objectives are revised and defined in more detail where necessary.

The individual scientific reports delivered on such occasions should be considered as the foundation of such a meeting but not as its sole purpose. Project group meetings should be inspired by a joint responsibility for any success and failure. Everybody should be aware that the failure of other parts of the project influences the project as a whole and has direct implications on one's own success. The achievement of objectives within time must be acknowledged, particularly those which were accomplished at the expected time despite unexpected problems.

Project Management Computer Software

The establishment of a complex project plan, scheduling and linking of project tasks, revision of project plans as well as the time, cost and resource planning and control can be made much easier by using computer programs. If however, the only purpose of a project management software package is to create a more professionally looking plan, which later on is filed away without fulfilling its main purpose, namely being used to monitor and continuously update the project, one can as well use a simple graphics program which costs much less and probably provides the desired result much faster!

If one wants to plan and control a larger project in a serious manner, project management software packages are essential and save a lot of time. These programs use entry data such as task descriptions, their duration, start or finish times, tasks dependencies and milestones to automatically sequence and schedule the project tasks. Conflicts and logic errors are identified and the project is re-scheduled after these have been corrected. A critical path analysis function reveals and

highlights those tasks which must not be delayed if the overall time frame is to be maintained. Resources, for example manpower, budget money, equipment or other limiting factors, can be added to the project tasks and may be used to allocate, plan and control these as well as to provide resource reports at any given time. Several format options for presentations are available with most software packages, including tables, resource histograms, Gantt and PERT charts.

The main virtue of these computer programs lies in the ease of the scheduling and revision process along with the ability to provide up to date reports at any time. As a side effect the availability of a supportive computer program may improve the motivation to create more detailed project plans and to update it as required.

Project management software packages need adequate hardware to support their features. Before buying such a package one must ensure that the available computer operating system, graphics card and memory is compatible with the software. Latest editions of computer magazines containing comparative test reports can be consulted to choose the right software for ones needs.

For most applications the mainstream project management software packages are fully sufficient, as these are easily able to handle projects with several hundred tasks per schedule. The main aspects to look for are the ease of use in establishing and surveying a more complex plan, the flexibility (additions, changes and re-scheduling must be simple and fast) and certainly also the reporting qualities. Reports must give a good and clear overview, but they must also provide all necessary details. The possibility to summarize tasks and to include breakdown structures (without interrupting the task links) enables separations of reports by sections, working groups, disciplines and so on, which can be of great value to make a project report understandable as well as workable.

Product Development

Product Development Follows Different Rules

Product development for biological pharmaceuticals might appear as a simple continuation of a research project after a sufficiently effective compound has been identified. From a scientific point of view there is no clear distinction between research and development. Until the clinical phase, product development utilizes the same basic skills and methods and - to a great extent - the experience of the same people who did the research. However, the rules change considerably as soon as innovative research turns into conservative testing of quality, safety and efficacy and into analytical and process development.

The decision to develop a pharmaceutical product transfers an active principle or compound from the resource-limited research laboratory into a new environment. In a multi-disciplinary approach the compound is subject to a variety of analytical, pharmacological, toxicological, and clinical tests and trials. From now on methods, results, documentation and the materials created are under strict scrutiny exerted by the developing organization itself and finally by several authorities. Research activities are hardly ever subject to such surveillance and control, concerning, for example the precision and consistency of methods and results. It usually takes time for a researcher to fully acknowledge and accept this fact.

Since there is no clear distinction between the research and development phase, projects quite frequently move into development while the people involved are unaware of the changed rules. This may result in neglecting essential aspects, in extra cost for the repetition of critical studies and in a considerable loss of time.

In larger organizations research and product development are usually separated in different units because of the fundamental differences between creative research and systematic, goal-oriented development and because development requires special knowledge and experience. In the field of biological pharmaceuticals, however, most companies and organizations are relatively small, since they traditionally operate on a national scale. They do not have several products under development which are subject to a similar development scheme. The methods are more complex and the materials created in the research phase are directly passed on for development. Furthermore, biotechnological products are still in their infancy, and pharmaceuticals from biotechnological processes are not yet routine products. Thus, there are many reasons why researchers in these areas in industrial and

non-industrial research organizations contribute to or perform product development. These scientists need to know more than just their science to understand their new task.

The general aspects of product development presented in this chapter, and the following chapter on registration requirements for pharmaceutical products were mainly written for researchers and scientists who are less experienced in product development. These two chapters are also meant to prevent the often observed, overly ambitious ideas about the commercialization of research results. Unrealistic expectations about the simplicity and duration of development may lead to inappropriate management decisions which may even endanger the future of research-oriented enterprises. The success of biotechnology ventures does not only depend on good research but also on a realistic assessment of the potential products and on the ability to adopt the required skills to effectively develop research results into commercial products.

Commercial Chances and Risks of Pharmaceutical Development

Pharmaceutical development is expensive, and the risk that the project fails during this process is high. The following facts and figures may illustrate the costs and risks that may be expected. Although these figures do not differentiate between research and development and are not specific for biological pharmaceuticals (they represent mainly chemical entities for human drugs), the general picture is similar for all types of pharmaceuticals, and the implications for product development are essentially the same.

The average capitalized cost to develop a human pharmaceutical product in the USA amount to US\$ 231 million (DiMasi et al., 1991). Comparable figures for 1982 are US\$ 91 million (Langle and Occelli, 1983) and for the time between 1963 and 1975 US\$ 54 million (Hansen, 1979). On one hand, these considerable increases in cost, which tended to double within ten years, reflect the increasing difficulties to find new and commercially attractive drugs, since these figures include the cost of aborted projects. On the other hand, a substantial part of the rising cost is due to the increasing regulatory demands which must be met to achieve marketing approval.

The average effective patent protection for human and animal health products approved in the USA between 1984 and 1989 was only 10

years and 7 months, including the possibility of restoration of patent terms of up to 5 years (Vangelos, 1991). This is because the average time to develop a newly discovered compound continuously increased over the past decades from less than 4 years in 1960 to more than 10 years in 1989 (Karia et al., 1992). Longer development times automatically reduce the effective patent protection period and thus significantly influence the revenue expectations.

Despite the sharp increase in development cost, the number of new products launched and their sales expectations remained fairly constant (Lumley and Walker, 1992). It has been calculated that in the UK even the best selling 10% new drugs require longer than the effective life-span of their patents to recover the research and development cost; the majority of new pharmaceuticals cannot recoup these cost even after more than 20 years (Prentis et al., 1988).

Comparable figures with reasonable validity for animal health products are not available. Veterinary product development cost are definitely lower, but the revenues are also much lower. Due to rising registration demands, influenced by both the pharmaceutical and the agricultural sector, veterinary product development cost follow the same trend as human health products.

In general the animal health market has stagnated since 1980. The international competition has increased and the more producers of biologicals and vaccines try to internationalize their products and sales in order to outbalance the price erosions by growth in sales volume. Whereas vaccine producers in the USA have been rather successful to penetrate European markets, European vaccines were prevented from access to the lucrative US market due to concerns about potential adventitious agents in these vaccines (e.g. FMD, BSE). At the same time European veterinary vaccines have to comply with increasing regulatory demands and the introduction of GMP (Good Manufacturing Practice) standards.

Relatively few really new and attractive products have been introduced in the animal health market. The recently developed new and expensive human therapeutics do not play a major role in animal health. Prophylactic vaccines against the major endemic diseases are already available and are difficult to improve for a competitive price. Several other interesting vaccine candidates are stuck in the research phase due to unsurpassable difficulties to achieve sufficient efficacy.

The continuing high interest and investment in pharmaceutical research cannot be attributed to guaranteed high revenues. Return on assets as a commonly used measure of industrial profitability for the

eight most successful health care companies in the USA in 1989 was approximately 16%, or 11% if research and development expenditures are included as gross assets for better comparability with other, less research intensive industries (Vangelos, 1991).

It seems that the general perception of high profits is very much influenced by the commercial success of a few "blockbuster" products like the H₂-receptor antagonists, ivermectin or the recently launched erythropoeitin. These are the exceptions, whereas extremely hopeful candidates rendering moderate success seem to be more the rule.

The pharmaceutical industry is much more research oriented than other industries and has to cope with higher risks. Due to the high development cost and long development times, risks must be eliminated as early and consequently as possible. Risk elimination must already start in the research phase and before the expensive industrial development commences. High-risk research projects need much time, thus they must be kept small and have to focus only on the major risk factors. Research projects should be clearly separated - if not physically, at least in mind - from the more rigid and much more expensive development.

Once an attractive product has been identified, the time factor becomes extremely important, risk and cost are no longer the only relevant criteria. From now on speed and efficiency are of paramount importance. A minor planning error which results in a delay of a task on the critical path for only one month can delay the entire project by one month. Almost inevitably it also adds 1/12 of the annual budget to the development cost. Thus, in a project with an average annual budget of \$ 2.5 million, a delay like this can cost more than \$ 200,000. Apart from these direct cost, later access to the market can cause much higher losses.

The following subchapters describe how to define the aim of a development project and propose a basic structure for a project plan which eliminates the main risk factors in the earliest possible stages but keeps the main dependencies in mind. Since the success of development projects depends on an efficient and well-organized use of human resources and because dealing with human resources is the most difficult task of a project manager, the human and organizational aspects of project work will also be discussed.

Product Profile and Market Assessment of Development Products

It has already been emphasized that a good knowledge of the entire scientific, medicinal and commercial background situation provides a sound base to define attractive aims for applied research projects. I used the term "creative market research" for this collection of information, to point out that despite the creative, research oriented purpose it is very much influenced by the market situation. In fact, a market assessment for a development product is based on exactly the same kind of information (compare Table 1).

A market assessment for a product to be developed identifies the potential strength and weaknesses of a new product, as well as those of competitive programs or therapeutic schemes. This assessment should include the patent situation and the competitiveness of the organization in terms of the skills and resources to develop, manufacture and sell the product when evaluating the chances and risks of the intended development product. From this information one or a series of potential products can be identified and defined.

The definition of a product candidate and the description of essential commercial aspects of this product and its development process should be summarized in a product profile. The product profile describes essential product qualities such as the indication, form of presentation, intended application and use pattern, efficacy, safety and other critical aspects, e.g. patent restrictions and cost limitations for the compound or for the formulated product. The expected date of product launch and sales expectations as well as the expected development cost are important elements of the product profile. Table 2 summarizes and explains the aspects which should be covered by a product profile.

Based on the product profile a cost benefit analysis can be calculated. Such an analysis helps in deciding whether, under the given circumstances, a potential product is sufficiently attractive to develop and which indication for the new compound is more or less attractive. It is mainly a means to prioritize and to compare the particular development product with other products under development or under consideration. This may be necessary since several development candidates may compete for the same resources, such as personnel, development budget, capital investment and production capacity.

It should be noted that cost-benefit calculations for the same development product may vary considerably between different organizations (see for example Hodder and Riggs, 1991). First, the calculation methods may be different. Second, the assumptions that go into these calculations, e.g. the expected sales of a certain product, may

vary considerably. These figures depend on company-specific factors such as available sales force and presence on relevant markets, as well as on certain personal opinions and other subjective judgements. Apart from this, it is obvious that already existing manufacturing facilities without the need for a major investment can significantly influence the result of a cost-benefit analysis. A cost-benefit analysis is a scenario, and the assumptions that formed the basis of the described situation should be specified and carefully taken into account, before general conclusions are drawn.

Besides the aspect of providing information to assist in decision making, a precise product profile has several other benefits. It creates a common vision about the direction of the development by defining the aim unmistakably to all people involved, thus assisting in tight project planning without the need for endless discussions about the goals. (About the importance of a common vision for projects see also Hardaker and Ward, 1991.) Critical aspects of the project are exposed at the beginning and measures to solve these problems can be included in the development plan at the best, most convenient and cost-effective time. Defining the product profile helps to recognize changes in critical parameters (e.g. in efficacy) and deviation from the decided development route earlier, so that counter-measures can be initiated before these become too costly. The later changes are initiated, the more expensive they are.

Product profiles frequently tend to describe an ideal or almost ideal product, because this is much easier and less controversial to define. In order to become a meaningful base for planning and decision making, the essential product characteristics in a product profile should be described as minimum criteria which define what must be achieved and where the product must not fall short. Only minimum criteria are useful to define potential milestones for the development plan which in turn are used as an objective guide for decisions to continue a project or to abandon it, if the milestones cannot be achieved. Desirable goals for further improvements can be added where appropriate.

Of course, a product profile is not a one-sided instruction. It requires input from research, preclinical and clinical development, marketing and sales departments and is developed by an iterative, stepwise procedure.

Table 2:Contents of a Development Product Profile

The product profile should address all essential aspects of the product and the development. It describes the agreed development task and assists in management decisions.

I. Essential Product Characteristics

Indication	Condition or disease to be treated. Target species for veterinary products.
Presentation	Type of product and formulation, e.g. live or inactivated vaccine, vector vaccine, type of vector, liquid or lyophilized product, adjuvant, special formulations.
Application/Use pattern	Mode and frequency of application, e.g. route of application, single or repeated use, duration of use, booster intervals.
Efficacy	Specified or in comparison to other products or treatment schemes.
Safety/Tolerability	Specific demands, e.g. standards set by other products or treatments.

II. Commercial Aspects

Cost of development	Per year until product launch, updated during development.
Cost of product	Active ingredient, formulation and packaging, limitations.
Investment costs	Manufacturing plant and equipment.
Sales expectations	Differentiated by medicinal indications, by major countries.
Expected date of launch	Month and year for major countries.
Patent protection	Duration in major countries, quality of patent protection.
Major product advantages	Major selling arguments, strategic importance.
Major development risks	Reasons for failure, e.g. efficacy, safety, regulatory risks, competing products or developments.
Cost-Benefit analysis	With annotations on critical limitations and including the important assumptions upon which the analysis is based.

Planning and Managing Product Development

The development of a modern pharmaceutical product is a complex task with has additional complications for biological or biotechnological products due to the potential variabilities of the biological production system and the resulting consequences. Apart from considerations of adequate skills and resources, careful and very detailed planning is imperative for the development. The basic rules of project planning described in a previous chapter using a research project as an example can be applied in exactly the same way for development. However, the controlling function is much more important for development plans.

Knowledge of the essential registration requirements is mandatory for the planning of a development project. If these are neglected, the development process will be like navigation in unknown waters without a compass or a map. The risk of a shipwreck is high, in any case the journey will take much longer and will cost more.

Provided that a reasonable and useful product profile (see Table 2, above) has been established, the general aim of the project and the most relevant objectives have already been decided. As with most research projects, these will most likely address the efficacy, this time with more qualifications concerning the exact indication, the type of product, its formulation and application scheme.

Another important general objective which has been defined in the product profile may be the expected price limit for the production of the active ingredient or the formulated product. Specific tasks and measurable success criteria for process development and manufacturing, e.g. in terms of yields and recovery after purification, can be deduced from this price limit. Other very specific objectives and the majority of project tasks relate to specific registration requirements.

It may take several months to establish a workable development plan and most of this time will be required to collect the necessary information. At the beginning the project plan will probably be a rather simple outline which then grows while the project progresses. A project master plan which covers the major sections, milestones and decision points can be established far ahead and - if prepared thoroughly- will remain essentially unchanged from then on. More specific and detailed planning and updating for the nearer future is done in the subordinated plans for the individual sections and must be performed continuously.

Development plans must be much more detailed than research plans. The simple reason for this is that the commercial environment in which

development takes place requires much stricter planning, use and control of time, budgets and manpower.

Significant time savings can, for example, be achieved by preparing tasks and trials early and by careful and extensive evaluation of trials. Often time is lost, since in negligent project plans resources for the planning and evaluation phase of larger studies were ignored. Several aspects can be tested simultaneously in the same study and do not require separate studies or experiments. This applies especially to clinical trials which need considerable time to get under way and where it is possible to collect data on efficacy, pharmacology, safety and tolerability aspects at the same time.

Many tasks have to be performed according to very detailed legal and quasi-legal standards which may differ from country to country. Relevant countries' guidelines must be checked and considered in planning the individual tasks. Studies performed according to GLP standards, animal trials and clinical studies can only be performed, after internal or external examinations of protocols or approval procedures have been passed. In this situation it is essential that all people involved start their activities with precise and detailed instruction and are given sufficient time for a careful preparation of their tasks. Good project plans include the preparation of relevant studies and trials as specific tasks in order to avoid delays.

Effective project controlling also needs detailed planning. Under normal circumstances the plans must be exact enough to allow progress to be monitored at intervals of 2-4 weeks. (Some industrial sectors and companies have much tighter schemes!) In critical situations or for activities on the critical path, more frequent checks and corrections may be necessary. Where possible, progress should also be monitored before a task is finished. Requesting information about the progress halfway through a job can create a better awareness for time limits and target dates. If problems are likely, means to solve them can be planned and implemented before these problems cause major concern.

Risk Oriented Planning

The most difficult and controversial part in the planning and managing of a development process is to keep the right balance between the three cornerstones cost, risk, and time. Using more time reduces the risk but increases the cost and delays the product launch. Controller and marketing manager will raise their protest. Taking more risks increases

the possibility of not meeting the milestones and everybody is concerned. There is no way to do it right for everyone!

The willingness to take risks can be a key element for a rapid and cost-effective development program. Making assumptions about the likely outcome of a piece of work and commencing the next step which depends on a particular result before it is available, does increase the risk, but it also permits to shorten the development time considerably.

The most relevant risk to be considered during the development of a biological pharmaceutical is the efficacy and safety in the target organism. Despite extensive preclinical tests, many product candidates are abandoned after first tests in humans. The problems encountered at this stage are often due to pharmacological or immunological differences between the model used in the preclinical tests and humans. Thus, it is necessary to plan Phase I clinical trials as early as possible.

Similarly most veterinary development projects fail due to a lack of efficacy and unexpected adverse effects which remain unnoticed until the product is tested in the target species. Veterinary products should be tested in the target species as soon as sufficient product is available. Tests under practical conditions should follow as soon as possible. Quite often major progress, but also unexpected negative results, come from experiments in humans (or primates) or in target animal species.

Tests in the target organism are crucial, but the importance of animal and in vitro models for pharmaceutical product development should also not be neglected. In most cases the available range of models and in vitro tests needs to be extended for the development phase, because the models used in research are not adequate or not sufficient. Considering the fact that all potential facets and variations of a new active component (different protein conformations, concentrations and formulations, the mode of action, immunology, pharmacokinetic, safety and efficacy under various conditions) may have to be studied, the availability of models can be an important asset for a fast and cost-effective product development.

Models allow certain aspects to be investigated in more depth, but they reflect only a part of the entire situation. Therefore, they need to be validated, preferably by comparing their results with those in the target organism. Models should be considered as a valuable addition, not as a replacement for tests in the target organism.

The economic feasibility of a product can be another major risk which needs continuous attention during the development. This is especially true for animal health projects and for all the products which will compete with simple and effective alternative treatments, for

example with existing vaccines. Factors directly affecting the economic assessment are those listed in the product profile under "commercial aspects" (compare Table 2). A project manager will have to control the development cost and pay special attention to details like yields and recovery rates during the process development. Critical limits for the manufacturing should be addressed by setting specific objectives.

One should not forget that the economic aspects of a project depend also on the underlying assumptions about the product's characteristics. Less efficacy than assumed or a slightly compromised tolerability may seriously affect a product's performance and viability on the market.

Product Development Phases

As a starting point for the planning of a development project, Tables 3 and 4 propose and summarize a phased scheme of a risk-oriented development plan. Several important milestones and decision points have already been included. Each phase must fulfil certain criteria in order to be accomplished before the next phase may start. Management decides whether a project is advanced enough to proceed to the next phase, since this decision is usually associated with the involvement of more people in different departments or of external participants and has significant financial implications. The data and information needed for an assessment of progress and criteria for the decision should be known beforehand. Most of these criteria, which are included in Table 4 as proposed milestones (and need to be specified in detail for a given project), address the critical aspects of the project and the question of what should be done to reduce these risks and to allow the project to enter the next phase.

The first management decision will be to forward a research proposal and component to development. This decision should not be made if the active principle (the active component) is not yet available or insufficiently defined. A recombinant antigen which is incompletely characterized most likely needs much more research before it can be considered a development candidate. It should stay in the less costly research laboratory until sufficient efficacy with a clearly characterized antigen is achieved. There would be no point in testing safety features or to develop a process for a component if its essential features are still unknown. The ability to complete the product profile to a reasonable

degree could serve as a prerequisite for a decision to enter development.

An important element, which is frequently used in drug development, is the introduction of a pre-development phase which serves the purpose of reducing major project risks before the full development commences and before extensive resources are allocated to the project. It can also serve as a time buffer to complete missing points of the product profile. In order not to delay the project too much, this project phase must have a limited duration of usually 1 year, but not more than 2 years. As far as possible, the crucial risk factors efficacy, safety, and economical risks should be investigated, e.g. by performing efficacy trials under the best available conditions. These could be target species experiments for veterinary indications and a range of animal model studies or perhaps even a small study in primates for human indications. Short-term safety tests can be performed to indicate where potential problems may be and which range of toxicity tests will address them. Most likely the methods used in research to generate the active component are unsuitable for later production, and the pre-development phase may be used to identify, investigate and calculate better options.

The introduction of defined project phases and management decisions before each new phase mainly intends to create a clear basis and an overall agreement before major new activities are initiated. These management tools should be handled pragmatically in order not to cause unnecessary complications and time delays. For example it could be necessary to approve preparations for clinical trials months before the preclinical development has been finished and before the formal decision to enter clinical trials is envisaged. The planning of such trials and the recruitment of trial cooperators and trial subjects can take a long time, which would be lost if decision procedures were not flexible enough.

Table 3: Product Development Phases, Main Risks and Tasks

PROJECT PHASE	MAIN RISKS	MAIN PROJECT TASKS
RESEARCH	Scientific feasibility Efficacy	Proof of a reproducible active principle. Achievement of sufficient efficacy.
PRE-DEVELOPMENT	Efficacy Safety Economic feasibility	Confirmation of efficacy in best available models or in target species. Limited, orientating safety studies. Establishment of a small-scale process, scaleable and with acceptable quality. Calculation of economic parameters.
PRECLINICAL DEVELOPMENT	Efficacy Safety	Evaluation of efficacy for all indications. Full pharmacological, immunological and safety evaluation. Process development and validation. Analytical development and validation.
CLINICAL DEVELOPMENT	Efficacy Safety and Tolerability	Phase I: Dose-finding, pharmacologic action, metabolism, side-effects: Intensive studies in patients or healthy individuals, usually 20-80 subjects.* Phase II: Controlled studies on effectiveness and on side-effects: usually no more than several hundred subjects.* Phase III: Expanded, controlled and uncontrolled trials on efficacy, safety, risk-benefit relationship, practicability: usually several hundred to several thousand subjects.*
REGISTRATION	Formalities Safety Quality	Updating/ improvement of dossier. Additional safety studies. Additional quality assurance tests or validations.
POSTMARKETING DEVELOPMENT	Safety Acceptance/ Practicability	Drug monitoring/pharmacovigilance. Further safety assessment. Postmarketing trials.

