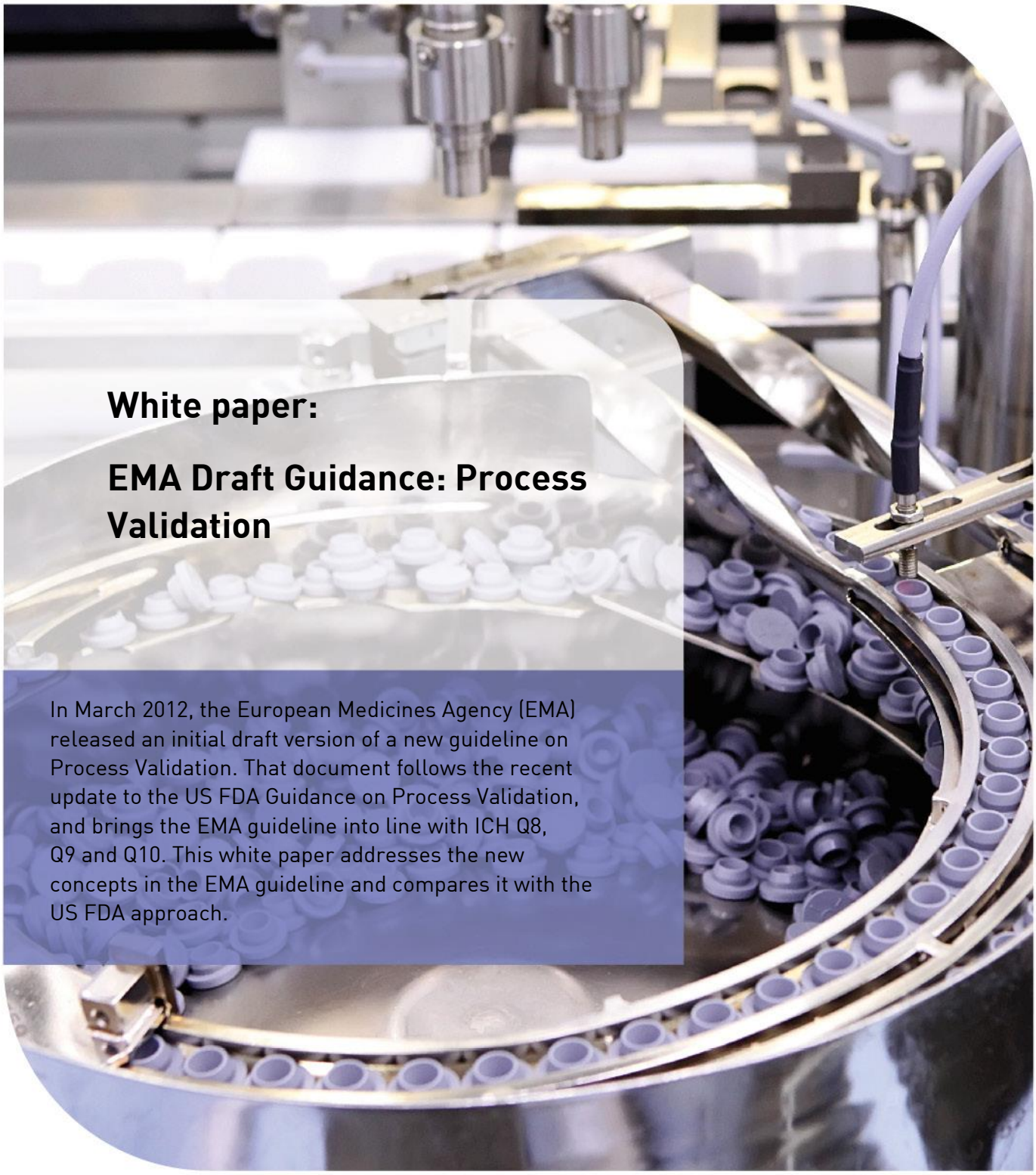

White paper:

EMA Draft Guidance: Process Validation

In March 2012, the European Medicines Agency (EMA) released an initial draft version of a new guideline on Process Validation. That document follows the recent update to the US FDA Guidance on Process Validation, and brings the EMA guideline into line with ICH Q8, Q9 and Q10. This white paper addresses the new concepts in the EMA guideline and compares it with the US FDA approach.

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Introduction

The European Medicines Agency (EMA) is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. The agency provides regulatory instruction and guidance to manufacturers to assist with the evaluation of such medicines. The EMA and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) are closely aligned and, as such, regulatory guidance from the EMA has relevance for Australia and other PIC/S aligned countries.

