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Expectations for Data to Support Clinical Trial Drugs

Presentation to:
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Overview

- Focus of Quality review for Clinical Trial Drugs
- Challenges presented by Clinical Trial materials
- Context for Review
- Summary of Quality (CMC) requirements & data expectations through Drug Development



Focus

Safety:

Ensure that participants in Clinical Trials are not placed at undue risk arising from unsatisfactory manufacture or control of Clinical Trial Drugs.



Challenge

- Production and control of investigational drugs involves added complexity in comparison to marketed drugs due to:
 - limited experience in the production of the investigational drug
 - lack of full validation of manufacturing process and analytical methods
 - incomplete knowledge of the potency and toxicity of the product
 - incomplete knowledge about the stability of the product
 - increased risk of product cross-contamination and mix up when using non-dedicated facilities and equipment and with packaging blinded materials



Context for Review


- What is the intended use, patient population, size of trial?
- What is the phase of trial and stage of development of the drug?
- What is already known about the product?
 - Previous trials
 - Drug development
- Is product type/class known to have specific quality concerns (e.g. problematic impurities, previous safety issues)
- What is the level of experience of the manufacturer and the degree of their involvement in drug development?
- Is there enough data present to assess the safety of the drug from a Quality (CMC) standpoint and is the data supportive?



Quality Expectations: Drug Substance





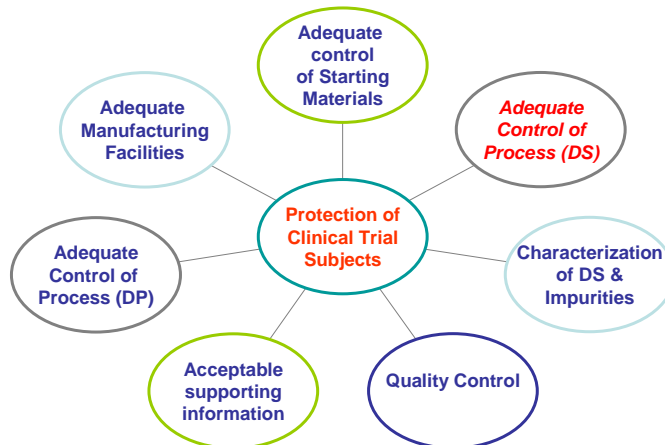
- ### Control of Starting Materials
- Is there adequate data to support starting materials and excipients as suitable for intended use?
 - Specifications/ Certificates of Analysis provided for non-compendial starting materials.
 - Adequate data to support suitability of animal-derived or biological starting materials (*e.g.* certification of compliance with EP Monograph 5.2.8).
 - For novel excipients is there adequate information about manufacture, control and link to acceptable pre-clinical study data?
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Control of Starting Materials (Biologics)

- Depending on product type, additional information may be required to support safety of complex starting materials such as cell lines, human or animal tissues or body fluids including additional characterization, screening or testing data.
 - Donor selection criteria, screening tests for plasma (or urine)
 - Descriptions of source and origin of animal derived materials or tissues
 - For products of prokaryotic or eukaryotic cell culture, derivation of cell stocks (ICH Q5D)
 - Testing for endogenous or adventitious pathogens for cell lines (ICH Q5A)
 - In some cases, excipients, adjuvants or process aids might need to be evaluated as products themselves (e.g. albumin excipient, MAbs used for purification, novel vaccine adjuvants)



Quality (CMC) Requirements



Manufacturing Process (DS)

- Given the stage of development for the product, is there an adequate description of the manufacturing process? Level of detail and in-process control should increase through product development
- Are starting materials, reagents, catalysts identified and consistent with other information supplied?
- For Phase II/Phase III materials is there a process narrative & does it agree with flow diagram and defined process scale?
- For Phase III materials, are critical steps identified and appropriate in-process controls in place for isolated intermediates?
- For Phase III materials is there an adequate description of process development and a discussion of evolution of the process to the current one?



