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PIC/S Guide to GMP PE009-13

Key Changes to Annex 15 – Qualification and Validation

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Key Changes to Annex 15 – Qualification and Validation

1. Principle and General sections
2. Organising and Planning section
3. Documentation section
4. Qualification stages
5. Process Validation (traditional, continuous, hybrid)
6. Ongoing Process Verification
7. Transportation
8. Utilities, Packaging and Test methods
9. Cleaning validation
10. Change control

Annex 15 – Principle

New Text	Impact
It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process.	No impact to inspection process
"…may also be used as supplementary optional guidance for active substances without introduction of additional requirements to Part II.	Annex 15 is not mandatory for API Manufacturing (Validation defined in Part II, Chapter 12)
The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.	Be aware of content of these ICH guidance documents

Annex 15 –General

New Text	Impact
A quality risk management approach should be applied throughout the lifecycle of a medicinal product.	No impact to inspection process
Retrospective process validation is no longer considered an acceptable approach.	**Major change to process validation (see implementation plan)**
Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.	Validation can include data from external sources (leveraging)

Annex 15 – Organising and planning (1)

New Text	Impact
1.2 Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures.	No impact to inspection process
1.3 Qualification/validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function. However, there should be appropriate quality oversight over the whole validation life cycle.	There should be appropriate quality oversight over the whole validation life cycle.

Annex 15 – Organising and planning (2)

New Text:	Impact
1.5 The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following: i. Qualification and Validation policy; ii. The organisational structure including roles and responsibilities for qualification and validation activities; iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status; iv. Change control and deviation management for qualification and validation ; v. Guidance on developing acceptance criteria; vi. References to existing documents; vii. The qualification and validation strategy, including requalification, where applicable.	No significant changes to inspection process Potential updates to VMP required

Annex 15 – Organising and planning (3)

New Text:	Impact
1.7 A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.	No significant changes to inspection process QRM is already an iterative process
1.8 Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.	Need to incorporate appropriate checks for data integrity

Annex 15 – Documentation Section (1)

New Text:	Impact
2.1 Good documentation practices are important to support knowledge management throughout the product lifecycle.	No significant changes to inspection process
2.2 All documents generated during qualification and validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.	No significant changes to inspection process
2.3 The inter-relationship between documents in complex validation projects should be clearly defined.	No significant changes to inspection process

Annex 15 – Documentation Section (2)

New Text:	Impact
2.4 Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.	No significant changes to inspection process
2.5 Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).	No significant changes to inspection process
2.6 Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.	No significant changes to inspection process

Annex 15 – Documentation Section (3)

New Text:	Impact
2.7 Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.	No significant changes to inspection process
2.8 Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation, and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report.	No significant changes to inspection process

Annex 15 – Documentation Section (4)

New Text:	Impact
2.9 The **review and conclusions** of the validation should be reported and the results obtained **summarised against the acceptance criteria**. Any subsequent **changes** to acceptance criteria should be scientifically **justified** and a **final recommendation** made as to the outcome of the validation.	No significant changes to inspection process
2.10 A formal **release** for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. **Conditional approval** to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a **documented assessment** that there is no significant impact on the next activity.	No significant changes to inspection process

Annex 15 – Qualification stages (1)

- DQ/IQ/OQ/PQ process supplemented
- Note the following statement in 3.1 allows flexibility of approach:

New Text:	Impact
3.1 Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some **suggested criteria** (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:	Flexible approach to qualification

Annex 15 – Qualification stages (2)

New Text:	Interpretation
User requirements specification (URS) 3.2 The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.	URS likely for qualification of new systems
Design qualification (DQ) 3.3 The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.	New DQ documents should reference URS

