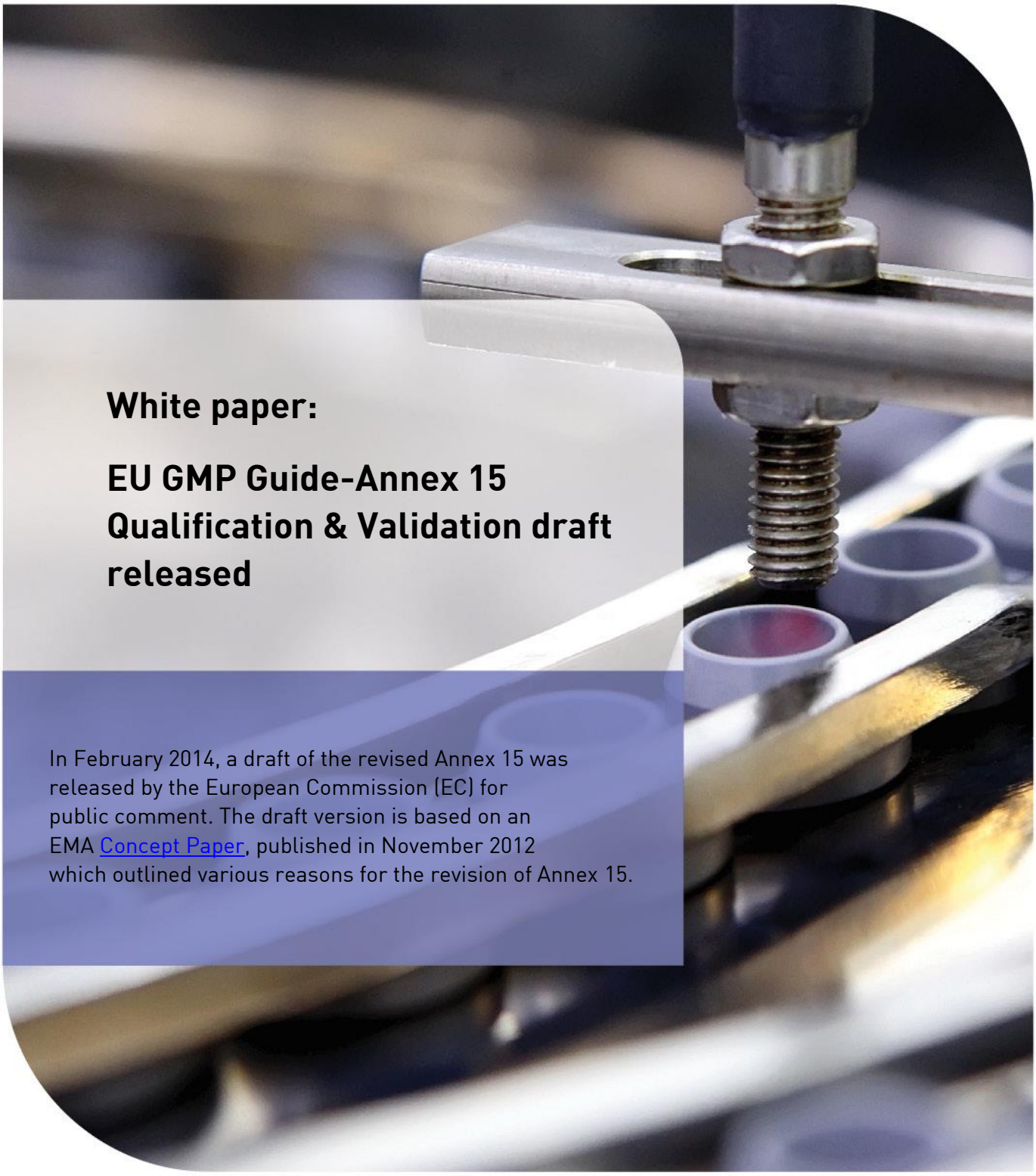

White paper:

EU GMP Guide-Annex 15 Qualification & Validation draft released

In February 2014, a draft of the revised Annex 15 was released by the European Commission (EC) for public comment. The draft version is based on an EMA Concept Paper, published in November 2012 which outlined various reasons for the revision of Annex 15.

