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Fully Automated Screening Systems

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1. Selecting the Hardware

1.1. Introduction

As a scientist or manager involved with high throughput screening (HTS), you have a wide range of options when selecting the degree of automation to support your discovery efforts. You will want to think about your anticipated needs 2–4 yr (or more) into the future and whether those projected needs will require a fully automated system.

Initially, many organizations use individual workstations for pipetting, incubating, mixing, washing, dispensing, plate reading, etc., with lab technicians moving the plates from station to station. This is simpler and requires less capital expense than a fully automated robotic system. The disadvantage with the workstation-based laboratory is that the processing of the assay and the overall plate throughput is very dependent on the lab technicians themselves. The results of the assay can vary significantly according to the attention to detail given by the laboratory technicians, and overall throughput also can vary significantly according to the staffing levels and the technicians' interest in processing the microplates as accurately, quickly, and efficiently as possible.

As throughput requirements and laboratory budgets increase, the disadvantages of manual workstations compel users to consider fully automated robotic systems. Fortunately, some types of fully automated robotic system are very flexible, can use many of the manual workstation instruments that you are already using in your laboratory, and allow the individual workstations in the fully automated system to be upgraded in the future as these devices are improved.

The degree to which you automate your laboratory will depend on many factors, including your throughput requirements and how this will grow in the

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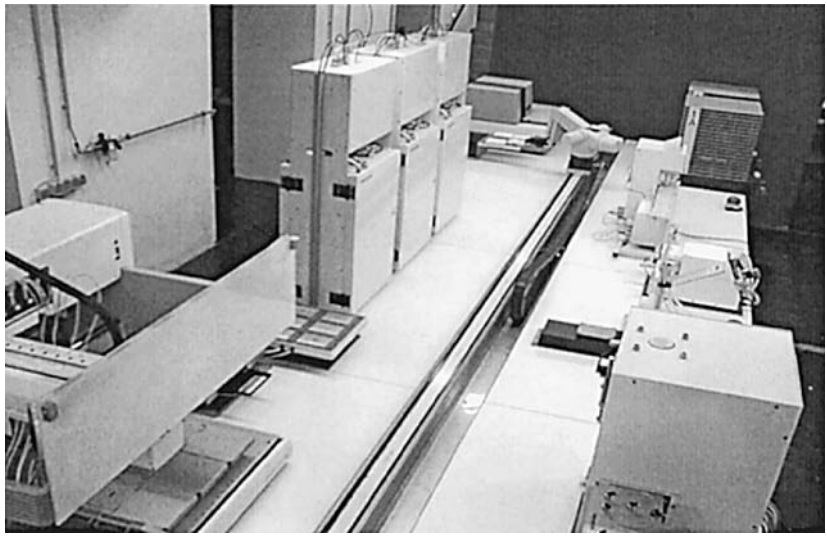

Fig. 1. Example of a fully automated high throughput screening system.

future and the amount of money that can be allocated to automation. A picture of a fully automated robotic system is shown in **Fig. 1**.

Some of the advantages of fully automated robotic systems or HTS include:

1. Assay steps performed consistently from run to run, independent of the operator.
2. Data and compound identification can be automatically tracked through the primary screen, confirmatory assays, and secondary screens with no errors.
3. Some types of fully automated robotic systems will run unattended continuously 24 h per day, 7 d/wk to provide maximum plate throughput.
4. Flexible robotic systems can run many different types of assays with no changeover time or learning curve.

The mantra of virtually every HTS laboratory is flexibility, reliability, and reproducibility. When considering various types of equipment, be sure to fully investigate the equipment and the vendor to make sure that they offer the best of these requirements. Reliability can be determined by checking with other users and investigating the equipment yourself. Reproducibility can be measured by performing standard evaluation tests, either within your department, by the vendor, or by a third party such as another user of the instrument.