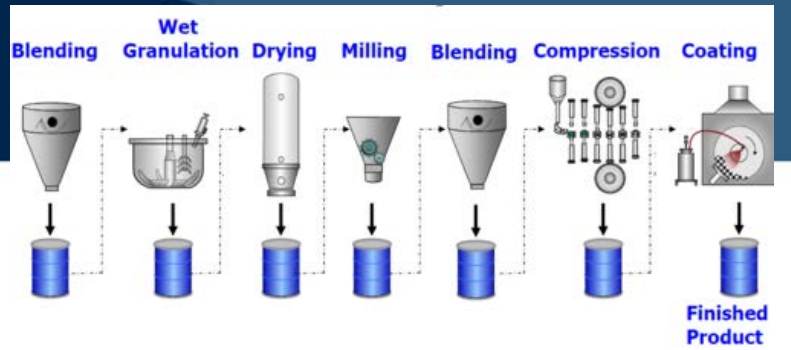
Annex 15 – Qualification stages (3)

New Text:	Interpretation
Factory acceptance testing (FAT) /Site acceptance testing (SAT) 3.4 Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery. 3.5 Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable. 3.6 Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation. 3.7 FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.	Flexible approach to qualification may include records from FAT and SAT FAT testing links to URS

Annex 15 – Qualification stages (4)

New Text:	Interpretation
4. RE-QUALIFICATION 4.1 Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control. 4.2 Where 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 small changes over time should be assessed.	No changes to inspection process

Annex 15 – Process Validation – General (1)



New Text:	Impact
5.1 The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and **ongoing process verification**. It is implicit in this annex that a robust product development process is in place to enable successful process validation.	Addition of ongoing process verification (refer later clauses)
5.2 Section 5 should be used in conjunction with relevant guidelines on Process Validation[1]. [1] In the EU/EEA, see EMA/CHMP/CVMP/QWP/BWP/70278/2012 .	TGA has adopted this guideline: *"Guideline on process validation for finished products - information and data to be provided in regulatory submission"*

Annex 15 – Process Validation - General (2)

New Text:	Impact
5.3 Manufacturing processes may be developed using a **traditional approach** or a **continuous verification approach**. 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 using the traditional approach should undergo a **prospective validation** programme wherever possible prior to certification of the product. **Retrospective validation is no longer an acceptable approach**.	Additional options for PV Must be performed before product is released Retrospective PV no longer accepted (for new products) Existing retrospective validations to be honoured

Annex 15 – Process Validation - General (3)

New Text:	Impact
5.4 Process validation of **new** products should cover all intended marketed strengths and sites of manufacture. **Bracketing** could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate **ongoing verification** programme.	No significant changes to inspection process Ongoing process verification (refer later clauses)
5.5 For the process validation of products, which are **transferred** from one site to another or within the same site, the **number of validation batches** could be **reduced** by the use of a **bracketing** approach. However, existing product knowledge, including the content of the previous validation, should be available. Different strengths, batch sizes and pack sizes/ container types may also use a **bracketing** approach if justified.	Reduced number of PV batches for transferred products – where justified

Annex 15 – Process Validation - General (4)

New Text:	Impact
5.6 For the site **transfer** of **legacy** products, the manufacturing process and controls must comply with the **marketing authorisation** and meet current standards for marketing authorisation for that product type. If necessary, **variations** to the **marketing authorisation should be submitted**.	No significant changes to inspection process Transferred product PV should refer to MA and whether any updates are required. (Grandfathered products?)

Annex 15 – Process Validation - General (5)

New Text:	Impact
5.7 Process validation should establish whether all **quality attributes** and **process parameters**, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being **critical** or **non-critical** should be clearly documented, taking into account the results of any risk assessment activities.	Introduces concept of CPP and CQA and criticality (ICH Q8 & Q11) Risk assessments justifying CQA and CPP should be incorporated into PV (5.21/22)

- A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8)

- A CPP is a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

Annex 15 – Process Validation – CQA & CPP risk matrix (6)

	Variables and Unit Operations					
DP CQAs	Formulation Composition	Blending I	Roller Compaction	Milling	Lubrication	Compresssion
Appearance	Low	Low	Low	Low	High	High
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	High
Impurities	High	Low	Low	Low	Low	Low
Content Uniformity	High	High	High	High	Low	High
Dissolution	High	Low	High	High	High	High

