13

Management and Maintenance of High Throughput Screening Systems

Barbara Hynd

1. Introduction

The object of all high throughput screening (HTS) laboratories is to provide the pharmaceutical research community with potentially active compounds rapidly and in the most cost effective manner possible. The most reliable way this can be achieved is by rigorous attention to the quality of the assays themselves, the quality of the compounds used, as well as the quality and condition of the equipment used. To effectively reach this goal all of the systems needed within the screening environment must function in a smooth, efficient manner. Since the complexity of the equipment used in screening labs is constantly increasing, the requirements for its continued maintenance are problems faced in all laboratories. An additional process that requires constant maintenance, but that is often forgotten, is management of personnel within the screening environment. This is, however, also an integral part of the efficient screening process.

In most companies HTS has evolved out of the research area and these groups have had to learn to adapt manufacturing principles for use in a research environment in order to become efficient. Since research laboratories do not have to conform to Food and Drug Administration (FDA) requirements as do the development and production laboratories, the concept of routine quality control has been alien to many that move into screening laboratories. Reliability has always been expected of laboratory equipment, but in research laboratories there was usually little impact if equipment was unavailable for a day or so. This situation is not acceptable in HTS since the whole premise is that nothing should stand in the way of the screens being run. Project timelines, which are set with the expectation that HTS is a fast process, can be adversely

From: *Methods in Molecular Biology, vol. 190: High Throughput Screening: Methods and Protocols*
Edited by: W. P. Janzen

affected if the equipment is unreliable or the screening assays are not robust and reproducible. Thus accuracy of equipment performance is a vital part of maintaining an efficient screening facility.

2. Equipment Requirements

The equipment found in HTS facilities varies from workstation like instrumentation to large multitasking robotic installations. All of these systems have evolved according to the requirements of the individual companies and their methods of working. Some laboratories only take a limited number of assay types as HTS and thus require a limited variety of instrumentation. Larger facilities may have the luxury of sufficient numbers of fully automated robotic platforms, which can be dedicated to individual assay types. There are also other groups intermediate to these two extremes who require as much flexibility in their screening repertoire as possible. All of these groups have the same core requirements: accuracy, precision robustness, and reproducibility, both for the equipment and the assays themselves. The equipment and support systems, discussed in this chapter, will be a representation of those commonly found in the chemical repository and assay throughput areas of an average HTS facility.

2.1. Chemical Repository

There is no current universally preferred format for a chemical repository and the maintenance methods depend on the equipment and format of the repository itself. The current storage methods depend on the library format and can range from storage as dry films in an inert atmosphere at −80°C to storage at room temperature in dimethyl sulfoxide (DMSO). Universal acceptance of one set of conditions for compound storage has not yet occurred for a number of reasons. The main one is lack of adequate data as to which conditions are really optimal since degradation studies performed by individual companies have not been published. The cost of replacing existing storage facilities is also a major concern to company management and has to be balanced against the value of the existing library. The result of this is that each company has developed a compound handling system that is peculiar to their situation.

Irrespective of the system used, control of the environmental factors must be recorded either by manual logging of temperature, humidity, and oxygen levels or by continuous electronic monitoring. The latter method is the one of choice since it is less prone to error and can give accurate timing of adverse events. Most older, manual or semi-manual storage instrumentation can be retrofitted with fully automated recording and alarm devices at a nominal cost. Continuous charting of the collected data will give indications of some potential problems but should not preclude regular visual examinations of known

problem areas such as seals and vents. In addition any robotic or mechanical component of the system must have a regular maintenance schedule set up and strictly adhered to (*see* equipment maintenance, **Subheading 4.**).

The quality control of any library, whatever the format, is very important and it is particularly advisable to have analytical checks done at regular intervals for any library that is held in a liquid format. The chemical composition of the compounds should be confirmed prior to addition to the library and the method used should be routine for the analytical services used to support the HTS facility. These results should be compared against the compound data provide by the synthesis laboratory, before the structures are stored in the library data base. Routine repetitive analysis of a representative set of compounds is advisable to monitor the status of the library over time. Contamination of the library can occur in several ways. Inattention to adequate tip-washing techniques, and in a microtiter plate, liquid format library, cross contamination from nearby wells, are the most common causes. However, contamination can occur from compounds extracted from the sample tube, the microtiter plate, the lid or sealer components, or from a combination of each. Studies are underway to investigate this and some information is already available from individual plate manufacturers. The larger companies, e.g., Becton Dickenson and Corning Costar, have undertaken such studies and information may be obtained by contacting their technical departments through the local technical representative. Some repository facilities require libraries held as dry films to be checked for chemical composition and concentration before use in a screening assay, since dissolution after drying may not be complete. This puts added strain on their analytical support groups as well as potentially slowing down the screening process.

