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Phase Appropriate Expectations for Analytical Methods and Process Validation for Expedited Programs: A Regulatory Perspective

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Outline of talk

- Clinical trials in Canada
- Analytical method validation expectations and issues
- Expectations for expedited programs (methods)
- Process validation expectations and issues
- Expectations for expedited programs (process)
- Conclusions

Clinical Trials in Canada

Clinical trials are required for testing the safety and/or efficacy of drugs that are not authorized for sale in Canada or for testing marketed drugs under new conditions of use

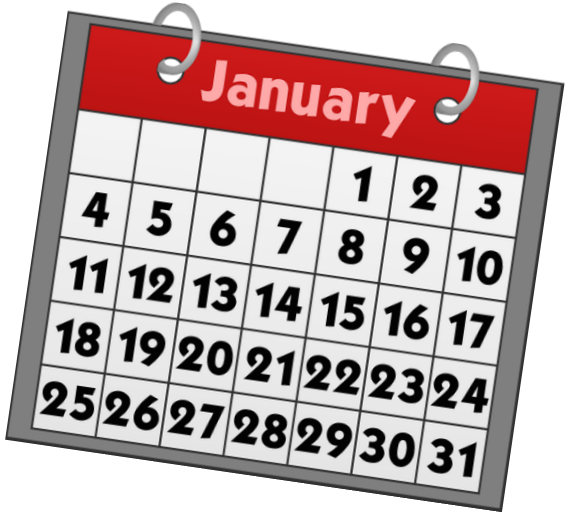
Health Canada is the federal regulator responsible for authorizing the importation and sale of drugs for the purpose of clinical trials in Canada

Health Canada regulates clinical trials by authority granted under The Food and Drugs Act and Regulations

Review of Clinical Trial Applications for Biotherapeutics

The Center for Evaluation of Radiopharmaceuticals and Biotherapeutics performs the review of clinical trial applications (CTAs) for biotherapeutics

Review Timelines



CTAs undergo Clinical and Quality review

Timeline for review:

- 30-day default (currently 45-day due to Ministerial Order)
- Sponsor response time to Information Requests: 2 calendar days

Expedited review:

- Allocate resources to support rapid review
- Dependent on quality of submission package and sponsor responses to requests for information

Objective of the Quality Review of CTAs

Ensure that subjects participating in clinical trials are not exposed to undue risk

Market Authorization

To obtain market authorization in Canada, sponsors submit a New Drug Submission or a DIN-B application. The information supporting product quality safety and efficacy are reviewed to determine whether the product benefits outweigh the risks, and if the risks can be managed.

If the submission is found to be in compliance with the Food and Drug Regulations, the sponsor may be issued an Notice of Compliance (once requirements of the Patented Medicines [Notice of Compliance] Regulations and data protection provisions in section C.08.004.1 of the Food and Drug Regulations have been met)/Approval Letter and a Drug Identification Number

Expectations for Market Authorization

Process consistency produces acceptable quality products within the commercial manufacturing conditions

Over the course of the clinical trials, the sponsor should be gaining knowledge of their product and process

Critical Quality Attributes

A critical quality attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

Critical quality attributes should be identified, suitable analytical methods put in place for monitoring, and the process characterized to establish the impact of variability on CQAs

Analytical Methods in Clinical Trials

Method qualification

- Performance capabilities assessed to ensure an acceptable level of method performance (accurate, precise, specific)

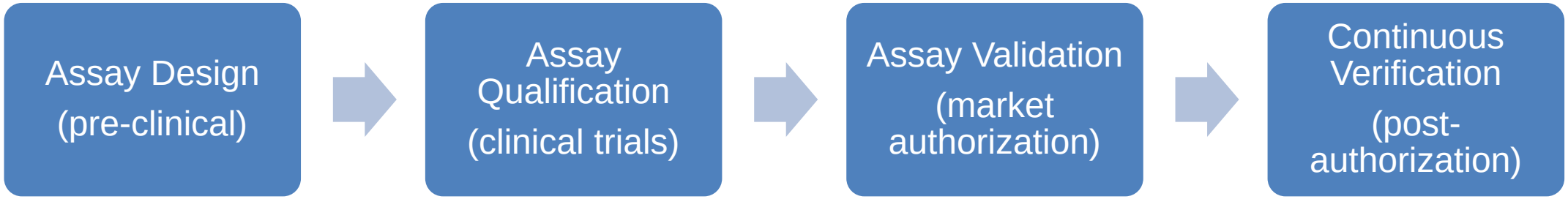
Analytical method validation

- USP<1225>Process by which it is established that the performance characteristics of the procedure meet the requirements for the intended use
- Performed in accordance with ICH Q2(R1) guidelines

Method verification

- USP<1226> Assessment of whether the procedure can be used for its intended purpose under the actual conditions of use for a specified drug substance or drug product matrix

Analytical Method Lifecycle



Regulatory Expectations for Analytical Method Validation in Clinical Trials

Health Canada does not expect validated methods in CTAs

Methods are indirectly assessed through the specifications, batch analysis data and stability data

Regulatory Expectations for Analytical Method Validation in Clinical Trials

Suitable methods should be in place to assess quality attributes including appearance and description, identity, purity/impurities, quantity and potency

Early in development the methods should support product safety and potency

Later in development, methods should support monitoring of manufacturing consistency

Methods should be fully validated by the NDS stage, and validated methods should be used to assess the process validation batches

Which methods need to be validated?