* Numbers quoted from 21 CFR 312.21 (USA)

Table 4: Product Development Phases, Milestones and Decisions

<u>MILESTONES</u>	<u>MAJOR DECISIONS</u>
RESEARCH Active component characterized. Efficacy proven.	>> Decision to enter pre-development. Decision on indications.
PRE-DEVELOPMENT Efficacy confirmed in reliable model(s) or in the target species for veterinary products. No safety risk identified. Scaleable process available; yields, cost and quality acceptable. Favourable economic feasibility study.	>> Decision to enter preclinical development. Decision on target countries. Decision on (preliminary) product specifications. Decision on manufacturing site and method.
PRECLINICAL DEVELOPMENT Proven efficacy for all indications. Acceptable safety/tolerability for all indications/conditions. Process details according to plan: scale, yields, cost, product specifications.	>> Decision on product specifications. Decision on final production process. Decision on indications to be pursued. Decision to enter clinical development.
Prelicensing serials passed quality controls; trial material available.	>> Decision to start clinical trials.
CLINICAL DEVELOPMENT Successful completion of Phase I. Successful completion of Phase II. Successful completion of Phase III.	>> Decision to file registration.
REGISTRATION Obtain market approval.	>> Decision to market product.

Decisions after completion of a phase should not exclude that preparations for later activities cannot be made before that decision. The actual activity in question (e.g. clinical trials, product sales), however, may only start with full approval.

Decision Making

Decisions are only the visible result of a process which is preceded by the generation of data, writing of reports and statements, exchange of information, meetings, and discussions. For large development projects, in which many people are involved and decisions imply significant expenses and investment, this process can take a considerable time. If decisions are well planned and prepared, they represent an important element of stability and support. If applied in the wrong way, they may severely hamper the progress of a project.

A well-founded decision to enter the development phase of a product usually takes several months. Often delays occur, because the decision was not anticipated and the necessary facts, figures and reports were not collected in advance. If the decision making individuals are not prepared and do not indicate early enough what kind of information and prerequisites they need to make the decision, months could be lost. For example, the existence of an acceptable product profile (compare Table 2) including the required information and evaluations may be used as a basis for a development decision.

Major decisions can and must be anticipated and prepared by both the decision makers and by those who's further work depends on the decision. The major decisions for a development project, as proposed in Table 4, should be integrated in the project plan along with the necessary tasks for their preparation. Management should provide guidance on the information needed for such decisions. Most larger companies have established routine schemes for the major project decisions and for the necessary information and prerequisites. If applied pragmatically, such schemes can shorten decision procedures considerably.

Minor decisions should not be made by the top management. Considering the number of people who are directly or indirectly involved, the time spent and the cost of this time at work, a decision can be more expensive than the expenditure for the object of the decision (Witte, 1969). If the suspicion arises that this could be the case, the project organization is probably top-heavy and delegation is done without giving appropriate authority.

Delegating responsibility to a project manager and to project team members also includes the delegation of decisions to them. Extent and limits of the delegated responsibility and authority should be defined in job descriptions. Only if there is trust and confidence in their capabilities, responsibility and decision making can be delegated.

Unless there are important and very convincing arguments which have not been taken into account, the subordinate's decision should be respected. Accepting a subordinate's decision can sometimes be very difficult for the superior manager, particularly if (s)he would have decided differently and the decision is questioned or criticized and must be defended. Overruling decisions of subordinates or facing them with already made decisions which would have fallen into their direct responsibility can seriously affect the working relationship.

Approval of a project requires the consent of many people, but a single "no" can cause the project to collapse. This mechanism has the potential of being misused by individuals to undermine projects they personally do not like. Risky projects (projects are by definition risky) are frequently surrounded by people who question the entire project by emphasizing one or the other inherent risk. If their concern has been recognized before and was considered during previous decisions, such criticism seems inappropriate and the critics should be requested to provide more constructive proposals.

Decisions to stop a project are the most difficult decisions. Although perseverance and full support by everybody are essential for the success of any project, there is a point where "the plug must be pulled". A feeling of personal failure if the project fails, selective perception and reporting of information, major setbacks being considered as temporary problems and the hope to recoup at least part of the investment are strong forces which hinder a reasonable decision at the right time. Staw and Ross (1991) have discussed the personal interests of people involved in such situations in more detail.

Simple recipes do not exist to prevent the project dragging on in a hopeless situation. But things can be done to make decisions to stop a project more rational and less painful for those affected by it.

First, the feeling of personal failure must be eliminated. Many organizations still consider the fear of failure and direct or indirect punishment (status, salary, no further promotion) as an important driving force - according to the "carrot and stick" method to keep a donkey moving. This method seems hardly adequate for the needs of project work with responsible and highly skilled individuals.

Project groups and their managers need recognition of their work and praise if they did a good job. This also applies to a project group which could not solve the scientific or economic problems of the project despite all reasonable efforts. The only reason to blame somebody personally would be if she or he refused to do what could have been done. In this case the person needs to be retrained to solve the problem.

Second, honest reporting also of negative results must be encouraged. The best encouragement is a modest, rational response and the offer of active help if unexpected problems arise.

Finally, one must not accept the argument that too much money and effort already went into the project and that it needs only some further investment to rescue it. Decisions must be based on the future perspective of the project. The past, including all money spent, does not count. The project should be evaluated in exactly the same way as a new project proposal and using the same kind of information. If in the new scenario, chances and risks, cost and time to develop the product do not justify the continuation of the project, it should be stopped based upon objective and rational arguments, but not because someone failed.

Project decisions tend to take a long time, and even projects which eventually finish up successfully are sometimes subject to several critical decisions during their life-span. In these times the individuals in the project group may frequently ask themselves, whether their efforts are worth it. The rule should be that as long as there is no official decision to discontinue a project, everyone should continue unharmed by the ongoing discussion.

The Project Manager

The success of any larger and complex project depends to a great extent upon an effective project management. Development projects for medicinal products need project managers with a variety of skills and personal qualities to cope with the very demanding job (see Table 5). Good knowledge or experience in many different scientific fields (for example in medicine, microbiology, immunology, protein biochemistry, pharmacology, toxicology) as well as in technical subjects (biotechnology, process development, analytical methods, formulation, manufacturing) are valuable assets for the planning and management of a project. Project managers must be prepared to continuously learn about these aspects. It is not sufficient to rely entirely on the specialists, because good decisions and judgement need overview. Furthermore, it could be helpful to know the subject in detail, if resources and time performances have to be negotiated.

Table 5: Responsibilities of a Project Manager**Project Planning**

- Development of a project concept.
- Definition of objectives, milestones and decision points.
- Definition of project tasks.
- Scheduling of project tasks.
- Planning of resources.
- Replanning and updating of plans.

Project Coordination

- Identification of shortages.
- Re-allocation of resources.
- Negotiation of use of resources versus time performance.
- Preparation and initiation of major decisions.
- Organization and chairing of project meetings.
- Special tasks as required ("putting out fires").
- Development and provision of missing skills.

Project Controlling

- Cost monitoring.
- Compliance with time frames (milestones).
- Compliance with quality criteria (objectives).
- Effective use of resources.
- Adequacy of documentation.

Information

- Effective communication among project group members.
- Initiation of scientific and technical reports and documentation.
- Progress reports.
- Project presentation and justification to the management.

Management skills, certain personal characteristics and a lot of psychology are required to coordinate and control the project and to maintain progress despite the inevitable setbacks. Project managers must always think ahead, sense potential problems before they actually appear and devise measure to avoid them. Nevertheless they must be prepared to spend much of their time by solving unexpected problems and conflicts and defending their project against criticism which is raised from various sides as soon as a project does not proceed smoothly. Project managers are always in the most prominent position when problems are tackled. They are the scapegoat and need a high level of resistance against frustration. Success will be claimed by everyone.

Project managers need clear and adequate organizational structures with delegation of defined duties and authority. Delegating the responsibility for a project to the project manager means that the "ability to respond" (in French: responsabilité) must be given. Resources and authority should be at the project manager's disposition to react according to the needs of a situation. For the benefit of the project, this must include the full authority to use the planned and agreed resources plus a certain degree of flexibility in special cases - without the need for extensive discussions, negotiation and approval procedures.

The assistance and support of all project group members is essential for a project manager. Considering the fact that project managers have to impose very unpopular time, cost and quality control measures on their work, some individuals in the group may have difficulties with accepting this.

Project managers can fulfil their task only by delegating work to the project group. (There will always be enough left for them to do.) The presence of unqualified or less agile project team members reveals itself by the repeated inability of certain individuals to achieve agreed objectives and milestones or much earlier by the fact that others (usually the project managers) have to do essential parts of their job. Another indication for weak spots in the project group are people who's planning and reporting needs constant assistance and who do not actively and in time collect the information which they need for their work.

If permanent pressure must be applied to ensure that objectives are met completely and in time, this could either indicate that necessary skills are missing or that the project plan was too ambitious and unachievable. Since the individuals should know best what they can or

cannot achieve in a certain time, this can be avoided by a delegation of the planning of details (and provision of assistance where necessary) to the functional groups and to the individual project members. If the problems remain the same, the project manager faces the very difficult task of changing the general attitude and motivation of the project group. But who motivates the project manager?

For further reading about this subject the classic article "The Project Manager" by Paul Gaddis as well as the Harvard Business Review volume on Motivation are recommended (see References).

Organizational Structures

An organization which focuses entirely on only one project should not have major internal conflicts about resources. Such a "task force" represents a largely independent group within an organization with far-reaching competences, which is created temporarily and in exceptional situations to solve a critical problem or for very large projects.

Under normal circumstances different departments or groups with different skills contribute to one or several projects besides their own routine work, e.g. in research. Somebody within these departments is nominated as project leader and continues to report to the head of his department. Quite often the different leaders of these functional departments actually lead the project, each of them with a particular personal opinion and preference. An overall responsibility and a coordinating person with adequate authority is missing.

A common solution to accommodate the needs of development projects is the creation of a matrix management structure. In a matrix organization a project manager is appointed, who reports directly to the higher management and, as far as it concerns the project, is usually on an equal level with the functional managers who control the resources. The authority of the project manager reaches across the functional departments.

A matrix organization clearly puts more emphasis on project work. Since in a commercially oriented organization research projects with a higher priority than development projects rarely exist, it also strengthens development activities. In other words, if the functional departments conduct research and development, conflicts between these

two activities are usually resolved by giving the higher priority to the development project.

The matrix organization does not abolish resource and priority conflicts between different projects and their managers. If necessary, these conflicts have to be resolved on a higher level, either by the upper management or by a project steering committee. This steering committee acts as project mandator, approves project plans, decides in case of conflicts and has the overall responsibility for product development. The project managers should be members of the steering committee.

Matrix organizations provide for an efficient use of resources and a better coordination across the functional departments. However, much time must be spent on proper planning, coordination, negotiation and finding agreements about details. Project team members report at least to two bosses and have to organize, negotiate and prioritize their work between their functional manager and one or several project managers.

The individual in a matrix organization can be caught in a difficult situation and bears the unpleasant consequences if the structure does not function properly. This, as well as the inherent instability of the system, may result in a situation where the individuals disregard projects and set their own priorities.

Organizational structures and administration have a significant potential for dissatisfaction among the staff and thus may severely influence the overall performance of the organization. Table 6 lists the five major factors which can result in positive motivation or dissatisfaction at work. It was summarized from 12 different investigations and covers all hierarchical levels and jobs in various organizations (Herzberg, 1986).

The message given by this table is rather clear: Dissatisfaction seems to be caused mainly by internal structures, supervisors and general work conditions. Discontent about the salary ranks relatively low on this negative side of the list (and did not appear at all among the motivating factors!). Changing the dissatisfaction factors which are criticized only by an individual person seems inadequate because this would in most cases affect the entire organization. If, however, the majority of staff complains about such aspects, changes must be considered seriously.

Motivation can quite simply and effectively be created by the delegation of recognizable sections of work or independent parts of a project along with adequate authority to make own decisions

concerning these parts. This allows the individual to assume responsibility, creates more interest in a given job and makes sure that the individual's achievements become visible and are recognized.

Motivation appears to have much in common with biotechnological products: they both have a tremendous potential and are inexpensive and highly effective. In practice, however, their availability is limited because their application is more difficult than expected.

Table 6: Main Motivation and Dissatisfaction Factors on the Job

The five most important factors on the job which motivate or lead to dissatisfaction, ranked according to their importance.

Motivation results from:

1. Achievement
2. Recognition
3. Work itself
4. Responsibility
5. Advancement

>> Motivation is achieved on the individual level!

Dissatisfaction results from:

1. Company policy and administration
2. Supervision
3. Relationship with supervisor
4. Work conditions
5. Salary

>> Dissatisfaction must be avoided on the organizational level!

Technical Aspects of Product Development

Medicinal products must have a consistent quality in order to be reliably effective and safe. Achieving consistency in all aspects is a cumbersome technical and analytical task which takes much time and which is usually not the main virtue of research work. Scientists without experience in product development tend to neglect the technical aspects which lead to a consistent product quality.

Increasing registration requirements for the product and the production process as well as environmental issues also add a significant technical and analytical dimension to the development. This particularly applies to products derived from biotechnology. Compared to conventional biological products, the final product is usually much better defined and its manufacturing process can be better controlled. But it requires the application of a variety of quite sophisticated techniques to do so.

For most new biotechnological products, processes and analytical methods have to be newly established. This represents a major and costly part of product development. In newly founded biotechnology firms pertinent technical experience and practical knowledge about the application of regulatory requirements is usually missing and must be developed. Early information and consideration of these aspects may considerably shorten this learning process.

Process Development and Manufacturing

The active ingredient of a potential product as it was identified in research is initially produced in minute amounts and by a process which in most cases is not acceptable for a pharmaceutical product or for large-scale production. Process development represents a link between research and manufacturing and adapts the research methods to the needs of production or develops new methods where necessary. Process developers must take multiple aspects into consideration (Table 7). Their task would be much easier, if researchers were aware of these aspects.

In the worst case process development can imply that an entirely new procedure to obtain the active ingredient must be found and established. Frequently master seed stocks (cells, viruses, bacteria) must be newly generated and tested, since those from research are not suitable because

**Table 7: Process Development for Biological Pharmaceuticals:
Major Points to Consider in Process Development**

Starting Materials and Excipients

Availability: appropriate quantities, regular supply.
Quality: specifications and consistency (compliance with pharmacopoeia specifications if these exist).
Safety acceptable for a pharmaceutical product.
Freedom of adventitious agents, e.g. from human serum components or bovine serum!
Master seed cultures: quality, documentation, suitability.

Safety and Environmental Aspects

Work safety, e.g. organic solvents, aerosols containing microorganisms.
Contamination from the environment.
Contamination of the environment.
Cross-contamination and separation of activities.
Waste material decontamination and disposal.

Legal and Regulatory Aspects

Registration requirements for product and process.
Licencing of facilities.
Good Manufacturing Practice (GMP).
Infringement of existing patents?

Economical Aspects

Cost of goods.
Yields.
Recovery rates.
Investment into equipment/facility.

of their quality (contaminants, inhomogeneity) or unclear history and documentation.

Unacceptable starting materials used in research must be replaced by those which meet the regulatory quality and safety criteria. Reference to standard volumes of pharmaceutical ingredients and excipients should be made to decide whether a certain ingredient can be used. Standards are described in the pharmacopoeias of relevant countries, the "Handbook of Pharmaceutical Excipients" or its Swiss ancestor the "Katalog pharmazeutischer Hilfsstoffe". Fiedler's "Lexikon der Hilfsstoffe" (Lexicon of Excipients) provides many useful informations about the safety and about applications for excipients. (For references see Annex B to the registration requirements chapter.)

Components used and approved for human food may also be considered as potential ingredients for certain applications. Hazardous components cannot be used at all or have to be removed during the process. Special conditions (see Registration Requirements and specific guidelines on this topic) apply to the use of starting material of human or animal origin to avoid the presence of adventitious agents in the final product.

Process developers should check existing patents and patent applications in order to avoid patent infringement with any use or process patent. On the other hand, there may be possibilities to patent the particular process newly developed or critical elements of it. Economic aspects such as yields from cell culture or fermentation, product recovery after purification and cost of materials and equipment also need constant attention. Production cost forecasts should be calculated and updated regularly.

A variety of product safety, work safety, environmental safety aspects and other legal aspects must be taken into consideration when a process is designed. Good Manufacturing Practice standards for facilities, equipment, and working procedures must be met. GMP approval is subject to inspection and requires constant attention and updating. Extensive documentation must be provided to comply with these requirements.

Manufacturing facilities are approved for their specific purpose, e.g. for the manufacturing of one particular product. If it is intended to manufacture another product in the same facilities, this must also be approved and requires very strict measures to avoid any cross-contamination and mix-ups. Either the facilities have to be separated or production runs for different products have to be performed at different times with intensive cleaning and decontamination in between.

The preferred option is of course to develop a manufacturing process for an already existing manufacturing plant. If adequate and approved facilities are not available, the possibility should be considered to develop the product in cooperation with somebody who has free capacities in a suitable plant. (Many vaccine producers have free capacities.) If this alternative is unacceptable, considerable investment and time will be required to establish manufacturing facilities. They have to be planned, built, equipped and approved first, and it will be necessary to gain sufficient experience with the new plant and the manufacturing process in these facilities.

The use of existing manufacturing facilities also overcomes another common limiting factor in product development: the availability of product for test purposes and clinical trials. All critical tests must be done with a product which is essentially the same as the final product, if the data from these tests are to be used for the registration application. Research material of dubious quality is definitely not appropriate.

It may take months or years to develop a controlled process which reproducibly leads to a product with adequate quality. As a consequence, process development must start very early in the development phase. The product specifications should not simply evolve from the process; the main parameters should be fixed beforehand. This does not only provide clear objectives for process development, it also makes sure that no time is wasted by testing products of inadequate quality which may render the data obtained useless for registration purposes.

In some cases it may be unavoidable to change relevant product specifications. If major pharmacological and safety tests have already been done, it may not be necessary to repeat all of these. Comparative tests (bioequivalence studies) with the earlier and the new product should be performed to check whether both are equivalent in all critical aspects. In the case of higher standards, (e.g. for purity) this may be relatively simple, lowering these standards, however, will be difficult to

justify and requires thorough studies about the nature and the effect of the additional impurities.

Analytical Development and Quality Assurance

Quality assurance schemes for medicinal products have evolved mainly from experience. Whereas initial quality controls were carried out only with the final product - with elimination of batches which did not pass the test - nowadays quality assurance covers the entire manufacturing process and continuously develops towards a more holistic system. Presently quality standards cover everything that goes into the product (starting materials, excipients, the active ingredient and its by-products), everything that could come into contact with the product (e.g. air, water to clean vessels, packaging materials) or has the potential to influence product quality without being noticed by the usual checks (e.g. personal qualification, management responsibilities, the validity of methods, documentation). The given examples may illustrate the general scope of modern quality assurance for pharmaceutical products.

Analytical procedures have to be developed for the active ingredient as well as for starting materials and the excipients used in the final formulation. These tests should be able to specify and confirm the identity, purity, potency, stability and consistency of these materials. If significant impurities, degradation products or critical metabolites occur, analytical methods for these will also be required. In-process control methods must be devised and developed to observe all relevant steps of the manufacturing process in order to have adequate control over the inherent variants and to detect potentially harmful contaminants at a stage where they may be easier to trace.

The spectrum of tests to be employed comprises methods from microbiology, immunology, protein and peptide biochemistry, genetic engineering and physico-chemical methods as well as animal experimentation. If these exist, for example in pharmacopoeias, standard method descriptions have to be followed.

Critical steps of the manufacturing process and analytical methods have to be validated carefully. Process validation will be required for example for the inactivation or elimination of potentially pathogenic microorganisms (e.g. viruses in cell cultures) from the product. This can be done by running spiked samples through the process or through

a smaller laboratory version of the process which exactly mimics all relevant parameters. Volumes, methods and test sensitivity must be considered carefully and statistically for such experiments.

Analytical methods are validated by investigating the specificity, sensitivity, detection limits, quantification limits, accuracy (of the individual result), precision (variation between different tests), applicability and practicability under laboratory conditions and the robustness (susceptibility to interference) of the method. This enables the organization itself to employ these tests much more consciously and with better results, but it also serves the purpose of enabling the registration authorities to use these tests for the regular batch control tests. Official guidelines by the regulatory authorities for the validation of analytical methods and processes are available for consultation.

Good Manufacturing Practice (GMP) standards are a further step towards the concept of "total quality". Implementing and maintaining a GMP status requires commitment of the entire organization and constant attention by those who are in charge of quality assurance. Because of the complexity and wide scope of the subject and the amount of paperwork (some translate GMP as "Give Me Paper") extra personnel or external consultants will most likely be required.

GMP includes for example:

- The organization, management structure, personal qualifications and training;
- Standard Operating Procedures (SOPs) with appropriate documentation and implementation systems ensuring their effective application;
- Detailed instruction concerning production, packaging, labelling, handling, testing and approval of starting materials, intermediate and final product;
- Construction, infrastructure and maintenance of buildings and equipment;
- Regular inspections and self-inspections and many more details.

In general GMP guidelines are fairly similar and attempts are made to harmonize these further. Difficulties arise if different organizations and their inspectors interpret certain points in these guidelines differently. All documents released by the inspecting authorities about the interpretation of guidelines should be traced and carefully studied.

More information about GMP for pharmaceutical products can be obtained from specific guidelines and from books about this subject. A selection of these is listed in the Annex B to the registration requirement chapter.

Whereas GMP as well as GLP (Good Laboratory Practice) and GCP (Good Clinical Practice) are mainly acting on the operational or technical level, other quality assurance standards have been established by the International Organization of Standardization (ISO) to assure quality at the organizational level. Inadequate organizations with unclear tasks and responsibilities can severely influence the quality of products and services.

In the near future quality assurance elements as recommended by the quality guidelines ISO 9000-9004 will certainly also be applied to pharmaceutical developers, manufacturers and to sales organizations. A formal accreditation of compliance with these standards requires the implementation of quality assurance schemes, covering for example the following aspects of a business:

- Management responsibility and commitment;
- Organizational structures with explicitly defined and delegated responsibilities;
- Quality assurance systems covering all functions in procurement, production, control of production, handling, storage, product identification, packaging, delivery, marketing, after-sales servicing, product supervision and in "design" (design = product development and improvement);
- Identification of non-conformity and corrective actions;
- Means to ensure product traceability, facilitating recall and planned investigation of products or services suspected of having unsafe features;
- Use of statistical methods to enhance and maintain quality at all stages and of all activities in the product cycle.

It is to be expected that by the year 1996 adoption of these standards will be recommended and compliance with these will soon be obligatory. The personnel cost of implementing and maintaining these quality assurance systems should not be underestimated.

Patents for Biomedicinal Products

A patent is certainly the most adequate means to protect an invention, if a product derived from this invention can be developed and sold on the market within the foreseeable future and if one expects major financial revenues from this product. The expected revenues should be high enough to recoup the cost of product development and to justify the expense of obtaining and maintaining a patent.

The majority of patented pharmaceuticals cannot recoup the cost of product development during the life-span of their patents (Prentis et al., 1988). Thus, patents do not guarantee high profits, but -depending on their quality- patents can significantly improve the chances of commercial success of innovative products. The quality of patents does not only depend on the quality of the research which led to the patented invention, but also on the quality of the patent application and a skilful patent strategy.