Annex 15 – Process Validation - General (7)

New Text:	Impact
5.8 **Normally** batches manufactured for process validation should be the **same size** as the intended commercial scale batches and the use of any **other batch sizes** should be **justified** or specified in other sections of the GMP guide.	No significant changes to inspection process Allows flexibility
5.9 **Equipment, facilities, utilities and systems** used for process validation should be **qualified.** Test methods should be validated for their intended use.	No significant changes to inspection process

Annex 15 – Process Validation - General (8)

New Text:	Impact
5.10 For all products irrespective of the approach used, process knowledge from development studies or other sources should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities.	No significant changes to inspection process
5.11 For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding.	No significant changes to inspection process ICH Q10

Annex 15 – Process Validation - General (9)

New Text:	Impact
5.12 The **suppliers** of critical starting and packaging materials should be **qualified prior** to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.	Vendor qualification required for validation materials
5.13 It is especially important that the underlying process knowledge for the design space justification (if used) and for development of any mathematical models (if used) to confirm a process **control strategy** should be available.	QbD approach Multivariate data analysis tools understood & validated Control strategy concept (ICH Q10)

Annex 15 – Process Validation - General (10)

New Text:	Impact
5.14 Where **validation batches** are **released** to the market this should be **pre-defined**. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any **continuous process verification** criteria (if used) and with the marketing authorisation or clinical trial authorisation.	The intent to release must be documented and justified CPV relates to QbD approach

Annex 15 – Process Validation – Concurrent Validation

New Text:	Impact
5.16 In **exceptional circumstances**, where there is a **strong benefit-risk ratio for the patient**, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, **documented in the VMP** for visibility and approved by authorised personnel.	Concurrent only where justified VMP states circumstances in which it is used
5.17 Where a **concurrent validation** approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The **results** and **conclusion** should be **formally documented** and available to the **Authorised Person** prior to certification of the batch.	Conclusion from PV made available to AP

Annex 15 – Process Validation – Traditional Approach (1)

New Text:	Impact
5.19 The **number of batches** manufactured and the **number of samples** taken should be based on **quality risk management** principles, allow the normal range of variation and trends to be established and **provide sufficient data** for evaluation. Each manufacturer must **determine and justify** the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.	Flexibility to PV approach We should accept 3 batch approach (5.20) Justification required for less
5.20 Without prejudice to 5.19, it is generally considered acceptable that a **minimum of three consecutive** batches manufactured under routine conditions could constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An **initial** validation exercise with **three batches** may need to be **supplemented with further data** obtained from subsequent batches as part of an on-going process verification exercise.	Flexibility to PV approach We should accept 3 batch approach Justification required for less Ongoing process verification may >3 batches

Annex 15 – Process Validation – Traditional Approach (2)

New Text:	Impact
5.21 A process **validation protocol** should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on **development data** or **documented process knowledge.**	CQA & CPP (ICH Q8 & Q11)

Annex 15 – Process Validation – Traditional Approach (3)

New Text:	Impact
5.22 Process validation protocols should include, but are not limited to the following: i. A short description of the process and a reference to the respective Master Batch Record; ii. Functions and responsibilities; iii. Summary of the CQAs to be investigated; iv. Summary of CPPs and their associated limits; v. Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion; vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status; vii. List of analytical methods and method validation, as appropriate; viii. Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected; ix. Additional testing to be carried out, with acceptance criteria; x. Sampling plan and the rationale behind it; xi. Methods for recording and evaluating results; xii. Process for release and certification of batches (if applicable).	Additional requirements for new PV exercises Document (template) and VMP updates potentially required