Should a compound prove active, further analytical confirmation of purity can then be performed using more specialized techniques such as liquid chromatography/mass spectrometry (LC/MS). All of the data gathered about the composition of the library compounds should be recorded within the repository database for future reference.

2.2. Screening Facilities

HTS facilities vary in their charters and hence in their requirements. At one end of the spectrum, some HTS facilities are specific for a restricted type of assay format and at the other end are those facilities that have to accommodate any type of assay required by any therapeutic area within the company. It is generally easier to set up a facility for specific assays than to set one up to cover all eventualities. With a specific assay format, the physical plant of the facility can be arranged to give the optimum working environment for both people and instrumentation, whereas compromises have to be made for more complex and flexible installations.

2.3. Controlled Environment Screening

Many screening laboratories require that some of the instrumentation be able to be run in a sterile environment. Performance of cellular or microbiological assays requiring live cell seeding followed by addition of reagents and incubation are best carried out in completely sterile conditions. This is easier to arrange in a dedicated facility, as sterile areas can be arranged and maintained with specific parameters in mind and issues of equipment arrangement can be optimized. In a large open laboratory area or in a screening facility covering multiple assay types, this is more difficult to arrange. One solution to the sterility problem is to position individual pieces of automation beneath a series of ceiling mounted fans with high efficiency particulate air (HEPA) filters attached. Installations of this type are commercially available from companies manufacturing clean rooms but are also found as "in house" installed units in some facilities. A selection of address for companies specializing in this type of installation can be obtained from Cleanrooms.com of San Mateo, CA. (www.info@cleanrooms.com). The filtered fans provide a down flow curtain of "sterile air" which directs environmental contamination away from the equipment. These fans need to provide airflow of at least 90 cu ft/min when measured 6 inches from the fan outlet.

The best method for validating the efficiency of the air curtain is by electronic checking of the airflow velocity, followed by smoke testing, and is best done by a qualified external company. This monitoring does not preclude checks for surface contamination by airborne organisms. A simple check for viable organism levels can be performed by exposing unlidded petridishes, containing bacterial growth or fungal media, in the area under the running fans for a standard time period. The petri dishes should then be incubated and the growth level checked at 24 and 48 h ***(1)***.

Another solution to the problem of robotic sterility is to use some form of structural enclosure around the individual open automation units and have HEPA filtered air pumped in as an air curtain at approx 100 cu ft/min. Several manufacturers produce enclosures of this type, which have clear plastic walls and are capable of supporting the air-handling equipment on their roofs. In an open facility, use of these enclosures enables even bacterial and cell-culture screens to be done in close proximity to one another without worries of cross-contamination. This type of enclosure can also be used for odor containment in the chemical repository area by reversing the airflow and passing it through activated charcoal filters as it exits. Monitoring of the efficiency of the air-handling mechanisms in this type of enclosure is best contracted to an independent, biological hood certification company. In the absence of such a company, the airflow through the filters must be checked at least yearly using a simple

airflow gauge, and the filters changed when the flow drops below 90 cu ft/min or after 3 yr, whichever comes first. Further details on the optimization of clean room systems can be obtained from standard texts ***(2)***.

3. System Management and Support

The smooth running of a HTS facility requires attention not just to instrumentation, but also to the personnel who work in the facility. The performance of an HTS facility has more in common with a manufacturing process than with academia or research from which most of the screeners are recruited. The heavy emphasis on automation of repetitious tasks necessitates that engineering support be available at all times since the robotic complexity obviates the usual laboratory methods of self-support. It is not imperative that small HTS groups employ individual engineers if they feel that traditional equipment maintenance agreements and in-house expertise are adequate. Larger groups often find it necessary to have continuous engineering support and this comes either from internal company expertise or from specialist engineers hired directly into the screening group. Unless dedicated engineering support is very comprehensive, it is advisable that some form of service agreement be available for all the systems within a facility, so that highly specialized repairs can be done as quickly as possible. Most equipment vendors operate on a priority system for parts and supplies, and lack of a service contract often removes a company from the vendor's priority list. One attractive alternative to the previous solutions is for a service support contract to be developed with the instrument company providing the majority of the automation. This contract would ideally provide permanent on-site engineering support for the automation as well as blanket coverage for peripheral instrumentation attached to the robotics. Such contracts do exist and, although expensive, have proved very valuable to the companies able to implement them.