This chapter describes the main characteristics of a patentable invention and of a patent application with special emphasis on patents on medicinal products of biological or recombinant origin. It is intended to help the inexperienced applicant in deciding if and at which stage of research a patent application should be made and to assist in drafting a patent application with an optimal patenting strategy. For researchers in non-profit organizations, it might be of interest to read about the opportunities for converting their intellectual property into money or into funds for further research.

As far as the subject allows, only the general principles will be outlined which apply to patents in the field of biomedical products, rather than dealing with specific cases (as the interpretation of their patentability changes with time). For practical reasons emphasis will be laid on the patent policies of the European Patent Organization (EPO) and of the USA, since these are most advanced in this field and strongly influence other countries' policies. Patents are usually applied first in the USA and in EPO countries, as they represent major markets. Important deviations from the EPO's or USA's policies in other countries will be mentioned and summarized where necessary. Alternatives to patents will also be briefly discussed.

The Purpose of a Patent

The basic purpose of the patent system is to provide incentives for innovation, industrial development and industrial investment. A patent entitles its owner to exclude others from the commercial exploitation of the patented invention for a limited time. In exchange for this temporary monopoly the public receives an accurate and detailed description of the invention, which makes the knowledge available to the public at an early point of time and, after the patent has expired, enables others to exploit the invention.

A patent does not only contain patent claims in order to exclude others from using the invention commercially, the patent specification also contains a technical teaching to solve a problem and thus contributes to the advancement of science and technology. A patent cannot be granted for something that is not innovative or is already in the public domain. Novelty, (industrial) utility and inventiveness are the three prerequisites for a patentable invention which must be fulfilled to ensure that a patent serves its purpose.

Owning a valid patent alone does usually not generate profit. Selling the patent rights and ultimately manufacturing, selling or using a potential invention may eventually yield a profit. A patent owner will only enjoy the full benefit of a patented product, if the patent is not easily circumvented and is strong enough to be enforced against infringers. However, the main purpose of a patent is not to prevent others from doing something, it is also necessary that a patent is used. Patent rights can be lost if the patent is not used in a constructive manner.

The quality of a patent, i.e. its scope, the chances to get it granted and its enforceability, is to a great extent dependent on the quality and depth of the underlying research. The most cunning patent description and wording of the patent claims cannot cover weaknesses in the research upon which a patent is based.

Due to the commercial interest in patents, their basic purpose as a means to promote science and technology tends to be neglected. Patent examiners might appear pedantic or narrow-minded when they are reviewing a patent application, but it should be kept in mind that they do so because they are protecting the interests of the public in an attempt to grant patent rights which are balanced against the contribution to innovation.

Alternatives to Patents

Most national laws provide specific legal protection of intellectual property not only for patents but also for registered designs and copyrights. Registered designs refer to the visual appearance of an industrial product. They are not suitable to protect scientific inventions aiming to achieve a certain effect or to fulfil a certain function. Copyright was conventionally intended for products of the arts, but nowadays it is also extended to instruction manuals, architectural drawings, computer software and (under special legislation) to integrated circuit layouts.

The idea of extending copyright to the information embodied by DNA or RNA molecules seems to suggest itself. However, copyright is limited to the information itself or to a certain form in which the information is presented. Copyright is not intended as a tool to control the use of the information. If genomic sequences would be subject to copyright provisions, the owner of a copyright could theoretically control all products derived from the use of these sequences by granting or withholding licences on the reproduction of the information. Copyright provisions would not exclude that the sequences may even be a product of the author's imagination or of a computer programme which generates random sequences. Without major adaptations, copyright provisions thus seem to be inadequate or useless for genomic information.

An important alternative to patents for certain minor inventions in the field of biology and biotechnology is to keep the information secret and to control its release by confidentiality agreements. It can be very useful for a company to keep a manufacturing process as a trade secret and enjoy the benefits of the developed technology as long as possible, rather than releasing patent information which might stimulate others to work around it.

Keeping research results secret for a long time is hardly a realistic option for academic scientists. However, if it is intended to patent research work, it is essential to make this decision early and to keep an invention secret until its full potential has been explored. Publications of new results in short intervals and a later ad-hoc decision to file a patent application on the same subject will, at best, result in weak patents. In the worst case, premature publications by the inventor can render patent claims or the entire patent invalid.

When patents for registered medicinal products expire, others may apply for a registration of an essentially similar product by referring to the pharmacological, toxicological and clinical data of the first applicant and without providing own data on these parts. For certain products second registrations of imitations are excluded for a limited period of time.

In the EEC "high-technology" products, including biotechnological products, which are registered according to the centralized European registration procedure are protected from second registrations for a period of ten years (EEC Council Directives 87/21/EEC and 87/22/EEC). Similarly in the USA "orphan drugs" for rare diseases or conditions are protected from second registrations for a period of 7 years. For commercial enterprises these provisions may be considered as an addition to patent protection but not as an alternative.

Basic Requirements for a Patentable Invention

Novelty

A patentable invention must be new. Novelty excludes the "state of the art" (also "prior art") which is what was "made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the ... patent application" (Article 54, European Patent Convention, EPC). Under the EPC the content of an earlier European patent application (which is not yet published) is also considered as state of the art.

All scientific publications and other written articles, oral presentations, interviews, potentially even casual non-confidential talks among researchers prior to the filing date of a patent application can be detrimental to patentability. This includes publications by the inventor anywhere in the world, therefore it is essential to check all publications before they are released to determine whether they contain anything that could be used in a patent application. Since most researchers have a confidentiality clause in their employment contract, discussions among colleagues within the same institution usually do not make the discussed matter "available to the public".

The most diligent study of all available information may not rule out the case that a patent application lacks novelty, because the matter to be patented was already subject to an earlier patent application which was not known to the inventor at that time. Patent applications in most countries are published 18 months after filing.

According to the United States patent law, "a person shall be entitled to a patent unless (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent or (b) the invention was patented or described in a printed publication in this or a foreign country more than one year prior to the date of the application for patent in the United States". (United States Code, Title 35: 35 USC §102; emphasis added). The differentiation between the point of time when an invention was made and when the patent was filed (according to the EPC only the filing date of a patent application is relevant) gives several advantages to inventors in the USA: An earlier state of art will be applied when their invention is judged in terms of novelty, and they may publish the contents of their patent application up to one year before filing. Other more important advantages of this paragraph of the US patent law will be discussed below in context with the priority date.

Non-obviousness

It is not necessary for a patentable invention to be the result of an ingenious idea. Article 56 EPC requires an "inventive step" which is "not obvious to a person skilled in the art", regarding the state of the art at the time the application was filed. Similarly in the USA "... a patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 USC, §103).

Despite the conformity of both definitions (not obvious regarding the prior art to a person skilled in the art), there is considerable room to speculate how these terms are defined in each individual case. Almost inevitably these terms are interpreted differently by the applicant and the patent examiner during the prosecution of a patent application. In the absence of official general explanations for "non-obviousness to a person skilled in the art" the following attributes may help to decide whether an alleged invention meets this requirement (see also Vossius, 1982).

For the average expert in the field an invention may

- be surprising or unexpected,
- be unpredictable,
- be unconventional or against a general prejudice of experts,
- solve a major problem or a problem that existed for a long time,
- teach a method that has been considered not feasible,
- demonstrate an advantage over prior techniques,
- be the result of a serendipity, e.g. the selection of a microorganism, cell strain or monoclonal antibody with new, favourable attributes (selection invention),
- present a new use for a known product.

The last point of the list seems to be in contradiction with the requirement for novelty. However, novelty must apply to the patented matter, which in this case would be the new use. The inventiveness lies in the fact that the new use for a known product was not obvious in light of what was known in the field.

The first really unbiased "persons having ordinary skill in the art" to judge a patent application will be the patent examiners. If they come to the conclusion that an invention is obvious (for example because it combines two pieces of well known prior art), this may be due to the

application failing to clearly emphasize the inventive step and might be overcome by providing further evidence and appropriate arguments. However, it would be better if such doubts were not raised at all. To avoid unnecessary arguments about the inventiveness of an invention, it is advisable to strongly emphasize the inventive step in applications for a patent: Almost invariably patent applications contain a separate paragraph which explains the non-obvious and surprising step of the invention, for example by quoting previous, unsuccessful attempts to solve the problem.

Utility or Industrial Applicability

Patentable inventions must be useful, "reduced to practice" (35 USC, §102) and, by legal definition in most countries, also amenable to an industrial application. The German concept of a patentable invention describes it as "*Lehre zum technischen Handeln*" (teaching of a technical operation). The Polish law even requires a strictly technical character of the invention and currently excludes from patentability any biological product as well as pharmaceuticals and chemicals, even if these derive from a technical process. The technical process which is used to make such products, however, is patentable in almost all countries, irrespective of whether these refuse to grant patents on certain or all products of nature.

According to the general purpose of a patent, its utility must be described in such detail that the average expert is able to reproduce the invention. Thus, the descriptive part of a patent application closely resembles the materials and methods section of a scientific paper. This requirement of utility prevents patents on mere theories.

The famous example of Samuel Morse's patent application for the telegraph is particularly well suited to illustrate the limitation to patentability set by the utility requirement. As an extension to his invention, Morse applied for a claim as follows: "I do not propose to limit myself to the specific machinery ... described in the foregoing specification and claims; the essence of my invention being the use of the motive power of the electric or galvanic current, which I call electro magnetism, however developed, for making or printing intelligible characters, signs or letters ..." (quoted after Bent et al., 1987). This extensive claim which literally includes still non-existing appliances ("however developed") was not accepted. Theoretically such a claim would have given Morse patent rights on electric typewriters,

photocopiers and even computers, had they been developed within the patent life.

Every patent applicant will, of course, try to extend the scope of his patent as far as possible by claiming all obvious and imaginable applications besides those which are described. Whereas the obvious extensions are likely to be accepted, speculative applications are probably claims on theories or on a principle of nature, which are excluded from patentability. Claims on theories without utility in the present form would be against the spirit of patents. They would be an attempt to control future inventions in this field and thus are not acceptable.

The first isolation and characterization of a viral protein from infected cell cultures may be sufficient to apply successfully for a patent on a serological diagnostic test based upon this antigen. If an ELISA test is described in detail, including a few results which prove that this test really fulfils the claimed purpose, it seems legitimate to extend the patent claims to variations of the described ELISA method. Most likely, extensions to other well known serological tests can also be included in the patent, since it can be assumed that the average expert in the field will be able to apply the patented protein in these methods without undue experimentation. Further claims, e.g. for a vaccine, would need to be substantiated and reduced to practice, at least by the ability to induce an immune response and some evidence that this immune response is protective in an animal model or a meaningful in vitro test.

It is currently unclear whether, based on the current state of the art, a patent following the above-mentioned example could be extended to recombinant derivatives of the native protein. One might argue that, once the native protein is known and accessible, it needs no inventiveness to sequence the amino acids for parts of this protein, synthesize the corresponding DNAs, use these as probes to identify and isolate the entire coding sequence of the protein, which is then inserted into a suitable expression system to produce the protein in any desired form and quantity. Experience, however, teaches that it still requires some non-obvious steps and usually more than a limited degree of experimentation (often even a stroke of luck) to get there and to achieve the desired utility with recombinant polypeptides. For a vaccine it may be necessary to find and express the important epitopes in an appropriate (still unknown) way and to develop adequate purification and further processing protocols (with unpredictable technical

problems) to achieve the desired and claimed protective effect in the target species.

The fact that some methods are obvious to try does not mean that the desired result is also obvious!

The degree to which utility limits a patent depends not only on the enabling descriptions or on the current technical standards. Another aspect to be considered is the characterization of the claimed substance matter. If a native protein can be defined by its exact amino acid sequence, the chances are much better to cover any recombinant form of the same protein or of one with minor, irrelevant variations by a patent on the native molecule. In this case and with today's technical standards, it may be argued that the knowledge of the amino acid sequence avoids many of the uncertainties and unpredictable problems mentioned above. The problem of limitations and possible extensions of patent claims for biological molecules is discussed in more detail in the section on patent claims below.

Inventions, Discoveries and Products of Nature

Inventions are patentable, but in almost all countries mere discoveries and products of nature as such are not. The distinction between invention and discovery, however, is difficult to define and new technological developments, e.g. in the field of biotechnology, may require new interpretations of the official definitions.

According to the European point of view, discoveries only recognize something which exists, but remained unnoticed. Thus products of nature as such can be discovered but not invented. A product of nature may be very useful, but its discovery lacks technical teaching and an inventive step, thus it cannot be patented. This does not mean that products occurring in nature cannot be patented. If, by a technical operation, a product of nature is isolated, enriched, purified or somehow changed into a hitherto unknown form and can be utilized, it can be patented. For example the discovery of a natural antibiotic effect alone is not sufficient to be patented, whereas an antibiotic which is isolated from a microorganism or which is utilized by feeding whole microorganisms from a fermentation process to animals may represent a patentable invention.

The first identification of a certain DNA sequence coding for a defined polypeptide which can be used for a diagnostic or therapeutic

purpose is in principle patentable. The construction of a link between the DNA sequence and the functional polypeptide is the result of a mental act which might be considered as non-obvious and inventive. Utility can be provided by a technical description of how the polypeptide was expressed, purified and by evidence that it can be used as a diagnostic or therapeutic agent.

For a detailed discussion and interpretation of discoveries and products of nature the interested reader is referred to the articles or editions of Utermann (1978), Bent (1982), Bent et al. (1987) and Plant et al. (1982) which are mentioned in the reference section. Recent events, however, have stimulated new discussions on this subject and it remains to be seen whether the interpretation of the above definitions will be changed.

The Human Genome Project and the decision of the US National Institutes of Health (NIH) in 1991 to file patent applications on randomly selected partial cDNA sequences of unknown function [potentially useful, for example "as genetic markers for forensic identification or for tissue typing" (utilities quoted after Eisenberg, 1992)] challenge hitherto valid interpretations of the terms discoveries, products of nature and utility. One might argue that the Human Genome Project "reads" and describes products of nature using an established methodology and without an inventive element. Even the term "discovery" may be considered as too sophisticated for the result of a repeated routine process which produces new - but hardly surprising - results, since the function of the DNA remains unknown.

Besides doubt about the inventiveness of these patent applications, there appears to be a lack of utility (a new technical teaching) of the claimed subject matter. The utility for such a vast number of cDNA sequences will most likely be based upon theoretical examples without a constructive reduction to practice. There is hardly any doubt that the intention is to use the given examples of utility to fulfil a requirement only formally but to claim patent rights on all potential utilities.

With the European Patent Convention in mind, these patent applications appear hopeless. But rather pragmatic or missing definitions provided by the US Code do not exclude discoveries from being patented. The USC states that "patentability shall not be negotiated by the manner in which the invention was made" (35 USC, §103). Based on this definition of inventiveness and generally low requirements to prove utility, it appears less hopeless to get the above-mentioned patent application granted. This is especially true if

there is a political moment involved: The applicant of these patents are "The United States of America", and in France and the UK similar patent applications were filed as a response to the US policy.

This controversial issue is discussed in more detail in three articles by Adler, Eisenberg, and by Kiley, published in Science in 1992 (see references).

Decisions on these or similar patent applications will hopefully be made with the basic purpose or spirit of patents in mind. But even if these patent applications would be granted, it is questionable whether commercial applications can be developed within the life-span of these patents.*)

Patentable Inventions and Exclusions

As a general rule, the US policy on patentable subject matters represents an extreme with the most liberal definitions. 35 USC, §101 states that "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof may obtain a patent therefor.

At the other end of the spectrum, a number of countries still exclude several inventions - mainly on food and medicines - from patentability. (For a discussion of the underlying ethical and commercial considerations see, for example, Tobias, 1992.) In the last few years many of those countries have abolished these exclusions, others also consider changing their policies.

The standard set by the EPC lies between these extremes. Many countries throughout the world have similar policies or have adopted the EPC statutes on patentable subject matter either literally or with minor modifications. It is likely that, wherever future changes of patent statutes are expected (e.g. in Eastern European and South American countries), these will also adopt at least major parts of the EPC standards.

The EPC defines patentable inventions mainly by exclusions. Parts of Articles 52 and 53 EPC are quoted here since they also reflect the view and the exclusions valid for most other countries:

- "(1)European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step.
- (2)The following in particular shall not be regarded as inventions within the meaning of paragraph 1:

*) Recently the NIH and the Medical Research Concil in the UK announced their intention to withdraw their patent applications on cDNA sequences without known function.

- (a) discoveries, scientific theories and mathematical methods;
 - (b) aesthetic creations;
 - (c) schemes, rules and methods for performing mental acts, playing games or doing business and programmes for computers;
 - (d) presentations of information."
- (4) Methods for treatment of the human and animal body by surgery or therapy or diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods." (Article 52, § 1,2,4)

Article 53 EPC also excludes "plant or animal varieties or essential biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof".

The European Patent Convention explicitly demands an industrial application and excludes therapeutical and diagnostic methods practised on the human or animal body (but not therapeutics and diagnostics or related instruments) and plant and animal varieties (but not microorganisms). None of these exclusions exist in the USA where patents are permitted on basically anything that is man-made, including agricultural or breeding methods as well as on clinical therapeutic and diagnostic methods.

Definitions like those quoted above for patentable inventions in the EPC, which are mainly based on exclusions, always appear somewhat unsatisfactory. A list of examples for principally patentable subject matters in the field of biological or biotechnological medicines may provide a more positive orientation (see Table 8). It should be noted that until recently numerous countries still excluded many of these inventions.

Several countries do not accept patents on pharmaceuticals and medicines or provide only limited patent protection. Based on latest available information, Table 9 summarizes restrictions which are relevant to pharmaceutical products.

Of course these tables should not be used as legal advice. For more specific information it will be necessary to check the latest statutory provisions, patent office policies and probably even judicial decisions

in the individual countries with a specific invention in mind. This should be left to patent specialists in the specific field.

Special provisions for a variety of inventions were established in communist states. In these cases "Certificates of Inventorship" were issued. The right of exploiting the invention commercially was usually exercised by the state. Following major political changes in recent years, most of these certificates were abolished and replaced by full patent protection.

Almost all countries and regional patent conventions have provisions that do not allow patents on the grounds that these are contrary to national laws, principles of humanity, public morality, public health, public safety and for other ethical reasons.

Table 8: Patentable Biological Subject Matter

Under the general provisions of novelty, non-obviousness and utility/technical applicability the following examples of biological subject matter with biomedicinal applications may be considered as patentable. For products which also occur in nature, this applies to a form which is isolated from nature or changed from how they exist in nature. See also Table 9 for country-specific exclusions.

Microorganisms Including Viruses

Specific strains of microorganisms.
Manipulated/engineered strains of microorganisms.
Mutants and variants of microorganisms.
Particular formulations of specific strains or cultures.

Macromolecules

Peptides and proteins.
Enzymes and hormones.
Specific antibodies, monoclonal antibodies, antibody conjugates.
Adjuvants.

Cells

Cell cultures.
Hybrid cells.

Recombinant DNA

Isolates sequences, isolated genes.
Promoters, plasmids, expression vectors.
Transformants and genetically engineered cell cultures.

Process Inventions

Processes preparing the subjects listed above.
Processes using the subjects listed above.

Products derived from processes using objects listed above

Table 9: Statutory Exclusions of Inventions from Patentability

Pharmaceuticals/Medicines

South and Central America:

Argentina*, Costa Rica, Cuba#, Guatemala, Nicaragua, Uruguay.
Andean Group (Bolivia, Columbia, Ecuador, Peru, Venezuela):
inventions relating to pharmaceutical products appearing on the list
of essential medicines of the WHO.
Brazil*, Honduras: chemical-pharmaceutical substances and processes.
Bermudas: patents which are mischievous or "inconvenient" to the
state may not be granted.

Asia: India*, Iran, Iraq, North Korea, Syria, Thailand, Turkey, Vietnam.
People's Republic of China*: chemical pharmaceuticals only.

Africa: Egypt, Ghana, Libya, Somalia, Tanger, Tunesia, Zambia.
Zimbabwe, Malawi: mixtures of known ingredients.
(No exclusions in OAPI member countries and in Algeria, Kenya, South Africa,
Uganda.)

Europe: Bulgaria#, Hungary*, Iceland*, Romania#, Poland.

Chemicals (patentability excluded or limited)

Brazil*, Bulgaria#, P.R.China*, Cuba#, Hungary*, India*, North Korea,
Poland, Romania, Vietnam.

Therapeutic and Diagnostic Methods Practised on Humans or Animals

Not patentable in almost all countries except in the USA and the
Philippines.

Microorganisms and Biological or Biotechnological Products

Bulgaria#, Cuba#, Romania#.
Poland: strict technical character of the patent required.

#: Certificate of Inventorship issued

*: Changes are under discussion

Processes for making the excluded substance matter are patentable in most countries!
Collected from Jacobs (1993) and updated by own information sources.

Product, Process and Use Patents

The separation of patent claims into those on a product, a process or on use is not only a theoretical division; in practice these three categories are of great importance for the enforcement of a patent. They differ considerably in their effectiveness to exclude competitors from using the invention.

The product patent category comprises:

- substances, e.g. adjuvants, isolated proteins or microorganisms, a cDNA sequence coding for a certain protein, (genetically engineered) cell lines;
- composition of matter, e.g. composite vaccine stabilizers, peptide conjugates, cell culture media,
- apparatuses and devices, e.g. a vaccination gun, a pulse release system.

Product patents are the key patents and generally offer the most effective protection against potential competitors. This is especially true for end products which are sold to the consumer or user, since infringement is easily detected. Less protective and enforceable are product patents on intermediate or starting products which are used during a manufacturing process. In many cases the commercial end product does not reveal the fact that a patented starting or intermediate product was used. The situation becomes obscure, when a patented product (e.g. PCR tools) was used only during the development of a commercial product. However, in most of the latter cases, patent claims which are broad enough to cover the end product of such a development stage will rarely be granted.

Process patents contain methods to prepare substances. Possible examples in the context of biomedicines are, e.g. isolation or purification methods, cell culture techniques, attenuation schemes and other more directed genetic manipulations of microorganisms, cloning techniques, and expression techniques for recombinant polypeptides. Since process patents are usually admitted in countries where certain products cannot be patented (see Table 9), process claims are a possibility to protect inventions in these countries.

Process patents can be difficult to enforce due to the fact that an infringement is less overt. Furthermore, process patents are easier to circumvent. Once a new and attractive method is disclosed, it stimulates others to invent around the disclosed process, which is legal

and even in line with the purpose of the patent system. As for all patent categories, this can be prevented by a thorough exploration of possible variations of the invention along with an adequate description, which allows broader patent claims.

But even the best possible process patent does not preclude others from exercising the invention in a country where patent protection is not available, no patent application was made, the particular invention was not patentable, or an available patent cannot be properly enforced. Since a mere process patent does not always cover the product derived from this process, the product may be imported and sold in countries which are covered by the process patent. Certain South and Central American states as well as some Eastern European countries with restricted patentability of pharmaceuticals and chemicals are the base of companies which exploit this situation, particularly with regard to products covered only by process patents.

Whenever products which are made by an invented process are new, useful and non-obvious (e.g. have advantages over existing products), the products derived from the inventive process should be included in the patent claims. Combined process and product patents are quite common, in fact many countries including the USA and the EPO extend patent protection to the products directly obtained from a patented process.

