New Annex 15 –
Practical Implications

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Regulatory Knowledge, Practically Applied.

Who is impacted by the Annex 15 update?

From October 1:

- Manufacturers who export to EU markets without an MRA with the TGA
- *Potentially* manufacturers who export to EU markets with an MRA with the TGA
- *Potentially* manufacturers who export to other PIC/S markets

From the undefined TGA adoption date:

- Manufacturers requiring licensing by the TGA

New in Annex 15

REVISION CONTENT	CURRENT CONTENT
Principle	Principle
General	X
Organising and Planning for Qualification and Validation	Planning for validation
Documentation including VMP	Documentation
Qualification stages for equipment, facilities utilities and systems	Qualification
Re-qualification	Revalidation
Process Validation	Process validation
General	General
Concurrent validation	Prospectve, Concurrent, Retrospective
Traditional Process Validation	x
Continuous process verification	x
Hybrid approach	x
Ongoing process verification during Lifecycle	x
Verification of Transportation	x
Validation of Packaging	x
Qualification of Utilities	x
Validation of Test methods	x
Cleaning validation	Cleaning validation
Change Control	Change Control
Glossary	Glossary

New in Annex 15

Manufacturers used to the old Annex 15 will find that the new parts of Annex 15 fall generally into three categories:

- New explicit requirements that most manufacturers (if not all) already do
- New requirements that some do routinely, some do some of the time and some don't do
- New requirements that few, if any, are currently doing

New requirements/opportunities that are well implemented in Australia

- Apply Annex 11 for Computer Systems Validation
- Combine qualification phases where appropriate
- Write URS and execute DQ for EFS and systems
- Perform FAT and/or SAT for novel/bespoke/complex equipment
- Bracketing
- Implementation of the new sections (Transport, Packaging, Method Validation and Utilities)

New requirements/opportunities that are partly implemented in Australia

- Prohibit retrospective validation
- Quality Risk Management approach (general)
- Leverage vendor documentation and testing during qualification
- Write URS and execute DQ for **every** EFS and system requiring qualification
- Ongoing/Continued PV (FDA stage 3) and evaluation of the qualification status of EFS periodically
- Understand QbD principles and application of CQA/CPP in validation

Retrospective Validation

Twice stated '*retrospective validation is no longer an acceptable approach*'

- Gaps in validation should practically no longer exist
- If they do, they should be identified through Continued PV
- Actions from CPV include impact and risk assessment to determine extent of remediation required
- May result in use of retrospective data to justify limited action
- May result in new PPQ (PV) batches
- All contained within 3 stage PV approach.

QRM - General application in Validation

Risk assessment as part of validation life cycle is increasingly common, areas for improvement include:

- Documentation - How RA is used needs to clearly documented (proceduralised, not just policy)
- RA lifecycle – what happens to initial RA as life cycle evolves (now mandated that they are revisited as appropriate)
- Use of RA – QRM is intended to justify scope and extent of validation activities. Not just 'another step'
- Change control – required to revisit RA as part of changes.

Leveraging of 3rd Party Information

Concept has gained popularity since the release of ASTM E2500:

- Must always have appropriate site level approval
- May include:
  - Third party validation protocols and execution
  - Commissioning testing and/or certification
  - Specification
  - Anything else acceptable to QA to support validation activities

Ongoing/Continued Process Validation

Technically not a new requirement:

- Section 45 of old Annex 1 (Revalidation), not well understood, implemented or inspected until recently
- FDA PV guide has prompted many sites to implement
- Periodic documented reporting required, but should be more than a PV version of PQR
- FDA requires input of data from every batch and corresponding statistical assessment of the data pool
- New Annex 15 not quite so specific: '*monitored throughout product lifecycle*', '*process trends evaluated*', '*extend and frequency … reviewed periodically*'
- Use of statistics (scientifically justified) to support conclusions

New requirements/opportunities for us to come to grips with

- Use prospective validation except in exceptional circumstances
- Understand the regulatory limitations on concurrent validation and adequately justify its use
- Quality Risk Management specific to numbers of validation batches
- Realise the potential of Continu**ous** PV (eg. PAT)
- Fully understand both the expectations of Continu**ed** PV and the power of an effective CPV program
- New requirements for cleaning validation

Prospective vs Concurrent Validation

Concurrent validation widely used in Australia for to validate changes to existing processes:

- PIC/S PI006 (validation guidance for non-steriles) encouraged concurrent validation for a range of low risk activities
- New Annex 15 and FDA PV guide expressly discourage concurrent validation
  - FDA expects '*concurrent release will be used rarely*'
  - New Annex 15 states concurrent validation is only acceptable '*in exceptional circumstances, where there is a strong benefit-risk ratio for the patient*'

Prospective vs Concurrent Validation

Circumstances that meet the "exceptional" criteria according to FDA (and presumed to be accepted by EMA):

- Infrequent manufacture of drugs due to limited demand
- Short half lives of drugs
- Medical necessity (drug shortage) upon agreement with regulatory agency

Note: Processes determined to be low risk through QRM do not meet the criteria for concurrent validation

BUT …

Quality Risk Management – How many batches?

3 batches is no longer a set-and-forget golden rule for validation:

- Yes, this may mean more than three batches when the RA indicates higher risks
- But, low risk validation may be able to be supported by lower batch numbers
- 1 batch essentially constitutes concurrent validation!
- Need a robust, justifiable QRM approach to determining batch numbers
  - ISPE Gold Sheet on Stage 2 Process Validation a good example
  - Can create your own risk based approach

Continuous Process Validation

New term, introduced by EMA to confuse us:

- Essentially refers to the control strategies in place
- Highly effective control strategies which continually provide assurance of product quality can be used to reduce or even eliminate prospective validation
- PAT, multivariate statistical process control mentioned
- Local manufacturers typically see as too expensive or too hard
- Currently optional, and therefore likely to gain little traction in local market in the short term

Continued Process Validation

Increasingly adopted, rarely to full effect. Effective CPV program will:

- provide knowledge base to reduce validation batch numbers for process changes or similar products
- reduce OOS and other deviations
- Aid continuous improvement in process design, even for unrelated process

Continued Process Validation

New Annex 15 is disappointingly light for detail. FDA PV guide much more detailed. Expectations go beyond collection and reporting of data:

- Detailed statistical analysis by statistician or adequately trained personnel
- Scrutiny of intra-batch and inter-batch variation
- Focus on CQAs and CPPs
- Other aspects, similar to PQR should have 'timely assessment' (calibration, maintenance, defects, OOS, batch records, etc.)

Cleaning Validation

Adapting to new Cleaning Val requirements is the biggest jump in new Annex 15:

- Visual check unlikely to be acceptable criterion alone in future
  - Visual inspection needs to be quantified
  - Should usually be accompanied by some form of analytical support
- Section 10.3 sounds suspiciously like concurrent validation is acceptable for cleaning

> 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.

Cleaning Validation

Acceptance Criteria is the big issue:

- '… should be based on toxicological evaluation'
- Should be established for products and for cleaning agents
- Should consider the cumulative effect of multiple equipment items in process train
- Some exceptions to toxicological evaluation are provided (substances than may degrade during cleaning)
- TOC and conductivity are suggested when it is not feasible to test for product residues

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Thank you for your time.
Questions?

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