3.1. Routine System Management

Management of a multitasking HTS facility requires accurate scheduling of equipment use, which should be revisited on a regular basis. The method used for this must be easily understood and should include time for routine equipment maintenance as well the actual time the instrument is being used for assay runs during the day. A convenient time frame for the routine equipment use schedule is two weeks, but a master schedule is also needed to apportion assay campaigns during the year. Combined use of these two schedules allows for planning and information sharing between assay groups. Placing the routine schedule on a shared drive allows screeners to update equipment usage and improves the efficiency of the whole HTS facility.

3.2. Performance Tracking

One of the most important concepts in laboratory management is to understand the necessity of tracking performance *(3)*. This is done easily by the generation of "Key Indicator Tracking" data. A key indicator is a measure of a process of prime importance to the task under scrutiny. The workflow together with the key indicators required by a typical HTS facility is described in **Fig. 1**. Key indicators need to be in place for process and quality measurements when operating in the true high-performance work-team manner that has proved so successful in the manufacturing world *(4)*. Each key indicator measures progress towards a team-determined goal and is approved by the team members before implementation. These goals are revisited each year and are revised as necessary. The key indicators that have most relevance within the screening environment are the three quality measurements (Q1–Q3) and the three process measurements (P1–P3) described in **Fig. 1**. These indicators cover both instrument and personnel performance within the facility and are vital to ensure reliable performance and rapid resolution of problems. The key indicator data is determined by the team goals and collated into a visual form such as a graph by a designated team member. Most of the key indicators are updated weekly, with only two (P1 and Q4) being updated quarterly. All the indicator graphs are then displayed for the team's information at a central location within the screening facility.

3.3. Team Composition

The balance between the engineering, chemistry, and biological personnel in a screening group is peculiar to each individual company. Some companies have a preponderance of scientists relative to engineers, others have the reverse. Smaller groups with staffing problems often find it cost-effective to employ temporary personnel for the more routine portion of screening. All groups have the same difficulties in maintaining continuous quality control across all members. One effective method of making sure that continuous quality control occurs is to form a high-performance work team using cross-functional teams within the HTS unit. Teams within the unit have responsibility for defining the direction of a specific area within the overall unit and develop a work plan specific to their area. Examples of these teams could be an Assay Team, a Data Handling Team, and a Compound Team. Open communication channels need to be maintained within the overall HTS unit to ensure continuity. The efficiency of each team is monitored by quarterly feedback documents that are requested from each teams customers. In the case of HTS, customers are defined as groups, such as therapeutic areas, which accept data from the unit, or other teams within HTS. Within HTS, upward feedback is generated by the technical