Introduction:

The current version of Annex 15 of the EU Guide to GMP was originally published in September 2001, and since then there have been significant changes in the GMP environment. The EMA is in the process of updating its guideline on Process Validation (a draft version is currently available), and there have been advancements in manufacturing technology and continuous manufacture processes. There has also been many changes to other Chapters and Annexes in the EU GMP guide, which have an impact on Annex 15, and therefore the revision of this Annex is required. Also the current version of the US FDA Guide on Process Validation, as well as the approaches in ASTM E2500-07 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment "may have also justified the change.

Who is affected by the changes?

Manufacturers may be directly affected by the changes if they sell the following categories of products into EMA regulated markets once the Annex is revised and effective:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Active pharmaceutical ingredient (API) manufacturers

Medical devices manufacturers are not directly affected; however, the guidance may contain useful information for qualification and validation activities.

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

What are the key changes in the new guidance?

The key change in the draft is the inclusion of the principles of ICH Q8, Q9, Q10 and Q11 (see Figure 1 below). These principles allow the use of concepts such as knowledge management (ICH Q8 & Q10) and science and risk-based approaches (ICH Q9) to support lifecycle validation & qualification activities, and the use of a design space (ICH Q8) for Process Validation.

Figure 1: ICH Q8, Q9, Q10 & Q11.

Other major changes within the draft are detailed in the list below, some of which will be discussed in greater detail later:

- Cross-reference made to Annex 11 Computerised systems
- Planning and documentation for Qualification and Validation
- Added information on the qualification stages for equipment, facilities and utilities
- Major revision of the Process and Cleaning Validation and sections
- New sections added on:
    - Ongoing Process Verification during Lifecycle
    - Verification of Transportation
    - Validation of Packaging
    - Qualification of Utilities
    - Validation of Test Methods

Planning and documentation for Qualification & Validation

During the planning phase, it is now expected that all stages of the lifecycle for equipment, facilities, systems and processes /products need to be taken into consideration. In terms of organisation during qualification and validation, the draft indicates that the Pharmaceutical Quality System (PQS) should define the Validation staff requirements (suitably trained to follow procedures) and the responsibility for oversight over the whole validation lifecycle, in alignment with Chapter 1 of the EU GMP Guide. The Annex indicates that this responsibility (including validation document approval) may not necessarily be a quality management or quality assurance function, but needs to be "appropriate over the whole validation lifecycle". This shift in "appropriate oversight" aligns with the thinking in ASTM E2500, which does not mention responsibilities for someone within a quality function, but instead allows for Subject Matter Experts (SME's) to "confirm acceptance of verification and release of the manufacturing systems, authorising fitness for its intended use".

The draft still states that the Validation Master Plan (VMP) should define the key elements of the validation program but now should also contain the "current validation status" of "facilities, systems, equipment and processes" and also define the "ongoing validation strategy", including requalification/revalidation. It does not mention utilities, but may be assumed under "systems". The VMP should now also cross-reference the template formats used for protocols and reports, as well as assessment of resources required for the entire project. The VMP should also summarise how acceptance criteria will be handled and provide clarity on deviation management during validation. To align with the lifecycle approach, the VMP should confirm that materials used for validation are of "sufficient quality" and obtained from appropriately qualified suppliers.

Assessment of risk:

As part of the alignment with ICH Q9, a well-documented quality risk management approach should be used to justify validation activities. As knowledge and understanding increases during the project phase and during commercial manufacture, the risk assessments should be repeated as required, with changes clearly documented and their impact understood.

Third Party Documents

The Documentation section of the draft outlines the importance of Good Documentation Practice (GDP) for knowledge management throughout the validation lifecycle. For complex projects, the inter-relationships between documents should be understood and visible and in particular, when third party documents are used, they must be "suitable and compliant" with company procedures before approval.