If a conventional vaccine for a certain disease exists, a new process/product patent would, for example, claim a process for the manufacture of a recombinant vaccine and the resulting new vaccine itself. Patent claims for the vaccine could be deduced from a higher purity, an improved efficacy or a reduced risk of adventitious agents. Of course, these advantages should be substantiated by experimental data or by conclusive evidence from the literature.

Process patents on improved and critical manufacturing steps, filed and granted after the initial product patent, can be used as an effective means to extend the time of patent protection for a product indirectly and at a lower level.

Use patents comprise the application of a product or process for a particular purpose. Examples for pure use patents which are independent of product or process patents are:

- the use of a known compound in a fermentation process, e.g. to enhance yields,
- the use of a known excipient or pharmaceutical as an adjuvant,

- the application of a known expression system to produce a protein.

Independent use patents offer the weakest patent protection. They almost invite others to seek possibilities to circumvent them and they do not cover the products that result from the invented new use. Wherever the necessary requirements are fulfilled, product patents should be applied for. In the first example given above, it seems hardly justified to construct product claims for (all) products made by the modified fermentation process. The excipient with adjuvant effects could probably be patented as a product patent, claiming "vaccines containing substance X as a novel adjuvant" with the non-obvious advantage of a better tolerability or efficacy over existing adjuvants. As for the third example, any advantageous characteristic of the resulting product may be used to justify a product patent.

In the USA mere use patents are not accepted. If possible, these inventions should be specified as process patents, e.g. as a "method of use".

Dependent Patents

A new patent may depend on other, earlier patents by using the entire earlier invention or elements thereof to achieve the desired result. Classic examples are improvements on earlier inventions. Pioneer inventions may stimulate a whole series of dependent patent applications.

When granted, dependent patents cannot be worked without infringing the pioneering patent. Thus the patentee of the dependent patent needs approval by the owner of the prior patent. This may be achieved by buying a licence or by a mutual cross-licence. In some countries there are legal provisions to prevent the owner of superior patents from blocking other, inferior patents. Licences must be given but are, of course, subject to remuneration by the licensee. Alternatively the owner of the prior patent may in return receive a licence on the dependent patent (reciprocal licences). If both parties cannot reach an agreement, the conditions and licence fees will be set by a court.

The Patent Application

The Patent Description

A patent application must fulfil different purposes. First, it must provide the necessary information to prove the novelty, non-obviousness and utility of the invention in order to successfully pass examination by the patent office and, if required, to defend the invention against opposition and infringement by third parties. Second, it must describe the invention in sufficient detail to enable others to reproduce the invention. Third, it must specify what exactly the applicant intends to claim.

As for scientific papers, a certain scheme has been shown to be most suitable to meet the necessary requirements, and applicants or scientists who draft a patent application for their invention are well advised to adhere to this scheme. Studying earlier patents or patent applications will enable an applicant to become acquainted with the usual form of patents. Alternatively applicants can have patent attorneys prepare the application for them.

The title of a patent describes the invented subject matter and usually also the patent category (e.g.: Therapeutic agent against disease X and process for preparing the same) and is followed by a short abstract identifying the field of the invention. The background of the invention or prior art is then described and discussed and is often quoted from earlier patents or patent applications which may be newer than scientific publications. This requires a diligently performed patent and literature search to set the invention apart from the prior art and to determine the potential novelty of the invention, as well as indicating the allowable breadth for patent claims. It should be kept in mind that granted patents or patent claims can be denied at any time during the life of a patent, if obtained by false or incorrect statements.

A short paragraph usually outlines the unsolved problem, which the invention addresses, and emphasizes the inventive, non-obvious element of the invention. This is followed by a detailed description of the invention. It is a statutory requirement that the invention must be disclosed completely so "as to enable any person skilled in the art ... to make and to use the same, ...and shall set forth the best mode contemplated by the inventor of carrying out his invention" (35 USC, § 112; similar wording in EPC, Article 83).

All materials used, including microorganisms and cells, should be identified according to a generally accepted nomenclature. The origin or method of isolation must be revealed, and all necessary

characteristics defining any biological material should be given. If necessary, drawings or formulas may be added.

Due to the diversity of microorganisms or cells it may be impossible for a person skilled in the art to repeat the invented solution without undue experimentation (a certain degree of experimentation to gain experience is acceptable) or without some inventiveness of his own. Therefore, it is mandatory in such cases to deposit a sample of the microorganisms or cells at an approved depository institution in order to provide the necessary enabling disclosure and to meet the requirements of a patent application (see below: Deposition of Microorganisms).

If certain parameters can be varied, the possible range of these variations should be experimentally explored and specified in the patent description, followed by an indication of the preferred range as demanded by 35 USC, §112 as quoted above. A description of the general methodology is not sufficient to describe and enable the invention. Specific details must be given which is generally done by describing examples and results. The broader the scope of the patent, the more specific examples will be required to teach the invention and to show its utility. It is self-evident that the methodology must reproducibly give the desired results.

A patent application ends by specifying what is to be protected in one or more claims. The exact wording of these claims is of utmost importance for the enforceability of the patent. A separate paragraph below is dedicated to the patent claims.

Patent applications are usually written in the official language of the country where the application is filed, with translations being provided where necessary. European patent (EP) applications must be written in one of the three official languages, English, French or German, unless nationals of an EPC member country choose to file an application in the official language of their country along with a translation.

Deposition of Microorganisms

Inventions involving microorganisms or cell cultures are often difficult to characterize sufficiently in writing to enable the average expert to reproduce the isolation, construction, attenuation or other processes performed with these materials. However, this does not release the applicant for a patent from the essential obligation to disclose the invention clearly and completely.

A practical way to solve this dilemma is to deposit the microorganism or cell culture at a depository which will provide samples upon request. According to the Budapest Treaty on the "International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure", such deposits can be made at internationally recognized depository authorities. The applicant is not obliged to deposit specimen(s) in different countries individually; a single deposit can be sufficient.

Having confirmed that a certain depository is recognized by the patent office of the country where the patent application is due to be filed and that the depository is able to handle the specimens in question (for safety reasons certain samples may not be acceptable in some institutions, and some countries may not accept certain biological samples for quarantine reasons), the deposit must be made by the date of filing of the application. The institution where the deposit was made, the accession number which identifies it and the date of the deposit must be mentioned in the patent description.

The depository must be authorized to dispense samples of the deposited specimen to the authorities involved in the examination of the patent application and to third parties upon request. Access to the samples by third parties (interested researchers, but also opponents) may be restricted until the publication date of the patent application (EPC members and other states) or until the patent is granted (USA). As long as the patent is valid, the patent owner may make arrangements with those requesting a sample that the sample is used for experimental purposes only and may not be passed on to another party.

Viable samples must be maintained at least during the life of the patent, usually for 30 years or 5 years after the last sample has been requested - whatever the latter is. If the depository becomes unable to maintain the deposited specimen or to supply samples, a new, identical sample must be deposited within 3 months. (This indirectly requires that the patent owners maintain samples themselves or deposit them at different institutions.)

Selected international depository authorities under the Budapest Treaty accepting bacteria, yeasts, fungi, viruses, and strains containing recombinant DNA molecules or isolated DNA preparations are listed below.

ATCC, American Type Culture Collection
12301 Parklawn Drive
Rockville, MD 20852, USA

AGAL, Australian Government Analytical Laboratories
1 Suakin Street
Pymble, NSW 2073, Australia

CBS, Centraalbureau voor Schimmelcultures
Osterstraat 1, Postbus 273
NL-3740 AG Baarn, The Netherlands

CNCM, Collection Nationale de Cultures de Micro-Organismes
Institute Pasteur
Rue de Docteur Roux 25-28
F-75724 Paris Cedex 15, France

DSM, Deutsche Sammlung von Mikroorganismen und Zellkulturen
Mascheroder Weg 1b
D-38124 Braunschweig, Germany

NIBH, National Institute of Bioscience and Human Technology
Ministry of International Trade and Industry
1-3, Higashi, 1-Chome
Yatabe-machi, Tsukuba-gun, Ibaraki-ken 305, Japan

A complete list of approved, international depositories is given in the PCT Applicant's Guide (see references), detailed information about conditions and restrictions is summarized in the "World Directory of Collection of Cultures of Microorganisms" edited by Staines, McGowan and Skerman.

Patent Claims

A patent must end with one or more patent claims which describe the patented subject matter as unambiguously as possible. Patent claims may be considered as the definition of the patent scope for legal purposes. The precedent patent description has to justify all aspects of the patent claims and will be used for this purpose during the examination process. But only in cases of doubt will details of the patent description be used later on to interpret the patent claims. Thus, patent claims must be formulated with the utmost care. The three basic requirements novelty, non-obviousness and utility have to apply to

anything that is covered by the claims and should be used to check the drafted claims.

On the other hand, patent claims should read as broadly as possible to cover all patentable aspects of the invention. In practice, this conflict between the inventor's intention to keep patent claims as broad as possible and the public's interest to grant patents only on what has actually been invented, disclosed and reduced to practice, has led to the situation that patent applications contain rather broad claims which are subsequently narrowed down during the examination process.

Since patent examiners on their own initiative cannot recommend to extend the scope of the proposed patent claims, it is probably best to reach for a maximum in the patent application and revise the claims according to the objections from a patent office. However, it is useless to go too far, e.g. by extending patent claims to mere principles, products of nature or undisclosed analogous subjects as well as to known and obvious things.

Japan and the USA formally limit the protection of a patent to what is literally defined by the claims. In the USA "equivalents" are also covered by a patent, i.e. infringers using equivalents may be sued. Equivalence is defined by the US Supreme Court as doing "substantially the same thing in substantially the same way to get substantially the same result" (Graver vs. Linde, 339 U.S. 605, 608, 1950) as a patented invention without literally infringing it.

The "Doctrine of Equivalents" applies to the interpretation of claims to establish infringement of existing patent rights in those cases where there is no literal infringement. Anything that comes under the definition of equivalents would have been patentable at the priority date (and should be included in the claims). Thus the Doctrine cannot be used as an argument to negotiate broader claims for a patent at the time of application or prosecution (Kushan, 1992).

The requirement to exactly define and limit the scope of a patent has implications for patents on biological molecules because it leads to patents which can be easily circumvented. This is illustrated by the following example: A polypeptide X is claimed and defined by its complementary DNA (cDNA) sequence. An equivalent according to the above-mentioned US definition and covered by this claim, would be the same polypeptide which is expressed by a modified cDNA, containing different base sequences but coding for identical amino acids. Polypeptide X with an exchange of amino acids would currently not be considered as equivalent since innumerable analogs would be possible

and the patent description would be unable to specify the scope of the patent. For example over 3600 different analogs of the erythropoietin molecule can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids (Amgen vs. Chugai, as discussed in Kushan, 1992). Furthermore, it is possible that an exchange of amino acids might alter the entire molecule in its three-dimensional structure and function. A molecule with such an exchange would not be substantially the same.

This opens up many possibilities for introducing minor variations into patented polypeptides with the aim of circumventing existing patents. One way to avoid this or at least to make it more difficult, would be to test and patent variants having the same effect or to identify the functional region or the most relevant epitopes and claim these specifically. This can be an endless task and does not seem practical for most molecules.

Another possibility would be to define the molecule to be patented by its function and claim forms of this polypeptide having the same function. Highly innovative patents will have better chances with this approach than less innovative ones. In the USA this may be considered as an attempt to claim patent rights on the end result rather than on the particular means by which the result can be achieved. Except for pioneering inventions, functional claims without sufficient qualifying structural elements are usually rejected, since these do not define the patented novelty with a reasonable degree of particularity and distinctness (see US Manual of Patent Examining Procedure, "MPEP", 5th. ed., Rev. 9; 706.03 c,d, 1988).

Due to the different policies in the European countries, the chances of achieving a broader patent protection, for example based on functional claims, are somewhat better. The European Patent Convention partly reflects the German patent policy with stronger emphasis on the protection of the basic idea of the invention ("Erfindungsgedanke"). According to the EPC patent claims should not be applied by the strict literal meaning of the wording used in the claims - nor should claims serve only as guidelines. Of course this does not mean that a proof of technical applicability or an exact description of the patented subject matter is not required.

In practice broader claims in European patent applications on biological substance matter have a better chance of being accepted, although they extend, for example, beyond the disclosed DNA or amino acid sequence (e.g. to related molecules from other species which can

reasonably be expected to fulfil the same purpose). Acceptability will be improved if the extensions are supported by at least some experimental evidence. For claims extending to not exactly defined DNA or amino acid sequences, such evidence may be presented by means of cross-hybridization results or by showing cross-reactivity of antigens.

Giving numerous examples for the exact wording of successful patent claims would require discussing these at length along with the disclosed description and the state of the art at a particular time. An idea of patent claim formulation for a specific invention can be obtained by studying recently granted patents which are related to one's invention and by seeking advice from specialized patent attorneys.

If patent claims on highly variable biological molecules are restricted to the literal wording of the patent claims and if functional language is rejected, these patents may become useless. Many conventional biological pharmaceuticals were considered as generics because, under the existing patent policies, they suffered from insufficient patent enforceability. Technical advantages over competitors, kept as trade secrets, were more effective than patents.

Modern products from biotechnological processes will probably be even more affected by insufficient patent protection. They usually require higher investment into research and development and thus need better protection against product piracy than mere trade secrets. It is likely that imitators of successful products will emerge as soon as the technical risks are eliminated by pioneers and analogous products can be developed without the initial high rate of failure experienced by the first developer. This may take ten years or more, but the encouragement for imitating products is dependent upon the current policies and the present approach to patent claims and their scope for biological inventions. It appears that the EPC guarantees a slightly more adequate patent protection for this eventuality than does the US system.

Filing a Patent Application

A draft of the patent application by the inventor usually requires several amendments and must be transferred into the correct form before it can be filed at a patent office. The scientific part of a patent relies largely on the inventor(s), but patent specialists should be consulted to help drafting the claims, to decide on the countries where

an application should be made and to attend to the formal aspects. These formal aspects (abstract length, paper format, filing procedures, authorization documents, priority date declaration, payment of fees, time limits, etc.) are sometimes extremely detailed and differ from country to country.

After submission to a patent office, the file is examined for some basic formal requirements and, if adequate, is given a filing date. A first indication about the chances of a patent application may be obtained from a search report which is issued by the European Patent Office and also for international patent applications under the Patent Cooperation Treaty (see below). In most cases, the search report will list a number of earlier patents or publications and indicate whether these interfere with the proposed claims of the examined file. As a consequence of the search report the applicant can amend the proposed claims before the examination is initiated.

A substantive examination for patentability (novelty, utility, inventiveness) will be performed by a specialized patent examiner or a group of examiners and an official report will be issued. Quite frequently the official report indicates a complete rejection of all proposed claims. The applicant has the opportunity to review the references cited in the official report and comment on the validity of the conclusions drawn. Most patents and publications quoted should already be known to the inventor and should have been considered in the "background of the invention" section. If these appear in the report, it is a good indication that the invention was not convincingly set apart from the prior art. Further evidence (i.e. more detailed arguments or further supportive literature) can be provided illustrating that the invention is novel over the prior art. (Objections on the grounds of a lack of utility are rare.) The patent office will consider the response and, if matters remain outstanding, will respond with further official action. Some countries have general time limits for this process, some other countries limit the number of rounds of official action and response by the applicant. If the initially proposed broad claims cannot be defended successfully during this process, it will be necessary to amend them according to the examiner's objections or to abandon individual claims or even the entire patent application.

The prosecution procedure of official action and responses may be repeated in all of the individual countries where a patent application was filed. Fortunately, international patent cooperation treaties exist to shorten and simplify this awkward process for both sides.

The International Patent Cooperation Treaty (PCT) created the opportunity to file a patent application almost world-wide (most countries accept PCT applications) at international patent registration offices which are usually identical with the national patent offices. A search report summarizing relevant prior art will be issued and, if requested, a preliminary examination considering the prior art is performed. The preliminary international examination provides a non-binding opinion whether the claimed invention appears to be novel, inventive and industrially applicable. It does not investigate the patentability according to any national law.

The International Patent Bureau in Geneva initiates the submission of the application in all designated member states, for which the application is intended, thus saving a considerable amount of time, effort and cost. However, due to the differences of international patent laws, the definitive substantial examination and granting of a patent applied for under the PCT is still in the hands of the individual countries.

A "PCT Applicant's Guide" is issued by the International Patent Organization in Geneva.

The European Patent Organization (EPO) provides a system for the application and granting of a patent for all designated member states at only one authority. Members of the EPO are Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, The Netherlands, Portugal, Spain, Sweden, Switzerland and the United Kingdom. Norway has not yet ratified the European Patent Convention.

Patents granted by the European Patent Office in Munich and in The Hague confer on its proprietors the same rights as a national patent. Since the contracting countries have adapted their national laws, only one examination process takes place and only one common certificate is issued. Applications filed under the PCT system may also designate EPO countries.

Similar to the European Patent Convention are two African organizations, joining English speaking countries or former French colonies by a common patent application and examination system.

The African Regional Industrial Property Organization (ARIPO) has a central registry in Harare, Zimbabwe, which examines patent applications and notifies member states on favourable examinations.

Member states can object to granting a patent in their territory, a provision which is necessary because member countries have no common policy on certain statutory exclusions of patentable subject matter. Member states of the ARIPO are: Botswana, Ghana, Kenya, Lesoto, Malawi, Sudan, Swaziland, Uganda, Zambia and Zimbabwe. Sierra Leone, Somalia and Tanzania have not yet signed the Harare Protocol.

The Organization Africaine de la Propriété Intellectuelle (OAPI), also referred to in English as African Intellectual Property Organization (AIPO), with its central office in Yaounde, Cameroon, issues only one single patent which is valid in all member countries. The general patent policy in the OAPI is comparable to the EPC. Member states of the OAPI are: Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Ivory Coast, Gabon, Guinea, Mali, Mauretania, Niger, Senegal and Togo.

International (PCT), European (EP) and most other national patent applications are published 18 months after the priority date. PCT and EP applications are published along with the search report. (If a search report is not available at that time, it will be published separately.) This publication offers third parties the possibility of inspecting the file upon request and to inform the patent offices about their related observations. These must be considered by the patent office and will be transmitted to the applicant.

Considering the fact that the time between the patent application and the granting is normally around 5 years, the publication of an application also provides a means to inform the public as early as possible about the technical progress of the invention which, after all, is one of the main purposes of the patent system.

After being granted, the final patent description is published again. Within a limited time an opposition can be filed by any interested person. The window of time to oppose is between 9 months for EP patents and only 3 months for Australian patents.

Patent applications in the USA are not published before they are finally granted. As a consequence, attacking these patents is possible at any time thereafter by requesting re-examination by the US Patent Office or before a court.

Although it is theoretically possible for an individual to file a patent application, it is in most cases necessary and strongly recommended to

entrust a patent attorney with this task. Only a specialist can oversee all the formal and legal requirements of the patenting process and make sure that fees are paid in time and time limits to respond to the patent office will be kept so that patent rights are not lost due to formal mistakes and errors. Due to the different situation in other countries and the requirement to provide a local contact person, the patent attorney on his part will liaise with colleagues overseas to handle foreign patent applications. This delegation of work has, of course, its price but the applicant will soon appreciate the advice and support provided by a specialized patent attorney. Nevertheless the inventor must be prepared to spend some time during the next few years defending a patent application by scientific arguments.

Priority of Patents and Continuation-in-Part

A patent application is assigned a priority date for the art disclosed in the application. Any aspect of the patent application which was known to the public before the priority date cannot be claimed as an invention. From the priority date onwards the knowledge contained in a patent application must be considered as prior art and excludes others from any attempt to patent the same subject matter. In general the first filing of a patent application establishes the priority. Referring back to the initial priority date, further applications in other countries can be made within a period of usually 12 months. Applications first filed in the European Patent Office or in individual PCT member states can also be used to claim a priority date for a PCT application.

Although the same basic rules on the priority apply to USA patent applications, two special provisions of the US patent laws should be mentioned which have some influence on the effective priority date of an invention.

Until a US patent is issued, a "Continuation-in-Part"(CIP) may be filed by the applicant. The same or a similar invention is refiled with new information which may enable the inventor to change or extend the patent claims and to better define the subject matter and its use. If the CIP is based on the same invention and not on later art than the original application, the priority date of the first application may be maintained. To retain the priority is, in fact, the intention of most CIP applications. New patent claims which are based upon information added in the CIP ("new matter") will get a separate, later priority.

Similarly, in Australia, a provisional patent application can be lodged to establish priority; the complete application must be filed within 12 months.

A second exception in the USA which influences the effective priority date of an invention (but not the official priority of the patent!) is the so-called swearing-back according to the Code of Federal Regulations, Title 37 (37 CFR, 1.131). If there is an interference with other patents or patent applications, the US patent authority will ask the applicant of USA-derived inventions to provide detailed information on the actual time of conception of the invention, reduction to practice and on all further steps which finally led to the current application. Proof of those activities can be provided by laboratory notebooks and other relevant documents, e.g. those which prove the involvement of a patent attorney during the process of drafting and filing the application in question. This information will be considered in order to assess the effective time when the invention was made and when it was reduced to practice in order to fulfil the requirements for patentability.

This "Rule 131" only applies to inventions made and reduced to practise in the USA. Applicants from abroad have a clear disadvantage because they can only claim the official priority date in cases of conflicts in the USA. This, along with the long time lag until a US patent is finally published, urges applicants from abroad to file patent applications in the USA as early as possible, probably exploiting the possibilities of a Continuation-in-Part later on.

Duration of Patent Protection

Patents may be valid for 10 up to 20 years, depending on the individual country. With a few exceptions the patent duration starts at the time of filing of the application. EPO and OAPI countries as well as most other countries, including Canada, the Commonwealth of Independent States, the Czech and Slovak Republics, South Korea and Mexico, offer patent protection for 20 years from the date of filing. Patents in the USA are valid for 17 years after issue. In Japan patent duration is limited to 15 years after issue with a maximum of 20 years between the filing of the application and the end of the patent term. Patent protection in Australia and New Zealand is 16 years from the filing date.

Countries which offer a shorter patent protection (10 - 15 years) are mainly South and Central American countries. These countries also exclude patents on medicines and pharmaceuticals (see Table 9). In the

last few years many countries with short patent durations and other restrictions have changed their patent laws and in most cases have adopted many of the EPC standards.

In almost all countries (except the USA) there are legal provisions to prevent the abuse of patent rights by either not using ("working") the invention or by not granting licences to others to work the invention. If the holder of a patent fails to prove that the patent is worked in the country within a reasonable time (usually after 3 to 5 years) or does not provide sufficient evidence that the patent could not reasonably have been worked (e.g. due to regulatory conditions for pharmaceuticals), this may result in a compulsory licence being granted to a third party prepared to work the patent, at terms set by the authorities. Import of a patented product is not accepted by some countries as being sufficient to comply with the requirement to work a patent.

Extension of Patent Terms for Pharmaceuticals

Patents which are related to pharmaceuticals can provide a significantly shorter effective protection for the resulting products, since a considerable time of the patent life may pass before all conditions for the market approval of pharmaceutical products are fulfilled. For such cases, some countries extend the patent duration of pharmaceutical patents to cover or offset the time which is lost during the registration of the related product. Possible extensions are equivalent to the time required to get market approval but are not meant to compensate for time losses associated with the technical hurdles of product development.

