How to provide a flexible and responsive assay plate preparation system

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The demands on compound management groups are largely driven by the needs of individual assay teams for different therapeutic areas, or the specific requests made by customers to a CRO. The types of assay to be run will also vary according to the development of the compound or the phase of research, e.g. for primary, confirmation and secondary screens.

The multitude of assay techniques and assay platforms and moderate degrees of standardisation means that there is a significant variety of plate formats to be supported [1], e.g. 96, 384, 1536, 2280, and 3456 well plates to name just a few. For each project there are likely to be preferences for the concentrations and volumes, and dilution factors.

Within the compound management teams of each organisation (and sites therein) there are large variations in the instrumentation provided to support assay plate preparation: from variable-span, multi-tip dispensers, to fixed head array dispensers; microliter dispensing to nano-litre dispensing; and from syringe, to ultrasonic and acoustic wave liquid transfer devices[2].

There is no common configuration mechanism for all of these instrument types; they are usually supplied with proprietary user interfaces with different programming techniques, from pipette scripts to graphical programming. Local rather than central saving of the protocol to match the assay type is commonplace. Each type of instrument has different parameters for pipetting e.g. dead volumes, minimum and maximum capacities, dispense speeds and tip cleaning or changing demands, and unless these are understood, the quality of the created samples will impact on the assay results.

The correct selection of appropriate samples and the strategies employed to maintain collections of samples in standardised formats will also have a significant effect on the availability and quality [3] of the aliquots in the assay plates, and the turn-around times for assay plate production.

In cases where many assay plate requests occur, there is a corresponding multiplication of the number of individual samples that may require individual picking, weighing and solubilisation (if dry), and potentially multi-stage dispensing. This creates a logistical problem that, if not addressed, would result in significant errors and uncertainties that are expensive to track down and correct [4], unless a sample identity or sample movement confirmation, and workflow system is provided.

As the plates are created and the source vessels are depleted, there is a need to reconcile the inventory to record the changes that occurred, and typically each pipetting instrument type will generate data that needs to be carefully parsed and interpreted to faithfully reflect the changes made. The plates, once prepared, can then be used in the assay, however it is also necessary to have the well-specific information available to the assay data analysis tools, so a transfer of the well contents is usually necessary, and if this can be done automatically, the risk of translational errors is eliminated.

Mosaic's approach to assay plate production

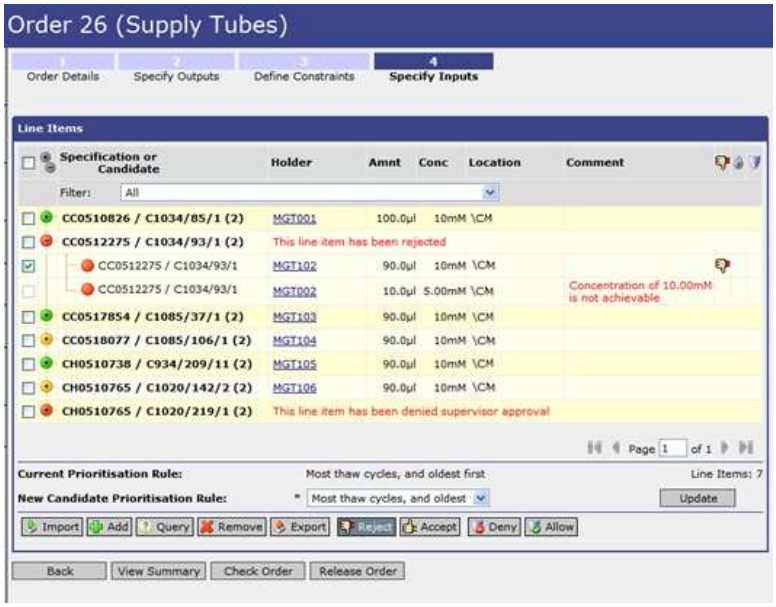
To support assay plate production, Mosaic has a number of features that provide consistency, convenience, and efficiency in the requesting, management and preparation of assay plates.

From a user-perspective, the first advantage that Mosaic has is a comprehensive, web-based ordering system. The ordering system is configured to provide order types that match the format of samples that are needed, to the format of samples that are available. The order types can be configured to precisely match the assay requirements, and also allow some flexibility in the specification of parameters, where this is needed.