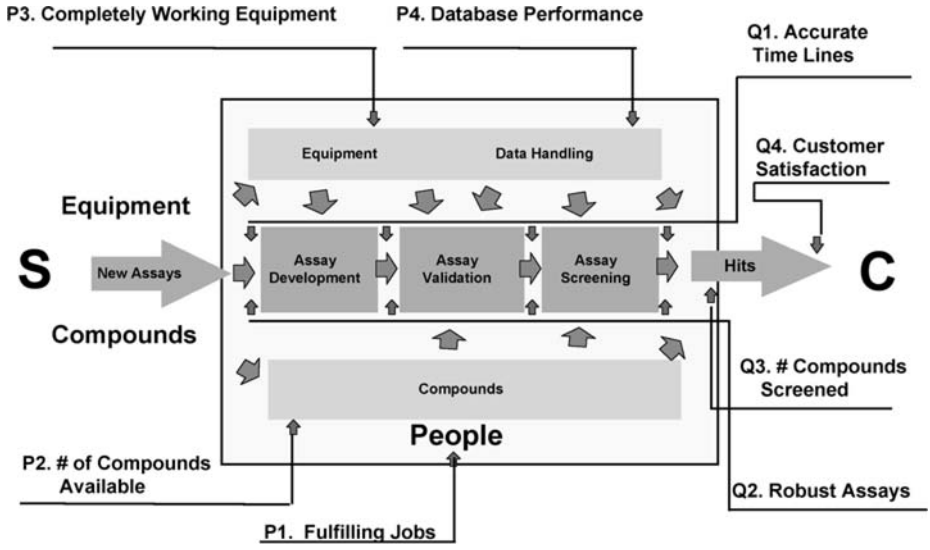

Fig. 1. HTS process chart: Diagrammatic representation of the indicators for performance (P) and quality (Q) used to measure the efficiency of the HTS system.

staff providing feedback on the supervisor's performance using the same basic system as for the customers of the whole team. All types of feedback forms are designed to provide constructive comments that can be acted on for future improvement and are generated quarterly. The forms can be completed anonymously and collated by someone outside of the group, preferably from human resources. An example is provided in Appendix 1. The data is then collated and graphs plotted showing progression towards the team's published goals. This data is reported out quarterly as the Q4 indicator. The HTS team holds annual workshops to analyze the previous year's results and to define the next year's challenges. An example of the graphs developed is shown in **Fig. 2**.

3.4. Equipment Performance Tracking

The function of the in-house engineering staff of an HTS facility is crucial. Their primary function is to provide engineering support to the robotics for reconfiguration or in a breakdown situation. An equally important part of their function is to oversee the records of each piece of equipment and to produce the historical information to enable the operators determine the equipment efficiency. When a new piece of instrumentation is received into the laboratory, all the manuals and software should be placed together in a well-defined

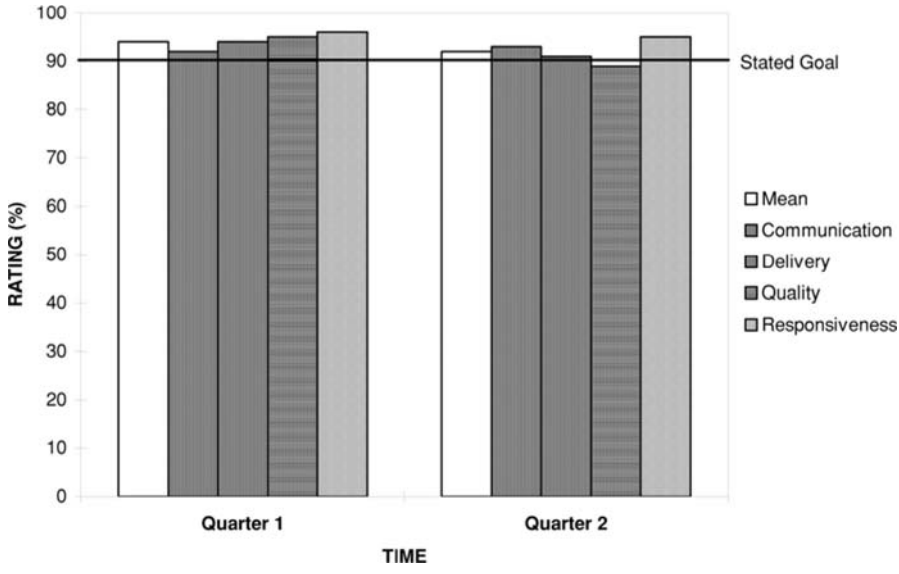

Fig. 2. Graphic representation of customer feedback measured over time identifying areas of potential improvement.

area for future reference. The first document, which needs to be written for every piece of equipment, is a description of the instrument and it's mode of action. This document need not be as detailed as a Standard Operating Procedure (SOP) required by manufacturing facilities, but detailed enough to provide easily followed instructions for casual users. In our hands these are dynamic documents that are updated regularly and are known as Current Best Approach documents or CBA's (*see* **Appendix 2**). In addition, each instrument has a laminated "cheat sheet" attached to it outlining the basic procedures of the instrument, such as how to switch it on and emergency procedures for shutting it down. The third document developed for each instrument is a logbook that is used for performance tracking. The information required held in the logbook is a historical, factual account of every procedure performed on the instrument, together with all the service reports for the equipment or its components. The operator must accurately fill in this record every time the equipment is used, even if the instrument performed perfectly. Correct use of this system allows slowly developing situations to be identified and dealt with before they become major problems. Basic laboratory general use equipment such as refrigerators, incubators, centrifuges, and hand-held pipetting units should be included in this performance documentation, with practical adjustments made to the paper work (e.g., no "cheat sheets" for individual hand-held pipettors).