Extensions of patent duration for pharmaceuticals are available in the following countries:

Australia:	maximum 4 years, for human pharmaceuticals only.
EPO countries:	maximum 5 years.
Japan:	maximum 5 years, if working delayed for more than 2 years.
New Zealand:	no specific time (and product) limitations.
USA:	no specific time limitation.

It should be noted that applications for a patent term extension must be handed in as early as within 60 days (USA) or 6 months (EPO) from product approval.

Opposition against Patents

In most countries the formal process of patenting includes several regulations and steps which enable third parties to prevent the grant of patents which are not justified. These steps are: early publication of a patent application, publication of the search report, access to the files upon request, provision of an objection period after publication of a patent grant and finally the possibility to submit objections against granted patents.

During the early stages of patent examination anyone may submit information relating to a patent application that has been published. This information will be considered by the patent office and will also be forwarded to the applicant. Since most patent claims are modified during the examination procedure and many patent applications are withdrawn, it seems more relevant to file an opposition against a patent as it is published after acceptance - as far as this is still necessary.

A patent opposition may be based upon evidence which shows that an invention lacks the basic requirements for a patentable invention and may aim for the invention as a whole or for individual claims or the scope of such claims.

Lack of novelty may be indicated by all kinds of earlier publications or other disclosures of the invention to the public. As already mentioned, prior publication by the inventor or applicant also interferes with novelty and can be used as an argument against their own patent application. This does not fully apply to US inventions, the content of which can be published by the inventor within 12 months before filing a patent. Novelty of an invention may also be contested by the proof that the invention was already in use, for example, as a manufacturing process which was kept secret.

Oppositions on the grounds of obviousness also depend on earlier publications, patents, and other evidence which demonstrates that the invention could have been deduced by a person skilled in the art without an inventive step. Objections against the utility of a patent are rare, because in most cases it will be very difficult to call into question that the subject of the invention will (also in future) be of no use.

Evidence that the patent description does not sufficiently enable others to reproduce the invention to the extent given by the claims can be used successfully to render an entire patent or certain individual patent claims invalid. In practice, this would be a very expensive and difficult exercise, however, this situation can emerge if two competitors simultaneously work on the same invention.

The inability (as well as the unwillingness) of the owner of a granted patent to use or "work" the patent may result in a loss of privileges provided by the patent. Whereas some countries require a proof of working in regular intervals, other countries take actions against the owner of such a patent only upon request of a third party. This includes cases in which a third party is in a position to practice and exploit an invention while the owner of the patent is not (yet) able to use it. In such a situation a compulsory licence will be given to the objecting third party.

Patent Costs

The costs of filing and maintaining a patent vary, of course, from country to country and depend on the complexity of any particular case. Thus, only a few examples and estimates will be given below.

Applications for a national patent or at the International Patent Office may cost up to an equivalent of US \$ 3,000 per application for a search report and the examination. A similar amount can be assumed for the involvement of a patent attorney as long as only formalities are concerned. Creative work by a patent attorney office (e.g. formulation of the claim or of defending statements) as well as translations result in the extra cost of about US \$ 100-300 equivalent per hour, depending on the qualification of the person who deals with it. Thus, the effective cost of the patent application may rise up to US \$ 8,000-10,000 per country. Annuities for a national patent are raised as a constant rate per year or increase during the life-span of a patent. The figure of US \$ 100-300 per year and country (or per patent certificate from international patent organizations) may serve as a clue for what must be expected.

Patent office fees may be reduced to 50 or 60% of the normal fee, if the applicant agrees to a "license of right" notation, in which case everyone may obtain a license to exploit the patent. If no agreement can be found with the patentee on the terms of such a license, the terms will be set by the court.

While the above-mentioned estimates assume that the patenting process is rather straightforward, considerable expenses must be anticipated if an opposition has been filed, or if an interference is to be expected in the USA. Due to the complicated procedure, especially of a US patent interference, several ten or hundred thousand dollars are spent readily and the entire cost of an interference procedure may well

exceed one or even several millions, especially if the case is fought in court. Direct negotiations between the parties involved may settle such cases easier, provided that compromises are acceptable.

Patent Information

Any serious research effort directed towards achieving a commercial reward and patent protection needs assistance from adequate information services. Besides the scientific literature, related patents and patent applications must be available and can be traced through patent data bases and patent libraries. Computerized patent data bases (Table 10) usually contain all front page information of a patent or patent application, such as patent number, applicant, inventor, filing and priority date, title of the invention and the abstract, in some cases also the patent claims. Full copies of selected patents can be ordered from national patent libraries or from the patent office.

If a scientific library does not provide an online patent and literature service, the patent office library may be approached directly. Patent attorneys may also offer a patent search service. Furthermore, contacts with companies which are interested in the field may be established in order to use their patent information network.

Compared with the cost of fruitless re-inventions, the expenses of patent searches are minute and comparable to scientific literature searches. The information obtained may be extremely valuable considering the fact that patent descriptions usually are very detailed and may also refer to alternative methods and possible variations of important parameters.

Table 10: Major Patent Data Bases

File	Host	Scope	From
EPIOS (INPADOC)	Orbit, EPO Vienna	international	1968
CA- FILE	STN	international	1967
WPI/WPIL	Orbit, Dialog , Telesystems Questel	international	1963
CLAIMS/CITATION	Dialog	USA	1947
CLAIMS/ US Patent Abstr.	Dialog, Orbit, STN	USA	1950
JAPIO	Orbit	Japan	1976
PATOS	Bertelsmann	Germany	1968
PATDATA	BRS	USA	1975
FPAT	Telesystems Questel	France	1969
PATDPA	STN	Germany	1981
EPAT	Telesystems Questel	Europe	1978
BIOTECH ABSTRACTS	Orbit	international	1982

Check List for Prospective Patent Applicants

Considering all aspects discussed above, the applicant for a patent should respond positively to the following questions. These may serve as a check list whether an invention should be patented at the current stage.

Negative or questionable answers indicate weaknesses, which may result in unsuccessful patent applications or in weak or unattractive patents. Activities for improvement should be considered, e.g. by discussing the proposal with patent and marketing specialists or by additional, targeted research.

	<u>yes</u>	<u>no</u>
1. Has a complete and up-to-date patent and literature search been conducted?	<input type="radio"/>	<input type="radio"/>
2. Does the invention meet the requirements of novelty and non-obviousness?	<input type="radio"/>	<input type="radio"/>
3. Does the invention have commercial or industrial applicability?	<input type="radio"/>	<input type="radio"/>
4. Are the intended patent claims sufficiently broad to avoid an easy circumvention of the patent?	<input type="radio"/>	<input type="radio"/>
5. Can a commercial product based upon the invention be developed and marketed before the life-span of the patent expires?	<input type="radio"/>	<input type="radio"/>
6. Is (are) the resulting product(s) likely to render sufficient profit to recoup the patenting and development cost?	<input type="radio"/>	<input type="radio"/>
7. Is the invention patentable in those countries which represent the major markets for the resulting products?	<input type="radio"/>	<input type="radio"/>
8. Is the applicant of the patent prepared to pay the expenses of patenting and to actively sell the invention or are there potential licensing partners who are prepared to promote further development and marketing of the resulting product(s)?	<input type="radio"/>	<input type="radio"/>

Selling an Invention, Licences and Royalties

Most inventors are not independent private persons but employees of a company, institute, university, or the state. Inventions emerge from work for which they are paid or were the objective of their work. Thus, the resulting patent rights belong to the employer. (However, the inventor(s) must be named on a patent.) Many employment contracts for researchers contain specific provisions which transfer the rights to commercially exploit inventions to the employer.

The question arises whether there is any incentive for an employed researcher to patent an invention, apart from the contractual obligation to do so as an employee. Filing and defending a patent often results in a lot of additional work for the inventor which in the case of a patent defense may be related to work done months or years before, while the inventor's research proceeded in the meantime. Publications on the subject and on later improvements may be held back in order to avoid supporting potential competitors. Thus the interest of a researcher to patent an invention interferes with the interest to publish and to turn the attention to new research fields. Specific measures by the employer, for example a bonus for a successful patent application or other awards, but at least an adequate recognition of the achievement should be considered as incentive for inventors. In this context it is noteworthy that a rather unique law in Germany entitles inventors to compensation payments by the employer.

If the employer is not interested in making use of the invention, the inventor is usually free to file a patent application himself and at his own expense. Otherwise, the employer will act as applicant, in which case it is most likely that a legal/patent/licence department and a patent attorney will provide the necessary support. Many universities and government funded institutes have established independent groups, departments or even companies in order to commercially exploit the inventive potential - especially in biotechnology - directly. These organizations may also provide service and advice in patenting.

In the absence of adequate support to file and defend patents, individuals or institutes may decide to approach companies with the aim of licensing the invention. This is often done already before the draft stage of a patent application. The invention as a whole may be offered to the company, in which case the company may act as applicant or licensee of the patent and will request exclusive exploitation rights in exchange for the payment of patenting costs and for later royalties.

Continuous payment of the patenting expenses by the company will ensure that the industrial partner of such an agreement does not lose interest in the project but nevertheless keeps the patent. As an alternative joint ownership of the patent can be negotiated. Provisions may be included in an agreement to the effect that the licence of the patent shall be terminated if the company does not wish to exercise these rights or does not exert serious efforts to develop or market the invention.

The main advantages of such agreements are that the inventor avoids the patent costs in a stage where the chances of getting a patent are still unclear and that the industrial partner has early access to the invention and may gain a significant advantage over competitors. These agreements also often link the two parties together in a common research and development project in which both have a strong interest in a fast and efficient commercialization.

Joint development agreements in which both partners share effort and cost can be of significant benefit for both sides because of the necessity to cooperate early and closely and to exchange information in two directions. If researchers agree to participate in the further research and especially in the development-related activities which are funded by the industrial partner, it must be anticipated that tight time schedules must be met and that funds are dependent on the accomplishment of certain tasks or measurable milestones.

In the case of major inventions the inventor may prefer to apply for a patent without foreign participation and try to sell non-exclusive patent rights to different industrial companies or to negotiate country-specific or use- and indication-specific exclusive agreements. At first sight this looks much more attractive for the inventor and may be possible for important inventions which can be split into reasonably sized, separate market segments. Any attempt to do so with minor inventions will most likely result in much less interest of the industrial partners and lower royalty rates for the inventor. Similar development cost will be calculated against smaller market shares due to restricted market access and immediate competitors and the overall benefit for all will be smaller.

Of course, the strength of the patent strongly influences the position of the inventor during licensing negotiations. However, in order to improve one's position it is not recommended that negotiations are delayed until a patent is granted. The long time lag between application and the issue of a patent would delay the development of the related product and could lead to the loss of a major competitive advantage.

The effective patent protection would be shortened and less valuable. A favourable search report, however, may be useful to considerably strengthen the position of the patent applicant.

Possible variations of licence contracts are lump sum payments (the licence is sold for a single, larger payment), royalties on sales, and combinations of up-front payments or option payments in certain intervals with royalties.

Reasonable agreements which are satisfactory to both contract partners for the entire life-span of the patent are the result of negotiations in good faith. The industrial partner needs to know all technical details and the scientific background of the invention, its gaps and technical risks and the inventor's party should be informed about the potential market expectations and especially on the product requirements on which these are based. If definite products can be envisaged, estimates of the development and manufacturing cost for the product and information on trade relations of the company, transfer prices, sales cost, and customary trade margins, may be helpful to establish optimal agreements for both sides.

For those who believe that after deduction of all cost the profit margins are still "huge", it may be necessary to mention that for real key patents (which cover a whole new area and are rare in the field of biological or biotechnological inventions) the usual licence agreement aims at a 50% profit share. This may probably result in royalty rates of the order of 10% of the sales. Standard royalties for "dominant" patents that cover a whole product class, are more likely to be around 5%. Less significant patents may render 2-3% royalties and improvements of existing methods or products may even be valued below this. The above figures are mentioned to give potential inventors an idea about the dimension of royalties in general. They are not intended to serve as a guideline for licence negotiations, which should be based on detailed information and sound calculations.

Registration Requirements

During the last few decades, pharmaceutical regulations in the western world soared to a degree that the system now faces substantial problems. Despite proliferating staff numbers and cost in industry and at the authorities, there is currently a massive backlog of unevaluated registration dossiers. The evaluation periods can last several years. If the increasingly complex registration regulations are not applied with flexibility, the system has the potential to paralyse progress and to become inoperable for both the regulated industry as well as the regulating authorities.

The registration of medicinal products is governed by relative values which cannot be clearly defined or limited, for example by ethical considerations and the endeavour to ensure the best possible quality and safety of pharmaceuticals. What is possible and achievable, may soon become a standard by which subsequent products will be measured. This leads to continuous and desirable improvements, but since there is no limit, very costly and undesirable extremes may be another consequence. According to today's standards, the most successful and beneficial pharmaceutical products, such as the vaccinia virus vaccine, live poliovirus vaccine and other live vaccines, would probably not be registrable for a wide-spread use in humans.

The technical and analytical progress of the recent decades as well as the increasing safety requirements became standards which have been laid down in various legal documents and persuasive recommendations. During the late 80's the flood of newly issued registration guidelines reached its peak. Due to the detailed nature of these documents, the diversity among different countries increased.

Triggered by the consolidated EEC regulations, attempts to harmonize the international registration requirements finally found sufficient support and led to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which at the moment concentrates on a harmonization between the leading pharmaceutical producer and user countries, the USA, EEC and Japan. The ICH can only identify the differences and make recommendations for harmonized procedures and requirements. It can take several years, until agreements are found and implemented in the national regulations. But even if guideline are harmonized it is to be expected that substantial differences between countries will remain, for example with

respect to the interpretation of results and to different attitudes and practices in different countries.

With this in mind, the following chapter endeavours to give an overview and basic understanding of regulatory requirements by pointing out the common elements which are applicable in most countries and to most products. But in order to understand the complexity and diversity, it is necessary to mention and to discuss the details and differences as well. The topic of preclinical pharmacology and safety testing was selected to illustrate the "devils in the details", since this development phase represents as a very costly element of the development. However, the diversity of regulations is not limited to the safety requirements. Substantial differences also exist in quality specifications and related methods as well as in the clinical and efficacy requirements and procedures.

To achieve the necessary level of information which is required to develop a product, the relevant guidelines have to be studied and compared with a specific product and question in mind, and latest trends and opinions have to be gathered from experienced people in the field.

The appended tables in Annex A summarize the main regulatory requirements for pharmaceuticals for man and animals and may answer many initial questions. Those who need more detailed information should consult the information sources and references listed in Annex B to this chapter.

Three Basic Elements

Market approval or registration of a pharmaceutical product depends on the fulfilment of three main requirements:

Quality
Safety
Efficacy

This sounds fairly simple, but these three basic terms must be interpreted in a very wide sense; every single aspect within these categories must be substantiated and proven under practical conditions. The scope and definitions change with time and with scientific, pharmaceutical and methodological progress.

The definitions for quality, safety and efficacy vary between product groups, countries, authorities and between people within authorities. In fact, there are no exact definitions at all. There are directives, guidelines and recommendations describing what must or should be done and which data should be provided, but the application for marketing approval is judged on relative criteria.

Quality - as far as it can be judged independently of safety and efficacy - is in principle assessed by a comparison with the state of the art, i.e. with similar products. Products with inferior quality than other products may need improvements before they can be registered, products which surpass current standards will raise the general standards. Safety and efficacy, too, are no absolute values which can be easily defined. Market approval depends on a reasonable relationship between safety and efficacy, between risks and benefits.

Quality, safety and efficacy are no independent criteria. The quality can significantly affect the safety and efficacy. A highly efficacious and beneficial product may be acceptable, even if it has serious side-effects. Keeping these interdependencies in mind, product development must address and emphasize the three basic registration requirements in the same order as listed above, starting with the product quality, although project risks suggest a different strategy which concentrates more on efficacy. Without a defined quality, all safety and efficacy tests may be irrelevant, and without an adequate safety, efficacy trials under natural conditions cannot be carried out.

Quality

Quality does not only comprise the final product itself and its attributes that can be tested. The high variability, in particular of biological products, demands that all variables of the manufacturing process are evaluated. Product quality commences with the starting materials and their attributes, runs through the entire manufacturing process and extends to the manufacturing facility and its infrastructure.

Everything that can affect the product quality must be assessed, tested and documented. For example, if one intends to harvest a product continuously from a culture, it must be specified what "continuously" means. If it is intended to harvest a hundred times over a hundred days, one has to prove that the product is still the same after the hundredth harvest - and probably even beyond that limit to add some safety margin.

Of course, it is necessary to validate all in-process control and product quality control tests, i.e. to substantiate that the tests really measure what they are supposed to do and within which limits.

All claims on product safety and efficacy depend on the specified quality; if the quality is not consistent, the safety and efficacy may not be the same. Safety and efficacy data for the product are only valid if they were established with material of the specified quality. The practical implications are that test material must meet the relevant specifications of the final product before safety and efficacy data can be generated. For biological products, this means that the test substances have to be made by a process which must not deviate from the final manufacturing process in essential elements. If the manufacturing process is changed during the development, all previous data with earlier material may be worthless, unless bioequivalence can be proven.

In order to emphasize the importance of a product's purity for its quality, the US FDA tends to mention purity as a fourth basic registration requirement and put purity on the same level than quality, safety and efficacy.

Safety

Safety of a product comprises any aspect of its production, use and disposal. This includes the manufacturing premises and their environments, starting materials (especially cells and microorganisms), the active component of the product as well as metabolites, impurities

and the excipients. Excipients are components which are added to the product, for example preservatives, vaccine adjuvants, stabilizers, emulsifiers and release controlling substances.

Safety of the manufacturing process and the facilities is covered by a variety of regulations concerning the layout of facilities, work organization, procedures and related controls and inspections. General national regulations on work safety and biohazard control measures, specific regulations for manufacturing pharmaceutical products and quasi-legal GMP requirements have to be applied. These are an inherent part of the registration dossier and market approval to ensure consistent quality and safety of the product and its manufacturing.

Safety of the product itself for the target organism, the user (who applies it) or the environment is addressed by a range of preclinical and clinical assessments which depend on the product and its use pattern. The range of safety features to be assessed includes local and systemic tolerance, acute and chronic toxicity, mutagenicity and tumorigenicity, reproductive toxicity, immunotoxicity and, for veterinary medicinal products, also the ecotoxicity. The safety tests will be described in more detail in a separate chapter below on preclinical pharmacological and safety test procedures.

For a safety assessment of a pharmaceutical product in the target organism it is necessary to know the action and fate of the product and its components within the body, after it has been administered. This knowledge derives from pharmacodynamic and pharmacokinetic studies, the results of which will influence the choice and setup of safety tests to be conducted. Pharmacodynamic studies investigate the influence of pharmaceutical substances on the human or animal organism, such as their mode of action and mechanism of side effects along with dose-effect relationships. Pharmacokinetic studies address the influence of the organism on the absorption, distribution, metabolism and elimination ("ADME") of pharmaceutical products in adequate models and in the target species.

For biological products (the chemical) excipients are often overlooked. They, too, may have effects or side effects and can leave residues in animals that end up in human food. Their choice for a development product must be considered carefully. Either one uses ingredients with a well established quality and safety profile or one must face the fact that a variety of analytical and safety data have to be established for these excipients. Safety studies for new excipients may cost more than the safety assessment of the biological product itself.

It is essential to demonstrate that pharmaceuticals for food producing animals do not have harmful effects on humans, particularly if residues of the active component or of excipients and of their metabolites may occur in meat, milk or eggs. This means that extensive studies regarding the safety for humans and residue depletion studies must be performed with these products.

As a general rule, products that are used only once or a few times have to undergo fewer safety tests than products which will administered regularly or over a longer time. Less - if any - side reactions are tolerated for products intended to be used in healthy individuals (e.g. vaccines) than for products which are used in diseased individuals. In any case the benefits must clearly outreach any potential side-effects.

Efficacy

A pharmaceutical product must fulfil its purpose under all recommended conditions and it must do so reproducibly. Experience shows that efficacy in controlled experiments does not guarantee that the product does the same and to the same degree under practical conditions. Pharmaceuticals for humans must be tested in human beings for their pharmacodynamic and pharmacokinetic characteristics to prove their effectiveness and safety. These clinical trials are normally carried out in three stages, each phase involving an increased number of patients. Clinical trials in humans are usually the most critical, most expensive, and most time-consuming developmental step and can account for more than one half of the development costs.

Concerning the proof of efficacy for animal health products, there is often the misconception that controlled experiments in the target species (pen trials or a challenge experiment under controlled conditions) which show that the product is efficacious, are sufficient to register a product. Animal health products also have to undergo clinical or field trials to prove their efficacy and safety under practical conditions. Quite often, these trials reveal several hitherto unrecognized weaknesses of the product. Clinical trials for veterinary medicinal products are much less critical, less expensive and usually less time-consuming than human clinical trials. Due to the preclinical pharmacological, efficacy and safety tests performed in the target species, the clinical trials are mainly designed to confirm preclinical efficacy data and to provide a broader basis for the safety evaluation.

Clinical trials are an important base of efficacy claims for the product. As a logical consequence, all indications for which the product is recommended, all proposed routes of application, treatment schemes, doses, relevant age groups and, in the case of veterinary products, all recommended species must be tested. It is often better to initially concentrate on only one or a few of the potential indications to reduce the risk and to get the product on the market earlier, than to follow up all variants at the same time.

Registration Applications and Procedures

Approval for Clinical Trials

Before a new pharmaceutical product can be tested in clinical trials, the test product, its labelling and the intended trials must be approved. This is usually done by the same authority that is responsible for the market approval of the final product. The formal procedures to obtain permission for clinical trials vary. Some countries require only a notification to the authority, which may then object within a certified period, other countries require a formal application in order to obtain approval, e.g. by issuing a Clinical Trial Certificate (CTC), before the trials can commence.

Notifications or applications for clinical trials are supported by summaries or full reports on the preclinical pharmacology and safety assessment. The kind of safety data (e.g. the type and duration of toxicity tests), which are expected at this time, should correspond to the intended route and duration of application. Data on process details and on the quality of the product are not always required. But it must be kept in mind that clinical trials can only render useful results for the later product registration, if the quality characteristics of the tested product and its method of production are the essentially same as for the final product. If available, clinical data from trials in other countries must also be provided. Protocols for the intended clinical trials are an essential part of the application.

The applications are examined mainly with respect to the safety for the clinical test subjects. Incomplete pharmacological data or safety studies, which do not comply with the standards of Good Laboratory Practice, may be reasons for a refusal of applications. Pragmatic compromises concerning the completeness of analytical and process validation or other quality data (e.g. of the real-time stability tests) are acceptable. It is also commonly accepted that in many situations clinical trial products cannot be made in the final manufacturing facilities and at the final scale. Where these exist, special GMP guidelines for the manufacturing of clinical trial product should be studied (see e.g. EEC document III/3004/91). The submitted trial protocols are checked for compliance with the required standards, for formalities according to relevant guidelines and Good Clinical Practice (GCP), but mainly for proper planning, especially with respect to statistical methods.