Annex 15 – Process Validation – Continuous

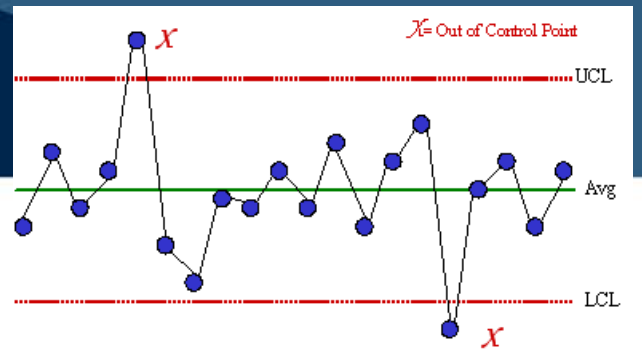
New Text:	Impact
Continuous process verification 5.23 For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation. 5.24 The method by which the process will be verified should be defined. There should be 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. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product. 5.25 The general principles laid down in 5.1 – 5.14 above still apply.	Normally applies to products developed by QbD approach Control strategy In-process monitoring May be used for “hybrid” approach

Annex 15 – Process Validation – Hybrid Approach

New Text:	Impact
Hybrid approach 5.26 A **hybrid** of the **traditional approach** and **continuous process verification** could be used where there is a **substantial amount of product and process knowledge** and understanding which has been gained from manufacturing experience and historical batch data. 5.27 This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.	CPV may be applied to products validated by the traditional approach Used normally to demonstrate re-validation of the process (not for new products)

Annex 15 – Ongoing Process Verification (1)

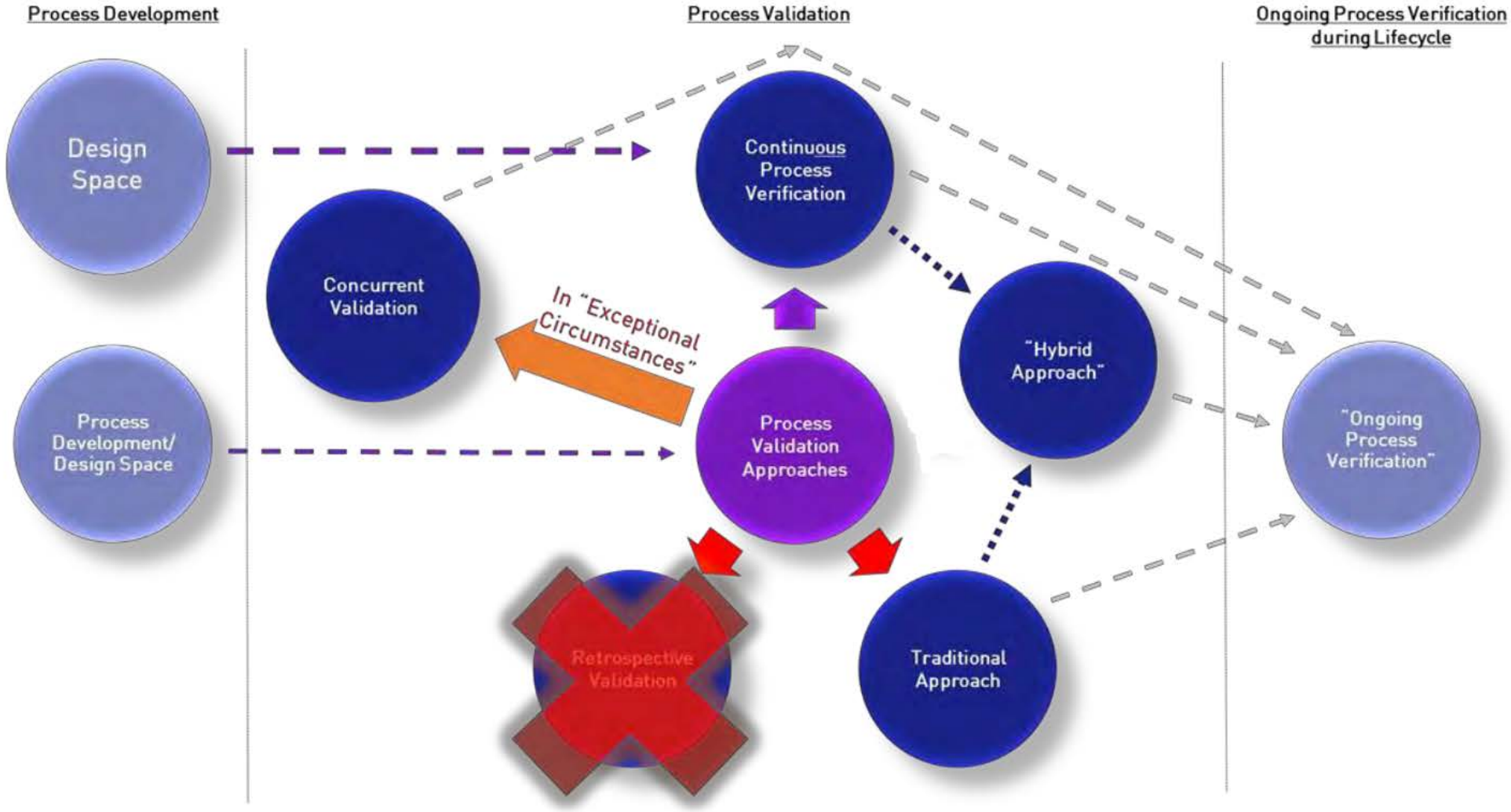
New Text:	Impact
5.28 Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.	New requirement - OPV applies to all validated processes
5.29 Manufacturers should **monitor product quality** to ensure that a **state of control** is maintained throughout the product lifecycle with the **relevant process trends evaluated.**	Monitoring at higher frequency than PQR. Uses SPC tools to detect issues
5.30 The **extent and frequency** of ongoing process verification should be **reviewed periodically**. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.	Additional review and trending of batch process data required New products monitored at higher frequency.



