Real Time Release Testing from an EU regulatory perspective

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EU regulators interest in Real Time Release Testing (RTRT)

- **EU regulators drafted NfG on Parametric Release in 1999**
  - Came into effect 2001
  - Emanated from and focused on terminal sterilisation
  - Did foresee the use of the concept in other parts of pharmaceutical manufacture
- **Revision and extension started in 2009**
  - triggered by the publishing of ICH Q8, Q9 and Q10
  - a request from the Commission
- **Resulted in**
  - Guideline on Real Time Release Testing
    EMA/CHMP/QWP/811210/2009 Rev 1

Overview

- **Definitions**
- **Regulatory aspects**
- **RTRT and Control Strategy**
- **Submission requirement**
- **Biologics and RTRT**
- **Importation from third country**
- **Parametric Release and sterility**
- **Regulatory experience**

Definitions

- **RTRT**
  - The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (ICH Q8 (R))
- **Parametric Release**
  - One form of RTRT. Parametric release is based on the review of documentation on process monitoring (e.g. temperature, pressure, time for terminal moist heat sterilisation) rather than the testing of a sample for a specific attribute (ICH Q8 Q&A).

ICH Q8, Q9 and Q10

- **Pharmaceutical development can lead to an enhanced understanding**
- **Need to involve**
  - Risk Management
  - Quality System
- **Often utilises e.g.**
  - formal Design of Experiment
  - Process Analytical Technologies (PAT)
- **May result in some flexible regulatory approaches**
  - RTRT is one such possible flexibility

Regulatory aspects of RTRT

- **Requires pre-authorization by Competent Authority**
- **May be applied**
  - as part of a new Marketing Authorisation (MA) Application
  - as a variation of a MA of an existing product
- **Applicable to Drug Substance & Drug Product**
- **Assessed by assessors and GMP inspectors**
- **Approval/withdrawal is at the discretion of the Competent Authority**
- **Variation required to return from RTRT to end testing**

RTRT as part of a Control Strategy

- **QP decision to release a batch takes into account among other aspects**
  - conformity of the product to its specification
  - traditionally based on end product testing
- **With RTRT one or more quality attribute replaced by**
  - a valid combination of measured material attributes and process controls
- **Typically not all attributes replaced**

RTRT and specification

- **Specifications are still needed when using RTRT**
  - Needed for the stability program to establish shelf-life
  - Needed for controls by Official Medicines Control Laboratories (OMCL)
- **Specification requirements in case of RTRT**
  - Complies if tested
- **RTRT acceptance criteria and associated specification test**
  - Relationship must be well understood
  - Supported by substantial comparative data (parallel testing)

If something goes wrong when utilising RTRT

- **When approved, RTRT should be used routinely for batch release**
- **If the criteria for the release fails/trend toward failure**
  - you cannot revert back to release based on end testing
  - failure to be investigated and trends followed up
  - batch release decision must be based on these investigations and must be in compliance with the MA and with GMP
- **A contingency plan with temporary testing procedure in case of equipment failure.**
  - any "fall-back" options should be discussed and justified

Certificate of Analysis

- **Attributes that are replaced by RTRT in the Control Strategy**
  - should still appear in the Certificate of Analysis
  - results given as e.g. “Complies if tested”
  - or indicating the alternative ways (see example)
  - footnote stating e.g. “Controlled by approved Real Time Release Testing”

Certificate of Analysis - example

Test	Method	Acceptance criteria	Results
Appearance and description	Visual	Round, glossy, white debossed with 5 on one side and # on the other side	Pass
Identification	HPLC	Major peak is within 2% retention time of reference peak (HPLC)	Complies if tested[1]
Uniformity of dosage units	Ph.Eur. 2.9.40. Content by HPLC.	Ph.Eur. 2.9.40	Complies if tested[1]
Assay	HPLC or NIR	95-105 %	101.1 % (NIR)[1]
Dissolution	HPLC or chemometric prediction	Not less than 80% (Q) released in 15 minutes	Complies if tested[1]