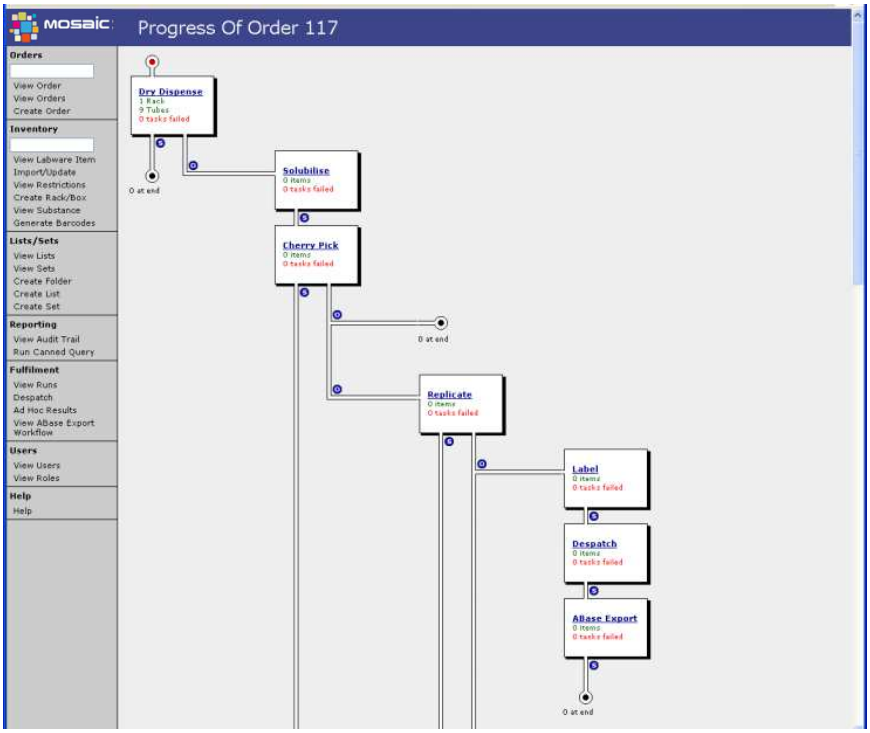
In this example, Mosaic allows plates to be related to specific projects and assay types. It can be seen also from this screen shot that different plate types are accommodated, and for some assays it may be preferable to fix the plate type to a standard value.

Plate layouts are managed within Mosaic, with specific wells and plate areas being assigned for different purposes. The plate layouts can be easily edited by users using the Mosaic Layout Editor.

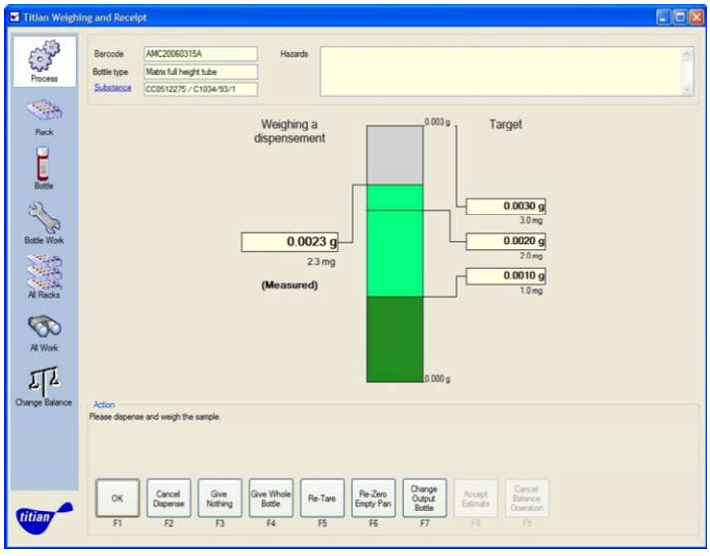
The inventory management and ordering features within Mosaic mean that it is possible to plan the usage of samples, create intermediate stocks, and track the usage of samples. For the fulfilment of orders, the selection of samples is controlled by configurable criteria, e.g. select samples with the fewest freeze/thaw cycles, or closest to the sample expiry date, or belonging to a specific set.