Abbreviated approval procedures may be applicable for products which are essentially identical to existing products, e.g. for clinical

trials with registered products in new indications. Exemptions may also be acceptable for important products, which promise benefits in areas for which no adequate treatment exists.

The formalized application procedure in the USA at the FDA (Food and Drug Administration) is referred to as "Investigational New Drug Application" (INDA) or INADA for animal health products. Products which are defined as "biologics" (see below under Registration in the USA) are subject to a different formal procedure and require an Establishment Licence Application (see 21 CFR 312, 511 and 601). Clinical trial approval by the US Department of Agriculture (USDA) for veterinary biologics requires less formal "brief descriptions", however, the permit will not be issued until facilities and equipment have been inspected and are licenced for the specific product (9 CFR 104). This can be a time-consuming procedure.

In the EEC, applications or notifications for clinical trials have to be lodged with the individual national authorities. A common procedure or even mutual recognition of clinical trial certificates does not exist. A list of the different national requirements is provided in "The Rules Governing Medicinal Products in the European Communities" Volume III, Annex 1. A discussion paper (III/ 3044/91) released in 1991 by the EEC Division for Pharmaceuticals (DG III) addresses various issues on the harmonization of approval of clinical trials and may eventually lead to common, non-binding recommendations.

Applications for Market Approval

An application for market approval of a pharmaceutical product contains all data to demonstrate the product's quality, safety and efficacy. Data are documented, summarized, evaluated and arranged according to the individual country's requirements. Considering the number of studies, trials, analyses and assessments which have to be carried out over a period of several years and the detailed documentation all these activities that must be provided, it is hardly surprising that the amount of paper forwarded to the registration authorities is not measured by pages, but by kilograms, numbers, or even meters of folders. More specific and detailed requirements and guidelines, but to a great extent also GLP, GMP and GCP standards, contribute to a permanently rising flood of paper.

Registration dossiers should not be written and collected at the end of the development. The development process should start with an

appointed person who is responsible for the registration - and with an especially prepared folder. According to the recommendations of the registration authorities, this folder should be subdivided into different sections, carrying headlines such as, for example, those listed in Tables 11, 16 or 17 in Annex A to this chapter. Incoming reports, after being checked for completeness and compliance with the requirements, will be continuously filed into the registration dossier folder(s).

If possible, early contacts should be established with the regulatory authorities to discuss and agree on the type of preclinical studies to be performed and on the protocols. (Clinical studies are subject to prior approval anyhow.) Of course, this does not guarantee that the trial results will be accepted later on, but it minimizes the risk of refusal of registration applications or of individual results for formal reasons. During these contacts, the applicant may also receive valuable advice from the specialists in the authorities. And finally one cannot neglect the fact that in each country the regulatory authorities - and probably even individuals within these authorities - have certain preferences and dislikes. There is nothing to be criticized about this, however, not being aware of these preferences can cause considerable delays of the registration.

US authorities actively and officially encourage early and direct contact and discussion about trial protocols and general development strategies. Authorities in many other countries foster a more authoritarian attitude. They tend to discourage direct contacts and avoid to commit themselves by giving advice. In some cases responses will only be given after the full application has been received.

A registration application is initially examined for completeness and compliance with the formal requirements, before the technical and scientific examination by specialized groups commences. The first official response from an authority may be a notification of the deficiencies of the dossier. Partly the objections may address only formal faults, other problems may be clarified by reference to the existing data, in other cases additional studies may have to be conducted to provide the required information.

The review procedure can last anywhere between a few months and several years. An important factor determining the duration of this process is of course the quality of the data and the dossier. But there are also considerable differences between different authorities and countries dealing with the same application.

Vaccines and similar products are often registered by specialized and smaller authorities which seem to have less complex ways of reaching a

decision. Responses from these authorities are normally faster and may take only 3-6 months. Other pharmaceuticals, including biotechnological products, regularly take much longer. Project plans for these products have to assume a duration of 2±1 years for the registration process.

With these high variations, the registration period is one of the most unpredictable parts of the project plan. Due to the time that is lost on the market, the necessity to maintain resources during this period, and due to sometimes considerable registration fees (e.g. those envisaged in the EEC), registration is also a very costly part of the development. Time limits for the registration procedure, which have been introduced, have not yet shown any significant effect. The time limit of 120 (+90) days, as it was initially specified for an EEC registration, has been mere theory. Experience indicates that the extension to 210 (+90) days may also be very optimistic.

Approval to market a pharmaceutical product is not a free ticket for an unlimited time. The licence must usually be renewed at regular intervals, which can be a formality, but may also require new data. Further conditions apply, concerning production records, sample provision and storage, and the duty to notify the authority of any intended changes to the manufacturing process, product packages or labels. The surveillance and reporting of any unexpected side-effects by the company is an essential part of pharmacovigilance procedures.

In some cases approval may be given under the condition that further clinical trials must be performed to address unknown aspects, such as efficacy and safety in population subgroups. These trials are referred to as post-marketing or Phase IV clinical trial.

Biological pharmaceuticals are subject to a formal approval for each individual batch, which often includes regular tests of all batches by the authorities. This also applies to imported products. Long test and response times by the authorities, often associated with the requirement to store the product batches in quarantine during that time, can act as an efficient import barrier.

Registration in the EEC

The harmonization of the national legislation on pharmaceutical products in the EEC is well advanced and covers almost all aspects. Although national registrations are still possible and the EEC-wide

registration uses the national authorities and their experts, the EEC regulatory system overrides national laws. The system was implemented by means of Council Regulations and Decisions which are directly binding to the member states. More specific Council Directives have to be transferred into national law to come into force. (Most directives are adopted, although with some delay.) The instrument of Council Recommendations is used for guidelines which are not legally binding. The relevant EEC regulations and guidelines are listed in Annex B to this chapter.

A central EEC registration authority (European Agency for the Evaluation of Medicinal Products) will be established and "shall take up its responsibilities on 1 January 1995 (Council Directive 2309/93 of 22 July 1993). The Committee on Proprietary Medicinal Products, CPMP, which consists of members of the Commission and from the states' authorities, plays a central role in the existing and future system. It is assisted by different working parties for specific areas. The CPMP coordinates the procedures, assesses applications and provides "opinion reports" and acts as arbitrator in the case of national discrepancies. However, the opinion reports and decisions of the CPMP are not (yet) binding to the member states. For veterinary products identical rules apply; here a CVMP acts as the central body.

In the EEC member states, three different routes can be used to register a human or veterinary medicinal product.

1. National registration in individual countries:

From 1996 onwards, a national registration will only be available for local products, registered in a single member state. Similar to the provisions in Council Directive 87/22/EEC, such products cannot be registered in another member state within five years. Accordingly, national registrations will not be possible for products for which a registration application in another member state has been lodged within the preceding five years.

2. The decentralized and multistate procedure:

Based upon a market authorization in one member state, applications of the same dossier are lodged with the authorities of other member states. The second country's abbreviated evaluation will be mainly based upon the assessment report by the first authority and on the expert reports on the main sections of the dossier. If the applicant chooses to make parallel applications in several member states, rather than waiting for approval in the first country, one country will be appointed as rapporteur. The other countries await the assessment

report of the rapporteur before dealing with the application. If, despite an approval by the first state, second countries raise objections against the approval on their territory, the CPMP arbitrates and may involve the applicant in this stage by written or oral hearings. However, the Committee's opinion is not binding, and if the arbitration fails, the matter will be subject to national appeal procedures. It is envisaged that in the future a positive evaluation by the CPMP or CVMP leads to a mandatory recognition (93/39/EEC and 93/40/EEC).

Until the end of 1992, the multistate procedure, which also relied on a mutual recognition of national approvals, operated on a very similar basis and has been very disappointing. Objections against the initial assessment and approval as well as against CPMP opinions were not exceptions, but the rule. The introduction of time limits for the evaluation and responses by the national authorities must also be considered as illusory. The average period to grant or refuse a national licence, after the CPMP opinion was formulated, varied between six months in Luxembourg and 26 months in Italy (Charlesworth, 1992). The limitation for this step was initially 30 days and was subsequently extended to 60 days!

3. The centralized procedure:

In the future, a centralized registration will be handled by the new European Agency. The CPMP and rapporteurs, drawn from the national authorities, will evaluate the application and provide an opinion, which is either accepted by the individual member states or referred to a Committee of the EC Commission for a final, binding decision.

A similar system, the "concertation procedure" is already in place and is obligatory for products from biotechnological processes. The CPMP becomes involved as soon as the first application in any member state is lodged. One country's agency acts as rapporteur and prepares a full evaluation report, other countries provide "monitoring reports". Based on these reports and the expert reports in the dossier, the CPMP summarizes its assessment in an opinion report which is considered by the national authorities, before they make their decision.

The concertation procedure was introduced by Council Directive 87/22/EEC. The Annex to this Directive lists biotechnological products for which the procedure is obligatory. These are products which are developed by processes involving recombinant DNA technology or by the controlled expression of genes, coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells and hybridoma and monoclonal antibody methods.

For other high-technology medicinal products listed in part B of the Annex to 87/22/EEC, the concertation procedure is optional. Products in this category use either new and technically advanced processes, delivery systems, or new substances for entirely new indications. Council Regulation 2309/93, which replaces 87/22/EEC after 1994, adopted the same Annex and added new human blood or plasma products and products containing new active substances for use in humans and food producing animals, which have not been registered in any member state before, to part B of the Annex.

Products which are registered via the concertation procedure are given a 10 year protection from a second applicant, who would otherwise be able to obtain registration for an "essentially similar" product without provision of pharmacological, toxicological and clinical data (Council Directive 87/21/EEC).

Expert reports to accompany registration dossiers were introduced in the EEC as an instrument to facilitate the evaluation of registration applications and as an internal review within the applying organization, before the application is lodged. Expert reports are summaries and critical evaluations of the key sections of the registration dossier and cover the quality/analytical, the pharmaceutical/toxicological and the clinical section (see Volume II, Annex II and Volume V B). For non-immunological veterinary products for food producing animals, a further expert report on the residue file must be provided by the applicant. These reports must be prepared by experts in the relevant field. Experts may be employed by the company, which applies for the registration or may be external specialists. They have to substantiate their expertise by providing biographic details.

Registration in the USA

Pharmaceuticals for human use and veterinary drugs in the USA are controlled by the Food and Drug Administration (FDA). Drugs are regulated by the Center for Drugs Evaluation and Research (CDER), Biologics by the Center for Biologics Evaluation and Research (CBER). The regulations, by which the FDA controls these products, are specified in the Code of Federal Regulation, Title 21 (21 CFR), which consists of several volumes and is revised at least once each year. The relevant subchapters and parts are listed in Annex B at the end of this chapter. Veterinary biological products are regulated by the US

Department of Agriculture (USDA) in accordance with 9 CFR, parts 101-123 in subchapter E on serums, toxins and analogous products, organisms and vectors.

As opposed to the newly established, systematic and occasionally somewhat hypothetical EEC regulations, which attempt to embrace future developments, the US regulations have been developed pragmatically, usually following technical progress with some delay. This is reflected in the CFRs, which on one hand contain rather general rules, but are very detailed in other parts which usually relate to existing products and techniques. Whereas conventional products seem to be well covered, new product categories require the establishment of new rules and opinions within the authorities; this needs time to develop. Considering the long approval periods in the USA, early and regular consultation with the authorities is essential for an expeditious development, particularly for innovative products.

As in other countries, biological products and drugs in the USA are regulated differently. However, the definitions for these two categories of products in the USA overlap. Drugs are cleared by a "New Drug Application", biologics by separate licences for the establishment and the product. Biologics require a lot-by-lot release permit by the authorities, export and import of product and intermediates is more restricted, and licensing and inspection for biologics follows different rules. Thus, it is important to know how and by which center a new product will be regulated. Unfortunately there are no clear rules to assign products to one of the two product categories. The FDA decides on a case-by-case basis.

Some guidance may be obtained from the official definitions: According to 21 CFR 600.3 a biological product means "... any virus, therapeutic serum, toxin, antitoxin or analogous product...". Further explanations state that a product is analogous

- to a virus, if it is prepared from or with a virus or agent actually or potentially infectious,
- to a therapeutic serum if it is composed of whole blood or plasma or contains some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma or serum,
- to a toxin or antitoxin if, irrespective of its source of origin, it acts through a specific immune process.

Hormones (and related molecules) are clearly regulated as drugs, and it appears that biological products are those which are made from the

natural source (blood, serum, plasma, microorganisms) or which act through a specific immune response.

Apart from the origin of a product and its manufacturing process, existing expertise with a certain application form or indication within the CDER or CBER may also influence the decision to allocate a new product as a drug or a biologic. This leaves considerable ambiguity, particularly with respect to biotechnological products, which are neither vaccines nor hormones. For example tissue plasminogen activator (TPA) was licenced as a biological product, erythropoietin (EPO) was regulated as a drug.

Similar difficulties with the definitions affect veterinary biologics. Based upon a different definition of a biological product than the one quoted above, the USDA claims responsibility for the licencing of biological veterinary products, whereas veterinary drugs are regulated by the FDA. But, as discussed above, the FDA also considers certain products of biological origin as drugs.

The definition for veterinary biological products in 9 CFR 101.2 reads: "... all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live and killed microorganisms and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment or prevention of diseases of animals."

In a Memorandum of Understanding between the USDA and the FDA, regarding each authority's responsibility for the regulation of animal biological products (published in: 47 Fed. Register 26458, 1982), it was agreed that "animal biologics generally act through a specific immune process". The USDA tends to use the word "generally" as an extension of the scope of the definition rather than a restriction, e.g. to vaccines only. However, the decision was made to regulate bovine alpha interferon by the FDA (and as an animal drug), because it does not function through a specific immune process (Korwek, 1989). This example shows that the FDA applies the definition very strictly. It is to be expected that veterinary biological products which do not exactly fall under the definition of 9 CFR 101.2 as quoted above (e.g. products which are not used in the diagnosis, treatment or prevention of diseases) will be regulated by the FDA. This could apply for example to performance enhancing biological products and antihormonal vaccines.

The matter is not yet resolved in a satisfying way. Further committees discussed the separation of competences between the FDA and USDA, but a reasonable compromise could not yet be found. As long as these discrepancies exist, it will be necessary to discuss a product candidate

with both authorities and to find acceptable compromises concerning the technical and formal requirements which define the development strategy.

Imports of biological products into the USA are restricted by the requirement to have the manufacturing facilities licenced and inspected by US inspectors or by local inspectors, if these are recognized by the USA. Furthermore, biological products are subject to a permit for each individual shipment, quarantine for the product and tests by the authorities before release. Veterinary biological product licences will not be issued for products from countries "...known to have exotic diseases, including but not limited to, foot and mouth disease, rinderpest, fowl pest (fowl plague), swine vesicular disease, Newcastle disease, and African swine fever (9 CFR 104.2).

Data from clinical studies in foreign countries are, in principle, acceptable in the USA, as long as the trial protocols comply with the US regulations and GCP standards. However, as in most countries, at least a part of the studies will have to be performed or repeated in the USA because, for example, the population may be different and the medicinal practices differ. Besides for these reasons, clinical trials are frequently conducted locally because the data tend to be more convincing.

Products for a rare disease or condition may be too small to recover their development and registration cost from sales. If this situation is expected, the developer may ask the FDA for written recommendations for the required preclinical and clinical trials. In addition, the manufacturer and sponsor can ask for an official designation as "orphan drug" (also for biological products). Orphan drugs are entitled to tax reductions and a 7 year monopoly on their use for the designated indication.

Registration in Japan

In Japan the Ministry of Health and Welfare's Pharmaceutical Affairs Bureau (PAB) regulates human health products and the Division of Veterinary Drugs in the Ministry of Agriculture controls veterinary products, including biological products. Applications are initially and rigorously checked by a single examiner, who ensures that the application complies with the Japanese requirements and guidelines. This can include inspections of facilities and laboratories. (GLP and GMP standards apply, for human clinical trials GCP is also essential.)

Only after the initial assessment by the examiner has been successfully completed (which may require working off a long deficiency list), the application is reviewed by specialized subcommittees. The initial examiner remains the only contact person for the applicant. However, there is a possibility for the applicant to receive direct instructions from the scientific subcommittee during a very short "hearing". The standard period for the evaluation of a dossier by the PAB is set at 18 months. This appears to be a reliable estimate.

Foreign documents and reports have to be provided in the original language along with Japanese translations by certified translators. Essential documents and studies must be supplied with an original signature by the investigator. Information on the qualification of those, who conduct essential preclinical and clinical studies, are also important in Japan. Only parts of the clinical data generated in foreign countries are acceptable for a registration in Japan. Due to differences in body size, metabolism, diet, etc., of the Japanese population and due to a different attitude regarding the balance between dosage, efficacy and safety margin, Phase I clinical trials and comparative efficacy and safety studies in Japan will be required.

As in most countries, the import and registration of pharmaceutical products requires a local resident who is legally responsible for the registration and post-marketing surveillance. This person or local company must have adequate skills and appoint a pharmacist or, for biological products, a microbiologist or physician as responsible person. For the import and sales of biological products, adequate and licenced biological facilities are also essential.

Requirements for the Preclinical Pharmacology and Safety Assessment

This section mainly addresses the purpose and technical aspects of preclinical studies which are described and recommended in the registration guidelines of the EEC, Japan and the USA. The following brief descriptions of commonly used test procedures cannot replace the detailed study of guidelines by those who conduct these trials. They are intended to give the less experienced an idea about the safety standards, which have to be fulfilled by a medicinal product and about the purpose and conduct of these tests. This enables scientists in research and development to judge essential parts of a project for themselves and to make better and informed decisions. It also assists in planning time and cost of a project.

There are no strict rules, demanding a certain set of studies for a certain product. The FDA recommends that the specific testing be addressed on a case-by-case basis with the appropriate FDA office. More specific guidance on testing strategies is given in the tables in the Annex B to this chapter. For products derived from biotechnology the most specific recommendations are given by the EEC "Notes to Applicants" which are summarized in Tables 12 and 13.

Unlike most other parts of product development, the preclinical investigation of a new product and/or ingredient in animals follows rather firm standards how to conduct the individual studies. Unfortunately these differ from country to country. The EEC tries to give guidelines on preclinical investigations which are flexible in details, such as animal numbers in toxicity tests. Other countries tend to formulate and apply their guidelines in a stricter and more formal way. Thus, the wording in guidelines and recommendations varies from "is essential" to "must be", "should be" or "may be". This suggests more flexibility than actually exists in the current competitive environment, in which rapid development is of utmost importance. The decision to omit simple details of examinations which appear unnecessary or of an entire study which, according to the wording of the guidelines, "may be required", can result in significant delays and costs for the repetition of studies, if an authority subsequently demands these data. Wherever possible, the proposed test strategy and the test protocols should be reviewed by the authorities before the trials commence.

Attempts are underway to harmonize guidelines for preclinical test procedures in the EEC, Japan and USA in order to avoid the unnecessary duplication of animal tests due to different formal requirements. Other countries will adopt such common recommendations for their own interest. However, this harmonization process has just begun and for several more years it will be necessary to study the specific guidelines and recommendations for these and other countries, before trials are planned and conducted. Toxicologists will need to know beforehand in which major countries the results of their safety tests will be used and will have to plan their experiments and test strategy accordingly.

Quotable figures for the cost of safety tests are difficult to obtain. They may also be misleading. Despite standardization, the test protocols can vary considerably, e.g. if different routes of application have to be tested, other test species have to be used or added, and if the observed effects need to be clarified by further, specialized trials. The figure of about US\$ 200,000 for a 3-month repeated dose toxicity test in rodents may serve as a guide on the costs of safety test procedures according to GLP standards. One has to assume direct costs anywhere between US\$ 2 and 5 million for a basic safety assessment of a new substance in laboratory animal trials and similar costs for a preclinical pharmacology package. This figure will be exceeded rapidly, if a range of specific tests (e.g. neurotoxicity tests, safety tests in primates) are required to address specific issues. Products to be used in food producing animals are also likely to incur higher costs for the safety assessment and for residue depletion studies.

Exceptions and Variations for Biological Products

The standard test procedures described below have been established to assess pharmacological and safety features of chemical compounds, such as drugs and newly introduced excipients. With some qualifications these tests are also used for biological pharmaceuticals, which act pharmacologically (as opposed to an immunological mode of action) and are applied frequently or in regular, short intervals, e.g. cytokines or blood clotting factors.

The choice of test animals presents a major difficulty if the repeated application of the biological product results in immunological reactions. Tests exceeding four weeks should be carried out in immunological

low-responders. Biological products may also require a different dosing rationale, which partly depends on the clinical use of the product and on the maximum doses to be used. However, it must be kept in mind that toxicity studies are designed to generate and reveal toxic symptoms, i.e. the highest dose in each test should normally be toxic. It is, however, accepted that even extremely high doses of biological products may not always be able to induce any toxicity (compare EEC, Volume III).

Most toxicological test procedures were never intended for vaccines. However, the requirement to test the pharmacokinetics, pharmacodynamics and reproductive toxicity for human vaccines means, that at least the basic rationale of these studies also applies to vaccines. The test methods may vary considerably.

If, for example, reproductive toxicity studies are required for vaccines, the trial duration and details of clinical and pathological investigations of standard trial procedures may be adopted, whereas the dosing must be chosen individually for each product to be tested and should be justified in the study protocol. Most likely it will be similar to the clinical use of the vaccine.

The terms "single dose toxicity" and "repeated dose toxicity" are easily confused with the EEC terminology "safety of the administration of one dose/an overdose" or with "safety of the repeated administration of one dose". The latter are test requirements for immunological veterinary products and refer to less rigid safety studies in the target species, using the clinical route of application and application schemes, which are more oriented towards the clinical use. Similar requirements apply in the USA, where repeated administration of overdoses (2, 3, 5 or up to 10-fold) are part of the safety assessment in the target species (see also Table 19). Extensive pathological investigations are normally not required in such studies.

New Vaccine Adjuvants and Other Excipients

Vaccine excipients (adjuvants and other substances used in the formulation) are treated in the same way as chemical substances. If new substances are introduced, a full safety assessment is required. It may be necessary to assess their toxic potential separately from the vaccine, since the vaccine formulation may interfere with a proper testing. In addition the normal pharmacological and safety tests for vaccines must be performed with the final, formulated product.

For this reason vaccine formulation tends to follow the traditional routes; innovative formulations are rare. Aluminium hydroxide, aluminium phosphate and calcium phosphate are still the only registered vaccine adjuvants for humans. Veterinary vaccines have to rely on the same components, however, a few vaccines containing a mineral oil adjuvant (Marcol) or saponin (Quil A or derivatives) have passed the registration hurdles. It remains to be seen whether and under which restrictions these adjuvants can be used in the EEC after 1996 (see also below in "Additional requirements for veterinary products").

The implications of those safety requirements for urgently needed new adjuvants are significant. The adjuvant issue appears to be caught in a vicious circle. Risky vaccine projects cannot afford the extra risk and cost of an adjuvant development project, which could cost several million dollars. On the other hand, the success of several recombinant vaccines under development seems to depend on new and better adjuvants. The lack of clearly superior adjuvant candidates with reproducible effects aggravates this current situation.