1.2. Your Future Needs and HTS Trends: Divining The Future

Certainly it is very difficult to predict your future needs, as well as future trends in the industry, but you want your fully automated HTS system to be as compatible as possible with the methods and protocols that you'll likely use in

the future. Some trends can be identified and are listed below. The key word for any system, however, is "flexibility". In order to protect your investment as well as ensure the continued throughput in your department, you need equipment that is flexible so it can be adapted to your future needs.

Some of the continuing trends in high throughput screening are:

1. Increased density of microplates;
2. Newer detection technologies including various imaging devices for fluorescence and luminescence assays; and
3. Movement away from assays which require separation steps such as washing and filtering, and away from radioactive assays.

By definition, flexible, fully automated robotic systems are reprogrammable and can easily adapt to new assays and new or upgraded instruments required for the assays. Some of the things that you'll want to do to improve the implementation of the fully automated system are:

1. Involve the users in your laboratory to define the system requirements and select the vendor.
2. Gather information from other users and vendor references regarding the desired features of various systems, things that they would do differently, and other recommendations. Experienced users usually have suggestions that are gained through trial and error, and you want to minimize your trials and errors.
3. It will be helpful to have frequent meetings possibly weekly, as the members of the task force report on various assignments to collect your internal needs and report on the investigation of various possible vendors.
4. Remember that the time spent reviewing the system and vendor-selection criteria BEFORE placing an order will be well spent and give you a more optimum robotic system to meet your needs.

1.3. What to Do Before Placing the Order

1.3.1. Defining Your Needs

The process of defining your needs and selecting the appropriate equipment and vendors can be a time-consuming, tedious process, and the temptation is to treat this as an interruption to your other job responsibilities. If you will take the time to define your needs and specify that the equipment must first be tested to meet those requirements before shipment to your laboratory, you will save yourself considerable headache and heartache after the equipment arrives at your laboratory.

1.3.2. Check the Details and Fine Print

Define the system acceptance criteria and get the vendor's policy on who pays for the transportation, site installation, and training. Most robotic systems

are sold FOB the factory, although the vendor will usually prepay and bill the freight. Many vendors have an additional charge for the time and expenses for the installation engineers to install the robotic system in your laboratory. It is usually difficult for either organization to estimate this cost, and most users don't like the open-ended nature of this type of billing.

Some vendors include the cost of installation in the overall price of the robotic system and this is better for you. First, you are not subject to additional invoices over which you have no control and which can be difficult to justify to your management, particularly if you didn't have enough money in the budget to cover these expenses. And secondly, vendors that include it in the overall price are confident that the system will be installed and accepted by the user well within the budgeted time. This tells you that the supplier is more confident of the successful operation of the robotic system as soon as it is installed.

Note that it is quite common for the vendor's delivery to slip. This is obviously can be a serious problem, particularly if you are on a tight time schedule to begin actual screens. You can reduce the chance of this happening by thoroughly investigating the vendor's references, verifying that your fully automated system is very similar to previous systems that have been delivered on time, and possibly writing into the purchase contract a penalty for late delivery.

1.3.3. Training is Very Important

You will also want to have as many people as possible trained on the robotic system. With personnel turnover and transfers, you want a pool of people who are trained and can operate the robotic system. The first people to be trained should be those who: 1) have operated a robotic system before, or 2) will be operating the system, or 3) have a good mechanical aptitude. There are many details and nuances in the operation of fully automated systems, and you will find your organization relying heavily on the supplier's manuals and training program. Many fully automated robotic systems will use third-party peripherals for dispensing, detecting, or other specialized functions, and those devices may have their own manuals and training programs.

Because there are many details to learn in order to operate and use the fully automated system, you will find a 'catch 22' with the factory training. Of course, people must have some training before they can operate the robotic system, but they will learn the most after they have had some experience with the system. This is because after a few months of operation, they will have developed an appreciation for why some information is of value and they will also ask questions specific questions that might have been omitted by the trainer. You will find that the best solution is to have training when the robotic system is installed (or before), but also have a follow-up training session 3–12 mo after installation. This will be invaluable as a refresher course and you will find

that your team will make a quantum leap in their understanding of the automation system after the second training course.