Once samples are selected, Mosaic assists the user to retrieve the samples, or where automated stores are provided, Mosaic can integrate with the stores to transfer pick lists and reconcile the stored inventory. The request is translated into a workflow, where each sample is tracked through from picking to despatch.



Depending upon the sample collections, and the configured business rules, it may be appropriate to source samples from dry powder stock. In this case the workflow towards the assay plates will include a dry dispensing step, carried out at a weighing station. Mosaic guides the operator through the required dispensing steps and collates the dispensed samples. The measured dispense weight is noted by Mosaic, and this information is then used to calculate the amount of solvent required to compensate and provide a solution of the desired concentration.



For the preparation of mother plates from the original samples, Mosaic can interface with a number of Liquid Handling instruments to perform the first stage dissolution and mother plate creation. Where instruments are fully integrated in 'on-line' mode, there is no need for the operator to enter or edit the pipetting protocol in order to produce plates.

Mosaic guides the operator on how to load the instrument, with source racks and destination plates (or other vessels), and then Mosaic is responsible for the protocol on the instrument. Mosaic is configured to be aware of the instrument capabilities and limitiations, and takes care of minimum volumes, dead volumes and tip cleaning and exchanging.

For instruments that are less frequently used, there is also the option to exchange a file-based description of the desired pipetting outcome and to read in the actual outcome – this is the 'off-line' mechanism and in this case the pipetting instrument set up is done by the operator, and the protocols used must use the exchange file format.

Once the preparation steps are completed, the Mosaic inventory is updated to reflect the creation of the new plates and any deductions from the source vessels. A Despatch mechanism is provided to record the despatch of samples from the preparation facility, and if Shipping is required, the shipping details can be recorded and can be checked by the requestor.

After the plates are used in the assay(s) it is likely that the results analysis will use the assay plate information from Mosaic to assist in the calculations. For this Mosaic can export the assay plate data (substance, concentration, volume, well position) to applications such as IDBS Ltd's 'ActivityBase'.

Mosaic has an Ordering API (Applications Programming Interface) which allows plate requests to be automatically placed by other systems such as Electronic Lab Notebooks (ELNs). This can provide an extremely efficient link, for example, if plates are required for a specific assay, an order type can be configured in Mosaic to contain all of the standard settings required for the assay. Once this is in place, requesting is as simple as the other system requesting an assay type (= order type), and providing a list of substances required for the assay, Mosaic manages the logistics and updates the status of the order.

Overall Benefits that Mosaic users have experienced

With Mosaic in place, users have reported improvements in overall sample quality e.g. lower CV in requested concentrations in plates. This is partly due to the compensated dispensing that is supported at solubilisation, but in addition the more rapid turnaround times mean less evaporation variations across a plate or rack of tubes.

The Workflow Management aspects of Mosaic mean that samples are much less likely to go astray mid-process, and mis-placing can be detected and corrected at an earlier stage. This obvious benefit has greater implications; since the time spent correcting such occurrences would normally take a significant fraction of available resources, and the audit trail that records the workflow events provides valuable supporting evidence, so unnecessary re-ordering is avoided.

The web-based ordering of samples provides a high degree of convenience, especially when the order types are configured to match the most frequent assay types. With the order template recording the plate types and parameters, this means that the plates for assay can be standardised, capturing best practice.

In general, Mosaic has allowed users to support greater plate preparation demands, and be more responsive to requests, with some compound management groups providing an 'express service' for assay plates with a turn-around time of one day, compared to one week before Mosaic was introduced.

The separation of requestors from the sample preparation, and the provision of multi-site despatch and receipt within Mosaic mean that an organisation can set up a cost-efficient centralised compound management service.

References, further reading:

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3. Lipinski, C (2005). Compound precipitation from DMSO and the synergy between water uptake and freeze/thaw cycles. Oral Presentation at LRIG Meeting, January 2005

4. Harrison, WJ "The importance of automated sample management systems in realising the potential of large compound libraries in drug discovery". J. Biomol. Screen 2.203

5. Report: "Small-Scale Benchtop Automation Trends 2011" Dr. John W. Comley, HTSTech Ltd

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