Manufacturing Process (Biologics DS)

- Is there a process narrative and flow diagram describing the manufacturing process and its control, including definition of scale and any blending or pooling?
- Are critical process intermediates identified with summary of quality control and storage parameters for any isolated intermediates?
- Any existing process validation/ evaluation should be summarized (this is expected to progress through development).
- Steps to control adventitious agents should be described and summary data provided.
- A brief summary of process development and comparison of material derived from various processes where the changes have been significant (this is expected to progress through development).





- ### Characterization (DS)
- Are the basic physicochemical properties of the Active ingredient defined quantitatively?
 - Is there a potential for polymorphism... if so is there data supporting properties of forms present?
 - If solubility is limited, is particle size distribution addressed and controlled?
 - For pharmaceutical Active Ingredients, is there enough data to confirm intended structure based on synthetic route?
 - For existing drugs this could be achieved through spectral comparison with a suitable reference.
 - Where isomeric forms can or do exist is this addressed?
 - Are possible isomers that can arise from the manufacturing process discussed, and summary data available to indicate their physical, chemical and biological properties?
 - It should be specified if a specific stereoisomer or a mixture of stereoisomers will be used/have been used in previous studies, and a rationale for this decision provided.
 - For complex actives (e.g. peptides) absolute structure may not be feasible and purification and control of purity take on more importance

Characterization (Biologics DS)

- In most cases for biologics, the active substance will be a “family” of closely related species reflecting the desired product and product-related substances.
- Is there adequate data in place to support primary and higher order structure and biological activity?
 - Typically multiple methods will be required to address structure and activity.
- Is there adequate data in place to describe presence or absence of expected post-translational modifications?
- Is the purity established and adequate for the intended use?

Guidance on methods in ICH Q6B



Impurities

- Based on route of synthesis or extraction and available characterization are potential or actual impurities adequately addressed?
 - Product related (intermediates, by-products, metabolites)
 - Process related (solvents, reagents, catalysts)
- For Phase I expect structure (or identifier) and origin
- For Phase II expect Limit of Detection & Quantification and actual impurity levels to be established (ICH Q3A, Q3C)



Impurities (Biologics)

- Are potential impurities arising from the expression or extraction process or the purification and/or potential degradation of the desired product adequately addressed?
 - Product Related (variants, related species, glycoforms, truncated species, multimers, aggregates)
 - Process Related (host cell DNA, Host cell protein (or unrelated proteins), affinity ligands, residual solvents)
- Are levels of impurities in batches produced to date described (for batches used in non-clinical studies and clinical trial where available)?



Adventitious Agents (Biologics)

- Are adequate measures implemented to control endogenous and adventitious agents (ICH Q5A, Q5D, Q6B)?
 - For non-viral agents (bacteria, mycoplasma, fungi) are measures in place to test, evaluate and eliminate risks during production?
 - Where relevant, is information available on measures in place to address risks from prions (EU Guide on TSE agents)?
 - For viral agents, are controls at the level of starting materials in place and testing conducted during appropriate stages of production?
- Are the results from viral clearance studies present and adequately discussed?
- Where applicable is there a calculation of estimated particles/dose?





- ### Specifications (Pharmaceutical DS)
- For Phase I while a specification is not necessary, expect the results for the batch(es) to be used to be provided.
 - Expect at least an interim specification for Phase II drug substances with appropriate tests and acceptance criteria based on the nature of the drug substance, and that reasonable limits for impurities and residual solvents have been established.
 - Acceptance criteria should be based on manufacturing experience, stability data and safety considerations. These are expected to be firmed up as development proceeds towards commercial process and scale.
 - By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6A).
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Methods (Pharmaceutical DS)

- For Phase II and III trial applications, is there a brief description of any non-compendial analytical methods used? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6A)? Complete validation is not usually necessary at Phase II but expected at Phase III.