1.3.4. Include an Unattended Run in the Acceptance Criteria

As part of your purchase order, you should include an acceptance criteria that includes at least one 12 h (or longer) unattended run in your laboratory using all peripherals. Although you should also insist on an acceptance test at the vendor's factory before shipping, you should still insist on an acceptance test in your laboratory to make sure that any damage that might have occurred during shipping is found and that the fully automated system is properly installed in your laboratory.

1.4. What to Do Before Your Robotic System Arrives

After you have selected the vendor and placed the order, there are still many things that you can and should be doing before the system arrives. The temptation is to get back to your work, whether on the bench or in the office, and let the vendor 'do their thing.' In reality, you have considerable work to perform to get ready for the equipment installation.

Users who are part of a large site will usually have their site engineering departments assist in coordinating the various installation steps with the vendor. This will include having the appropriate utilities brought to the proper place in the lab so they will connect to those on the automated system. Experienced vendors will have specifications that you can actually review before placing the order so you can evaluate the site-installation costs and put the appropriate amount into your budget.

The utilities can include electricity, computer connections, compressed air and vacuum, liquid drains, vapor recovery, etc. The vendor will be able to give you a drawing of the robotic system and the specific ratings (electrical amperage and voltage, for example) that the system will require.

You should begin writing your Standard Operating Procedures (SOPs) for the operation, calibration, and validation of the major third-party peripherals and the fully automated system as a whole. Unfortunately users commonly delay these details until after the robotic system arrives, but, at that point, you'll be busy trying to run your assays on the system, so the ideal time to begin researching and writing these documents is before the system is installed.

2. Assay Development for Fully Automated High Throughput Screens

2.1. Introduction

Development of assays which will be implemented on HTS systems in fully automated mode requires one to address the same issues as the development of

the assay to be run in workstation or partially automated mode. Among these considerations are detection format, signal/noise window, assay chemistry, reproducibility, signal and reagent stability, compound concentration /presentation, assay artifacts, and overall assay quality (as quantified by such metrics as % CV or *Z'* factor ***[1]***). Although these considerations are common to both fully automated and workstation approaches, often additional attention to several of them is required to implement the HTS on a fully automated system.

Fully automated systems may run the HTS for extended periods of time, some even completing the full screening library in a single run extending for more than a week. The stability of the reaction components (cells, enzymes, substrates, compounds) and the resulting signal often becomes a major focus of the assay-development effort. Bulk reagent preparation and storage conditions, as well as the storage capacity for assay consumables on the system, are also related issues. The stability of the complete assay is dependent on the combined stability of all components, therefore an understanding of the stability of all parts of the assay is required.

Specific examples of the development of fully automated HTS for cell-based and in vitro assays are described below. Issues that were critical to successful implementation of these assays as fully automated screens are discussed.

2.2. Cell-Based Assay

2.2.1. Introduction

The first example is a 384-well growth inhibition assay using a hypersensitive strain of the yeast *Candida albicans*. The goal of the HTS was to identify growth inhibitory antifungal agents. This microbial growth assay was originally developed for a workstation assay and later reconfigured to run on an automated system in fully automated mode. The assay involves a 20 µL dispense of a dilute (50 mOD_{600}) *C. albicans* culture in liquid growth media into a clear 384-well plate containing 5 µL of dilute screening compound dispensed previously by the compound dispensary and stored at –20°C in vacuum bags prior to the HTS. Control compounds are added and the plates are incubated with lids at 30°C. Final assay conditions are 25 µL/well, 5 µ*M* test compounds, <1% dimethyl sulfoxide (DMSO). In the workstation version of the HTS, the cells were diluted from an overnight culture, grown out for 2 h with shaking, rediluted to 50 mOD_{600} and immediately dispensed into up to 80 microtiter plates using a Labsystems Multidrop 8-channel peristaltic dispenser with a sterilized dispensing cassette. Control compounds were added manually with an 8-channel pipettor prior to the cell addition. Following cell addition a zero time read at OD_{600} was acquired with a microplate reader with plate stacker.