1 Controlled by approved Real Time Release Testing

Submission

- **Highly dependent on the process and the controls suggested e.g.**
  - continuous or discrete process
  - sampling or continuous monitoring
- **RTRT granted for specified sites on basis of**
  - Product and Process Understanding
  - proposed Control Strategy
  - assessment of GMP compliance for the proposal

Documentation

- **Including e.g. (not unique to RTRT)**
  - development identified CQA:s
  - development done with a risk based approach
  - scientific basis for the control strategy
  - relationship between end testing and RTRT
  - justification of acceptance criteria
  - specified procedures for approval/rejection
  - parallel testing where applicable

RTRT for biologicals

- **Principles equally acceptable for biologics**
  - Product/process understanding and/or testing at earlier stages should be used to justify
  - Most likely to be applied at Drug Substance stage
- **Established practice**
  - validation of process to justify upstream control (e.g. virus testing) could fall under RTRT.
  - Usually not labelled as RTRT
- **Unlikely to cover all tests of a specification**

Retesting upon importation from Third Country

- **Directive 2001/83/EC as amended requires that:**
  - *each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least the active substance and all the other tests or checks that are necessary to ensure the quality*

- **Tests replaced by approved RTRT need not be repeated upon importation**
  - Identification upon receipt as part of GMP will still apply

Parametric Release

- **Parametric release**
  - One form of RTRT
  - Release based on monitoring of process parameters (eg. time, pressure, temperature for moist heat sterilisation) only, rather than also measured material attributes
  - Together with compliance with specific GMP requirements
- **Typically for replacement of sterility test for release**
  - Mentioned in Ph Eur in chapter 5.1.1 “Methods of preparation of sterile products”
  - EU GMP, Annex 17 “Parametric release” (Jan 2002)

Parametric release of sterility –why/when?

- **Shorten processing time i.e. time to release**
- **Statistical limitations of the sterility test**
  - small number of samples
  - limited ability of culture media
- **Sterilisation method according to Ph Eur**
  - terminal sterilisation by moist heat, dry heat, radiation
  - overkill process
- **Experience with the process**
- **Satisfactory GMP compliance record**

Parametric Release of Sterility - application

- **Submission of a variation application**
- **Application to be supported by the following data**
  - description of sterilisation cycle
  - methods/procedures and specifications applied for e.g. bioburden control, monitoring of cycle parameters, verification of load sterilisation
  - a validation report (demonstrating acceptable conditions throughout the load)
    - heat penetration and distribution
    - microbiological performance qualification
    - level and heat resistance of microorganisms
  - Package integrity data (if applicable)

Parametric release –
a product specific inspection will focus on

- **Relevant SOPs of significance for product sterility**
- **Applied system for segregation of non-sterilised and sterilised products/batches**
- **A risk assessment containing**
    - consistency of performance
    - experience with the product/similar products
    - risks associated with any changes since first approval
    - steps taken to assess and control risks

Parametric Release Approval

- **Basis for approval**
    - close collaboration between assessor and inspector
    - in general, **no new** data need to be created
    - reference can be made to already submitted data where applicable
- **Once approved, parametric release should be used routinely.**
- **If results fail or are trending towards failure it may not be substituted by end product sterility testing.**

Regulatory experience

- **Limited experience of applications with RTRT**
- **Increase in applications with extensive development and enhanced understanding (the QbD concept) without claims for RTRT**
- **Reflects that enhanced understanding is beneficial also without any regulatory relief**
- **Concept established for**
  - some aspects regarding biologics
  - parametric release for sterility

Examples RTRT for biologicals

- **DNA/HCP should normally be tested at Drug Substance level.**
  - May be tested upstream taking validated downstream removal into account to assure that acceptable levels in drug substance
  - Would fulfil the specification, if tested
- **Apart from this, few examples seen in applications.**

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Parametric Release – Regulatory Experience

- **No significant increase in applications after release of the first guideline in 2001**
- **Majority of approvals concern standard over kill processes**
- **Reduced processes**
  - in combination with antimicrobial properties of formulation assuring a low bioburden level
  - sufficient experience in combination with monitoring of bioburden
- **Radiopharmaceutical with limited stability ($t_{½}$ = 50 days)**

Thank you for your attention

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