Review Article

Real Time Release Testing-A Review

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ABSTRACT
QbD is a systemic approach to attain a intended product quality, the tools which assist the QbD principle are design space and Process Analytical Technology(PAT).Now Modern application called Real Time Release Testing has came in to existence which can be accompanied with or without design space and PAT tools. Real time release testing is set of In-process controls that provide greater assurance of product quality than end – product testing under specific conditions. RTRT involves at-line and on-line measurements of critical quality attributes for eg., (tablet weight after compression, moisture measurement during drying, blend uniformity)where they are generated to ensure the product quality in real time. This real time release testing challenge is to perform the right measurement at right time and at the right location. RTRT improves and enhances analytical testing without affecting either product quality or manufacturing cycle.
Keywords: *Real Time Release Testing, PAT, End-Product Testing.*

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INTRODUCTION

Definition

RTRT can be defined as "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"

RTRT can replace end-product testing,but does not replace the review and quality control steps called for under GMP to release the batch.RTRT is moving the "QC lab into process and measure the (CQAs) Critical Quality Attributes where they are generated"[1]

Examples of RTRT:

1. On-line or At-line measurements

   Tablet weight after compression
   Particle size measurement after granulation or milling
   Moisture content during drying
   Blend uniformity

2. Fast At-line measurements

   NIR for tablet assay
   Disintegration in lieu of dissolution

3. Models as surrogate for traditional release test

   Multivariate model as a surrogate for dissolution

4. Process signatures

   An evolving approach

PARAMETRIC RELEASE

Definition:

A system of release that gives the assurance that product is of intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release

It is recognised that a comprehensive set of In-process tests and control may provide greater assurance of finished product meeting specification than finished product testing

Parametric release may be authorised for certain specific parameters as an alternative to routine testing of finished products. Authorisation for parametric release should be given, refused or withdrawn jointly by those responsible for assessing products together with GMP inspectors

Parametric release is based on process data(eg., Temperature, Pressure, Time for terminal sterlization) rather than testing of sample for specific attributes(ICH Q8,Q&A)[2]

Controlling CQAs and CPPs

The QbD approach helps to identify what is critical for the product quality including

what to control,where and how.Focuses on what matters and not controlling everything

Reduced risk of failure of important controls**.**Critical quality attributes can be measured in

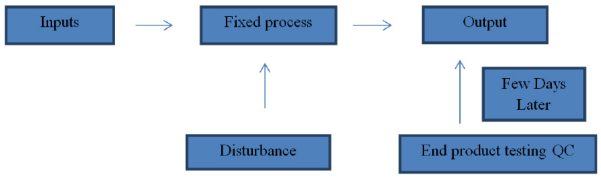
real time during manufacturing.Quaity decisions can be made using the measurements to

Control and adjust the process as needed.Real time release testing to replace end-product

Testing

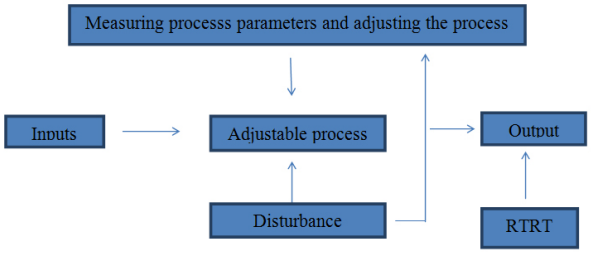
END PRODUCT TESTING

Figure 1: End Product Testing



REAL TIME RELEASE TESTING

Figure 2: Real Time Release Testing



BACKGROUND

A medicinal product must comply with requirements stated in authorised specfication for release and shelf life.RTRT is a system of release that gives assurance that the product is of intended quality,based on information collected during 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.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.Enhanced product knowledge and process understanding,the use of quality risk management principles and the application of appropriate pharmaceutical quality system provide the platform for establishing RTRT mechanism for other applications,for new products as well as established marketed products.Release of a product can be combination of RTR approach for certain CQAs[3]

METHODOLOGY

Sampling procedures

To use RTRT,a specific approach for sampling should be present on when and where to take the sample and how much amount of sample to be taken.As RTRT is an on-line measurement, automated sampling is done.The quantity collected is lesser and sample preparation is simpler than that of traditional method sampling.The overview of sampling plan should be such that it should facilitate real-time control,to gain knowledge of the next manufacturing step and to measure critical material attributes.the probe or sample location,frequency

should be the representative of entire batch,sample acquisition time,sample volume and environmental factors sholud be constant over entire process[4]

Equipment failures

In case of equipment failures,the manufacturer should not stop the RTRT measurements and return to conventional methods like In-process,end-product testing unless there is a proven evidence of equipment failures.After provision of evidence,alternative methods can be used without disturbing the acceptable level of quality.The failure should be investigated and followed