The plates were then lidded and incubated at 30°C for 18–20 h prior to the final OD_{600} read.

2.2.2. Procedure

The goal was to convert the assay to run on the automated system. The assay plates would still be loaded onto the system already containing the test compounds, however now the control and cell additions, the incubations and the reads would all be processed on the system. The robotic system that we used has a capacity for 216 plates in its 4 incubators, so we targeted 216 plates (75,000 tests) as our desired capacity for each HTS run. Approximately 4 L of cells would be required to source the 216 plates. One major change in the method necessitated by the switch to full automation was the requirement for the cells to be dispensed over a long period of time. In the workstation version, 80 plates could be dispensed in as little as 30 min (less than half of 1 doubling time for this culture at room temperature.) In a 216 plate full automation run, the time to dispense the cells would take almost 18 h. Using the original workstation SOP, the cells would continue to grow following dilution into the room temperature media. Therefore at the time of the dispense into the assay plates, there would be increasing cells, leading to an inconsistent and insensitive assay. Continuously providing dilute cells to the system (for example, every hour) would be impractical over the 18 h necessary to process all 216 plates and increase the risk of contamination.

Since online refrigeration was available on the system, we attempted to determine the stability and sensitivity of the strain held at 4–6°C for extended periods prior to dispense into the assay plate. We addressed a number of growth-related issues including the growth rate (if any) of cells held in the refrigerated reservoir and the incubation time necessary for the cells grown out from this storage condition. We also determined the viable cell number as a function of time held in the refrigerated reservoir. If the cold storage altered the sensitivity of the strain to inhibitory compounds, it might invalidate this approach to the assay.

To prepare the cells, the workstation protocol was followed from the overnight cell growth until the final dilution of the cells into the room temperature media. The dilute cell suspension was then placed in the refrigerator for 2 h prior to the initiation of the dispense to the assay plates. Viable cell counts were determined by plating out dilutions of the cell suspension at various times included just after the final dilution into the room temperature media (Time 0) and at numerous subsequent time points out to 40 h at 4–6°C. To our surprise, the cell number and viability remained constant during the full 40 h of the

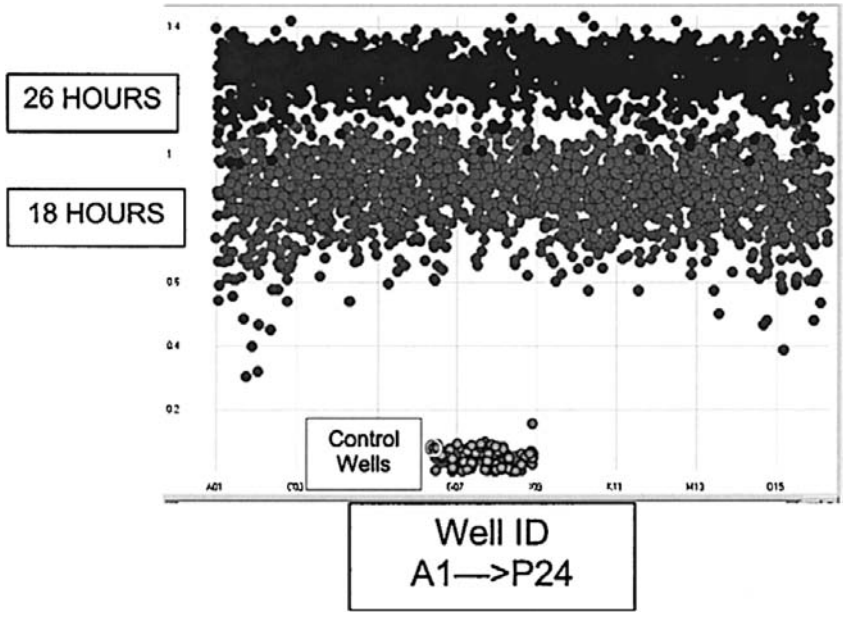

Fig. 2. Growth of cells in a 384-well microplate over 18 and 26 h.

experiment, suggesting that this method could be used to maintain a consistent cell number for dispensing throughout the course of the automated HTS.