There are several widely used systems for tracking instrument performance, varying from completely manual to fully computerized. The major problem with any tracking system is that it usually relies on human introduction of information. The simplest method of information gathering is the previously mentioned logbook. This is attached to each instrument or workstation and into which information is entered as each run is performed. Transfer of data from this logbook to a spreadsheet for historical tracking is time-consuming and error-prone. One of the most efficient methods is for each instrument's 'run program' to have an electronic spreadsheet attached to it that must be completed before any run data can be archived. The information required by this spread sheet is identical to that required in the logbook method and a similar format can be devised. The collected data is then automatically downloaded into an historical data file and stored. Currently there are no commercial programs able to do this and those in use are site specific. An example of the basic data required maintaining historical tracking of instrument reliability is to be found in **Fig. 3**. This is an example of the instrument-reliability graph posted as HTS key indicator P3. Recording runs completed both with and without operator intervention enable distinctions to be made between simple malfunctions and those requiring engineering intervention. On multitasking systems differentiation between errors of software and peripheral hardware are often picked up in this manner. A similar graph can be produced from the electronic data-acquisition system should that be available. The results from either method must be reviewed on a regular basis and remedial action taken if necessary.

4. Examples of Requirements for Maintenance Programs

4.1. Pipetting and Dispensing Equipment

Routine checking of all pipetting and dispensing equipment for accuracy is one of the primary requirements of any HTS maintenance program. Any valid quality-control program should require all pipetting and dispensing units, both manual and automated, to be checked independently at least twice yearly. This procedure can be performed either in house or by a reputable outside contractor. All calibration records should be kept by both the contractor and the owner laboratory as a safeguard in case of future problems. In all cases the operator should be aware that the quality of the disposable tips used with any type of aspiration pipetting or dispensing unit has direct bearing on the reliability of the whole system. At no time should tips be used that are not recommended by the equipment manufacturer. Some tip manufacturers apply strict quality controls to their manufacturing processes and statistical details of the manufacturing batches can be obtained if requested. Common variations in pipetting accuracy are blocked tips or dispensing head mandrels, failure of the dispense

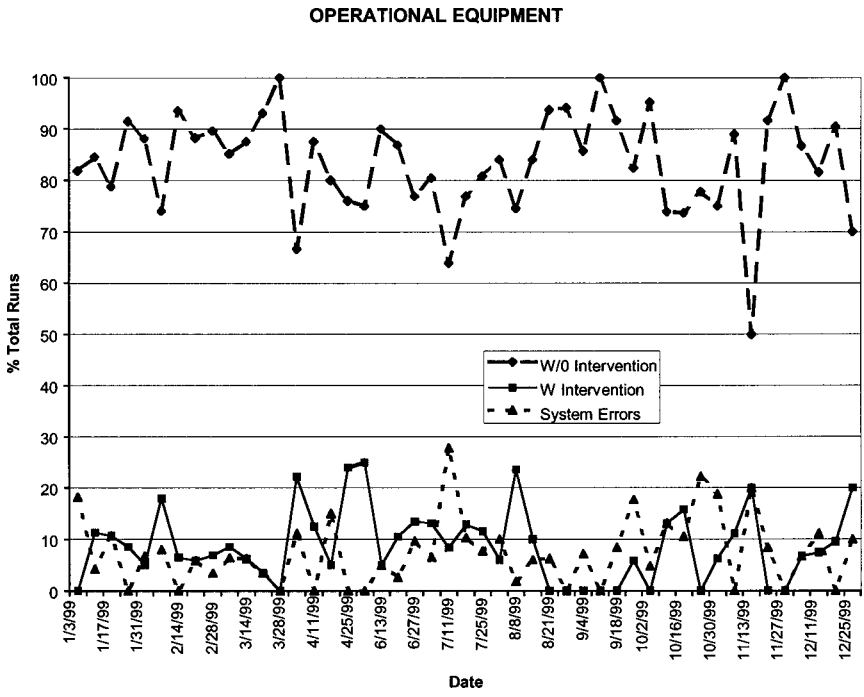

Fig. 3. An example of historical reliability data and error charting for a routine HTS laboratory.

