EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2010
EMA/CHMP/QWP/811210/2009 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)

Draft

Draft Agreed by Quality Working Party	November 2009
Adoption by CHMP for release for consultation	17 December 2009
End of consultation (deadline for comments)	31 August 2010

This guideline replaces the Note for Guidance on Parametric Release CPMP/QWP/3015/99

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Parametric release, batch release, sterilisation, Process Analytical Technology, Quality by Design, real time release testing

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Executive summary

Medicinal products must comply with the approved specifications before they are released into the market. Compliance with release specifications can be demonstrated by performing a complete set of tests on the finished product, according to the approved specifications. Under certain conditions, an alternative strategy to routine testing is possible. So far this concept has been only applied to sterility testing of terminally sterilised products (parametric release). Recent guidelines adopted in the ICH context (ICH Q8, Q9 and Q10) have made possible to apply a similar release strategy to tests other then sterility, this approach has been called Real Time Release testing.
This guideline addresses the requirements for application of RTR testing to different kinds of products e.g. chemical and biological products and its scope is to facilitate the introduction of RTR testing. The guideline replaces the previous guideline on parametric release and does not introduce new requirements, so the parametric release part on the previous guideline is retained unchanged.

1. Introduction (background)

Medicinal product must comply with the requirements stated in the authorised specifications for release and shelf life. Real Time Release (RTR) is a system of release that gives assurance that the product is of intended quality, based on the information collected during the manufacturing process, through product knowledge and on enhanced process understanding and control. RTR recognises that under specific circumstances a comprehensive set of in-process controls (Real Time Release testing (RTR testing)) may provide greater assurance of product quality than end-product testing.). The RTR principle is already authorised for use as an optional alternative to routine sterility testing of products terminally sterilised in their final container i.e. parametric release[1,2]. Enhanced product knowledge and process understanding, the use of quality risk management principles and the application of an adequate pharmaceutical quality system, as defined within ICH Q8,Q9 and Q10[3,4,5,6] provide the platform for establishing RTR testing mechanisms for other applications, for new products as well as established marketed products,
This guideline elaborates on the application of RTR testing to a number of areas of pharmaceutical development and manufacture, in addition to sterilisation. It will thereby replace the “Note for Guidance on Parametric Release.

2. Scope

This document is intended to outline the requirements for applications that propose RTR testing for active substances, intermediates and finished products. The guideline highlights the different requirements that have to be fulfilled in the application and the role of related inspections (pre authorization and routine GMP inspections).

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

4. Real Time Release Testing

4.1. Real Time Release Testing and Specifications

Before a medicinal product is released for sale, the Qualified Person responsible for its release should take into account, among other aspects, the conformity of the product to its specifications[7]. In the case of approved RTR testing, this conformity would not routinely be supported by results of end product testing. Nevertheless product specifications have to be established and each batch of a product should comply with them if tested. Product specifications are also necessary for stability studies, in order to establish a product shelf-life as well as for OMCL controls. The application for RTR testing should contain adequate data of a running in period with both end product testing data and RTR testing data.
When RTR testing has been approved this should be routinely used for batch release. In case the test results of an approved RTR testing fail or are trending toward failure it may not be substituted by end-product testing. Any failure should be investigated and trending should be followed up appropriately.

Batch release decisions will need to be made based on the results of these investigations, and must comply with the content of the marketing authorization and current GMP requirements.
The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in case of equipment failure. In this situation, the alternative approach could involve use of end-product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown needs to be managed in the context of a deviation under the Quality Management System and can be covered by GMP.
For products coming from third countries into the EU it is a requirement in Directive 2001/83/EC "that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorization" (9). This normally means a complete reanalysis of the product according to the approved specifications. When a company has got approval for RTR testing for one or more tests in the specifications, these tests would not be considered a "necessary test or check to ensure the quality of the medicinal product in accordance with the requirements of the marketing authorization". Therefore a relief from this testing will be accepted.

4.2. Application of RTR testing

Process monitoring may be applied to various manufacturing processes, such as tabletting, on the basis of appropriate testing at various stages in the process. Some parameters are usually checked routinely at defined intervals regardless of the design of the manufacturing process of a tablet. Uniformity of mass, crushing strength and disintegration are such examples. The results of a comprehensive set of in-process tests and controls in these cases may constitute sufficient grounds for replacing the corresponding end product testing and may also offer greater assurance of the finished tablet meeting certain criteria in the specification, without the tests being repeated on a sample of the finished product, as the number of tested units will in general be substantially larger.
RTR testing will in general comprise other technologies such as process analytical chemistry test methods, e.g. vibrational spectroscopy techniques like near infrared spectroscopy (NIR) and Raman spectroscopy, usually applied in combination with multivariate analysis. Spectral data monitored on-line controlling content of active substance, polymorphism, water content, blending homogeneity, particle/powder properties or film thickness could thereby replace end-product testing like e.g. uniformity of content, tablet strength and drug dissolution.
When RTR testing is applied, the attribute that is indirectly controlled (e.g. sterility, uniformity of content) together with a reference to the associated test procedure, should still be included in the specifications. The relation between end-product testing and material attributes and process monitoring, including acceptance criteria, should be fully explained and justified, including the use of any prediction models.