2.2.3. Results

Although the viable cell counts remained constant, because of previous experiences, we suspected that the refrigerated cells may experience a greater lag in growth by the automation method compared with the workstation version in which the cells were immediately dispensed from the room temperature media. In the workstation method, the cells reached their maximum growth in the wells following 18–20 hours at 30°C. We set up a series of experiments on the automated system which varied the incubation time of the cells from 18–40 h. **Figure 2** shows these results.

Compared with the previously developed workstation HTS (manual), the time required for completion of cell growth in the wells was extended by approx 8 h, requiring an extension of the incubation time from 18 h to 26 h. This finding suggested that the cells experience a prolonged lag phase before initiation of growth and division when held at the lower temperature.

One key validation issue was the sensitivity of the strain following prolonged storage at the refrigerated temperature and comparison of these results with the Minimal Inhibitory Concentrations (MIC) determined by the workstation

Table 1
Comparison Between Manual (Workstation) and Full Automation Minimum Inhibitory Concentrations (MICs) for a Range of Antifungal Compounds

	Manual MICs	Automation MICs
Test compounds	µg/mL	µg/mL
Tunicamycin	0.81	1.79
4-nitroquinilone	0.02	0.05
Cerulenin	0.20	0.20
Amphotericin B	0.20	0.28
Fluconazole	0.10	0.10
Ketaconazole	0.03	0.07
Nystatin	20.80	12.48

method. A panel of known antifungal agents with different modes of action were prepared by serial dilution and included with the uniformity plates during the robotic validation runs. MIC determinations (**Table 1**) determined that no significant change was observed for any of the compounds tested by the changes made in the SOP to accommodate the automated version of the assay.

2.2.4. Sterility

Sterility is an additional area of concern in the development of an automated version of an assay. Contamination of the cell reservoir or the assay plates could lead to false negative results. All possible sources of contamination including incubators, reagent-dispensing lines, pipeting canulas, and exposed surfaces were cleaned with 70% ethanol prior to and after each run. Special attention was paid to the handling of the compound plates. The room containing the system was monitored regularly using settling plates. The completed assay plates were disposed of promptly into the appropriate bio-waste bins and removed from the premises immediately.

2.3. Noncell-Based Assay

2.3.1. Introduction

Scintillation proximity assays (SPA) are a popular format for prosecuting kinase screens. In the following example, the goal was to develop a 384-well SPA assay for a purified kinase enzyme. The enzyme phosphorylated a small peptide substrate, which was biotinylated to allow for capture to Streptavidin-coated SPA beads. The benchtop assay was optimized for the Km's for the two substrates, ATP and the peptide. The amount of Streptavidin beads and ^{33}P-ATP

were also optimized to provide the best signal/background window. The reaction time-course studies suggested that the reaction was linear for at least 6 h ***(2)***.

2.3.2. Procedure

The automated system that was used for this HTS was designed specifically for SPA assays, but isotopic assays are widely performed on fully automated systems that also run nonisotopic assays. The only additional equipment that is required accommodates the 'hot' or radioactive compounds and detects the assay results. This particular fully automated robotic system consists of a central robot on a 3-foot track; two high-capacity temperature controlled incubators; a 96–384 channel pippetor; three Multidrop® 384 dispensers and two Wallac® 12-detector Microbeta Trilux® readers for detection of the SPA signal. The plates and datafiles are tracked using a bar-code reader on the system. Due to the relatively long time required to read the SPA signal (15–>30 min/plate) the system throughput is typically limited by the number of readers.

Because of the long plate-reading time, in order to achieve the maximum throughput (plates/d), the system should operate as close to 24 h/d as possible. The initial automation attempt used preformatted 384-well DMSO compound plates already containing controls in the appropriate wells. To these plates, 15 µL of substrate buffer and 10 µL of enzyme were added to the compound plate using two of the Multidrops. Following incubation of 90 min at room temperature, a stirred stop solution containing Strepavidin beads was dispensed into the plates using a third Multidrop.