mechanism itself, and lack of attention to the viscosity of the liquid being pipetted. Maintenance of peristaltic dispensing units also requires similar dispensing volume validation. Most dispensing heads on this type of equipment are calibrated during manufacture and need rechecking during use to confirm their performance efficiency. They should be replaced at regular intervals or when performance efficiency begins to deteriorate. It is considered good practice to run check plates of each liquid handling device prior to each assay run to prevent potential pipetting errors. There are two commonly used methods for checking the reliability of any type of dispensing tool. The first is a spectrophotometric method using a colored solution and is of most use for pipetting units with capacities above 50 µL and thus is used for 96-well microtiter plates. The microtiter plates used for this procedure must have flat-bottomed wells and be as optically clear as possible to cut down on optical-reader distortion. Some laboratories prefer to use glass microtiter plates for this procedure. The optical density of the dispensed liquid in each well is read at the peak wavelength of the chosen dye. This procedure can be performed with food coloring,

which is easily obtained, and the spectrum of which can easily be determined on any scanning spectrophotometer. The second method employs fluorescene, which is used for much smaller pipetting volumes and requires the use of a fluorescence spectrophotometer with a 490 nm excitation filter and a 520 nm emission filter to read the results ***(5)***. Solid black or white microtiter plates should be used with the fluorescence technique to reduce the well to well cross-talk and to obtain the most sensitive signal. The concentration of the dyes in both cases should be adjusted to give values within the center of the readers sensitivity range so maximum accuracy is obtained.

All dispensing is into microtiter plates and the results read on microtiter plate spectrophotometers or fluorometers, which allow visualization of the results in a plate format, thus easily isolating problems with individual mandrels and/or tips. Analysis of the results from these tests should give the operator the mean well volume with the standard deviation. Two other useful parameters are the standard deviation of the rows and columns across the plate. If there is a suspicion of problems with disposable tips then several iterations of the method should be performed to check the reproducibility across a series of tip loads. The same method can be used for 384-well dispensing units and the same calculations performed. An alternate method of reading is to use the weight of the microtiter plate before and after dispensing a fixed volume of liquid. This does not enable checks to be made on individual mandrels but just records the total volume dispensed. If the pipetting head is found to be defective, a document recording all the observed parameters should accompany the freshly cleaned head when it is returned to the manufacturer for refurbishing.

4.2. Detection Equipment

The detection equipment found in a screening laboratory depends on the type of assays done by that facility. Usually equipment for fluorescence, spectrophotometric, luminescence, and radiometric measurements are all required. Detection units, which are automation-friendly, are readily available for each measurement type and it is advisable to purchase multiples of the same type of detector if finances allow. Use of identical equipment permits assays entering screening to be developed using the same parameters as will be required when they are transferred to full-scale automation. This is a simple method if using a modular robotic system, but often difficult if custom designed systems are used. A common misconception about detection instruments is that identical models will perform in identical fashion. This is not necessarily the case since the majority of detection equipment still uses photomultiplier tubes (PMTs) and these can vary significantly from instrument to instrument. This misconception becomes very obvious when several instruments with unmatched PMTs

are used to perform fluorescent polarization. In some cases the software can be manipulated to "balance" the results of a single assay between differing instruments to give consistent results. " Balancing" should always be carried out with the knowledge of the instrument manufacturer since some parameter changes could lead to confusion when a routine service engineer is called in for unrelated problems. This balancing process has to be repeated every time a lamp or PMT is changed. Misunderstandings due to lack of adequate operator training often result in little attention being paid to the type and quality of the filters used within detectors. This is of great importance in fluorescence assays using several endpoint detectors in one assay or on one robotic unit where it is imperative that all filters be identical to ensure data integrity. Information on standard filters is usually easily obtained since most companies provide details of the filter parameters in their instrument manuals. Lists of the filters used within individual instruments should be kept in the instrument logbook and alteration of the filter profiles restricted. Alteration of filter positions within an instrument must be also noted in the instrument logbook and software. Failure to do this will result in measurement errors when the wrong filter is used. Routine checking of filter sensitivity should be carried out if at all possible. Microtiter plates containing stable fluorescent indicators can be obtained for this procedure and checking the results of these plates over time will give an indication of the reliability of the detector light path.

