Product conformance and 'registration drift'

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Abstract

Product conformance discrepancies in the bio/pharmaceutical industry can occur for a number of reasons but typically they result from notable events such as mergers and acquisitions, or situations involving third-party manufactured products. This article underlines the importance of ensuring product registration details remain aligned with manufacturing documents, and shares a number of solutions that have been successfully implemented. The importance of a single, consistent change control process that spans the full manufacturing, testing and registration disciplines is also discussed.

Introduction

Throughout the lifecycle of a pharmaceutical product, it's known and accepted that manufacturing processes will drift within their specified ranges due to things like equipment wear-and-tear and operator variance. In order to maintain the validated state, and as diligent pharmaceutical manufacturers, companies spend a lot of time and effort in ensuring validation, and periodic re-validation, of manufacturing processes to ensure that we account for and control any process drift. Indeed, there is a lot of literature and expertise within the industry that provides guidance around process validation. Similarly, the registration file (and marketing authorisation) of a pharmaceutical product may in many respects be considered to be equivalent to the manufacturing process and changes can result in a drift from the actual manufacturing process – a phenomenon we describe as "registration drift".

For clarity, for the purposes of this article it should be noted that the term "conformance" is used to refer to the alignment of plant/manufacturing documents to the MA (CTD M3), whereas the term "compliance" is normally considered to be compliance to Quality and current good manufacturing practice (cGMP)/ICH requirements. While it's possible that a regulatory conformance review will cover some elements of product compliance, product/manufacturing compliance is often assessed as part of the Quality Assurance Unit's function under its audit programme; product compliance does not form part of this article.

Despite clear legal and ethical obligations to ensure MAs are updated as and when necessary, registration drift is a known phenomenon that until recently was not fully understood or addressed directly. Left unchecked, registration drift can result in serious conformance issues where the registered manufacturing process bears little resemblance to what actually happens during manufacture, testing, and release. Clearly this type of discrepancy can pose a risk to patient safety and can be subject to unwelcome regulatory action following Board of Health (BoH) audit.

Background

As expected, not all of the CTD sections in Module 3 are equally susceptible to changes during the product's lifetime. For example, a process that does not use materials derived from humans or animals will mean that Section 3.2.P.4.5 will not change; conversely, changes in the manufacturing process and test methods/specifications will impact numerous sections of both Module 2 and Module 3.

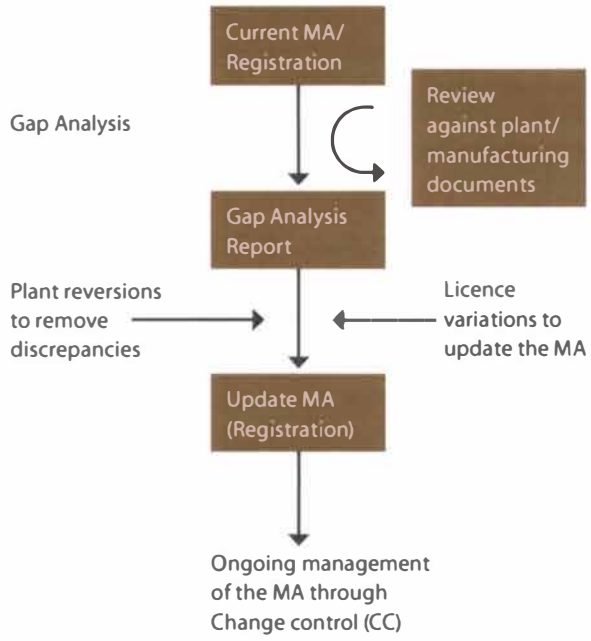
To begin to assess the impact of potential differences between the registration file and the manufacturing documents, one must perform a comparison (or "gap analysis") of these two sets of documents. While there are many different ways to tackle this issue, the general approach for the review of MAs against plant/manufacturing documents is summarised in Figure 1. This is a high-level overview that highlights many of the key stages and activities for licence review. It is worth noting that to ensure a complete and robust conformance assessment of the registration documents, they should be compared with the manufacturing documents to record any differences; comparing manufacturing documents against the MA will result in only a partial review, as not all of the plant details will be documented in the MA.