Annex 15 – Ongoing Process Verification (2)

New Text:	Impact
5.31 Ongoing process verification should be conducted under an **approved protocol** or equivalent documents and a **corresponding report** should be prepared to document the results obtained. **Statistical tools should be used**, where appropriate, to support any conclusions with regard to the **variability** and **capability** of a given process and ensure a state of control.	Protocols for OPV required SPC normally used
5.32 Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.	Report outcomes considered in PQR

Annex 15 – Process Validation Pathways (Summary)



Annex 15 – Transportation (1)

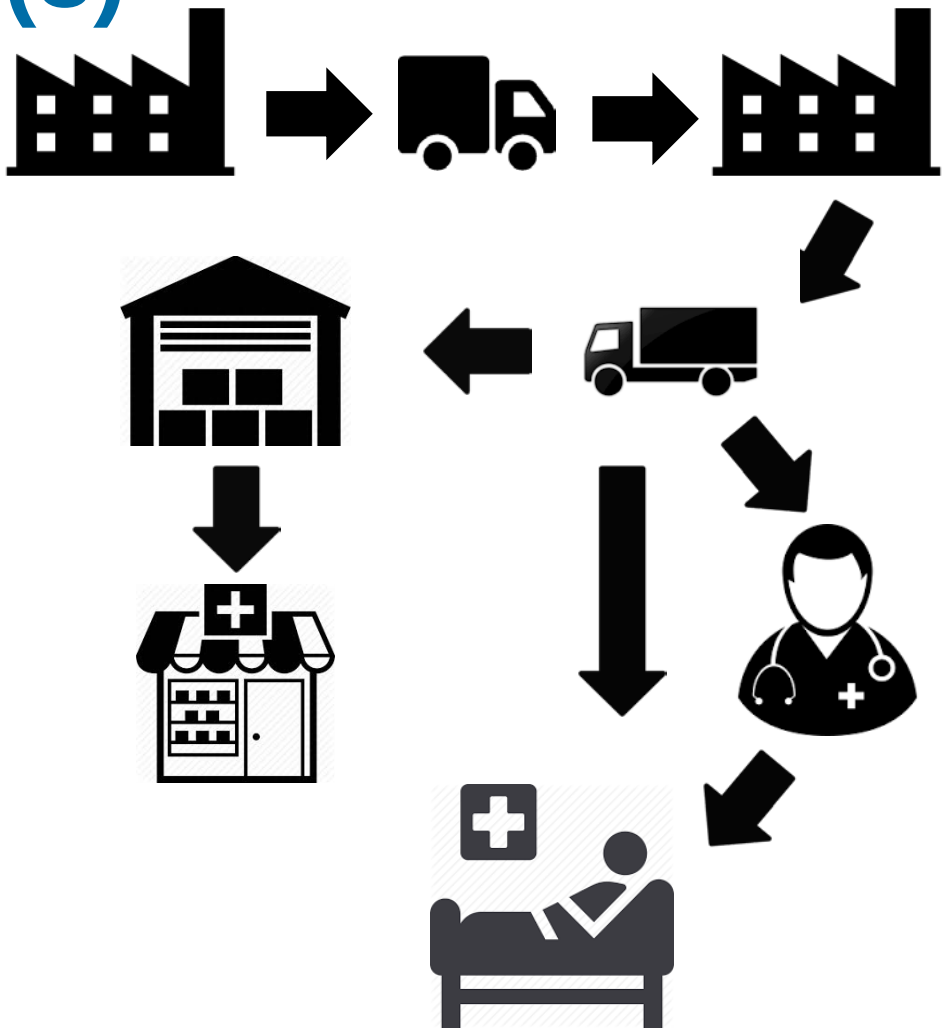
New Text:	Impact
6.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be **transported** from manufacturing sites **in accordance** with the **conditions** defined in the **marketing authorisation**, the **approved label**, product specification file or as justified by the manufacturer.	Evidence that transport chain is appropriate Cannot transport 'outside' label conditions
6.2 It is recognised that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport	Evidence of transport routes required

Annex 15 – Transportation (2)

New Text:	Impact
6.3 A **risk assessment** should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.	Risk assessments for transport routes required
6.4 Due to the variable conditions expected during transportation, **continuous monitoring** and recording of any **critical environmental conditions** to which the product may be subjected **should be performed**, unless otherwise justified.	Data loggers should be used unless justified

Annex 15 – Transportation (3)

- How does this apply in Australia?
- Consider responsibilities of TGA and State/Territory Health Departments
- Note that the manufacturing site may also hold a Wholesalers Licence
- Technical Agreements should provide responsibilities
- Inspection focus should be risk based and consider the supply chain
- Ask questions regarding the validation and monitoring of transportation