End-point detection in luminescent and radioactive assays is usually performed with the same instrumentation. These instruments were primarily designed for radioactive assays but were found to be suitable for luminescent measurements. Checking of this instrumentation for background and normalization must be done on a regular basis using the instructions provided by the manufacturer. The use of injection or "flash" luminescence has resulted in the introduction of reagent injection units into some radioactive detectors. These injection units are rugged but require regular cleaning methods to be in place to prevent clogging of the liquid-handling system. Since there are routinely only one or two injection ports per unit, it is a relatively trivial task for the operators to perform at the end of each run. One method that can be used is the fluorescence-dye technique outlined in the liquid-handling maintenance section followed by repeated flushing of the injection system to remove all contamination (*see* **Subheading 4.1.**).

In this discussion of the detection equipment only common instrumentation has been mentioned. There are many different manufacturers with a variety of alternate methods of detection, all of which provide some improvement for a specific assay type. If all available assay types are supported, it can result in a large number of differing designs of detection units being needed within the

screening facility. This scenario is expensive to implement and difficult to maintain. To address this situation some manufacturers have developed equipment with the ability to detect several different end-points, e.g., combined fluorescence and spectrophotometric readers. Many of these combination detector designs have a bias towards one of the detection mechanisms and thus need to be carefully evaluated before purchase.

4.3. Developmental Equipment

In addition to the robotic instrumentation within an HTS facility, the equipment used for development of assays and for development of novel screening technology has to be accommodated. In an ideal situation the dispensing and detection instrumentation required for development of potential screening assays should duplicate the equipment that will be used in the final automation systems in order to simplify cross validation. Such luxury is not possible for most laboratories and so accommodations have to be made that nearly always delay the speed of the screens. The equipment used for development of new screening technology is often from smaller vendors without adequate engineering support systems and no published methods for accuracy checking. In these cases, it is advisable that the operator develop both training and maintenance documentation for each novel item. Both of these types of equipment must also be regularly serviced and calibrated in line with the larger units.

4.4. Computer Maintenance

Nearly all of the equipment in a screening laboratory uses personal computers (PCs) to control both the robotics and to handle the generated data. PCs are powerful tools when operating properly, but they can cripple productivity when they fail. Laboratory PCs frequently have specialized hardware and software requirements dictated by the vendor of the equipment the computer is connected to. End users can save time and money by following a few basic guidelines in helping to maintain their lab computers.

When a new PC enters into the lab keep all the manuals and software together for future reference. This is especially important when there are numerous PCs in the lab. If serious problems develop in the future, one of the information technology (IT) professionals may need the specific disk or manual that came with the computer to troubleshoot and fix it. A logbook for each computer should be set up when the computer is received. The model and serial numbers must be recorded in it along with date and vendor. Each time the hardware is upgraded or new software is installed or modified the alterations to the system must be added to the logbook. This history can be very helpful when trying to troubleshoot problems.

A startup disk or emergency-repair disk should be made and updated at any time changes are made to the system. It's a good idea to run a check disc or utilities program once a week and to "Defrag" once a month. These utilities can often catch and fix minor problems before they turn into big ones. Old, unused log files, temp files, etc., that gradually fill up and slow down your hard drive (HD) should be cleaned out at the same time.

Statistically, the HD is one of the most likely hardware components to fail. When the hard drive fails, not only is all data lost but so is the operating system, application programs, and custom settings, methods, and tweaks, sometimes the hardest to recover. It is preferable to perform full HD backups for all critical computer systems. Backing up can be done to an outside server or independently to a hardware storage system. There are two parts to providing an independent backup: first the backup software and then the hardware storage device. If the HD fails and requires replacing, the same backup software can be used to restore (copy back) the entire contents of the original HD to the new one, complete with all custom settings, etc.

4.5. Data Management

Data files from detectors should be moved to an independent server or personal computer at the earliest opportunity. Reliance on the detector internal-storage system can occasionally lead to loss of data files due to mistakes from different operators using the same equipment. Backing up and general management of assay data files should be the responsibility of the screener in charge of that assay since "ownership" is a potent force in the efficient performance of a screen. Validation of data-handling packages is a complex procedure and should also be included in the continuous monitoring off a high-performance facility ***(6)***.