Batch Analysis (Pharmaceutical DS)

- Has a description of batches produced and the results of their testing been provided? For Phase I and II trials expect that analytical results for the batch to be used in the proposed clinical trial are provided.
- For Phase II if data from specific batches to be used in the proposed protocol are not supplied is there data from representative batches (produced by the same method of manufacture, equipment, specifications, and container closure and at a similar scale) and a commitment to provide data for the specific lot(s) prior to dosing?
- For Phase III, if specifications and analytical methods are well supported, representative batch analysis data may be sufficient.



Specifications (Biologic DS)

- For Phase I and II drug substances has an interim specification been provided with appropriate tests and acceptance criteria based on the nature of the drug substance, with reasonable limits for impurities?
- Is testing carried out at the appropriate stage of manufacture? Some tests (e.g. for adventitious virus) might be more appropriate at earlier stages of production.
- Acceptance criteria should be based on manufacturing experience, stability data and safety considerations. These are expected to be firmed up as development proceeds towards commercial process and scale.
- By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6B).



Methods (Biologic DS)

- Is there a brief description of any non-compendial analytical methods used? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6B)? Movement towards full validation is expected by Phase III.
- Is there an adequate description/characterization of the reference material(s) used?

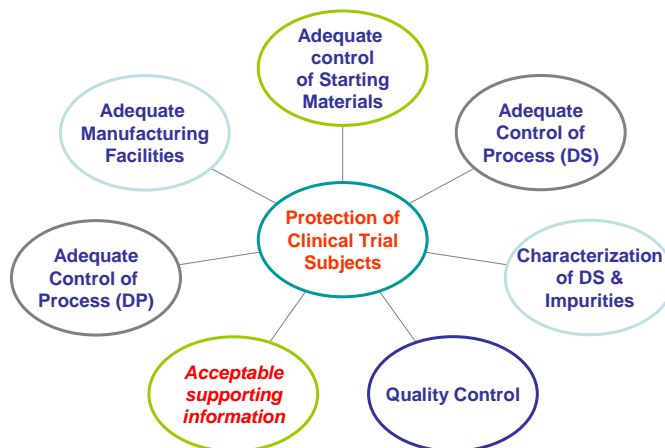


Batch Analysis (Biologics DS)

- Has a description of batches produced to date and the results of their testing been provided and discussed?
- For Clinical Trials of biologics expect that the analytical results for the batch to be used in the proposed clinical trial are provided.
- For lengthier protocols, have a Fax-back process providing a certification that the batch to be used met the specification in the Clinical Trial Application, and/or justification for any parameters that were not met.



Quality (CMC) Requirements



Stability (DS)

- Is there data in place to support the practices (e.g. storage, shipping and handling) in place at the time of filing the Clinical Trial Application?
- Was the data available collected on material representative of the intended material for the proposed trial (process, equipment, facility, container closure)?
- Is the data provided current (are there planned test points that could have been provided but weren't)?
- Are any gaps covered by commitments to evaluate stability on an ongoing basis?
- As development proceeds expect the amount of data to increase towards that necessary to cover the intended commercial practice



Plenary Discussion: Drug Substance

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Quality Expectations: Drug Product



Control of Starting Materials

- Is there adequate data to support starting materials and excipients as suitable for intended use?
 - Specifications/ Certificates of Analysis provided for non-compendial starting materials.
 - Adequate data to support suitability of animal-derived or biological starting materials (*e.g.* certification of compliance with EP Monograph 5.2.8).
 - For novel excipients is there adequate information about manufacture, control and link to acceptable pre-clinical study data?




Control of Starting Materials (Biologics)

- Depending on product type, additional information may be required to support safety of complex starting materials such as cell lines, human or animal tissues or body fluids including additional characterization, screening or testing data.
 - Donor selection criteria, screening tests for plasma (or urine)
 - Descriptions of source and origin of animal derived materials or tissues
 - For products of prokaryotic or eukaryotic cell culture, derivation of cell stocks (ICH Q5D)
 - Testing for endogenous or adventitious pathogens for cell lines (ICH Q5A)
 - In some cases, excipients, adjuvants or process aids might need to be evaluated as products themselves (*e.g.* albumin excipient, MAbs used for purification, novel vaccine adjuvants)