Handling Changes and Deviations

The instruction for the handling of protocols (pre and post execution) and reports has been refined. Protocols should now also include definitions of "critical systems, attributes and parameters which are important", along with their acceptance criteria. Section 2.6 states that "Any changes to the approved protocol during execution should be documented as a deviation and be scientifically justified." The Annex does not detail what types of "changes" could be defined as a "deviations". For example, obvious typographical errors that have no impact on protocol execution may require a change, but may not necessarily warrant a deviation. This should be dependent on the manufacturers own PQS.

The Approval Process

The Annex also now clearly states that the qualification and/or validation report should summarise the results obtained "against the acceptance criteria. Also, any subsequent changes to the acceptance criteria should be “scientifically justified” with a “final recommendation” on the outcome of the study detailed in the report. The formal release for the next step in the validation process is still evident, and can be part of the approval of the validation report or separate summary document authorised by the relevant responsible personnel. Section 2.9 now also states that where "certain acceptance criteria or deviations have not been fully addressed", with a documented assessment, "conditional approval" can be given to proceed to the next validation stage, provided that there is "no significant impact" upon the next stage by doing so.

Qualification stages for equipment, facilities and utilities

As part of the alignment with ICH Q8 to Q11, the activities undertaken during qualification and validation should "consider all stages from initial development of the user requirements specification or initial process development through to the end of use of the equipment, facility or process." This section goes on to suggest some of the "stages" and "criteria" that could be used, but it may depend on the individual project circumstances and may be different. This may allow for the implementation of other qualification and validation approaches such as ASTM E2500. The suggested stages are summarised briefly below.

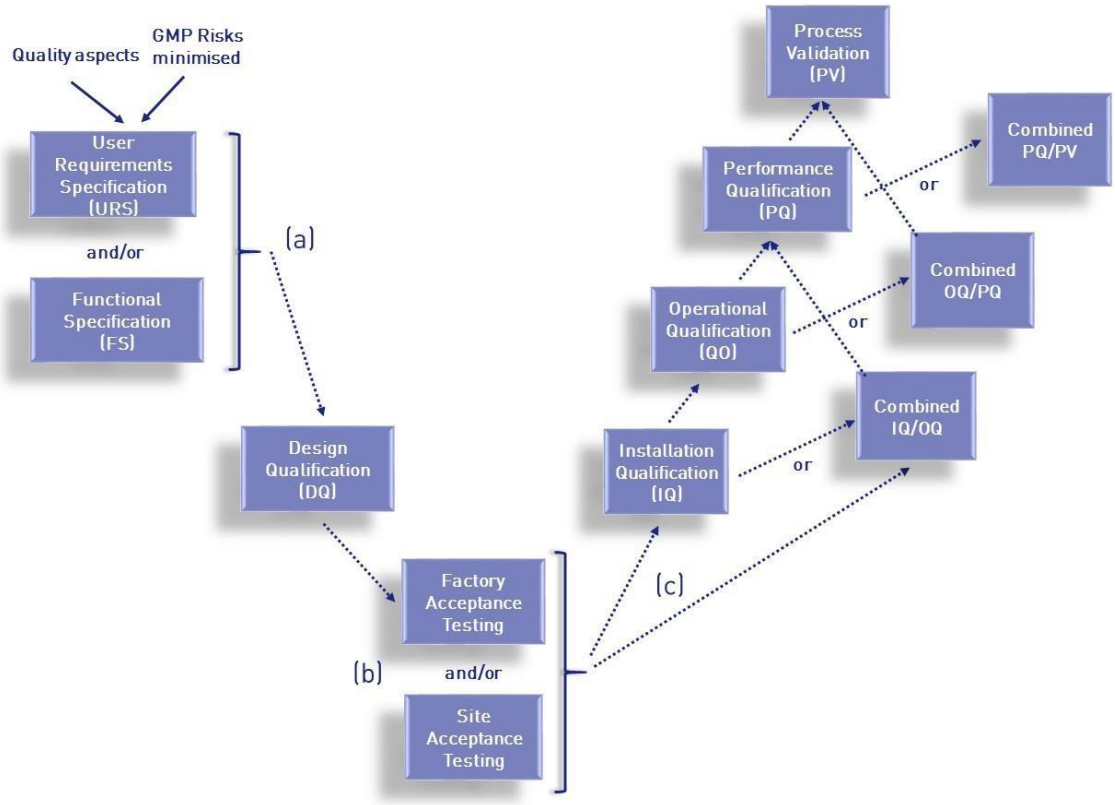

Figure 2: Possible qualification and validation stages from the Draft Annex 15.

