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

Final

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Executive summary

Medicinal products must comply with their 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 active substance and/or finished product, according to the approved specifications. Under certain conditions, an alternative strategy to systematic end product testing is possible. So far this concept has been mainly applied to sterility testing of terminally sterilised products and has become associated with parametric release applications. Recent guidelines adopted in the ICH context (ICH Q8, Q9 and Q10) have made it possible to apply a similar release decision process to tests other than sterility, this approach has been called Real Time Release Testing (RTRT).

This guideline addresses the requirements for application of RTRT to different kinds of products e.g. chemical and biological products and its scope is to facilitate the introduction of RTR testing. The guideline is a revision of the guideline on parametric release and does not introduce new requirements.

1. Introduction (background)

A medicinal product must comply with the requirements stated in the authorised specifications for release and shelf life. RTRT 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 process understanding and control. RTRT recognises that under specific circumstances an appropriate combination of process controls (critical process parameters) together with pre-defined material attributes may provide greater assurance of product quality than end-product testing and the context as such be an integral part of the control strategy. The RTRT 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 appropriate pharmaceutical quality system, as defined within ICH Q8, Q9 and Q10^{3,4,5,6} provide the platform for establishing RTRT mechanisms for other applications, for new products as well as established marketed products. Release of a product can be a combination of a RTR approach for certain critical quality attributes (CQAs) and a more conventional evaluation for other CQAs (partial RTR).

2. Scope

This guideline outlines the requirements for applications that propose RTR testing for active substances, intermediates and finished products. It also outlines the different requirements that have to be fulfilled in the application and the need for interaction between quality assessors and GMP inspectors in the approval process.

The principle of RTRT may be applied during the stages of manufacture of chemical and biological products resulting in the elimination of all, or certain, specific tests in the specifications of the finished active substance or finished medicinal product.

This guideline is not applicable to investigational medicinal products although a company may be at various stages of development aiming at RTRT of the final product.

3. Legal basis

This guideline should 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. General considerations

The application of RTRT may offer advantages to a manufacturer and from a regulatory point of view the enhanced knowledge gained is welcomed, however it is not a mandatory requirement. Potential benefits are e.g. to enable real time control and process intervention (feed-back or feed-forward options), assessment based on a larger set of data and reduced overall operational cycle times.

The introduction of RTRT requires pre-authorization by the competent authority. In general the documentation submitted for a new market authorization or a variation should address only those quality aspects that are specific for the medicinal product. Site specific quality aspects not specific to the product (i.e. quality systems and process implementation), fall within the remit of GMPs.

RTRT may be introduced as a part of an application that is based on an enhanced product understanding of what is responsible/critical for product performance or may be introduced following a variation of an existing market authorization when more experience has been gained with the manufacture of the product and sufficient product and process knowledge has been demonstrated. In both cases adequate risk management should be demonstrated in line with the relevant ICH guidelines.

Although the assessment of applications is primarily made by the assessors, close collaboration with inspectors is highly recommended as the input from both parties will form the basis for the approval where the assessors will focus on the product related issues and the inspectors more on the system related ones. Approval as well as withdrawal of RTR testing is at the discretion of the Competent Authority. A withdrawal may be based on the results of an inspection or on the receipt of other information.

If a company after approval of RTRT wishes to return to end product testing, a variation of the marketing authorization is required.

5. Real Time Release Testing

5.1. RTRT as part of a Control Strategy

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 specification⁷. In the case of approved RTRT, this conformity would not routinely be supported by results of end product testing. Nevertheless a specification has to be established and each batch of a product should comply with it if tested. A specification is also necessary for stability studies, in order to establish a product shelf-life as well as for Official Medicines Control Laboratory (OMCL) controls. The application for RTRT should be supported by adequate validation of the RTR test method. The relationship between the RTR test, including acceptance criteria, and the end product test and associated specification should be well understood and, where applicable, supported by substantial comparative data at commercial scale (parallel testing).

When RTRT has been approved this should be routinely used for batch release. In the event that the test results of RTRT fail or are trending toward failure, RTRT 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. Attributes (e.g. uniformity of content) that is indirectly controlled by approved RTRT should still appear in the Certificate of Analysis for batches. The approved method for end-product testing should be mentioned

and the results given as "Complies if tested" with a footnote: "Controlled by approved Real Time Release testing".

In case of equipment failure the control strategy provided in the application should include a contingency plan specifying the use of alternative testing or monitoring approaches on a temporary basis. 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.

5.2. Application of RTRT

The exact approach to RTRT will vary depending on the process requirements. The RTRT strategy may be based on control of process parameters, monitoring of product attributes or on a combination of both at appropriate steps throughout the process. Critically, the RTRT strategy should be based on a firm understanding of the process and of the relationship between process parameters, in-process material attributes and product attributes. Process monitoring may be applied to various manufacturing steps or unit operations, such as tableting, on the basis of appropriate testing at various stages in the process. Some parameters/attributes 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 amount of data will in general be substantially larger. If testing of units is part of the RTRT a sampling strategy should be defined that provides the number of locations sampled throughout the batch as well as the number of dosage units tested at each location.

RTRT will, in general, comprise a combination of process controls which may utilise process analytical technology (PAT) tools e.g. near infrared spectroscopy (NIR) and Raman spectroscopy (usually in combination with multivariate analysis), together with the control of relevant material attributes. 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 e.g. uniformity of content, tablet strength and drug dissolution.