In March 2012, the EMA published draft guidance for public comment entitled Guideline on Process Validation. On final publication, this document will replace the EMA's 2001 guidance document, Note for Guidance on Process Validation.

As the document is intended as guidance, it will not be legally binding in most jurisdictions. Additionally, the focus of the document is on the requirements for dossier submission, and it is therefore not an exhaustive reference for guidance on regulatory requirements for process validation.

It does, however, provide an insight into the future direction for process validation and the differences between a traditional approach and a contemporary approach that includes Continuous Process Verification (CPV).

The EMA document is not as comprehensive or prescriptive as the US FDA guidance released in 2011. As such, manufacturers who intend to move beyond traditional process validation may find the US FDA document a useful reference for further information.

Who is affected by the changes?

Manufacturers will be directly affected by the changes if they sell the following categories of products into EMA regulated markets:

- Human drugs
- Veterinary drugs

Biological and biotechnology products (although the complex nature and inherent variability of biologicals is acknowledged as impacting the direct application of the guidance).

Medical devices and active pharmaceutical ingredient (API) manufacturers are not directly affected; however, the guidance may contain useful information for such activities.

Manufacturers in other non-EMA PIC/S regulated markets are likely to be affected indirectly. The close alignment of EMA and PIC/S means that PIC/S may adopt the guidance in full, or develop its own guidance based on the EMA document.

What are the key changes in the new guidance?

The updated guidance has essentially the same scope as the 2001 Note. The intent is to provide advice on what to consider for dossier submission for market authorisation and, by implication, determine appropriate process validation strategies for commercial dosage forms.

Apart from the scope however, the draft guidance is a substantially different document from the 2001 edition. Of particular note, the new guidance:

- Formalises the life cycle concept for process validation and aligns with ICH Q8, Q9 and Q10
- Places new focus on non-standard methods of manufacture
- Provides scope for flexibility of approach, utilising traditional methods, CPV or a combination of both.

Life Cycle Concepts

Although not necessarily the original intent, one key shortcoming of traditional process validation has been the idea that a manufacturer can perform a minimum of three validation batches at product commercialisation and, if successful, make the product routinely in the future without further consideration to process validation.

In such cases, the validation effort 'dies' when the product is successfully launched, and there may be no ongoing life cycle considerations. The concept of product life cycle is a key aspect of the ICH guidelines (Q8, Q9 and Q10). The draft guideline formalises the concept of validation life cycle as part of product life cycle, and provides a framework to consider when preparing a dossier submission.

Unlike the US FDA guidance, the EMA document does not break down validation life cycle into stages. However, parallels can be drawn between the two approaches and broadly; the three stages described by the US FDA can be applied to the EMA guidance.

US FDA Stage 1 – Product Development

Although the EMA guideline does not specify what kinds of documentation or testing activities should be conducted during product development, it does encourage leveraging of development phase activities, such as Design Space and pilot scale production to assist with product understanding and development of validation strategies, including CPV.

US FDA Stage 2 – Process Qualification

This stage is the key focus of traditional validation, where the process validation batches are executed and approved, leading to routine commercial manufacture. The draft EMA guideline still permits this traditional approach, but offers alternatives (CPV and a hybrid approach), as well as providing some additional clarity around expectations for the traditional approach.

US FDA Stage 3 – Continued Process Verification

As difficult as it may be to avoid, 'continued process verification' should not be confused with CPV, or 'Continuous Process Verification'. Continued process verification is the ongoing monitoring of the validated state of a process, usually through tools such as statistical analysis of batch data, non-conformances, customer complaints and similar product quality feedback mechanisms. It is a cumulative process across multiple batches.

CPV is the assessment of a manufacturing process during a batch using on-line and in-process verification methods. The EMA draft guidance encourages the use of CPV as a tool to augment or even replace traditional process validation. Although not mandatory, the CPV concepts can be seen as a significant step forward in regulatory thinking and should be evaluated by manufacturers looking to increase process efficiencies and at the same time, enhance regulatory compliance.

Unlike the optional nature of CPV, continued process verification is expected as part of the formalisation of validation life cycle in the draft guidance. It is independent of the use of CPV, although clearly would benefit from the enhanced testing required by CPV.

Non-standard methods of manufacture

A notable difference from previous EMA guidance is the section on 'non-standard' methods of manufacture. The guideline advises that where CPV is not used, a dossier submission must nominate (with justification) whether a process is standard or non-standard.

Manufacturers are expected to supply full scale validation data with dossier submissions for non-standard processes. There is exemption/mitigation for this when the manufacturer can demonstrate adequate previous experience with the non-standard methodology.