The process outlined in Figure 1 has been followed by a number of manufacturers and the results of such gap analyses are summarised. The process depicted here also outlines a recently developed semi-automated process for gap analysis review and remediation of MAs. Following this process, Table 1 summarises the changes averaged for several hundred MAs and expressed as percentages. Taking the average over many products and several manufacturers enables a representative snapshot of the typical observations expected in the wider industry. It should be noted that only the affected sections of the Drug Product section of Module 3 are shown in Table 1; sections that did not show any discrepancies are not listed. Similar results are seen following the review of Drug Substance sections.

For the purposes of illustration, a typical selection of the most common discrepancies is provided in Table 2. There are numerous examples of individual discrepancies for each of the sections listed that have deliberately been excluded for ease of interpretation.

It is clear (and unsurprising) from Table 1 that not all sections of Module 3 are equally affected. Also, of the sections impacted, the potential discrepancies are not evenly distributed across them. Although the nature and extent of the discrepancies is difficult to generalise given the wide range of pharmaceutical products, and is beyond the scope of this introductory article, universally applicable solutions for the

Figure 1: Summary of the general approach for the review of MAs against plant/manufacturing documents and the subsequent corrective actions.



correction (or remediation) of these discrepancies have been developed and will be discussed later.

There are generally two main hurdles to overcome before starting to rectify conformance gaps. First is the recognition that a problem exists; such acknowledgment is usually viewed as being indicative of the failure of one or more of the Quality Systems, and can potentially have wider implications on the management and implementation of Quality Systems within an organisation. While this may be true, it is also indicative of a well-developed Quality System that is able to effectively self-audit to find discrepancies and manage their resolution. Secondly, having discovered gaps, knowing how to manage them is key to the success of any conformance programme.

Potential resolutions may involve introducing a combination of possible short-term and long-term solutions to re-align the registered details with the manufacturing operations; this will include giving due consideration to some of the sustainable solutions that a number of progressive pharmaceutical manufacturers have adopted in order to address this industry-wide problem. Amongst these solutions, and probably the most important element of any long-term plan, is the need to re-evaluate the purpose and scope of change control, and the re-implementation of this quality system to be inclusive of regulatory impact and actions following a change in the manufacture, testing or release of a product; effectively making change control a single, end-to-end system applicable across the entire business (operationally and geographically).

The following sections deal with how an initial assessment would be triggered and managed.

Do you have a problem?

This is quite an easy question to answer, using a number of pointers that are known to have a direct impact on the degree of registration drift. These risk factors include:

- Whether there are a significant number of products which are more than 15 years old. It is known that as products become an established part of the licence/lifecycle maintenance activities and responsibilities, they can become less well-resourced and thus tend to start to become neglected; sometimes referred to as the "poor cousins".
- Whether products are manufactured by third parties. Such products are not always subject to robust technical/quality agreements and therefore can be prone to changes in manufacture and testing at the third party, and not being reported to the marketing authorisation holder (MAH).
- If the company has been subject to a merger or acquisition in the past. Mergers which in reality are acquisitions tend to be driven by a select number of desirable target products/compounds. This inevitably means there will be a number of other less desirable products destined for divestment. Such products also tend to be subject to significant registration drift.
- Whether there has been a significant staff turnover; regulatory affairs departments tend to be organised around therapeutic areas, with the aim of helping minimise the impact of staff losses. However, experience shows that a poor hand-over of responsibility, poor communication and a general lack of structure and departmental processes (paper and electronic) can create a significant risk of registration drift.

Although there are probably other factors, those listed above are key contributors to the overall level of product conformance. There is some degree of certainty that when one of those factors is present, there will be registration drift.

Given the potential complexity of products and supply chains, the question of whether this problem actually exists in a particular organisation is most effectively answered by undertaking a targeted evaluation of a small selection of MAs. The answer is usually clear within a short time! However, before commencing this type of "look-see" pilot evaluation, it is important to document how potential discrepancies will be managed and corrected. Some possible resolutions are considered below.