User Requirements Specification (URS)

This section is new to Annex 15 and states that "the specification for new facilities, systems or equipment should be defined in a URS and/or a functional specification" and is shown by point (a) in Figure 2 above. This is a significant change as the current version of Annex 15 does not mention a specification phase. The URS should be written with quality elements in mind, as well as minimising GMP risks and "should be a point of reference throughout the validation life cycle". It does not state that a URS should be written for the process itself, and there is no reference to the benefits/use of other types of specifications generally used within the industry.

Design qualification (DQ)

The current version of Annex 15 indicates that Design Qualification (DQ) could be the first element for the validation of new facilities, systems or equipment. The draft version indicates that the "next element is DQ" which serves to ensure the compliance of the design with GMP and should be "demonstrated and documented". It also states that the "requirements of the user requirements specification should also be verified during the design qualification", but does not mention the Functional Specification, or indeed other specification such as design specifications. This section could also have adopted a lifecycle approach to design qualification preceding design reviews, with the same intent as described in ASTM E2500-07:

"Design reviews—planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions".

Factory acceptance testing (FAT) /Site acceptance testing (SAT)

The draft Annex now contains a new section on Factory Acceptance Testing (FAT) and Site Acceptance Testing (SAT) of equipment only as shown in (b) in Figure 2 above. The URS and DQ sections as above refers to "facilities systems and equipment", but only equipment is mentioned in this section. The section recommends the evaluation of equipment "incorporating novel or complex technology" at the vendor's site before delivery, and that equipment should be demonstrated to be in compliance with the URS/functional specification, unless otherwise justified. Testing and documentation reviews carried out during the FAT may not need to be repeated once delivered on site if transport and installation has no impact. The appropriateness of carrying out more testing or not should be assessed and documented.

Installation qualification (IQ)

The definitions and expectations of Installation Qualification (IQ) are the same in both versions of Annex 15, but the new draft also states that the installation should be "as detailed in the design and confirmation of current engineering regarding drawings and specifications" and the IQ must include "verification of the correct installation against pre-defined criteria". This is an obvious requirement for any protocol, but is not evident from the current version of Annex 15.

Operational qualification (OQ)

The OQ section in the draft now details that depending on the complexity of the equipment, a combined IQ/OQ may be performed. It does not state that the same is true for facilities, systems, utilities and/or processes. The draft no longer states that the completion of a successful OQ permits the formal "release" of the facilities, systems and equipment, but it can be inferred from point 2.9 of the draft that this approach is acceptable.

Performance qualification (PQ)

For Performance Qualification (PQ), the draft allows for the qualification activities to be performed in conjunction with OQ or Process Validation. Section 3.14 now details what a PQ "could" include instead of what it "should" include, as per the current version of Annex 15. Sampling and testing used to confirm process control should encompass what has been previously developed from knowledge of the process and the facilities, systems or equipment and justified. The tests should cover the process operating range "unless documented evidence from the development phases which confirm the operational ranges are available".