Guidance on what constitutes non-standard methods is provided, and is broadly categorised into four groups:

- Specialised dose forms
- New technology in conventional processes
- Highly specialised processes or highly complex processes
- Non-standard methods of sterilisation

Examples from each group are provided, but of particular note are some examples from group 3. Processes such as lyophilization and aseptic processing are included as highly complex and, upon publication of the full guideline, will warrant full scale validation data to support dossier submission, except where exempted through experience.

Flexible Approach

The draft guideline makes it clear that the traditional approach to validation is still acceptable, provided it incorporates the elements of validation life cycle (such as continued process verification) and complies with the expectations stated within the guidance.

In addition however, the guideline offers two alternative approaches to validation not considered in previous guidance:

- Continuous Process Verification (CPV), where a process is continually monitored and evaluated in real time to demonstrate that the process continually meets its pre-defined specifications. Such an approach requires appropriate analytical technology, and is expected to cover all aspects of production from starting materials to finished product. Note that a CPV approach must still be verified at commercial scale prior to marketing, although these batches would not necessarily feature the rigour of traditional validation batches.
- A hybrid approach of traditional validation and CPV, where some traditional validation is used in combination with CPV. Circumstances where a hybrid approach may be appropriate include where CPV is not possible, is impractical or not acceptable (e.g. non-standard manufacture).

Comparison with US FDA Process Validation Guidance

The US FDA Process Validation Guidance published in 2011 has created much discussion amongst validation professionals and marked a key shift in validation practices for the future. When comparing the EMA guidance with the US FDA document, it is clear that the EMA does not intend its guidance to be directly analogous to the US FDA guidance.

While there are similarities, there are many areas in the US FDA document not covered by the EMA guidance and there are some important differences between the documents.

Similarities

Areas where the two documents are in broad agreement include:

- Incorporation into validation practices of product life cycle, quality risk assessment and efficient quality system practices as described in ICH Q8, Q9 and Q10.
- Significant emphasis on continued process verification through analysis of pre and post release data to provide confidence of an ongoing valid process.
- Acknowledgement and provision of scope to emerging processing technologies, such as PAT, to assist the validation effort.
- Enhanced detail to provide understanding of regulator expectation on what constitutes an appropriate validation effort.

Points of difference

Some areas of conflict or at least differences of emphasis include:

- The minimum number of batches required for successful process validation prior to marketing. The EMA draft guideline states "a minimum of three consecutive batches", with justification to be provided (there are some exceptions to this statement). The US FDA guidance states that the number of batches must be sufficient to provide statistical confidence of the process. It is a subtle, but important distinction in the approaches.
- The US FDA guidance places significant emphasis on documenting the product development phase as part of process validation. The EMA document encourages the use of the product development activities, but is less prescriptive on requirements.
- The EMA guideline specifically allows the use of CPV to replace traditional validation efforts. This is a significant variation from the US FDA approach, which does not place high emphasis on CPV, and requires all three stages of process validation to be fully addressed, regardless of whether contemporary or traditional methods are utilised.
- The two documents utilise slightly different definitions of process validation. The EMA guideline uses the long-established definition:
    - "documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."
    - While the US FDA document has redefined process validation as:
    - "the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

The US FDA definition reflects their intent to redefine validation as a scientific rather than a documentation exercise.

Other notable issues

Apart from the key similarities and differences above, there are a few other issues to note when comparing the documents:

- The US FDA guidance is written to assist the development and execution of process validation activities. The EMA guideline is written as a guide of what to consider when developing process validation strategy for dossier submission.
- The US FDA guidance is much more prescriptive when it comes to the requirements of process validation activities. This is understandable when the above document scopes are considered.
- The US FDA guidance considers equipment and process design, as well as equipment qualification as part of the overall process validation effort. The EMA guideline sees process as independent from equipment and facility. Currently, the EMA still relies on Annex 15 of the GMP guide for instruction on equipment qualification. It is likely that Annex 15 will be updated in the near future to reflect the changes in process validation guidance.

What should you do?

You should review your current validation policies and procedures against the draft guidance to determine what extent of change is required. You may wish to consider whether CPV provides you with opportunities to reduce validation effort.

Regardless of the approach you plan to take in the future, it is likely you will need to consider policy and procedure revision, resourcing and training in order to continue to meet industry best practice.

As leading compliance experts within Australasia, PharmOut can significantly reduce this effort and allow you to focus on your everyday business operations of making and selling quality products.

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References

EMA Draft Guideline on Process Validation, March 2012.

US FDA Guidance for Industry – Process Validation: General Principles and Practices, January 2011.

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net

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