All data should be backed up on a daily or "each run" basis to minimize loss in event of an accident. The most efficient method for data handling is "real time data acquisition and calculation," which is available only to those screening groups having adequate IT support. Lack of foresight by some groups in the past has resulted in companies having data-handling packages, which have very rapidly become too small to handle all their requirements. When a data-handling package is purchased it should ideally be very flexible and have the ability to interface with all other software packages used within the screening group, chemistry, and the therapeutic areas. The ability of all groups to access and enter data into the same linked system cuts down on errors and misunderstandings and eases data mining. This type of system is always large and requires extensive IT support to maintain it reliably and the cost and requirements for its upkeep can make it an unattractive option for some facilities.

5. Conclusion

It is hoped that this chapter will provide both new and experienced screeners with fresh insights into the complexity of maintaining an efficient HTS facility and will provide a basis for improving the work processes within all screening facilities. Continuing improvement to the processes will result in even greater efficiency and reliability resulting in faster and hopefully better, identification of new drug entities that will result in benefits for all.

References

1. *Microorganisms in Clean Rooms, Standard IEST-RP-CC023-1.* (1993) Institute of Environmental Sciences and Technology (IEST), 940, E. Northwest Hwy, Mt. Prospect, IL 60056.
2. Liptak, B. G., (1998) *Optimization of Industrial Unit Operations*. CRC Press, Boca Raton, FL.
3. Shewhart, W. A. and Deming, W. E. (1990) *Statistical Method from the Viewpoint of Quality Control*. Dover Publications Inc., Mineola, NY.
4. Graham Brown, M. G. (1997) *Baldridge Award Winning Quality*. Productivity Press Inc., Portland, OR.
5. *CCS Packard/PlateTrak Service manual revision* (2000) Packard Bioscience, 2841, Lomita Blvd, Torrance, CA 90505.
6. Lewis, W. E. (2000) *Software Testing and Continuous Quality Improvement*. CRC Press, Boca Raton, FL.

Appendix 1

EMPLOYEE SATISFACTION INDEX

Appraising (Name): _____

Your Name: _____ Date: _____

GRADE		SCORE
A	Total Customer Satisfaction	>90%
B	Customer Generally Satisfied	70-89%
C	Customer Generally Dissatisfied	40-69%
D	Total Customer Dissatisfaction	<40%

* If Scoring is rated "B" or less, please explain your reason so that improvements can be made.

** Please give an exact numerical score as well as a letter grade.

	GRADE	SCORE
Communication: Use of basic principles, effective method established for two-way verbal and written message or instructions, and timely communication relevant to helping you do your daily work.		
Delivery: Timeliness, keeps promises, facilitates work flow, helps eliminate barriers to help you do your job.		
Quality: Provides quality product and/or service (i.e., accurate information), provides ideas, consistency, and clear priorities, communicates and follows up on short- and long-term career development needs.		
Responsiveness: Exhibits courtesy and professionalism, provides appropriate and timely feedback and advice resulting in total employee satisfaction.		

Comments:

_____

_____

_____

Appendix 2

CURRENT BEST APPROACH

High Throughput Screening Laboratory

Date	Equipment/Instrumentation	Page
		1/

Type of Instrument

Operation, Calibration, Maintenance and Identification

I. SCOPE: This CBA describes the general procedures to be followed by users of the instrument. General operating procedures, validation procedures and maintenance procedures will be described.

II. REFERENCES: Often reference to the instrument manual

III. COMPONENTS/PERIPHERALS: A complete list of instrument components if modular, including computer.

IV. RESPONSIBILITIES:

PERSONNEL	RESPONSIBILITIES
Scientist	For running, for repairs etc.

V. SPECIFIC PROCEDURES: What it can be used for.

VI. SUITABILITY: Description of suitability of instrument for task.

A. Operation	Detailed practical documentation.
B. Calibration	Specific protocol for instrument.
C. Safety Issues	Specific to the instrument
D. Documentation and Record Keeping	Where kept and in what format.
E. Identification and labeling	Model, serial number and other identification.

VI. ATTACHMENTS: Any other documentation.

Approval Signatures: Date:

_____ _____

_____ _____

Author: Date:

_____ _____