The beads were allowed to settle for 8 h prior to the read. The read for the first plate through the system was nearly 10 h after the start of the screen. The read time of 60 s/well limited us to about 4 plates/h using both detectors. To validate the automation, a uniformity run on the system was performed. The method used would process one plate per hour for 24 h. Enzyme and substrate solutions were dispensed from a refrigerated cabinet and the solutions in the Multidrop tubing were automatically withdrawn back into the chilled reservoir after each dispense. This kept the reagents in a chilled environment as long as possible. Modern peristaltic dispensers have commands to empty the lines and reprime after each dispense.

2.3.3. Results

Figure 3 shows the results of this first 24-plate uniformity run. The kinase activity appears to be reduced as a function of time, giving consistent (and expected) signal for the first 3–4 h but dropping off steadily. By the 16th plate, the activity is barely detectable above the background. This result suggested that one or more of the assay components was not stable during the assay. The

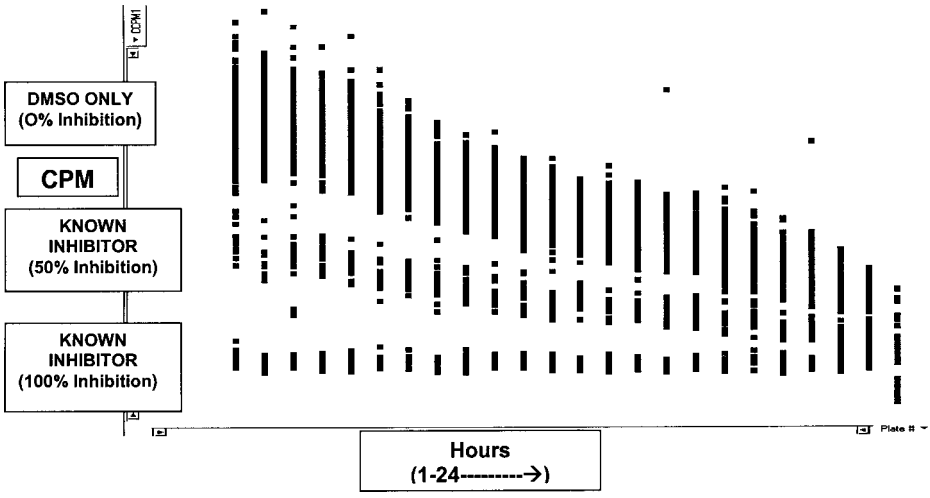

Fig. 3. Results of a 24 microplate uniformity run.

likely suspect was the enzyme. All previous stability studies had been done with the enzyme stored on ice.

On the system, a small refrigeration unit is used to hold and chill the enzyme to maintain its stability. Using temperature monitors, it was determined that the refrigerator was not holding temperature to specifications (2–6°C) but was in fact fluctuating up to 12°C. The uniformity plates were run again. This time the enzyme and substrate reservoirs were placed directly in an ice bucket next to the Multidrop dispenser. The bucket was covered to reduce the rate of the ice melting. This time the assay gave high and consistent signal for the full run of 24 h continuously. (**Fig. 4**).

The refrigeration system was adjusted and the HTS was run again, paying close attention to the monitoring of the refrigerator temperature. This illustrates the importance of performing a validation run before running the actual screen and potentially wasting valuable compounds and reagents.

3. Other Topics

3.1. Validation

3.1.1. Introduction

A key step in the commissioning of a fully automated HTS is the validation of the system. Obviously if the automation system hasn't been validated, then you can't rely on the data generated. So validation becomes first and foremost the most important task after system installation and acceptance from the ven-