- Non-compendial methods used for release and stability testing, in-process testing should be validated for the NDS
- Compendial methods should be verified
- Method used for characterization that are not validated should be qualified

Qualification of methods for CTAs

Ensures that the acceptance criteria are meaningful

Ensures that the sponsor can demonstrate comparability of the product across different manufacturing processes, manufacturing sites, testing sites

Case Study 1: Method Qualification

Background:

Phase III CTA, wide specification for protein content at drug product release

Sponsor indicated that the wide specification was due to the method, which was not sufficiently accurate to determine protein content

It was not possible to accurately determine the dose patients would receive

Sponsor was required to institute a different assay to determine protein content

Case Study 2: Method Verification

Background:

Phase I CTA, wide specification for endotoxin at drug product release

The proposed limit did not ensure exposure to less than 5 EU/kg/h

The sponsor was required to withdraw the maximum proposed dose from the Study Protocol

Expectations for Expedited Programs

Methods do not have to be validated for clinical trials; however, they should be appropriately qualified

The review of CTAs focuses on the safety of study participants

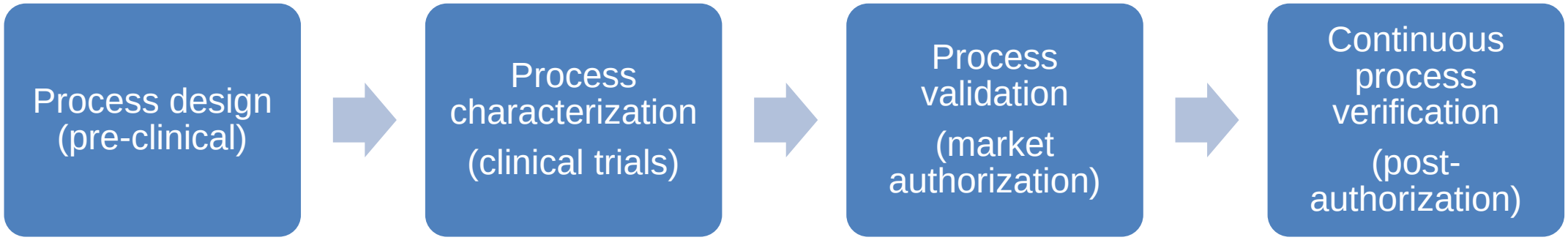
Qualification of methods used to monitor quality attributes that can impact safety should be the priority

Risk ranking of attributes based on impact to biological activity, PK/PD, immunogenicity and safety

Process Validation

A documented program that provides a high degree of assurance that a specific process will consistently produce a result meeting pre-determined acceptance criteria

Process Validation Lifecycle



Process Validation

Process validation at clinical trial stage not expected as the process is still in development

The clinical development timeline should be used to gain knowledge of the manufacturing process

Process Characterization- Clinical Trials

CQAs should be defined during clinical trials

Process parameters that can impact CQAs should be identified (Critical Process Parameters; CPPs)

The range of each CPP expected to be used during manufacturing should be defined, should be controlled and monitored during validation studies

Need to ensure appropriate controls in place to maintain product quality and appropriate methods in place to detect changes

Case Study 3: Process Validation

Background:

Phase III CTA

Transfer of the manufacturing process to a new site

Charge profile changed, sponsor determined this was due to a change in hold time at new site

Sponsor had determined that the charge variant was a non-critical attribute and would not impact safety or immunogenicity

Case Study 4: Process Validation

Background:

Phase III CTA

Manufacturing changes during product development resulted in an increase in sub-visible particles. The sponsor was required to decrease their drug product shelf-life while they updated their manufacturing process to address the root cause.

The sponsor had a robust development program, and was able to identify the issue early and appropriately manage the issue, ensuring market entry was not delayed.

Expectations for Clinical Trials

Early phase:

Process controls in place to ensure safety

Late phase:

Process controls to ensure safety and product quality/manufacturing consistency

A risk assessment to evaluate process parameters and their potential impact on the product can ensure control of process parameters that can impact CQAs

Expectations for Expedited Programs

Safety of clinical trial participants is the priority

Controls are expected to control for safety-related attributes and later on to ensure manufacturing consistency

Acceptance criteria should be defined based on information gained during characterization studies

Sponsor can leverage prior product knowledge to support approach

Quality risk management can help ensure that appropriate controls are implemented to ensure product safety and quality, especially when manufacturing experience is limited due to expedited quality program

Conclusions- Expedited Programs

- Submissions are assessed on a case-by-case basis
- Health Canada is flexible, and will consider proposal for alternative approaches
- It is the responsibility of the sponsor to justify the proposed approach
- Sponsors can use process development tools (risk management tools, data from prior experience/knowledge), to achieve better product/process understanding and justify alternative approaches
- Methods can be risk ranked, and higher priority given to methods that support safety
- Process can be set earlier to ensure sufficient data is available for market application
- Safety is the priority when Health Canada is reviewing CTAs

Planning for Expedited Programs

Sponsor should plan for expedited programs with the end in mind!

Pre-submission Meetings

Regulators in the Center for Evaluation of Radiopharmaceuticals and Biotherapeutics are happy to discuss specific submissions in pre-submission meetings

Sponsors can get feedback early on regarding the acceptability of their proposed approach

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