Annex 15 – Packaging

New Text:	Impact
7.1 Variation in equipment processing parameters especially during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components; therefore primary and secondary packaging equipment for finished and bulk products should be qualified.	No change to inspection process
7.2 Qualification of the equipment used for primary packing should be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other factors.	No change to inspection process

Annex 15 – Utilities

New Text:	Impact
8.1 The quality of steam, water, air, other gases etc. should be confirmed following installation using the qualification steps described in section 3 above.	No change to inspection process
8.2 The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.	No change to inspection process
8.3 A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.	No change to inspection process

Annex 15 – Test Methods

New Text:	Impact
9.1 All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in Chapter 6 of the PIC/S GMP guide Part I.	No change to inspection process
9.2 Where microbial testing of product is carried out, the method should be validated to confirm that the product does not influence the recovery of microorganisms.	No change to inspection process
9.3 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 recovery of microorganisms.	No change to inspection process

Annex 15 – Cleaning Validation (1)

New Text:	Impact
10.1 Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.	No change to inspection process
10.2 A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.	No change to inspection process

Annex 15 – Cleaning Validation (2)

New Text:	Impact
10.3 It is recognised that a **cleaning validation** programme **may take some time** to complete and validation with **verification after each batch** may be required for some products e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.	No change to inspection process Pragmatic provision
10.4 Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.	No change to inspection process

Annex 15 – Cleaning Validation (3)