Possible solutions

There are really just two mechanisms to correct regulatory file discrepancies. The first is one we all aim to avoid – regulatory action following an audit or at worst, a serious adverse event. The second is one we aspire to achieve – proactive action. Some of the elements of both of these approaches and the potential risks and benefits associated with them are discussed in the following sections.

Regulatory action: Pharmaceutical manufacturers are subject to a variety of assessments as part of a licensing authority's obligations; this includes regular audits. It's not unusual during compliance audits (for cGMP compliance) for the auditor to ask for product manufacturing details such as specifications (in-process, release, and stability) in order to undertake an evaluation of the conformance between what is registered and what is documented on site. Any negative observations at this point will trigger a more detailed review of the complete registration file and can include severe penalties for the MAH. Unfortunately, some successfully completed conformance programmes have resulted from such regulatory interventions.

Proactive action: This is by far the most desired approach to addressing potential conformance issues. However, before taking a proactive approach there needs to be recognition of the fact that there

Table 1: Summary of the percentage spread of discrepancies in affected sections of Module 3 and their relative order of ranking			
CTD Section	**Title**	**% of total**	**Rank order**
3.2.P.1.1	Description and Composition	8.0	5
3.2.P.1.2	Description and Composition	4.3	10
3.2.P.3.1	Manufacturer(s)	3.7	12
3.2.P.3.2	Batch Formula	7.9	6
3.2.P.3.3	Manufacturing Process and Controls	14.1	1
3.2.P.3.4	Control of Critical Steps and Intermediates	0.8	16
3.2.P.3.5	Process Validation	7.0	9
3.2.P.4.1	Excipient Specifications	1.4	14
3.2.P.4.2	Excipient Analytical Procedure	1.8	13
3.2.P.4.5	Excipients of Human / Animal origin	1.2	15
3.2.P.4.6	Novel Excipients	0.1	17
3.2.P.5.1	Specifications	7.8	7
3.2.P.5.2	Analytical Procedures	7.6	8
3.2.P.7	Container Closure	8.3	4
3.2.P.8.1	Stability Summary & Conclusions	13.7	2
3.2.P.8.2	Stability Data	3.8	11
3.2.P.8.3	Post-Approval Stability and Commitment	8.8	3

Table 2: Summary of the nature of the common discrepancies noted during the gap analysis of selected Module 3 CTD sections		
CTD Section	**Title**	**Description of main group of discrepancy**
3.2.P.1.1	Description and Composition	Changes to drug product composition and unit formula; changes in batch sizes; changes or updates to the container closure system
3.2.P.1.2	Description and Composition	Changes to drug product composition and unit formula; batch size change
3.2.P.3.1	Manufacturer(s)	Change in manufacturer; addition of new manufacturer
3.2.P.3.2	Batch Formula	Changes in drug product composition, batch formula, or batch size
3.2.P.3.3	Manufacturing Process and Controls	Batch size change; changes to in-process controls; change or update in method of manufacture
3.2.P.5.1	Specifications	New/replaced method resulting in specification change; replaced/updated specification, eg, shelf-life
3.2.P.5.2	Analytical Procedures	New/replaced method, eg, replacement with Limulus Amebocyte Lysate (LAL); change in method (change in sterility method procedure); removal of test, eg, removal of an *in vivo* test
3.2.P.7	Container Closure	Changes to stopper/flip-offs; container closure system changes, eg, dimensions, pack size
3.2.P.8.1	Stability Summary and Conclusions	Shelf-life change; stability specification.

is the potential for a problem to exist; this is mostly due to internal inertia. Following an initial mini-assessment, it quickly becomes apparent if there is registration drift – experience shows that there is almost always some degree of registration drift regardless of the company, therapeutic area, product type, etc. Approaches to address registration drift can include:

- Grade the differences based on their severity and implement actions to correct the most severe discrepancies first, followed by the less serious differences. There is a sound rationale behind this approach whereby the company is attempting to direct their resources most effectively. The reasoning behind grading the discrepancies must be clearly documented and justifiable under audit. Be aware that agencies may take the view that a "difference is a difference" regardless of any attempt to assign a measure of severity.
- Undertake a full programme of dossier review and remediation ensuring all differences are evaluated and corrected (remediated). This approach will almost certainly include the expansion and redefinition of any existing change control process to ensure manufacturing changes are captured within registrations. Following this approach allows the products to be scheduled and planned according to various criteria including route of administration and product age.