- ### Batch Definition
- Is there a description of the dosage form, it's composition (including all components used in the manufacture regardless if they appear in the final product)?
 - Are overages clearly indicated and the batch scale defined?
 - Does the batch scale described in the process narrative match the batch formula provided?
 - If there is a placebo form it should also be defined and it's composition provided.
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Pharmaceutical Development

- As development of formulation and manufacturing process proceeds expect some changes in formulation and process optimization. Is there a comparison of the current formulation (or process) with earlier iterations? Do these changes impact the relevance of earlier studies (e.g. stability)?
- Is there an assessment of the potential impact of changes on extrapolation of results from pre-clinical earlier clinical trials to the proposed trial?
- Is there data to support compatibility of the various components?
- The scientific rationale for the approach taken should be provided



Pharmaceutical Development (Biologics)

- For Biologics, the comparability of the test material during a development program should be demonstrated when a new or modified manufacturing process or other significant changes in the product or formulation are made.
 - Comparability can be evaluated on the basis of biochemical and biological characterisation (i.e., identity, purity, stability, and potency)
 - In some cases additional studies may be needed (i.e., pharmacokinetics, pharmacodynamics and/or safety)
- Overall, the goal is to demonstrate that improvements in processes lead to improvements in product quality while preserving or improving safety



Manufacturing Process (DP)

- Given the stage of development for the product, is there an adequate description of the manufacturing process? Level of detail and in-process control should increase through product development.
- For Sterile products is a complete narrative of the manufacturing process and details of the sterilization procedure provided?
- For Phase II/Phase III materials is there a process narrative & does it agree with flow diagram and defined process scale?
- Are any non-standard or novel manufacturing processes or technologies described in adequate detail?
- For Phase III materials, are critical steps identified and appropriate in-process controls in place, are specifications in place for intermediate tests, and isolated intermediates?
- For Phase III materials is there an adequate description of the process development and a discussion of evolution of the process?



Manufacturing process (Biologic DP)

- Is there a process narrative and flow diagram describing the manufacturing process and its control, including any blending or pooling of Drug Substance to make a Drug Product batch?
- Any existing process validation/ evaluation should be summarized (this is expected to progress through development).
- Are any steps to control adventitious agents described and summary data provided?
- Is there a brief summary of process development and a comparison of material derived from various processes where the changes have been significant (this is expected to progress through development)?





- ### Specifications (Pharmaceutical DP)
- For Phase I if a specification is not provided, are the results for the batch(es) to be used to be provided?
 - Is at least an interim specification in place for Phase II drugs with appropriate tests based on the nature of the drug substance and dosage form?
 - Are acceptance criteria reasonable based on manufacturing experience, stability data and safety considerations? These are expected to be firmed up as development proceeds towards commercial process and scale.
 - By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6A) and reflect the additional manufacturing experience and available stability information.
-
- The slide lists four key questions regarding specifications for pharmaceutical Developmental Process (DP). The questions cover Phase I, Phase II, and Phase III expectations. Below the list is a row of four small images: a nurse examining a child, a laboratory flask, a man and woman smiling, and a close-up of a pill.

Methods (Pharmaceutical DP)

- For Phase II and III trial applications, is there a brief description of any non-compendial analytical methods used that aren't already described for the Drug Substance? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6A)? Complete validation is not usually necessary at Phase II but expected at Phase III.



Batch Analysis (Pharmaceutical DP)

- Has a description of batches produced and the results of their testing been provided? For Phase I and II trials expect that analytical results for the batch to be used in the proposed clinical trial are provided.
- For Phase II if data from specific batches to be used in the proposed protocol are not supplied is there data from representative batches (produced by the same method of manufacture, equipment, specifications, and container closure and at a similar scale) and a commitment to provide data for the specific lot(s) prior to dosing?
- For Phase III, if specifications and analytical methods are well supported representative batch analysis data may be sufficient.
- Discussion of the results should include ranges and trends observed, and numerical data should be provided for quantitative tests.