New Text:	Impact
10.5 For all cleaning processes an **assessment** should be performed to determine the **variable factors** which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the **worst case situations** should be used as the basis for cleaning validation studies.	No change to inspection process

Annex 15 – Cleaning Validation (4)

New Text:	Impact
10.6 **Limits** for the carryover of product residues should be based on a **toxicological evaluation**[2]. The justification for the **selected limits** should be **documented in a risk assessment** which includes all the supporting references. **Limits** should be established for the removal of any **cleaning agents** used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.	Toxicological evaluations required based on HBEL (PDE) calculations

Annex 15 – HBEL Calculations

- EMA/CHMP/CVMP/SWP/169430/2012 – *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"*
  - Will be transcribed into PIC/S Guidance
- Based on ICH Q3C (R4) - residual solvents
- Clinical data used to calculate Permitted Daily Exposure (PDE) Limit
- Calculations should be performed by qualified toxicologist
- PDE is a safe dose that may be taken on a daily basis for a lifetime

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

- Where:
  - NOAEL = No observed adverse event level (mg/kg)
  - Weight adjustment = 1
  - F1F1: A factor (values between 2 and 12) to account for extrapolation between species
  - F2: A factor of 10 to account for variability between individuals
  - F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks
  - F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity
  - F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity

Annex 15 – Cleaning Validation (5)

New Text:	Impact
10.6.1 Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.	Pragmatic provision
10.6.2 If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.	Pragmatic provision

Annex 15 – Cleaning Validation (6)

New Text:	Impact
10.7 The risk presented by **microbial and endotoxin** contamination **should be considered** during the development of cleaning validation protocols.	No change to inspection process
10.8 The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean **hold times** for the cleaning process.	No change to inspection process Hold times
10.9 Where **campaign** manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the **maximum length of a campaign** (in time and/or number of batches) **should be the basis** for cleaning validation exercises.	No change to inspection process

Annex 15 – Cleaning Validation (7)

New Text:	Impact
10.10 Where a **worst case** product approach is used as a cleaning validation model, a **scientific rationale** should be provided for the selection of the worst case product and the **impact of new products** to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity, and potency.	No change to inspection process
10.11 Cleaning validation protocols should specify or reference the **locations to be sampled**, the **rationale for the selection** of these locations and define the **acceptance criteria**.	No change to inspection process
10.12 Sampling should be carried out by **swabbing and/or rinsing** or by other means depending on the production equipment. The **sampling materials and method** should **not influence the result**. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.	No change to inspection process Recovery validation

Annex 15 – Cleaning Validation (8)

New Text:	Impact
10.13 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.	No change to inspection process
10.14 Where a cleaning process is **ineffective** or is not appropriate for some equipment, **dedicated equipment** or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of the PIC/S GMP Guide.	No change to inspection process
10.15 Where **manual cleaning** of equipment is performed, it is especially important that the effectiveness of the manual process **should be confirmed** at a justified frequency.	No significant change to inspection process Manual cleaning verified

Annex 15 – Change Control

New Text:	Impact
Clauses 11.1-11.7 Essentially identical in intent	No change to inspection process
11.3 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.	Additional clause for QbD
11.7 Following implementation, and where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.	No change to inspection process

Q&A

- Add Q&A
- Questions

Useful references

- EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions.
- EMA Guideline on setting limits for use in risk identification in the manufacture of different drug products in shared facilities.
- ICH Q11 – Development and manufacture of drug substances (for an understanding of CQA, CPP, design space)
- ICH Q9 – Quality Risk Management.
- E2500 - 07 Standard guide for specification, design and verification of Pharmaceutical and Biopharmaceutical manufacturing systems and equipment. (Mentioned a lot in the consultation but not endorsed by IMB, FDA. Relies on SME rather than QA, overreliance on QRM, no qualification documents required, use vendor documentation.)
- FDA Process Validation Guide 2011

Australian Government

Department of Health

Therapeutic Goods Administration