Regardless of the approach selected, it is highly recommended that sufficient time be allowed for planning and risk assessment, ensuring that all of the factors typically related to product manufacture and supply are evaluated; these include (in no particular priority order):

- Medical necessity: will patients/supply be impacted; is there an alternative/equivalent supply?
- Variation requirements: are the data required to support a variation available; are there any particular strategies or regions that should be avoided/favoured? The use of grouped variations may help to mitigate some of the potential risk factors.
- Commercial impact: are there competitor products to consider? While this will enable an alternative supplier for continuity of supply to patients, it also presents a serious commercial risk .
- Current stock levels within the supply chain: can market supply be maintained?
- Will potential discrepancies result in stock write-off?
- Manufacturing schedule: when will the next batch be manufactured? Will it be possible to implement any necessary changes ahead of the next scheduled manufacturing campaign?
- Likely difference: what is already known about the product and it's MA? Are there any indicators to potential discrepancies already known?
- Local regulatory commitments: are there any local requirements/ arrangements that need to be considered? Will this expedite the programme or hinder it?

There is no single solution that can be recommended over another without specific details but, based on experience, some suggestions of possible courses of action that may be taken to re-align registrations are summarised below. It is difficult to quantify the time required to make these corrections as they are based on a number of factors including the number of gaps, the types of gaps, the available resource for review and remediation.

Recommendations

Following the completion of the gap analysis (MA conformance), there are a number of fundamental steps that need to be taken in order to ensure that the manufacturing details, tests, and specifications, etc are accurately captured within the MAs and remain aligned. Some of the main activities are discussed below.

Fix the errors: Following a review of the MA against the plant documents, any differences must be corrected and the registered details and manufacturing operations should be aligned. The approach to synchronise these documents may be either through licence variation or by altering the plant documents to reflect the registered details. It should be noted that although reverting to the originally-registered state will remove the discrepancy, a follow-on action to reinstate the preferred practice through licence variation will still be needed to attain the current state. Caution should be exercised in instances where an outdated release test is reinstated alongside the "current" procedures, as the tests may render conflicting results which will need to be justified and reconciled. It should be noted that all licence variations must be prepared and submitted in accordance with the current legislation and guidance.

Implement measures to ensure the errors remain fixed: This is probably the biggest activity in order to ensure that the registration drift is known and controlled moving forward. This fix is normally an extension of the existing change control processes to include the completion of any regulatory activities, and ensure that any pending regulatory actions are visible at the time of product release. Where there are a number of manufacturing sites and regulatory offices, the change control process would be extended to ensure all of the sites (plants and regulatory groups) are covered by the same single process. The use of electronic data repositories (such as EDMS) enable the visibility of registration details from remote locations, thus ensuring that product release by the Qualified Person (QP) is always against the currently approved licence.

Perform periodic checks: Periodic checks should be conducted to ensure ongoing conformance – with the best of efforts, there is still a chance that some regulatory drift will occur (particularly in supply chains where there may be multiple manufacturing sites, affiliates and/or third parties located globally). Recognising this, a periodic review programme should be developed in order to ensure ongoing alignment.

It's important to emphasise that changes to registrations should not be avoided, but should be embraced as part of the product improvement/refinement process, while ensuring that products and registrations remain synchronised. After the completion of a gap analysis, there needs to be a single, consistent procedure whereby MAs are maintained and managed. In order to enable this, a single repository of the registered information should be developed and maintained.

Conclusions

Given the nature of regulatory affairs, registration drift in product conformance is a problem that exists to a lesser or greater extent in all pharmaceutical manufacturers. Several pharmaceutical manufacturers have already started review programmes underlining the importance of this work, and a few have completed them. Regulatory bodies both here and elsewhere are showing a renewed interest in the quality of maintenance of established products and expect robust processes to ensure against registration drift. From experience, there are a number of solutions, and selecting the path of least disruption/resistance should be based on specific circumstances and the products affected.