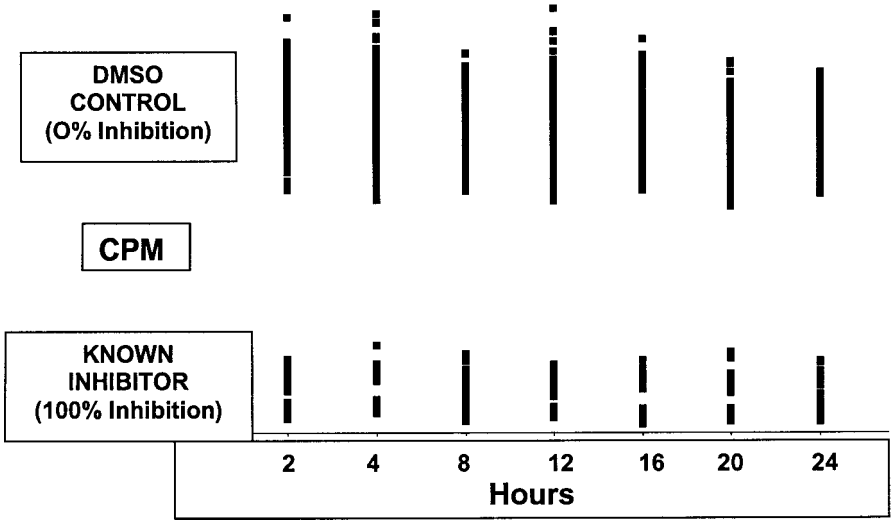

Fig. 4. Results of the assay using properly chilled enzyme.

dor. Some people may be tempted to take shortcuts, but the most methodical, although sometimes not the fastest method, is to first validate each instrument by itself, then validate the system as a whole.

3.1.2 What You Can Do Before the Fully Automated System Arrives

While you are waiting for your fully automated system to arrive, you can begin preparing for the system validation. Now is a good time to contact each of the suppliers for any of the instruments that will be part of the automation system. Ask for the recommended maintenance, calibration, and validation procedures for each of the devices that will be part of your fully automated system. In addition, find out what training is offered and recommended. You can decide whether to take the training before the system is installed or afterwards, but remember that it virtually always takes longer than anticipated to start running assays, so it's better to do things before installation than afterwards if you want to stay as close to schedule as possible.

3.1.3. System Validation

The steps of validation include first verifying that both the hardware and software were installed properly to become a qualified system ***(3)***. Then a method is performed and validated. Finally, complete validation is achieved when the suitability of the system is assessed for your specific purposes. All of

these steps must be documented and on file at the automation system for fast future reference in case there is a quality audit or if there is any question about the validation procedure ***(4)***.

Thus, in order to validate the automation system, you will first request and receive any information from all of the suppliers of any third-party instruments or devices for any validation information and procedures for their instruments. You must run these tests to verify that the instrument is performing within allowable tolerances. Keep the test procedures and results of these tests in your files. (Remember that you'll want to periodically verify that the instrument is operating within allowable ranges, so you'll need to periodically run the required procedures. Each instrument vendor should recommend how frequently their device should be verified to be operating properly.)

After validating the operation of each device, you are prepared to select a method and run it on the automation system. You must compare the results with those performed by a previously validated method and verify that the results are within allowable tolerances. When the results are comparable, you have now validated a method on the automated system. Document the method and results and file it with the previous validation results.

The final step is to list the types of assays that can be properly performed on the automated system. When all of these steps have been completed, you have validated your automation system.

Although the validation steps can be time-consuming ***(5)***, it is absolutely critical that they be performed precisely and correctly. You cannot begin to have confidence in the data generated by the automated system if you have not verified that the automation system is capable of producing accurate data. As scientists and technologists, we all recognize the importance of these basic steps before running actual assays. The investment in reagents, compounds and time is too great to risk it on running the assay on a nonvalidated automated system.

When testing liquid dispensing or pipetting accuracy, fluorescein or tartrazine are commonly used because the strength of the fluorescence reading is directly proportional to the amount in the plate well ***(6,7)***. Your instrument vendors will be able to recommend other materials and procedures for validating the operation of their products.