4.2.1. Application of RTR testing to biological/biotechnological products

RTR testing may be applied to biological/biotechnological products. For instance, the level of process related impurities such as residual host cell DNA or host cell proteins (HCP), which are typically tested on a routine basis on the active substance, may be evaluated using a routine testing approach and/or a validation approach.
A routine testing approach would be based on the monitoring, using suitable analytical tools, of the level of those impurities at appropriate step(s) of the process, in order to ensure acceptable levels in the final product.
A validation approach would be based on evidence of successful validation of the manufacturing process establishing that at given steps of the purification scheme, those impurities are removed in a consistent and reproducible manner to an acceptable level. This may be supported by demonstration the process clearance capability, based on reduction factors. In such situations, the review of the documentation on process monitoring may be carried out during manufacturing without direct measurements of the quality attributes. Therefore a relief from this testing may be accepted.
A combination of routine testing and validation approaches is also possible. Such approach could be used, for instance, where the application data alone are not sufficient to completely remove routine testing (e.g. reduction factor not sufficient). In this situation, routine testing at an earlier step, before a purification step which has been demonstrated to appropriate clearance capability with regards to the given impurities, in order to ensure acceptable levels in the final product level, if tested.

4.2.2. RTR testing examples

For illustrative purposes some examples are given, which are not intended in any way to limit the scope of the application of RTR testing.
A combination of in-process tablet weight, blend content uniformity measurement e.g. by NIR, drug substance purity and particle size could serve as a control strategy for drug content of a high dose tablet if the relationships has been demonstrated. Core tablet weight, blend uniformity, drug substance purity and particle size in this example are the RTR tests. The production batches are released by the Qualified Person based on the outcome of the RTR tests, any other required tests and GMP compliance.
Properties relating to the properties of a tablet granule such as porosity, particle size, surface area etc. could be shown to have a relationship with dissolution behaviour and serve as RTR testing surrogates for dissolution testing. These dependencies would have to be confirmed on a product-by-product basis.

5. Documentation for RTR testing

5.1. General requirements

For some substances and dosage forms, the different stages of manufacturing process will be discrete, thus allowing sampling at critical parts of distinct stages of the process. For other substances and dosage forms, the manufacturing process may be more or less continuous, necessitating a more integrated process monitoring. It is therefore not possible to specify in a guideline, specific details of how RTR testing can be applied. This must be assessed in each individual case verifying that the requirements of appropriate Notes for Guidance are met.
The authorization of the RTR testing programme will be granted for specified sites on the basis of an assessment of how well the manufacturing process concerned is founded. Monitoring of critical parameters must be capable of demonstrating that pre-determined validated conditions have been achieved throughout the batch. In addition, assessors will evaluate the choice and limits of the critical parameters in relation to their effect on the technical characteristics, stability and bioavailability of the product and its packaging. Methods of controlling critical parameters will also be assessed.
The introduction of RTR testing must be based on sufficient experience with the process and evaluation of the GMP compliance at the actual site.

5.2. Documentation

The application upon which an authorization may be granted should demonstrate:

- that the risk assessment identifies the critical quality attributes,
- that the manufacturing process is validated adequately,
- that it is reliably controlled,
- relation between end-product testing and process monitoring, including justification of acceptance criteria
- that in process requirements chosen for approval/rejection are decided on the basis of the acceptance criteria defined in the validation records,
- that clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection
- that the applied technologies gives an adequate quality

6. Parametric Release and Sterilisation

Parametric release is referred to in the European Pharmacopoeia monograph ”Methods of preparation of sterile products”[9]. This states ”When a fully validated terminal sterilisation method by steam, dry heat or ionising radiation is used, parametric release, that is the release of a batch of sterilised items based on process data rather than on the basis of submitting a sample of the items to sterility testing, may be carried out, subject to the approval of the competent authority.”
The statistical limitations of the sterility test in predicting sterility assurance are well known and based on a) the small number of samples required for testing in relation to the batch size and b) the limited ability of the culture media to enable growth of all potential microorganisms. Thus the sterility test will only detect major deviations in the process resulting in the contamination of a large number of units. By accurately monitoring relevant sterilisation parameters e.g. temperature, pressure and time, data derived from in-process monitoring of a validated terminal sterilisation process can provide more accurate information since the probability of product bioburden surviving the process in any single unit can be calculated to be less than one in a million. Approval for parametric release eliminates the

requirement for a finished product sterility test as a condition for batch release. The release of each batch is dependent on the successful demonstration that pre-determined, validated sterilising conditions have been achieved throughout the load.