It is important to note that the definition of "Performance Qualification" is somewhat different within the current PIC/S document PI 006-3 that covers recommendations on VMP, IQ and QO, Non-sterile Process Validation and Cleaning Validation. It includes a definition for Process Validation, but states that "the term Performance Qualification or PQ may be used also". There is also potential for confusion using the abbreviation "PQ" within industry as the US FDA Process Validation Guidance defines PQ as "Process Qualification" which has two elements:. (1) is the design of the facility and qualification of the equipment and utilities and (2) is the process performance qualification (PPQ). which combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches, and will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Process Validation

The requirements and principles outlined in this section are still applicable to the manufacture of all pharmaceutical dosage forms, and now also cover site transfers and ongoing process verification. The Annex should be used in conjunction with the EMA guideline on Process Validation, (currently in draft) which provides direction on what is required for regulatory submission and GMP requirements. A White Paper on the EMA Draft Guidance can be found on the PharmOut website, and a summary of the main sections of the EMA PV Guide are shown in Figure 3 below. Note that Retrospective Validation is not mentioned in the draft, nor is it mentioned in the draft EMA PV Guide. It is assumed that all validation will be either prospective or concurrent in exceptional circumstances.

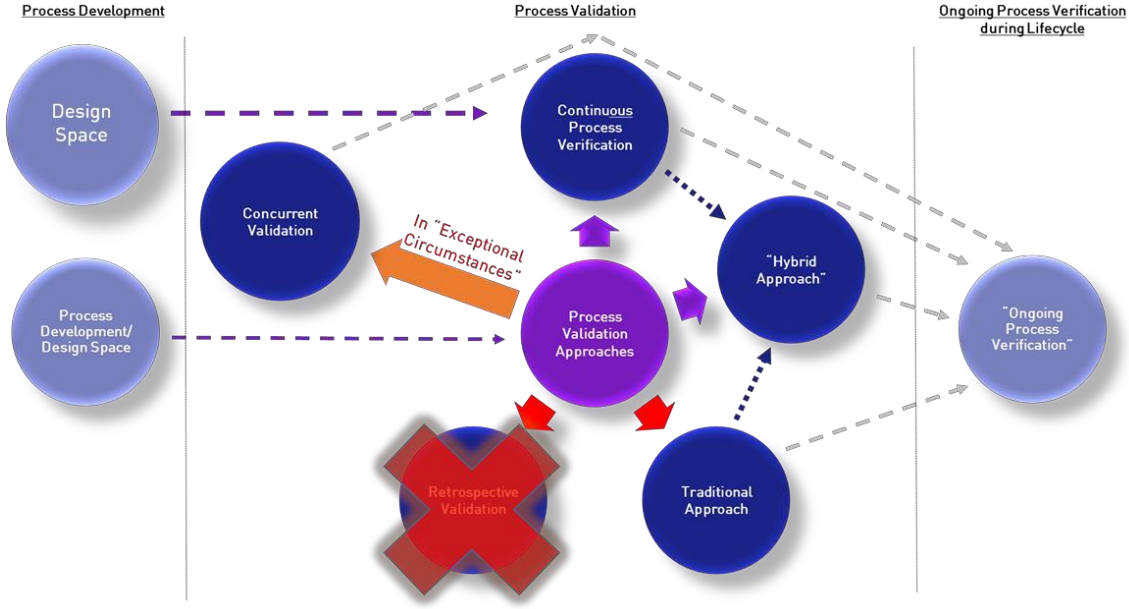

Figure 3: Process Validation approaches from the Draft Annex 15.

The Draft of Annex 15 has sub-headings with descriptions on Concurrent Validation, the Traditional Approach, Continuous Process Verification and Ongoing Process Verification. The only information on the Hybrid Approach is in section 4.24 where it states that "A hybrid approach using the traditional approach and continuous process verification for different production steps can also be used", and a definition is missing from the Glossary. Within the draft, the terms "Ongoing Process Verification" and "Continuous Process Verification" are used and are further described below. Both terms are described as being the same in the Glossary, but this may lead to confusion.

Section 4.3 states that "products may be developed using a traditional approach or a continuous verification approach" but again, does not mention the hybrid approach here. It goes on to say that "however irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market". Manufacturing processes should undergo a prospective validation programme wherever possible prior to marketing of the product.