Pharmacokinetics

The pharmacokinetic profile of a product or substance describes its fate in the organism with respect to the absorption, distribution, metabolism and elimination. For chemical compounds pharmacokinetic data form the basis for an assessment of pharmacodynamic and toxic effects and allow a rationale for a dosage regime to be established for preclinical and clinical studies.

Initial tests are usually performed in rodents, e.g. in rats, and thereafter in dogs. Different dose levels and routes of administration are used, which depend on, but are not restricted to, the intended clinical routes of application. The test species should represent a reliable model for the target organism. In practice this can only be achieved by comparing pharmacokinetic profiles from animal experiments with those in the target species. According to the available knowledge and if initial clinical trials reveal essential differences, specific models, such as primates may be required for human medicinal products. Not only different species, but also male and female individuals of the same species may give different pharmacokinetic profiles for the same substance.

Veterinary products for food producing animals require pharmacokinetic studies to investigate the depletion of residues. Based

on initial studies in rodents to narrow down the range of variables, these studies are carried out in the target species. Sensitive detection assays and probably also extraction methods are required to measure the product and its metabolites in various body fluids, organs and tissues. Radioactively labelled test substance may be required to trace the minute concentrations of the active component and metabolites.

Substances which are metabolized into several derivatives and breakdown products pose special problems. These compounds are sometimes abandoned because their pharmacokinetic behaviour presents too many problems for the later development.

For most vaccines and several other biological products full pharmacokinetic studies are unnecessary or impossible. Proteins, recombinant polypeptides or peptides which are to be applied repeatedly, over long periods of time, or in large quantities will require rather detailed pharmacokinetic studies. Similarly, products which are not identical to physiological molecules need to be investigated more thoroughly. As a specific requirement for vaccines in EEC guidelines, the retention at the injection site (adjuvants) as well as the further distribution and elimination via mucous membranes, urine and faeces (live vaccine organisms) needs to be addressed and investigated where necessary. For veterinary vaccines the possibility of vaccine components occurring in meat, milk and eggs may need to be investigated.

Pharmacodynamics

Pharmacodynamic studies investigate the pharmacological effects of a substance on the human or animal organism in order to gain an understanding of the active principle. Knowing the therapeutic rationale, enables many relevant conclusions to be drawn about the effects of the product in various situations and in population subgroups, about factors which may influence the effectiveness of the product and about potential side-effects. Investigations of dose-response relationships, of effects and side-effects are an essential part of any pharmacodynamic study.

Although the term is somewhat uncommon for vaccines, traditional investigations about their mode of action by assessing the type and duration of protective immune mechanisms under various conditions are based on a very similar approach.

For a comprehensive pharmacodynamic investigation, systematic studies on the effects of a product on different organ systems may be required and are obligatory for drugs to be registered for human use in Japan. These specialized studies investigate effects on the central nervous system, cardiovascular system, respiratory and digestive tract and on the general water and electrolyte metabolism.

Bioequivalence and Bioavailability

Modifications of a pharmaceutical product's specifications, its manufacturing process, formulation, dosage, strength or regime may be desirable after registration or during the development. In these cases it will be necessary to prove, that the modification provides an equivalent product with respect to efficacy and safety. Modified formulations and application forms, which affect pharmacokinetic parameters (e.g. controlled release forms), require investigations on the availability of the active ingredient in the organism and at the site of action. Evidence from in vitro experiments or in vivo studies in animals can be used to avoid safety and efficacy studies of the modified product in new, extensive clinical studies.

Bioequivalence and -availability can be assessed in vitro, for example in dissolution tests for controlled release forms, or in vivo in experimental animals in pharmacokinetic and/or pharmacodynamic studies. The results should be correlated with the pharmacological effects in the target organism. If the modified product is not bioequivalent or shows different therapeutic effects, clinical studies will be necessary. Products which have a narrow therapeutic ratio (e.g. a less than twofold difference between the minimum toxic and minimum effective concentration in the body; 21 CFR 320) require clinical studies under all circumstances.

Single Dose Toxicity (Acute Toxicity)

Single dose toxicity tests assess the effects of a single application of high doses of a substance. This allows conclusions to be drawn about the effects of accidental overdoses or about the effects on individuals with a higher sensitivity. Until recently, single dose toxicity tests required large numbers of animals to establish a statistical figure, the 50% lethal dose (LD₅₀), as a measure of the toxicity of a new

substance. Although morbidity is certainly a better indicator of toxicity than mortality, the LD₅₀ is still too often and uncritically used to characterize the toxicity of a substance.

In an attempt to reduce the high numbers of animals used to establish questionable LD₅₀ values, the test requirements in the USA and EEC have been reduced. These countries require only an "approximate lethal dose" along with a dose-response relationship. Single dose toxicity tests with this approximate lethal dose level now become more and more acceptable also in other countries (e.g. in Japan), although these countries' guidelines may not yet reflect the changes. In cases of doubt it may be necessary to negotiate the best procedure (beforehand) with local authorities. If the authorities still prefer statistically exact LD₅₀ values, it may be useful to refer to the fact that, as a result of the first "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use" (5.-7. Nov. 1991 in Brussels), the approximate lethal dose approach was clearly favoured and recommended.

Single dose toxicity tests are carried out as consecutive tests using increasing doses. Two different species (rodents, usually rats and mice) and both sexes must be tested in groups of 5 or more animals per group. The substance is given by at least two different routes (e.g. oral and parenteral). The application routes should reflect the proposed clinical applications and should also ensure systemic exposure. Test animals are observed for (7-)14 days, occasionally also for longer periods, if symptoms persist or to monitor the regression of symptoms. The study is completed by a macroscopic pathological investigation (autopsy) of at least all animals that died during the trial and by a microscopic pathological inspection (histopathology) of visibly affected organs.

Repeated Dose Toxicity (Subacute, Chronic Toxicity)

Repeated dose toxicity tests are usually performed in two species, one rodent and one non-rodent, using equal numbers of both sexes in each group and 10 rodents or 4-6 non-rodents per group. Rats and dogs are a commonly used combination. Veterinary products which are not used in food producing animals may be tested in only one species, e.g. the target species.

The test substance is given daily (seven days a week) by the expected clinical route and at three (or more) dose levels. The highest dose level should result in slight toxic effects, the lowest dose level

should not induce observable effects, an intermediate dose should preferably correspond to the therapeutical dose. The study is monitored by daily observations to detect changes of the behaviour and any onset, progression or regression of signs of toxicity. Additional examinations, which are performed at predetermined intervals complement the routine observations. Recommendations include clinical and analytical tests (as complete as possible), organ function tests, blood chemistry and urine analyses as well as neurological and ophthalmological examinations. Autopsies and histopathology conclude the studies.

US guidelines recommend a "short-term toxicity" study lasting for up to 28 days as a range-finding test, followed by a "subchronic toxicity" study for at least 90 days. According to the FDA "chronic toxicity" tests should be carried out over a period of 2 years. If carcinogenicity studies are necessary, they may be combined with chronic toxicity tests by adding 3 more satellite treatment groups which are sacrificed after 12 months. The USA recommendation for a short-term toxicity test can be regarded as a definite requirement. The EEC and Japan propose similar, preliminary and short-term tests over (2-)4 weeks which are not essential but may be useful to define adequate doses for the main study.

EEC and Japanese guidelines deviate considerably from those in the USA with regard to the recommended test duration. In the EEC and Japan the test duration depends on the expected duration of the clinical treatment. Products for single use (or for single day treatments with more than one application) need to be tested for only 2 (EEC) or 4 (Japan) weeks. Clinical applications for up to 7 days require tests to be carried out for at least 4 weeks, products for an intended use up to 30 days should be tested for at least 3 months, a longer clinical treatment requires tests for at least 6 months. Japan demands tests over 12 months if the product is to be applied for more than 6 months. Three month chronic toxicity tests are most common and the minimum for products for food-producing animals.

If applied to biological pharmaceutical products, the choice of test animals and the test duration may need to be varied to avoid the interference of stimulated immune responses against the test substance. If the test duration will exceed 4 weeks, immunological low-responder animals should be used.

Reproduction Toxicity

The evaluation of a potential reproductive toxicity comprises the observation of adverse effects during three different phases:

1. Fertility studies observe toxic effects on spermatogenesis, formation of ovarian follicles, mating, conception, implantation and organogenesis.

2. Teratology studies cover the organogenesis period and usually end shortly thereafter, near or at term of delivery.

3. Peri- and postnatal toxicity studies commence before mating or in early pregnancy and observe the effects during pregnancy, at delivery and during the entire lactation period until weaning.

In all reproduction toxicity studies at least three doses (minimally toxic, intermediate, non-toxic) should be given, preferably by the proposed clinical route of application. Fertility and peri- and postnatal toxicity studies require tests in only one species (usually rats or mice), the teratology segment must be tested in two species (e.g. rodents and rabbits). Pharmacokinetic data and differences in the placentation may suggest other modes of application and/or other test species, e.g. primates. Of course the minimum animal numbers for the standard tests do not apply to studies in primates.

For the fertility part, at least 20 (or 24 in the EEC) animals per group and of both sexes are required. Allowances for normal reproductive failures increase the group sizes. Males are dosed for at least one full spermatogenesis cycle (60 days), females usually from at least 14 days before mating onwards. Treated males and females are mated. If more reproductive failures occur in the test groups, treated animals must also be mated with untreated partners in repeated experiments. Males are usually autopsied after mating, females after organogenesis or near term. The examination includes the determination of fertility indices, as well as pathological observations of mothers and foetuses.

Teratology studies are conducted with usually 20 (30 in Japan) pregnant rodents and 12 pregnant rabbits per dosed or control group. Daily dosing during the foetal organogenesis is followed by an autopsy before or at term and investigations of the dams and fetuses.

Peri- and postnatal toxicity studies are recommended as a continuation of a part of the fertility or teratology studies, thus the treatment periods vary. At least 12 (-20) pregnant mice or rats per group are examined during pregnancy, delivery and during the lactation

period until weaning, before pathological examinations are performed on the dams and their offspring.

Various versions and combinations are proposed by the different guidelines. The US/FDA "Red Book" explains a detailed scheme of combined reproduction and development toxicity studies (at least 20 individuals per group) over 2(-3 if necessary) generations with an optional teratology phase with the F1 generation. As another alternative, fertility toxicity testing may be combined with a teratology study. The EEC guidelines recommend the use of at least 24 rodents for fertility studies and continue the peri- and postnatal phase with one half of these. Two (up to 3 if necessary) generations should be investigated. Japanese guidelines describe a more formalized three-phase procedure. For a combination study it is recommended that one third of the rodents used in the teratology phase be used for further peri- and postnatal studies.

The mentioned differences between the US, EEC and Japanese guidelines are only the major ones. Other differences concern the definition of organogenesis periods and the related treatment periods for the different species, as well as the type of recommended investigations. Depending on the regulating authority (e.g. for human or veterinary products) test recommendations can even vary within one country.

Mutagenicity

Mutagenicity tests are designed to detect gene mutations, chromosomal aberrations or DNA damage in prokaryotic and eukaryotic in vitro systems and in vivo. These tests are routinely performed with all new drugs. Although mutagenicity tests are in most cases not appropriate for biological products, they may be necessary for previously unknown excipients and for certain impurities.

Three or more of the following test categories are normally used in a mutagenicity test battery:

1. Gene mutation tests in prokaryotic systems, using *Salmonella typhimurium* and *Escherichia coli* strains to detect mutation reversions (e.g. Ames test). As with other in vitro tests, the substance is also tested in the presence of a metabolic system, the "S9 mix" from rat liver cell homogenates.

2. Gene mutation tests in a eukaryotic system in vitro, e.g. the Hypoxanthine - guanine - phosphoribosyl - transferase (HGPRT) gene mutation tests in hamster cells.

3. Chromosomal aberration tests in vitro (e.g. Cytogenetic test) and in vivo (e.g. Micronucleus test in rodents).

4. Tests for the induction of primary DNA damage, e.g. the Unscheduled DNA Synthesis (UDS) test.

Tumorigenicity (Carcinogenicity)

Long-term tumorigenicity tests in animals will be necessary, if the product, excipients or impurities in the product are suspected to be tumorigenic, or if the product is intended for regular applications over long periods, for example more than 6 months. Specific suspicions may arise from an analogy to known carcinogens, indicative results in mutagenicity or other toxicity studies, or from the pharmacological mode of action.

Tumorigenicity tests are normally performed in two species, usually in mice, rats or hamsters, and in strains with low spontaneous tumor rates. Species that gave rise to specific concerns in earlier toxicity tests should be preferred. For biological substances the target species should be selected following consideration of the immunological response and its potential interference with the study.

Preliminary studies over 3 months in groups of 10 animals each are an essential requirement in Japan. Since adequate dose levels for such a long-term study are difficult to define beforehand, short dose-finding trials may be useful for other countries, too.

The main tumorigenicity study with 50 animals per group and sex lasts 18-24 months in mice or hamsters and 24-30 months in rats (recommendations differ). Three dosage levels (toxic, intermediate, non-toxic) are recommended, all of which should be above the expected clinical dose. Recommendations may propose upper limitations, for example the 100-fold clinical dose or, in the case of an oral application, a maximum of 5% of the diet. However, different countries and authorities have a different view on such details.

As for all long-term and expensive toxicity studies, it is essential to discuss the study protocol beforehand with the relevant authorities to avoid later objections against the protocol and results of such trials. After all, including the time for histopathological investigations and

GLP-standard reports, tumorigenicity studies will take two to three years and cost more than a million dollars.

Immunotoxicity

Immunotoxicity tests for chemical pharmaceuticals address the potential of causing hypersensitivities or the allergic potential of a substance. Along with other pharmacological and safety tests, the term immunotoxicity has been included in EEC registration guidelines also for biological products and needs a wider definition. Some explanation can be obtained from the "Notes to applicants" on biotechnological products (Volume III) which paraphrase the area as "difficult" and does not recommend specific tests: "Suitable" tests should be carried out to address potential problems in more detail, if there is evidence that the product can cause a "dysfunction of the immune system". The suspicion that a certain product may cause dysfunctions may arise from findings of

- immune complex formation, e.g. with host immunoglobulins or with complement,
- release of pharmacologically active molecules which affect the immune system,
- interactions with immune cells which may affect their normal function and cross-reactivity of antibodies with intrinsic human antigens or tissues.

For new vaccines for humans it may be required to assess the immunological effects of adjuvants and undue cross-reactivities of the induced antibodies with a variety of intrinsic human antigens and tissues. This point is specifically mentioned in the EEC guidelines, and reference is made to a suggested list of human tissues and organs to be used for immunohistochemical or cytochemical investigations (see Biotechnology Guidelines and Annex II of the Guideline on murine monoclonal antibodies in Volume III).

For veterinary immunological products which "...might adversely affect the immune response of the vaccinated animal or of its progeny, suitable tests on the immunological functions shall be carried out" (92/18/EEC). Possible reasons to investigate the general immunological functions of vaccinated animals in more detail could be, for example, the intended use of in combination with other immunizations or live vaccines containing microorganisms which could cause immuno-suppressive effects.

If animal models are used, the difference between the model animal's immune system and that of humans or the animal target species must not be neglected. In exceptional situations homologous animal systems should be considered, e.g. by testing a mouse-specific variant of the product in a mouse model.

Local Tolerance

Pharmaceutical products which are applied intramuscularly, subcutaneously or locally need to be tested in preclinical animal studies and clinically for their local tolerance at the application site. For human vaccines this is an essential part of the preclinical safety assessment. Veterinary products should be tested in the target species. Mechanical effects of administration or purely physico-chemical actions should be distinguished from toxicological or pharmacodynamic effects by using appropriate testing strategies (91/507/EEC). This could be done by testing buffers, adjuvants or other excipients and the active ingredient separately.

Additional Preclinical Studies for Veterinary Products

User Safety

Veterinary products are applied by man and may, in certain cases, present hazards to the user, for example by accidental injection. Proper handling can avoid problems. Appropriate safety recommendations should be included on the product label or in the package insert. Certain products may require further safety measures concerning their storage, use and disposal, and it may be necessary to substantiate the problem by specific studies on the local skin or mucosal irritation, percutaneous irritation, inhalation toxicity or on the allergic potential (EEC, Volume VI, Part IV, Notes for Guidance).

User safety-related investigations are unlikely for most biological products. However, some excipients and special vaccines (e.g. poultry live vaccines for spray applications) may warrant studies addressing the user safety during application.

Tolerance in the Target Species

The separate listing of tolerance tests in the target species in EEC guidelines does not necessarily mean that separate studies have to be performed. Local and general tolerance data to establish the tolerated dose range with an acceptable safety margin can be obtained from other pharmacological, safety and clinical studies. This should be kept in mind when those trial protocols are drafted.

Ecotoxicity

With whole-herd applications of antimicrobial and antiparasitic substances and live vaccines in mind, ecotoxicity assessments have been included in the registration requirements for veterinary products in the EEC and the USA. A defined procedure exists in the USA where a "Finding of no significant impact" (FONSI) certificate by the Animal and Plant Health Inspection Service (APHIS) is a necessary prerequisite for the registration.

In a first phase of the assessment, the potential extent of exposure of the environment to the product is considered with reference to the use pattern, application method, potential excretion and disposal of the product. Based on the significance of exposure, further investigations

may be required, addressing the kinetic degradation, elimination and distribution into environmental compartments (agricultural land, aquatic systems) and the impact on the affected environment. Terrestrial and aquatic organisms, such as plants and earthworms, algae, daphnia and fish are used as test subjects.

The application of the same basic and formal principle to all biological products, including inactivated vaccines appears exaggerated. However, Commission Directive 92/18/EEC describes the same principle of a basic assessment ("shall always be carried out"), followed by ecotoxicity tests in the case of "potential exposure of the environment" also under Title II, which is specific for immunological veterinary medicinal products.

Safety of Residues

The development of veterinary products for cattle, pigs, sheep, poultry and other food producing animals also includes residue testing of all new pharmaceutical products, including adjuvants or other excipients in vaccines. Residue safety studies address the potential risk to humans due to the consumption of food from treated animals. Accordingly, the test substances in these toxicity studies are applied orally. Residue depletion studies (pharmacokinetic studies) in the target species must be carried out to define the occurrence, concentration and elimination of the substance and its metabolites in edible tissues, milk and eggs.

The "NOEL" (no observable effect level), defined as the highest non-toxic dose level in the most critical animal study, is used to estimate and calculate the acceptable daily intake (ADI) values for humans. The ADI value is calculated from NOEL-residues in a daily food package, consisting of meat (including fat, offal and skin), milk and eggs. Based upon the assumption that humans are ten times more sensitive than the most sensitive test animal used and that the sensitivity among human beings varies by a factor of ten, a safety factor of 100 is included in the calculation. Depending on the results and validity of the safety data, safety factors of 1000 or more are also possible.

Based on the residue studies and ADI values, maximum residue level (MRL) values for the substance or critical metabolites are defined. Methods must be developed and validated to detect these under practical conditions. Withdrawal periods will be set to ensure that no unacceptable residues occur in human food.

Usually the application for a residue assessment must be made and official MRL values must be set, before the product registration is handed in.

A particular situation currently exists in the EEC. Veterinary drugs and excipients intended for use in food producing animals, including those in approved products, must be registered in the Annexes I, II or III of Council Regulation 2377/90 (Volume VI), otherwise they will be effectively banned from use after 1996. This regulation came into force in 1992.

Annex I will list substance which can be used in food producing animals, as these substances do not present a health hazard for human beings, provided that the MRL is not exceeded.

Annex II will contain those substances for which no MRL is necessary to protect public health. However, this does not necessarily mean that these substances do not require safety testing or are exempt from withdrawal periods. As indicated by the application form for an Annex II listing, this category was created with (among other substances) adjuvants and excipients in mind. It is expected that at least those excipients with a long history of safe use in humans will be listed in Annex II.

Most previously used substances will initially be listed in Annex III. Within a limited period, results from additional safety and residue studies have to be provided for this category. After a final assessment, substances in Annex III will be allocated to Annex I, II or IV.

Annex IV will list substances for which no safe levels can be fixed. The use of these substances will be prohibited throughout the community.

Applications for MRLs for excipients in currently registered vaccines have to be made before 1994. The procedure and the MRL limits do not apply to products and ingredients for cats and dogs or for other animals, which are not used for human consumption. However, substances which are banned because of their toxicity for humans, could also be critical for those species.

Annex A

Outline of Major Registration Requirements

I. Major Registration Requirements for Human Medicinal Products.

Tables 11 - 15

Table 11: General Requirements for Human Medicinal Products in the European Community**I. Summary of the dossier**

Administrative data.

Summary of product characteristics; samples of packaging, labels, inserts.

Expert reports: critical evaluations of the

- Chemical, pharmaceutical and biological documentation;
- Pharmacotoxicological documentation;
- Clinical documentation.

II. Chemical, pharmaceutical and biological testing and documentation

Qualitative and quantitative particulars of the constituents.

Description of method of preparation.

Control of starting materials.

Control tests at intermediate stages of the manufacturing process.

Control tests on the finished product.

Stability tests.

III. Toxicological and pharmacological tests and documentation

The requirements of this part for biological medicinal products may have to be adapted for individual products; the testing programme shall be justified by the applicant.

Single dose toxicity.

Repeated dose toxicity.

Examination of reproductive function.

Embryo/foetal and perinatal toxicity.

Mutagenic potential.

Carcinogenic potential.

Pharmacodynamics.

Pharmacokinetics.

Local tolerance.

IV. Clinical documentation

General requirements.

Conduct of trials.

Presentation of results.

Clinical pharmacology.

Bioavailability/bioequivalence.

Clinical efficacy and safety.

Documentation for application in exceptional circumstances.

Post-marketing experience.

Valid for all categories of medicinal products.

See also Annex to Directive 91/507/EEC

Table 12: Safety Testing Categories for Products Derived from Biotechnology

Testing requirements for these categories are summarized in Table 13.

Category I

Polypeptides and proteins shown to be identical to naturally occurring human polypeptides and proteins.

Category II

Polypeptides and proteins closely related to human polypeptides and proteins, but containing known differences in amino acid sequences and/or post-translational modification(s) that may affect biological activity or immunogenicity or both.

This category also includes proteins whose structure may be identical to the natural product but where this cannot (yet) be verified.

Category III

Polypeptides and proteins distantly related or unrelated to human polypeptides and proteins (e.g. murine monoclonal antibodies and viral/bacterial antigens).

See also "Notes to Applicants on the preclinical biological safety testing of medicinal products derived from biotechnology" (EEC; Volume III, p. 73-88).

Table 13: Preclinical Safety Testing of Medicinal Products Derived from Biotechnology.