Specifications (Biologic DP)

- For Phase I and II drugs has an interim specification been provided with appropriate tests and acceptance criteria based on the nature of the drug and it's intended use?
- Is testing carried out at the appropriate stage of manufacture? Some tests might be more appropriate at intermediate steps rather than on the final container (e.g. residual solvent/detergent used for viral reduction).
- Are acceptance criteria based on manufacturing experience, stability data and safety considerations? These are expected to be firmed up as development proceeds towards commercial process and scale.
- By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6B).



Methods (Biologic DP)

- Is there a brief description of any non-compendial analytical methods used that wasn't provided for the Drug Substance? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6B)? Movement towards full validation is expected by Phase III.
- Is there an adequate description/characterization of the reference material(s) used?

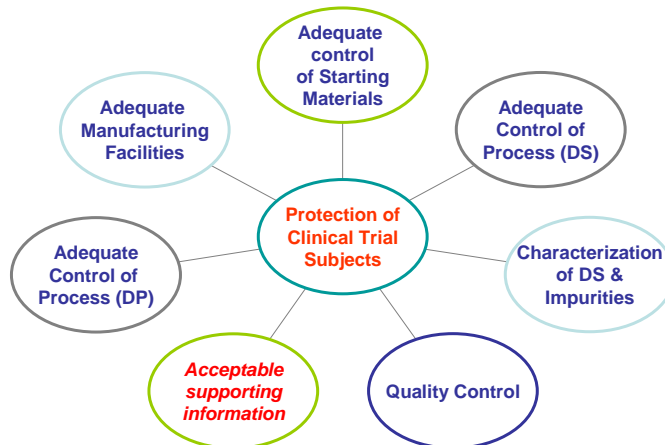


Batch Analysis (Biologics DP)

- Has a description of batches produced to date and the results of their testing been provided and discussed?
- For Clinical Trials of biologics expect that the analytical results for batches to be used in the proposed clinical trial are provided.
- For lengthier protocols, have a Fax-back process providing a certification that the batch to be used met the specification in the Clinical Trial Application, and/or justification for any parameters that were not met.



Quality (CMC) Requirements



Container Closure System

- Is there a description of all those components that contact product, help ensure stability or sterility, are used for drug delivery, support drug quality during transport?
- Is there data to support compatibility?
- For sterile products, is there a description of the preparation of sterile packaging components?



Stability

- Is there data in place to support the continued acceptability of the product for the duration of the trial?
- If full data isn't available, is there a commitment to monitor actual clinical batches (or representative batches) throughout the duration of the trial and a summary of the testing to be performed and the test stations?
- Is accelerated stability data provided?
- For drug products that are reconstituted or diluted, is there data to support the proposed in-use period?
- Should be using principles in ICH Q1A-E (Pharmaceuticals) and Q5C (Biologics)



Comparator Products (Pharmaceutical)

- Are comparator products to be used in the trial identified (proprietary name DP, common name DS, manufacturer, country of origin (market status) ,dosage form. strength)?
- Prefer comparator obtained from domestic market.
- Full Quality information required for comparators not obtained in EU, US, Australia or Switzerland.
- If comparator is modified (e.g. milling, encapsulation of tablets), data to support lack of impact on pharmaceutical properties (e.g. comparative dissolution). For sterile dosage forms that are repackaged, need evidence for maintenance of sterility.



Comparator Products (Biological)

- Where comparator products are not obtained from the domestic method either require evidence to establish equivalence of product with the Canadian version of the product, or full Quality data.