> *A lifecycle approach is applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during commercial production"*

Process Validation should be based on documented critical process parameters (CPP's) and critical quality attributes (CQA's) as a result of risk assessment activities as applicable. If a design space justification is used, the process knowledge and statistics used to confirm a state of control should be available. Validation batches (including continuous process verification) that are released to the market should fully comply with GMP & Marketing Authorisation and meet all validation acceptance criteria.

The draft also indicates that the number of validation batches could be reduced by the use of a bracketing approach for products which are transferred to another/within site where sufficient product knowledge exists, and if a continuous manufacturing process is used, the batch size for Process Validation should be justified. The options for Process Validation are discussed briefly below.

Concurrent validation

The draft Annex indicates that concurrent validation may be acceptable in exceptional circumstances "where there is a strong risk – benefit to the patient" but the decision must be justified and documented in the VMP and approved by authorised personnel.

The current US FDA Process Validation Guidance document provides greater detail on the potential benefits to concurrent validation. It indicates that concurrent release might be appropriate for "processes used infrequently for various reasons" including limited demand drugs, radiopharmaceuticals with short half-lives or drugs that are medically necessary and are being manufactured "in coordination with the Agency (US FDA) to alleviate a short supply".

Traditional approach to validation

The "traditional approach" allows the manufacturer to produce a number of batches under routine conditions, confirming reproducibility. The number of batches pre- defined and the sampling to be undertaken must be justified based on QRM principles to demonstrate "a high level of assurance that the process is capable of consistently delivering quality product". The section also goes on to say that a minimum of three batches may be justifiable, but the validation exercise may be supplemented with data from "subsequent batches as part of an on-going process verification exercise.

Continuous Process Verification

CPV can be used for products that have been developed by a quality by design approach as an alternative to traditional process validation, as discussed above. CPV should be based on a "science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation". This should also include regular evaluation of the control strategy and the use of statistical tools and Process Analytical Technology (PAT) may be used. The number of batches used to justify that the process is consistent and capable must be justified. CPV can also be used after changes or during ongoing process verification even if the process was initially validated using the traditional approach, but a substantial amount of product and process knowledge must have been gained from experience and historical data first, and again justified.

"A Hybrid Approach" using the "Traditional Approach" and "Continuous Process Verification" together for different production steps can also be used, but there is little detail on the Traditional Approach here.

Ongoing Process Verification during Lifecycle

Ongoing process verification is required periodically to ensure that "a state of control is maintained throughout the product lifecycle". The period of the verification should be based on the level of "process understanding and process performance" at all times during the product lifecycle. This ongoing verification should be used to support the Product Quality Review and should be conducted under an approved protocol with a report, using statistical tools to support conclusions made. The report should contain a detailed assessment of the "variability and capability of the process and ensure a state of control". It should also assess changes during the product lifecycle and their impact on the validated state of the process.

Cleaning validation

Within the Glossary of the draft, the definition for Cleaning Validation has changed from "will provide equipment which is suitable for processing medicinal products" to "will remove all traces of the previous product used in the equipment." This statement is weaker than the older definition as it only infers that previous product be removed and not potential contamination such as bioburden and endotoxin that might be present.

The draft identifies that "visually clean" is an important part of cleaning validation but not acceptable acceptance criteria on its own. The Annex identifies that cleaning validation may take some time to complete and that "ongoing verification" after each batch may be required for a period of time to gather sufficient data.

Section 9.5 states that the "*Limits for the carry-over of product residues should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value*" and should be documented in a risk assessment. This is not particularly helpful for non-toxic products/administration routes.

The PDE represents a dose that is unlikely to cause an adverse effect if an individual is exposed at this dose every day for a lifetime. This approach is not new and the PDE concept is already used in the ICH Guideline Q3C (R4) Guideline for Residual Solvents. The PDE determination is carried out substance-specific on the basis of all available toxicological and pharmacological data from clinical, preclinical or toxicological studies by means of the NOEL (no-observed-effect-level). The NOEL is the highest dose at which no critical effect is observed. This ties in with EMAs draft guide titled "*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*" released in December 2012. The acceptance criteria should also consider the "potential cumulative effect of multiple equipment in the process equipment train". The assessment for potential microbial and endotoxin contamination should also be assessed as applicable, along with the influence of dirty and clean hold times for equipment.

