New hope for overstressed compound libraries

AUTOMATION FACILITATES DISTRIBUTED COMPOUND MANAGEMENT

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The manual procedures used to manage, distribute, preserve, and monitor the quality of compound library assets from megastorage refrigerators to HTS (high-throughput screening) assay locations were conceived in an era when a large library contained only tens of thousands of compounds. Today, it is not unusual for two million compounds to be used in a single HTS assay, and some libraries are now approaching ten million compounds in storage.

No one would disagree with the observation that this system is breaking down. The remarkable thing is that research organizations have been able to sustain annual step increases in HTS assay volumes without labor-intensive compound management procedures crashing the system with untenable costs or shoddy results. However, there is only so far you can go.

The current practice is to archive compounds as highly stable dry powders, films, or beads at low temperatures. For distribution to HTS locations, master copies are prepared as concentrated solutions with a universal solvent like dimethyl sulfoxide (DMSO) and are typically stored frozen on microplates. Daughter plates are uncovered, thawed, and their contents withdrawn; these plates are then recovered and refrozen many times before the compounds are eventually discarded.

Compound library stress

The stresses to which compounds are subjected in the middle zone between the stable archive and the HTS include:

- Exposure: Diverse environmental factors including dust, light, temperature, water vapor, and oxygen cause accelerated degradation
- Covers: If used with care, covers serve as a barrier to dust and UV light but are not by themselves effective barriers to oxygen and water vapor
- Oxygen: This is the most destructive; plate lids actually seal a layer of ambient laboratory oxygen (21%) in place over the compound in the well
- Dilution: Since DMSO is very hygroscopic, the presence of water vapor causes dilution of the compound—up to 20% on the laboratory bench and even more in a refrigerator where relative humidity is higher. Excessive water may cause hydrophilic compounds to precipitate out of solution
- Tracking: With thousands of daughter plates in circulation at any given time, it is difficult to determine how long or how often a given plate has stayed on a benchtop thawing prior to or during assays. This leaves users with the unsavory choice of discarding the plate long before its predicted degradation under ideal conditions or risking compromised assay results due to overly degraded compounds
- Cross-contamination between wells may result from repeated manual sealing and unsealing.

Figure 1 *The Plate Management System (**TekCel**) features automation designed specifically to address plate management, from compound storage through the HTS process. Stress factors and costs associated with traditional compound management can be dramatically reduced with this type of platform.*

Associated costs

Traditional compound management carries with it a number of associated costs:

- Excessive compound use because in many laboratories each assay testing location finds it necessary to keep its own set of daughter plates replicating the master archive
- Acquisition of expensive, room-size refrigeration units to store these daughter plate collections
- Premature discarding of good compounds to provide a margin of error to ensure potency
  Loss of assay efficiency as a result of false positives generated by use of partially degraded compounds. False positives significantly increase the requirement of time-consuming confirmation assays
- Manpower costs, since up to half of the labor allocation in conventional HTS operations is typically consumed by the task of unsealing, loading, resealing, and storing microplates
- Manual operations significantly increase exposure of the staff to potentially dangerous compounds.

Distributed compound management

All of these stress factors and associated costs can be dramatically reduced with automation designed specifically to address plate management—from compound storage through the HTS process (*Figure 1*). Key components of the Plate Management System (**TekCel,** Hopkinton, MA) include:

- Proprietary reusable plate sealing technology that allows for rapid automatic sealing and resealing with no cross-contamination
- Portable refrigerated storage modules that can be maneuvered up to the HTS assay on a hovercraft-type air bearing to deliver any or all of 1000 plates on a random access basis. Multiple units can be linked in tandem to deliver millions of compounds per HTS assay campaign
- An automated server system that gently thaws, unseals, delivers, collects, and reseals plates in an inert atmosphere
- An integrated IT component that automatically tracks and monitors the condition of plates in the distributed compound management system and connects to a corporate database.

Remaining questions

Since a distributed compound management approach costs less than either conventional megastorage refrigerators (whole room refrigeration) or the level of manpower associated with manual daughter plate management, there is no question that it is worth implementing. Six of the largest pharmaceutical research organizations have taken delivery of the Plate Management System and many of these have also placed orders for additional units. The many remaining questions are concerned with the degree to which it is possible to finesse the distributed management concept to minimize costs in many different areas.

- To what degree can consistent distributed compound management retard compound degradation?
- What is the actual contribution of degradation to false positives and assay inconsistency?
- To what degree is it possible to extend compound life with tightly controlled monitoring and handling?
- To what degree is it possible to get greater utilization of existing compounds via electronic scheduling of shared daughter compounds, as opposed to allowing every HTS location to have its own collection of daughter plates?
- Can the scalability of distributed compound management hold the line on escalating manpower allocations due to increased compound library size and screening assay volumes?
- What is the optimal number of uses for compounds stored in daughter plates?
- Can random access to specific compounds and compound families dramatically reduce the number of compounds required per assay through improved automated selection processes?

Answering these questions is now possible because distributed compound library management gives pharmaceutical research organizations the means to stabilize storage and handling conditions that were previously chaotic. The IT component of the system gives researchers the means to collect real-time data regarding plate utilization and conditions of the system. These tools now allow researchers to control the numerous variables affecting compound integrity, while simultaneously improving process efficiency.

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