Product group	Product category					
	I identical	II closely related		III unrelated or distantly related		
(relatedness to naturally occurring human proteins/polypeptides; compare Table 12)						
Hormones,	demonstrate equivalence with					
Cytokines,	conventionally produced and					
Other	established medicinal product,					
Regulatory factors	otherwise:					
Pharmacodynamic	B	Pharmacodynamic	B	Pharmacodynamic	B	
Pharmacokinetic	C	Pharmacokinetic	B	Pharmacokinetic	B	
Acute toxicity	C	Acute toxicity	B	Acute toxicity	B	
Chronic toxicity	C	Chronic toxicity	B	Chronic toxicity	B	
Local tolerance	C	Local tolerance	C	Local tolerance	C	
Reproductive toxicity	D	Reproductive toxicity	C	Reproductive toxicity	C	
Mutagenicity	D	Mutagenicity	D	Immunotoxicity #)	C	
Tumorigenicity	D	Tumorigenicity	D	Immunotoxicity #)	C	
		(#) immunomodulating substances)				
Blood products (not including hormones)	Pharmacodynamic	C	Pharmacodynamic	C		
	Pharmacokinetic	C	Pharmacokinetic	C		
	Acute toxicity	C	Acute toxicity	C		
			Chronic toxicity	C		
Comparison with naturally derived counterpart where possible						
Vaccines (not including live vaccines)	Pharmacodynamic	D				
	Pharmacokinetic	B	(retention at injection site, further distribution)			
	Local tolerance	A				
	Immunotoxicity	B				
	Reproductive toxicity	C	(if intended for use in woman of child-bearing age or during pregnancy)			
	Vaccine adjuvants and other excipients may require independent or further pharmacological and safety studies.					
Monoclonal antibodies	The preclinical testing strongly depends on the type of product, intended frequency of application, dose, intended clinical therapeutic or diagnostic effect and should be decided on a case by case basis. Complement-binding and cross-reactivity with human tissue should be tested.					

Abbreviations for Guideline recommendations:

A: essential requirement

B: should be tested or applicable in most cases

C: may be applicable/necessary

D: applicable/necessary only in certain cases or unlikely to be required

The same testing strategy also applies to comparable products derived from chemical synthesis.
 Method of production, physico-chemical parameters, impurities and excipients may also have a bearing on testing requirements.

Compare Notes to Applicants, EEC Vol. III, p.73-88.

Table 14: Biological and Biotechnological Human Medicinal Products: Major Requirements for Production Methods and Quality Assurance/Quality Control Measures

Manufacturing

Licensed establishment with adequate infrastructure and separation of activities.
Good Manufacturing Practice (GMP) standards.
Production outline including all in-process controls and quality control tests.
Validated test procedures with results of the validation studies.
Seed lot system for cells and microorganisms with complete history, genotypic and phenotypic characterization; stability of seed lot beyond passage level used for production.
Freedom from potentially pathogenic adventitious agents or validated inactivation or elimination procedures with sufficient safety margin.
Removal of contaminating DNA and host cell antigens.

Starting materials

Specifications and quality control of all starting materials.
Starting material of biological origin: known origin, defined pools, testing for adventitious agents.
Starting materials not described in a Pharmacopoeia require description in the form of a monograph similar to a Pharmacopoeia description.

Consistency

Traditionally 3 (tendency 5) consecutive production runs with full characterization of the final product; also used to justify quality specifications and limits.
Consistency batch production may be pilot scale if it mimics full-scale production as described in production outline.

Stability

Real time stability tests based upon the identity tests for the active ingredient(s), physio-chemical and biological tests; nota: aggregation, degradation, modifications etc.!
Stability of product after reconstitution; tests under stress, e.g. heat, light, humidity.

Potency

Minimum titre, bacterial counts, amount of antigen, biological activity units with reference samples to be guaranteed until the end of the shelf life.

Identity

Identification and assay of active ingredient, e.g. electrophoresis, ELISA, HPLC profile, peptide mapping, amino acid analysis, tests for conformational integrity etc..
In vitro or in vivo biological assays (specific serum neutralization of microorganisms) may be necessary if other methods do not adequately define the active ingredient.

Purity

Proof of absence of contaminating microorganisms.
Characterization and quantification of impurities and degradation products.
Maximum acceptable levels of impurities to be defined.
Semi-official limits: purity : > 95-99%; impurities: <10 or 100 pg DNA/dose.

Sterility/bacterial contaminants

Tests for sterility, bacterial endotoxins, pyrogenicity.

Physical/chemical tests

pH, density, viscosity, emulsion droplet size, residual moisture in freeze-dried products etc..
Identification and assay of excipients such as vaccine adjuvants and preservatives.

Table 15: Clinical Testing of Human Medicinal Products

General requirements for all categories of medicinal products and exceptions and special requirements for vaccines. See also Annex to Directive 91/507/EEC.

Prerequisites for human clinical trials

Preclinical pharmacological and toxicological safety assessment in animals.

Safety from transmission of infectious agents must be ensured.

Pre-established, systematic written procedures for organization and conduct of trials, data collection, documentation and statistical verification of trial results.

Approval by relevant ethics committees and by relevant health authorities.

Conduct of human clinical trials

Good Clinical Practice standards.

Controlled trials, randomized where possible.

Control group treatment: established medical product or treatment, placebo less likely, due to ethical considerations.

Randomization and blinding important where effects cannot be measured objectively.

Safety assessment relative to the disease to be treated, in comparison with other therapeutic approaches, considering the characteristics of sub-groups of patients, and considering the animal toxicology and pharmacology data.

Results of all trials to be communicated, both favourable and unfavourable.

Clinical pharmacokinetics (inappropriate for most vaccines)

Rate and extent of absorption.

Distribution.

Metabolism.

Excretion.

Differences between man and animals used in preclinical studies.

Implications for dosage regime, especially for patients at risk.

Clinical pharmacodynamics

Dose-response relationship.

Dosage and administration scheme justification.

Mode of action.

Bioavailability/Bioequivalence

Necessary if therapeutic dose near the toxic dose, if absorption or other pharmacokinetic properties are variable.

Comparison of products if conclusions are drawn from data on other products or compounds.

Interactions

Influence of other medicinal products which are normally administered concomitantly.

Possible pharmacodynamic and pharmacokinetic interactions with other medicinal products or substances like alcohol, caffeine, tobacco, nicotine.

Vaccines

Local and general tolerance.

Immunological status and age distribution of trial subjects.

Local epidemiology.

Potential transmission of live vaccine microorganisms to non-vaccinated subjects; if transmission possible: genotypic and phenotypic stability to be studied.

**II. Major Registration Requirements for Veterinary
Medicinal Products.**

Tables 16 - 21

**Table 16: General Registration Documentation and Requirements
for "Non-Immunological" Veterinary Medicinal Products
in the EEC.**

Nota: These requirements also apply to certain biotechnological products with a pharmacological (non-immunological) mode of action, e.g. growth hormones, cytokines and other regulatory factors.

I. Summary of the dossier

Administrative data.

Summary of product characteristics; samples of packaging, labels, inserts.

Expert reports: critical evaluations of the

- Analytical documentation;
- Pharmacotoxicological documentation;
- Residues documentation;
- Clinical documentation.

II. Analytical (Physico-chemical, biological or microbiol.) documentation

Qualitative and quantitative particulars of the constituents.

Description of method of preparation.

Control of starting materials.

Control tests at intermediate stages of the manufacturing process.

Control tests on the finished product.

Stability tests.

III. Safety and residues tests and documentation

Safety tests/documentation:

- Single dose toxicity.
- Repeated dose toxicity.
- Tolerance in the target species.
- Reproductive toxicity including teratogenicity.
- Mutagenicity.
- Carcinogenicity.
- Immunotoxicity.
- Microbiological properties of residues (of antibiotics).
- Observations in humans.
- Ecotoxicity assessment/testing.

Residues testing/documentation:

- Pharmacokinetic studies.
- Depletion of residues.
- Routine analytical method for the detection of residues.
- Proposed safety factor, maximum residue limit (MRL), withdrawal period.

IV. Preclinical and clinical documentation

Preclinical trials/documentation:

- Pharmacodynamics.
- Pharmacokinetics.
- Bioavailability/bioequivalence.
- Tolerance in the target species.
- Resistance.

Clinical trials/documentation.

Table 17: Registration Documentation and Requirements for Immunological Veterinary Medicinal Products in the EEC

General requirements for products intended for administration to animals to produce active or passive immunity or to diagnose the state of immunity.

I. Summary of the dossier

Administrative data.

Summary of product characteristics, samples of packaging, labels and inserts.

Expert reports: critical evaluations of the

- Analytical documentation;
- Safety documentation;
- Efficacy documentation.

II. Analytical (Physico-chemical, biological or microbiological) documentation

Qualitative and quantitative particulars of the constituents.

Description of method of preparation of the finished product.

Production and control of starting materials.

Control tests during production.

Control tests on the finished product.

Stability tests.

III. Safety tests and documentation

Laboratory tests:

Safety of the administration of one dose.

Safety of the administration of an overdose.

Safety of repeated administration of one dose.

Examination of reproductive performance.

Examination of immunological functions.

Special requirements for live vaccines.

Interactions.

Residue assessment (for excipients, live vaccines for zoonotic diseases).

Field studies to support laboratory tests.

Ecotoxicity assessment/testing.

IV. Efficacy trials and documentation

Laboratory trials.

Field trials.

From Annex to Directive 92/18/EEC

Table 18: Biological and Biotechnological Veterinary Medicinal Products: Requirements for Production Methods and Quality Assurance and Quality Control Measures

General outline which is mainly based on the EEC and USA requirements. Most countries have similar requirements, although the interpretation of details may vary.

Manufacturing

Licensed manufacturing establishment with adequate infrastructure and separation of activities, esp. separation of steps involving microorganisms and cell culture.

Good Manufacturing Practice (GMP): EEC, Japan, USA (FDA, formally not USDA), in Australia expected by 1994/1995.

Production outline including all in-process controls and quality control tests.

Validated test procedures with results of the validation studies.

Seed lot system for cells and microorganisms with complete history, passage limitations.

Starting materials

Specifications and quality control of starting materials. (Culture medium = one starting material.)

Starting material of biological origin: known origin, defined pools, testing for adventitious agents.

Starting materials not described in a Pharmacopoeia require description in the form of a monograph similar to a Pharmacopoeia description.

Consistency

Prelicensing serials (3 consecutive consistency batches).

May be run at pilot scale if it mimics full-scale production as described in production outline.

USDA: at least 1/3 the size of the average serial.

Stability

Real time stability tests based upon the identity tests for the active ingredient(s) and/or physio-chemical and biological tests; accelerated tests may be acceptable in USA (USDA) on a provisional basis, e.g. 7 days/37°C for 1 year/4°C.

Stability of product after reconstitution; tests under stress may be requested.

Potency

Titre, bacterial counts, amount of antigen, biological activity units with reference samples.

USA: 2 times (bacteria) or 5 times (viruses) minimum effective dose for entire shelf life.

Identity

Identification and assay of active ingredient, e.g. electrophoresis, ELISA or other methods.

In vitro or in vivo biological assays (specific serum neutralization of microorganisms, specific antibody formation in animals) may be necessary, if other methods do not adequately define the active ingredient.

Purity

Freedom of extraneous material "except what is unavoidable"; dependent upon product, process and state of the art, resp. comparable products.

For vaccines proof of absence of contaminating microorganisms, directly or by lack of antibody formation in animals.

Sterility/bacterial contaminants

Tests for sterility, abnormal toxicity.

Physical/chemical tests

pH, density, viscosity, emulsion droplet size, residual moisture in freeze-dried products etc.

Identification and assay of excipients such as vaccine adjuvants and preservatives.

Table 19: Safety Requirements for Veterinary Vaccines

Summary of EEC and USA requirements

Tests in most sensitive category of each target species.

Test vaccines made according to the production method for which the registration application is submitted

If made at a smaller scale, evidence must be given that scaling-up does not alter the product.

Validated techniques and test procedures**Good Laboratory Practice (GLP) test standards**

For EEC; formally for USA only if registration by the FDA.

Tests with maximum titre or potency for which application is submitted (EEC)**Safety tests in guinea pigs and mice or in the target species**

Country and product (group) specific batch safety tests. See for example 21 CFR, 610 for FDA requirements or 9 CFR, 113 for USDA requirements and British Pharmacopoeia (Veterinary).

Single dose test

EEC: Systemic and local reactions in all target species and categories, pathology if necessary.

Overdose test

EEC: each recommended route of administration, no definition of overdose.

USA: see specific requirements and standard procedures for most existing vaccines and for certain types of vaccines in 9 CFR, 113); Overdose: 2-, 3-, or 5-fold and usually 10-fold for live vaccines.

Safety of repeated administrations of one dose

Product dependent, test duration depends on frequency and duration of clinical use; USA: overdoses and repeated administration.

Reproductive Performance

Test requirements depend on product characteristics and indication.

Examination of immunological functions

EEC: if adverse effects possible.

Ecotoxicity assessment and studies where necessary**Safety of Residues**

Determination of the Maximum Residue Level (MRL) and Acceptable Daily Intake (ADI) for human food. May be necessary, e.g. for adjuvants and other excipients in products for food producing animals.

Table 20: Special Safety Test Requirements for Attenuated Live Veterinary VaccinesSummarized EEC and USA (USDA) requirements

Genetic characterization of parent and attenuated (recombinant) strain**Master seed microorganism and master cell bank:** Extensive characterization at lowest and highest passage level

USA: to be tested and approved by USDA separately and before field trials commence.

Genetic stability/reversion to virulence

Investigation of at least 5 back-passages; 10 back-passages for poultry vaccines.

Recombination or genetic reassortment

Testing and methodology to be decided on a case-by-case basis.

Biological properties of the vaccine strain

Test requirements depend on microorganism and strain specific properties, e.g. neurotropism, abortigenic and other potential pathological effects.

Dissemination and persistence of the vaccine strain in the vaccinated animal

Persistence in specific organs? Dissimilation via mucous excretions, feces, urine or milk?

Spread of the vaccine strain

Dissimilation within the population and to non-target species?

Extent of release into environment and (non-) persistence in the environment**Probability of human exposure and potential pathogenicity**

Table 21: Efficacy Requirements for Veterinary Vaccines

Summarized EEC and USA requirements

Dose response study (USA)**Definition of minimum effective dose (USA)****Controlled efficacy tests with untreated controls**

EEC: Trials with minimum titre or potency for which application is submitted.

Controlled field trials to assess efficacy and safety

Large number of animals, different geographic locations, different husbandry practices, animals of all ages, breeds etc.

Test vaccines made according to the production method for which the registration application is submitted; Use of prelicensure serials recommended.

USA: prior testing and approval of prelicensure serials, i.e. approval of production method required.

Efficacy to be demonstrated in each target species**All product claims must be supported by data**

E.g. claims on specific effects, onset and duration of effect, intended or recommended concurrent treatments.

Application of validated techniques and test procedures**Combined/multivalent products:**

EEC: efficacy of each component to be proven;

USA: "compatibility" must be demonstrated.

Lesser combinations registrable using the same dossier: USA: yes, EEC: no.

All results obtained must be reported, whether favourable or unfavourable!

Annex B

References and Information Sources

on Regulatory Matters

General Information Sources

Summary of Registration Requirements

International Federation of Pharmaceutical Manufacturers' Association (IFPMA),
Geneva, 1988

Griffin JP, ed.

Medicines: Regulation, Research and Risk, 2nd edition

The Queen's University of Belfast, 1992

(Summaries of UK, EEC, USA and Japanese Regulations)

WHO Requirements for Biological Substances; WHO TRS 323

World Health Organization, Geneva

OECD Principles of Good Laboratory Practice (GLP)

Organization for Economic Cooperation and Development, 1981

and EEC Volume II, Annex 2

Willig SH, Stoker JR

Good Manufacturing Practice for Pharmaceuticals.

A Plan for Total Quality Control. 3rd. edition

Marcel Dekker, New York, Basel, Hong Kong, 1992

Anderson M

GLP Quality Audit Manual;

and

Steinborn L

Quality Assurance Manual for the Pharmaceutical and Medical Device Industry;

and

Anon.

International Drug GMPs; 1988

All available from Interpharm Press (ca. 200 £)

Spilker B

Guide to Clinical Studies

I: Guide to Clinical Studies and Developing Protocols, 1984;

II: Guide to Clinical Interpretation of Data, 1986;

III: Guide to Planning and Managing Multiple Clinical Studies, 1987;

Raven Press, New York

Pocock SJ

Clinical Trials: A Practical Approach

Wiley & Sons, New York, 1983

Friedman LM, Furberg CD, DeMets, DL

Fundamentals of Clinical Trials.

J.Wright, PSG Inc., Boston, 1982

Pharmacopoeias and Related Books

European Pharmacopoeia (EP)
Loose-leaf edition with continuous updates.
Maisonneuve S.A., France

US Pharmacopeia/National Formulary (USP/NF)
US Pharmacopeia Convention, Rockville MD, USA

International Pharmacopoeia; Vol. I - III, 1979 - 1988
World Health Organization, Geneva

British Pharmacopoeia (BP)
Her Majesty's Stationery Office, London

BP (Veterinary)
Her Majesty's Stationery Office, London

and other national Pharmacopoeias in their latest edition.

Martindale
The Extra Pharmacopoeia, 30th. edition
The Pharmaceutical Press, London, 1993

Information Sources on Excipients

Handbook of Pharmaceutical Excipients
American Pharmaceutical Association/The Pharmaceutical Society of Great Britain, Washington, London, 1986

Katalog Pharmazeutischer Hilfsstoffe
Ciba Geigy, Hoffmann-LaRoche, Sandoz, Geneva, 1974

Fiedler HP
Lexikon der Hilfsstoffe fuer Pharmazie, Kosmetik und angrenzende Gebiete.
(Lexicon of excipients for pharmaceuticals, cosmetics and related areas)
Editio Cantor, Aulendorf/Germany, 1989

EEC Registration Guidelines for Human Medicinal Products

EEC directives and guidelines as well as the volumes summarizing "The Rules governing Medical Products in the European Community" are available on sale from:

Office des publications officielles des Communautés Européennes
2, rue Mercier
L-2985 Luxembourg

or from the local offices to the Commission of the European Communities in the capitals of community member states and other countries as well as from publishing organizations, business centres and libraries in several other countries.

Collection of Directives and Guidelines

"The Rules Governing Medicinal Products in the European Community"

Volume I : The rules governing medicinal products for human use in the European community (1989)

Volume II: Notice to applicants for marketing authorization for medicinal products for human use in the member states of the European community (1989)

Volume III: Guidelines on the quality, safety and efficacy of medicinal products for human use (1989)
Addendum 1 (1990)
Addendum 2 (1992)
Addendum 3 (expected 1993/1994)

Volume IV: Good manufacturing practice for medicinal products (1989)

Major EEC Directives and Recommendations Applying to Human Medicinal Products

<u>General organization/procedures</u>	<u>Also in Volume</u>
65/65/EEC: Regulations or administrative action relating to proprietary medicinal products amended by the five following directives:	I
83/570/EEC	I+II
87/21/EEC	I+II
87/22/EEC	I+II
89/341/EEC	I
75/319/EEC	I
75/320/EEC: Setting up of the Pharmaceutical Committees	I
78/25/EEC: Colouring matters which may be added to medicinal products	I
86/609/EEC: Protection of animals used for experimental and other scientific purposes.	I
87/18/EEC: Good laboratory practice (for tests on chemical substances)	I
90/18/EEC: Adaptation of Annex to 87/18/EEC to technical progress	I
90/679/EEC: Protection of workers from risks relating to biological	

agents at work.
 88/320/EEC: Inspection and verification of Good Laboratory Practice I
 EEC1768/92: Council Regulation on Supplementary protection certificate for medicinal products

Council directives introducing special provisions for biological pharmaceuticals

87/21/EEC:	Protection against a second applicant for high technology products	I+II
87/22/EEC:	High technology medicinal products, particularly those derived from biotechnology	I+II
89/342/EEC:	Vaccines, sera and allergens	
89/343/EEC:	Radiopharmaceuticals	
89/381/EEC:	Blood and plasma products	
90/220/EEC:	Deliberate release into the environment of genetically modified organism	

Data requirements

75/318/EEC:	Analytical, pharmacotoxicol. and clinical standards and protocols	I+III
amended by the following directives:		
87/19/EEC:	Analytical, pharmacotoxicol. and clinical standards and protocols	I+III
83/571/EEC and 87/176/EEC:	Recommendations relating to pharmacotoxicological tests and tests for specific product groups	I+III
91/507/EEC:	Complete update of the annex to 75/318/EEC on analytical pharmacotoxicological and clinical standards and protocols	

"Future Systems" legislation package:

published in: Off. J. EEC, L214,(24.8.93)
 EEC 2309/93: Establishing a European Agency, new centralized registration procedures
 93/39/EEC: Medicinal products registration procedures
 93/41/EEC: High-technology products (EEC 2309/93 to replace 87/22/EEC after 1994)

3. Selected CPMP Guidelines

Quality guidelines

Development pharmaceutics and process validation (4/1988)	III
Chemistry of active ingredients (10/1987)	III
Stability tests of active ingredients and finished products (7/1988)	III
Analytical validation (7/1989)	III, Add.1
Drug master file procedure for active ingredients (7/1990)	III, Add.1
Radiopharmaceuticals (12/1990) and Radiopharmaceuticals based on monoclonal antibodies (12/1991)	III, Add.2
Good Manufacturing Practice of investigational medicinal products (7/1993); Ref. No.: III/3004/91	

Pharmacotoxicological guidelines

Single dose toxicity (2/1987)	III
Repeated dose toxicity (10/1983)	III
Reproduction studies (10/1983)	III
Testing of medicinal products for their mutagenic potential (2/1987)	III
Testing of medicinal products for their carcinogenic potential (10/1983)	III
Pharmacokinetics and metabolic studies in the safety evaluation of new drugs in animals (10/1983)	III
Non-clinical local tolerance testing of medicinal products (12/1990)	III, Add.2

Biotechnology guidelines

Production on quality control of medicinal products derived from recombinant DNA technology (7/1987)	III
Production and quality control of monoclonal antibodies of murine origin (7/1987)	III
Preclinical biological safety testing of medicinal products derived from biotechnology (9/1988)	III
Production and quality control of cytokine products derived from biotechnological processes (2/1990)	III, Add.1
Production and quality control of human monoclonal antibodies (7/1990)	III, Add.1
Validation of virus removal and inactivation procedures (2/1991)	III, Add.2
Radiopharmaceuticals based on monoclonal antibodies (5/1991)	III, Add.2
Guidelines for minimizing the risk of transmission of agents causing spongiform encephalopathies via medicinal products (12/1991)	III, Add.2

General clinical guidelines

Recommended basis for the conduct of clinical trials of medicinal products in the European Community (5/1987)	III
Clinical investigation of medical products	
- in children (9/1988)	III
- in the elderly (9/1988)	III
Pharmacokinetic studies in man (2/1987)	III
Investigation of bioavailability (2/1987)	III
Clinical testing requirement for drugs for long-term use (2/1987)	III
Fixed combination products (10/1983)	III
Good clinical practice for trials on medical products in the European Community (7/1990)	III, Add.1
Clinical testing for prolonged action forms with special reference to extended release forms (7/1990)	III, Add.1
Investigation of bioavailability and bioequivalence (12/1991)	III, Add.2
Discussion paper on the harmonization of approval of clinical trials; Ref. No.: III/3044/91	

Information Sources on Registration Requirements in the USA

21 CFR (US Code of Federal Regulations), Food and Drugs

Chapter I, Food and Drug Administration, Department of Health and Human Services.

Subchapter A, Parts 001-099: General

C, Parts 200-299: Drugs

D, Parts 300-499: Drugs for human use

F, Parts 600-699: Biologics

H, Parts 800-899: Medical devices

Revised annually; available from:

The Superintendent of Documents, Government Printing Office,

Washington D.C. 20402

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