Section 9.8 states that "*where a worst case product approach is used as a cleaning validation model, the rationale for selection of the worst case product should be justified and the impact of new products to the site assessed" and "when there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider toxicity and PDE value as well as solubility. Worst case cleaning validation should be performed for each cleaning method used*".

> *"Typically, the cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated"*

The Annex no longer looks for three consecutive batches to demonstrate that the cleaning process is validated. It now states that cleaning process be carried out an "*appropriate number of times based on a risk assessment*".

Cleaning verification may be used instead (but principles still based on the principles in the Cleaning Validation section of the Annex) of cleaning validation when manufacturing batches infrequently or for investigational medicinal products. If cleaning validation has been proven to be ineffective/not appropriate for some equipment, then dedicated equipment should be used for each product.

New Sections

Ongoing Process Verification during Lifecycle

This section has been discussed in the Process Validation section above.

Verification of Transportation

Verification of transportation ensures product(s) and samples are transported in accordance with the conditions defined in the Marketing Authorisation, product specification file or by the manufacturer. Seasonal variations should also be considered. The Annex states that a risk assessment should be performed to consider the impact of conditions other than temperature during transport and examples are given in this section.

Validation of Packaging

Packaging should be validated as variation in equipment processing parameters during primary packaging may have an impact on the product i.e. blister strips, sachets etc.

Qualification should encompass the entire operating ranges defined for the critical component parameters.

Qualification of Utilities

The quality of utilities such as water, steam, air, gases etc. should be confirmed following installation. Extent of qualification should reflect seasonal variation and intended use. A risk assessment should be carried out to mitigate any risks of failure and is particularly important for direct product contact systems like Heating Ventilation Air Conditioning (HVAC) systems.

Validation of Test Methods

Analytical methods (including microbiological methods) used for qualification, validation or cleaning should be appropriately validated. This section cross references Chapter 6 of the EU-GMP guide Part I.

8.3 states that where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the result.

Other notable changes within the Annex

Re-qualification

The "Re-validation" section has been retitled as "Re-qualification" and states that "Facilities, utilities, systems, equipment should be evaluated at an appropriate frequency to confirm that they remain in a state of control". Also, "Where additional re- qualification is necessary and performed at a specific time period, the period should be justified and, the criteria for evaluation defined. Furthermore the possibility of incremental changes should be assessed".

Change Control

11.3 of the draft states that "Where design space is used, the impact on changes to the design space should be considered against the registered design space within the Marketing Authorisation and the need for any regulatory actions assessed". QRM should be used to evaluate planned changes and assess their impact and to "avoid unintended consequences and to plan for any necessary process verification or requalification efforts". Once the change has been executed, an evaluation of its effectiveness should be carried out to confirm that the change has been successful.

Glossary

The glossary now contains descriptions of the following terms new to the draft:

- Bracketing approach
- Continuous process verification
- Control Strategy
- Critical process parameter (CPP)
- Critical quality attribute (CQA)
- Design Space
- Knowledge Management
- Lifecycle
- Ongoing Process Verification (also known as continued process verification)
- Product realisation
- Quality by design
- State of control
- Traditional Approach

Conclusion

The draft guide has been brought in line with updates to ICH Q8-Q11 and the lifecycle approach, as well as current trends in pharmaceutical manufacturing. There are a number of significant changes in terms of how equipment, facilities and systems can be planned and qualified, and how processes can be validated.

It is also no longer acceptable to have three consecutive batches to demonstrate that the cleaning process is validated-a risk assessment is required to justify the number required.

Included is guidance on the Verification of Transportation as well as separate sections on Validation of Packaging, Utilities and Test Methods.

The document is currently available for public consultation with the deadline for comments set for May 2014. The draft is subject to change and it may need further clarity on a number of sections as highlighted above to avoid confusion including CPV, ongoing process verification and deviations. It is expected that the new version will be adopted be the European Commission in October 2014.

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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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