The sterilisation process in an application for parametric release of sterility must be in accordance with the requirements of the European Pharmacopoeia. Consequently, parametric release can only be applied to products sterilised in their final containers by moist heat, dry heat or radiation[9]. The choice of a sterilisation process must be well founded considering both the knowledge of the stability of the product under relevant conditions and the data gained in development studies where critical process parameters are identified.

As regards inspections conducted based on an application for parametric release the inspector checks that standard operating procedures for the various stages in the manufacturing process that are of significance for sterility are in place. In particular, the procedures for quality control of starting materials, packaging materials, process water, steam and environmental monitoring are checked. Other aspects of importance are for example filtration procedures, equipment cleaning/sterilisation procedures, maximum holding times for bulk solutions and quality of the cooling medium as well as physical arrangement to separate non-sterilised and sterilised loads.

6.1. Sterilisation by heat

A sterilisation process shall be validated in accordance with GMP guidelines. Qualification of equipment and validation of the process which is applied at a particular time, including heat distribution and heat penetration studies with a given, established load pattern are thus carried out so that heat equivalents can be calculated. The technical validation of a heat sterilisation method shall be complemented by a biological validation. Consideration shall be given to the level and heat resistance of the microorganisms associated with the product. When the sterilisation process has been defined, its reproducibility shall be demonstrated. Compliance with specific GMP requirements as described in the annex 17 to the EU-GMP[2] should also be demonstrated. An example of such a requirement is the segregation of non-sterile products from sterilised products. There should be a readily apparent system of identifying sterilized and non sterilized products. The distinction may be enhanced when process monitors (color indicators and tapes which change after being subjected to the sterilization process) are used to indicate sterilization. However, these devices are only process indicators and do not constitute absolute proof that the correct process parameters have been achieved.

An application for parametric release of sterility should be supported by

- a description of the sterilisation process including type of cycle, load pattern, specifications for cycle parameters (time, temperature, pressure, F0-value) and chemical indicators (if applicable),
- specifications and methods/procedures used for in-process controls e.g. pre-sterilisation bioburden, monitoring of cycle parameters and verification of load sterilisation,
- a process validation report comprising heat distribution and heat penetration studies for at least three runs for each load pattern used, and a microbiological qualification showing sufficient efficacy (SAL) at the minimum level of the cycle including information on the biological indicators used (type, D-value, Z-value, stability), and bioburden characteristics (number, type, resistance) as applicable,
- package integrity data (if applicable).

Typically the specific sterilisation process for the product proposed for parametric release should be the same as the process already approved in the original application and reference could, where applicable, be made to the previously submitted data. It is suggested that the risk assessment presented in the application focus on the failure to achieve sterility in each unit of every batch. The risk assessment should include:

- consistency of performance of the sterilisation process within validated limits
- experience with the product applied for and similar products
- risks associated with any changes made to the product, or process or equipment since the first approval
- steps taken to assess and control identified risks

Once parametric release has been granted, decisions for release or rejection of a batch must be based on the approved specification, which means that batch release with regard to sterility is based on parametric data. Such a decision cannot be overruled by the use of a sterility test contrary to some other approaches of real time release (see section 4.1).

6.2. Sterilisation by radiation

Parametric release can also be applied in the case of sterilisation by radiation. The minimum absorbed dose should generally be 25 kGy. Lower doses can be acceptable if justified by low, routinely checked, bioburden levels and adequate validation data[10,11].
The same requirements regarding documentation as for sterilisation by heat must be met where applicable. The documentation shall comply with the guidelines defined by the EU in regard to ionising radiation.

Definitions

Real Time Release Testing (RTR testing): 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 type of RTR testing. Parametric release is based on process data (e.g. temperature, pressure, time for terminal sterilization) rather than the testing of a sample for a specific attribute (ICH Q8 Q&A).

Batch release: Approved RTR testing may form a basis but more aspects needs to be taken into account in the decision of a Qualified Person to release a batch. These aspects could include batch results of testing for an attribute not subject to RTR testing as well as specific GMP requirements[12].

References

1. Note for Guidance on Parametric Release (CPMP/QWP/3015/99, March 2001)
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3. ICH Q8(R2) Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/2004)
4. ICH Q9 Quality Risk Management (EXT/24235/2006)
5. ICH Q10 Pharmaceutical Quality System (EMEA/CHMP/ICH/214732/2007)
6. ICH Quality Implementation Working Group on Q8, Q9 and Q10, Questions & Answers
7. Directive 2003/94/EC (as amended) article 11
8. Directive 2001/83/EC (as amended) article 51 1b
9. Ph Eur 6th Ed, 5.1.1, Methods of preparation of sterile products
10. NfG on The use of Ionisation Radiation in the Manufacture of Medicinal products (III/9109/90)
11. EN 552:1994, Sterilisation of medical devices – Validation and routine control of sterilisation by irradiation.
12. EU Guide to Good Manufacturing Practice. Annex 16.