3.2. System Troubleshooting

3.2.1. Introduction

Troubleshooting an HTS robotic system requires a systematic analysis of the observed deviation and a careful consideration of the possible causes. It is

a two-step process: first establish where the problem is, then determine how to correct it. When analyzing a problem on the automated system, you must first determine if the problem is with the chemistry of the assay itself, or if the cause is with the automated system. Regardless of the cause, you must work to isolate it and then develop a solution. You will find that you must examine every step, including rechecking reagents and plasticware, verifying that instruments are still within calibration, etc.

3.2.2. Random and Systematic Errors

Sources of error might be systematic or random. Systematic error causes a general shift of the data, which is easier to observe than random errors, which can affect one or a few data points, but then disappear as quickly as it appeared. Systematic errors might have either mechanical or biological/chemical causes, but by isolating and testing each individual possible cause, the source of the problem can eventually be found.

Random errors are much more difficult to find, but the troubleshooter can take heart that most random errors have a mechanical cause that hasn't progressed enough to be consistent enough to become a systematic problem.

For example, incorrect readings that seem to be in one part of a micro plate more often than others might be due to occasional large variances in reagent dispensing, uneven heating during incubation, inaccurate plate reading, etc., all which would point to a mechanical component that is beginning to fail. In order to find the cause of the deviation, you will be required to carefully observe the movement of the various mechanical devices in the robotic system as well as devise experiments to test the various subcomponents.

Experienced users of automated systems keep a log at the system of everything unusual that is observed during any run. The log is just a simple listing of the following: Date, Time, What Was Observed, Any Action Taken, Who Reported It, etc. Forms should be pre-printed with these headings (make any changes to this suggestion) and hole punched so they can be kept in a three-ring notebook binder with the other manuals at the robotic system. Make sure that any unusual observations are written down. This error log history will be invaluable in trying to identify potential causes of problems.

3.2.3. Possible Problems That Might Occur

1. Dispensing of reagents.
   a. Temperature-sensitive reagents warm up waiting to be dispensed into the plate.
   b. Reagents that are suspensions (cells, beads, etc.) settle while waiting to be dispensed.

   c. The dispensing device doesn't dispense the same volume to each of the wells.
   d. The reagent coats or reacts with the inside surface of the fluid path, possibly losing some of its chemical properties or gaining unwanted properties.
   e. Uneven dispensing can be caused by restricted flow in the fluid path, nonuniform pumping action, incomplete valve actuation, etc.
2. Heating/incubation.
   a. Edge effects: some wells receive more (or less) heat, CO_2, or humidity than other wells.
   b. Temperature, CO_2, or humidity control isn't precise enough, causing too much variation between plates.
3. Plate washing: Not consistent or inaccurate, either from well to well within a plate, or from plate to plate.
4. Reader calibration: The reader may have the wrong or incorrectly calibrated plate definition.

4. Summary

A fully automated system is one of the most valuable tools available for HTS. However, proper sourcing, installation and operation of an automated system requires a thorough inventory of your needs and a strong attention to detail in the implementation and operation.

As you could see from the examples, assays can usually be transferred to an automated robotic system with minimum changes. However details must be reviewed to assure that the results will be consistent within a run and as compared to the same assay performed manually on the bench or on workstations.

Validation is a crucial element to assure that the integrated system and the individual components are operating within their designated tolerances.

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Other Suggested Resources

Although not specially referred to in this text, there are a number of publications that frequently print articles on fully automated systems for high throughput screening.

Journal of Biomolecular Screening, Society of Biomolecular Screening, Danbury CT. Publisher: Mary Ann Liebert, Inc., Larchmont, NY.

Proceedings: International Symposium of Laboratory Automation and Robotics, Zymark Corp., Hopkinton, MA (published yearly).

Journal of the Association of Laboratory Automation (JALA), Association for Laboratory Automation, Charlottesville, VA.

Associations

Association for Laboratory Automation, PO Box 800572, Charlottesville, VA 22908, www.labautomation.org

The Laboratory Robotics Interest Group (LRIG), 1730 West Circle Drive Martinsville, NJ 08836-2147, www.lab-robotics.org

Society for Biomolecular Screening, 36 Tamarack Avenue, #348, Danbury, CT 06811, www.SBSonline.org