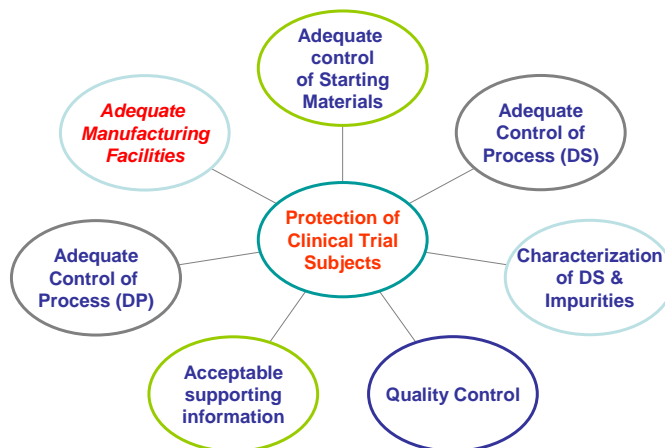


Diluents

- For reconstituted dosage forms, is there evidence supporting compatibility with the proposed diluent(s)?
- Is there a cross-reference or letter of access for diluents supplied with the Clinical Trial Drug?
- For non-commercial diluents provided manufactured by or for the clinical trial sponsor for reconstitution or suspension of clinical trial drugs, a separate drug product section should be completed.



Quality (CMC) Requirements



Facilities Considerations

- For Pharmaceutical Clinical Trial Applications expect an attestation that the facilities used to manufacture the drug in dosage form meet GMP (PIC/S Annex for Clinical Trial Drugs)
- For Biologics expect:
 - a descriptive summary of the facilities and the product contact equipment used (both for Drug Substance and Product)
 - for shared facilities and equipment, procedures or measures in place to prevent contamination or cross contamination (both for Drug Substance and Product)

Annex to the GMP Guidelines for Schedule D (Biologic) Drugs



Plenary Discussion: Drug Product

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Key Messages

- Use a systematic approach where every component of the quality information contributes to the overall assessment.
- Compare all drug substance and drug product batch results and look for variability, inconsistencies.
- Ensure stability testing is adequate for the type of product and intended use.
- Use a benefit / risk approach where other factors such as the phase of development, subject population, and manufacturer's experience contribute to the assessment.
- Available Quality (CMC) data is expected to progress through product development phases.
- Often involves a case-by-case judgement call on extent of quality data requirements at time of application or as a post-approval commitment



Thank You!

Questions?



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References: Pharmaceuticals

ICH Quality Guidance for Pharmaceuticals:	
Q1A Stability New Drugs/Substances	http://www.ich.org/LOB/media/MEDIA419.pdf
Q1B Photostability	http://www.ich.org/LOB/media/MEDIA412.pdf
Q1C Stability New Dosage Forms	http://www.ich.org/LOB/media/MEDIA413.pdf
Q1D Stability Bracketing & Matrixing	http://www.ich.org/LOB/media/MEDIA414.pdf
Q1E Evaluation of Stability Data	http://www.ich.org/LOB/media/MEDIA415.pdf
Q3A Impurities Drug Substance	http://www.ich.org/LOB/media/MEDIA422.pdf
Q3B Impurities Drug Product	http://www.ich.org/LOB/media/MEDIA421.pdf
Q3C Residual Solvents	http://www.ich.org/LOB/media/MEDIA423.pdf
Q6A Specifications: New Drugs	http://www.ich.org/LOB/media/MEDIA430.pdf
Health Canada Quality Guidance	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qual_cta_dec_e.pdf
GMP: Manufacture of Drugs Used in Clinical Trials	www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compl-conform/clin_trials-essais_cln_e.pdf



References: Biologics

ICH Quality Guidance for Biologics:	
Q5A Viral Safety Cell Lines	http://www.ich.org/LOB/media/MEDIA425.pdf
Q5B Analysis of Expression Construct (rDNA)	http://www.ich.org/LOB/media/MEDIA426.pdf
Q5C Stability Testing: Biotech/Biological	http://www.ich.org/LOB/media/MEDIA427.pdf
Q5D Characterization of Cell Substrates	http://www.ich.org/LOB/media/MEDIA429.pdf
Q5E: Comparability	http://www.ich.org/LOB/media/MEDIA1196.pdf
Q6B Test Procedures and Acceptance Criteria	http://www.ich.org/LOB/media/MEDIA432.pdf
EMA Note for Guidance Minimizing TSE Risk	http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf
GMP Annex for Schedule D (Biologic) Drugs	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compl-conform/sched_d_part1-annexe_d_part1-eng.pdf