Challenges by introducing RTRT

S.No	Challenges
1.	PAT tools in place (In-line analysers, PATdata management, multivariate data analysis, process control)
2.	Requires new skills and re organisation of work
3.	Risk associated with implementing PAT 1. Installation of probes, representative sampling, failure of instrument, failure of multivariate models 2. Backup strategy must be in place 3. Models need frequent update 4. If RTRT fails it cannot be replaced by end – product testing[5]

Relationship between RTRT, control strategy, PAT and QbD

RTRT when used,is part of the control strategy.	Can include some or all of final product CQAs
QbD is not directly coorrelated to RTRT.	1. You can have QbD approaches without RTRT 2. However,it would be difficult to justify RTRT without a science and risk based approach
Not all Process Analytical Technology(PAT) leads to RTRT	PAT systems can be designed to control CQAs of raw materials and not contribute to RTRT
A design space is not required for RTRT.	Having a design space can increase operational flexibility,without additional regulatory approval.[6]

APPLICATIONS OF RTRT

S.No	Challenges
1.	Outcome of high level of process understanding 1. Corrective actions may be implemented in real time
2.	Controlling the process
3.	Provides increased assurance of quality
4.	Increase yield, reduce waste, scrap
5.	Reduce the risk of losing a batch
6.	Reduced QC test
7.	Increased control activity on manufacturing shop floor
8.	Reduced cycle time
9.	Quality of finished product can be measured during manufacturing
10.	Provides increased manufacturing flexibility and efficiency 1. Reduction in end-product testing 2. Reduction in manufacturing cost 3. Reduced inventory

SUBMISSION REQUIREMENTS

To implement RTRT for a particular manufacturing operation with respect to that of a particular product. Application should be submitted to competant authority.The application would be granted only after the assesment of product,process and control strategy of particular product mentioned in submission.The competant authorities will evaluate the critical attributes selected in relation to their effect on stability and bio-availability of product. The control strategy presented in application should also mention the use of alternative methods in case of equipment failure while maintaining product quality.[7]

Documentation

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

1. That the pharmaceutical development studies have identified the critical quality attributes for the finished product.
2. That the risk based development program has been carried out.

3. That a scientifically based control strategy has been developed and implemented.
4. That the manufacturing process is, or will be,validated adequately(as evaluated on inspection)
5. That in-process requirements chosen for approval/ rejection are decided on basis of acceptance criteria defined in development studies.
6. The relationship between end-product testing and RTRT,including justification of acceptance criteria.
7. That clear,specified procedures are in place describing the reporting and actions to be taken on approval/rejection.
8. That the applied technologies gives an acceptable quality.
9. Comparative test results(parallel testing)supporting the relationship between the end-product specification and RTRT where applicable.
10. That the RTRT approach is equivalent to or better than end-product test.[8]

Considerations for implementing RTRT

Initially pharmaceutical quality system must support the control strategy.Later on risk assesment program should be done in case of failure of RTRT.RTRT strategy should incorporate data trending,OOS(out of specification) if any occurs and alarms.It should be able to recaliberate or verify the process when there is any change in the raw material,manufacturing equipment or measuring instrument

CONCLUSION

We can conclude that RTRT can provide a higher assurance of product quality as it involves

Enhanced process understanding

Real time analysis and control of process

Operational flexibility

Framework for continuous manufacturing

Support of continual improvement

RTRT relies on the information of materials,equipment and method employed in manufacturing.RTRT can be applied to new and marketed products. It efficiently supports the continual improvement of product. Generic industry is also very interested in RTRT-Help to reduce cost.The pharmaceutical sector is moving forward by adapting the principles of RTRT.FDA also supports the implementation of RTRT approaches and also has reviewed and approved applications using RTRT but less in count.

GLOSSARY

1. **Real Time Release Testing-**Ability to evaluate and ensure the quality of in-process and or final product based on process data,typically include a valid combination of measured material attributes and process controls ICH Q8(R2)[9]
2. **Quality By Design(QbD)-**A systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control,based on sound science and quality risk management ICHQ8(R2)[10]
3. **Process Analytical Technology(PAT)-**A system for designing,analysing and controlling manufacturing through timely measurements(i.e during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of assuring final product quality[11]
4. **Control strategy-**A planned set of controls,derived from current product and process understanding that ensure process performance and product quality. The control can include parameters and attributes related to drug substance and drug product materials and components,facility and equipment operating conditions,in-process controls,finished product specification and associated methods and frequency of monitoring and control(ICHQ10)[12]
5. **Critical Quality Attributes(CQA)-**A physical, chemical, biological or microbiological property or characteristics that should be within appropriate limit,range or distribution to ensure the desired product qualityICHQ8(R2)[13]

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