In active substance manufacturing, RTRT can apply to continuous manufacturing processes, but also to discrete unit operations such as distillations, hydrogenations, crystallisations and all sorts of other chemical reactions or separations (e.g. diastereoisomers).

When RTRT 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 specification as "Conforms if tested" (see 5.1). The relationship between end-product testing, material attributes, process monitoring and acceptance criteria, should be fully explained and justified. In addition, the use of any prediction models should be fully explained, justified and verified at the commercial site.

5.2.1. Application of RTRT to biological/biotechnological products

Alternate approach to routine end product testing could be considered for quality attributes included in the specification of a biological/biotechnological product, provided that it can be demonstrated that acceptable level would be maintained in the final product level, if tested. Product/process understanding, in-process parametric control and/or attribute testing at an earlier step in the process

are elements that can be used to justify the replacement of end product testing on a routine basis by RTRT.

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. In this situation, the demonstration of high process clearance capability, based on reduction factors, may be sufficient to justify the lack of end product testing of these quality attributes on a routine basis.

A justification based on 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, could also be used to justify the lack of end product testing of these quality attributes on a routine basis.

5.2.2. RTRT examples

For illustrative purposes some examples are given, which are not intended in any way to limit the scope of the application of RTRT.

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 tablet if the relationship 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.

Attributes relating to the properties of a tablet granule such as porosity, particle size, surface area, bulk/tapped density etc. if shown to have a predictive relationship with dissolution behaviour could serve as RTR testing surrogates for dissolution testing. These dependencies would have to be confirmed on a product-by-product basis.

RTRT for impurities for an active substance may be achieved through control of starting materials and process parameters which directly impact impurity levels, supported by empirical and mechanistic knowledge of impurity formation and purging during processing.

5.3. Retesting upon importation from third country

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"⁸. This normally means a complete reanalysis of the product according to the approved specification. When a company has approval for RTRT for one or more tests in the specification, 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. Identification upon receipt of material as part of GMP will apply even if this test subject to RTRT.

6. Submission requirements

6.1. General requirements

For some substances and dosage forms, the different stages of the 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 partially or wholly continuous, necessitating a more integrated process monitoring. It is therefore not possible to specify in a guideline specific details of how RTRT 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 RTRT programme will be granted for specified sites on the basis of an assessment of the product and process understanding together with the proposed control strategy as described in the submission and implemented in accordance with GMP. Monitoring of critical parameters/attributes 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, and their potential impact on stability and bioavailability of the product and its packaging. Methods of controlling critical parameters will also be assessed and adequacy of operations evaluated on inspections.

The approval of RTRT by the competent authority will be based on an assessment of the regulatory submission as well as the knowledge of sufficient experience with the process and the GMP compliance at the actual site.

6.2. Documentation

The application upon which an authorization may be granted should demonstrate (not unique to a RTRT application):

- that the pharmaceutical development studies have identified the critical quality attributes for the finished product;
- that a risk based development program has been carried out;
- that a scientifically based control strategy has been developed and implemented;
- that the manufacturing process is, or will be, validated adequately (as evaluated on inspection);
- that in process requirements chosen for approval/rejection are decided on the basis of the acceptance criteria defined in the development studies;
- the relationship between end-product testing and RTRT, including justification of acceptance criteria;
- that clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection;
- that the applied technologies gives an acceptable quality;
- comparative test results (parallel testing) supporting the relationship between the end-product specification and the RTRT where applicable;

- that the RTRT approach is equivalent to or better than the end product test;
- that a contingency plan as described in 5.1 is in place.

7. Parametric Release and Sterilisation

Parametric release is based on evidence of successful validation of the manufacturing process and review of the documentation on process monitoring during manufacturing, without direct measurement of quality attributes. It can be used as an operational alternative to end product testing for the drug product in certain cases when approved by the competent authority. Sterility testing for terminally sterilized drug products is one example. 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. for moist heat sterilisation; 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 radiation⁹. 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 product 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 used in heat sterilisation processes as well as physical arrangement to separate non-sterilised and sterilised loads.

When parametric release has been approved this should be routinely used for batch release. In the event that the results fail or are trending toward failure, parametric release may not be substituted by end-product sterility testing. Any failure should be investigated and trending should be followed up appropriately.

7.1. Sterilisation by moist and dry 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 should be complemented by microbiological performance qualification. Consideration should 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-GMP² 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/FH-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 performance 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.

7.2. 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 routinely collected bioburden data comprising both count and type of microorganisms as well as 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 (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)⁶. (Together with compliance with specific GMP requirements related to parametric release this provides the desired assurance of the quality of the product.)

Batch release: Approved RTRT may form a basis but more aspects need 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 requirements¹².

References

1. Note for Guidance on Parametric Release (CPMP/QWP/3015/99, March 2001);
2. The Rules Governing Medicinal Products in the EU: GMP Guidelines Annex 17 – Parametric release;
3. ICH Q8(R2) Note for Guidance on Pharmaceutical Development (EMA/CHMP/167068/2004);
4. ICH Q9 Quality Risk Management (EXT/24235/2006);
5. ICH Q10 Pharmaceutical Quality System (EMA/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/ISO 11137 Parts 1 and 2 (2006), Sterilisation of health care products – Radiation;
12. EU Guide to Good Manufacturing Practice. Annex 16.