



## Similarities and Differences between CMC Information required for EU IMPD CTA and US IND

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February 25, 2010

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## Objectives

- To understand the similarities and differences between the EMEA and FDA requirements for initial submissions of new medicinal products
- To take home practical suggestions for preparing the EU IMPD CTA versus the US IND

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## Definitions

- IMPD = Investigational Medicinal Product Dossier
- CTA = Clinical Trial Application
- IND = Investigational New Drug
- CTD = Common Technical Document

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## Overview

- EU and FDA Background
- Key differences between CTA and IND
- What is an IMPD?
- Use of CTD format in both regions
- Key CMC activities for IMPD and IND
- FDA Phase I guidance
- CMC risk factors and potential hold issues
- Recommendations

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## EU and FDA Background

- EU – multiple agencies
  - European Medicines Evaluation Agency (EMA) – administrative organization
  - Committee for Medicinal Products for Human Use (CHMP) of the EMA – scientific input
  - National Health Agencies
- FDA – one agency

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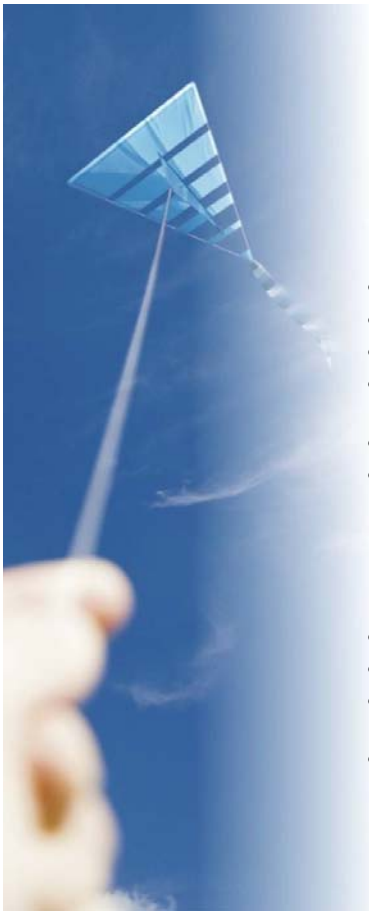


## Differences in Review Styles

- EMA is an administrative framework, and National Agencies are the scientific reviewers – differences in culture and medical practices
- FDA reviewers within the same Agency
- EU top down, FDA bottom up
- EU benefit/risk of entire data, FDA more specific
- Same data package to both will probably not result in the same outcome

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## IMPD - IND vs. CTA

### IND

- Form FDA 1571
- Table of Contents
- Introductory Statement
- General investigational plan
- Investigator's brochure
- Protocol:
  - Study protocol
  - Investigator data
  - Facilities data
  - IRB data
- CMC data
- Pharm and Tox data
- Previous Human Experience
- Additional Information

### CTA

- Application form (12 pg form)
- Cover letter
- NA
- Investigational brochure
- Protocol:
  - Study protocol
  - Investigator data (some MS)
  - Facilities data (some MS)
  - EC data (copy of opinion)
- IMPD:
  - Quality data
  - Pharm and Tox data
  - Previous Human Experience
  - Risk and benefit assessment

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## IMPD - IND vs. CTA (cont'd)

### • IND

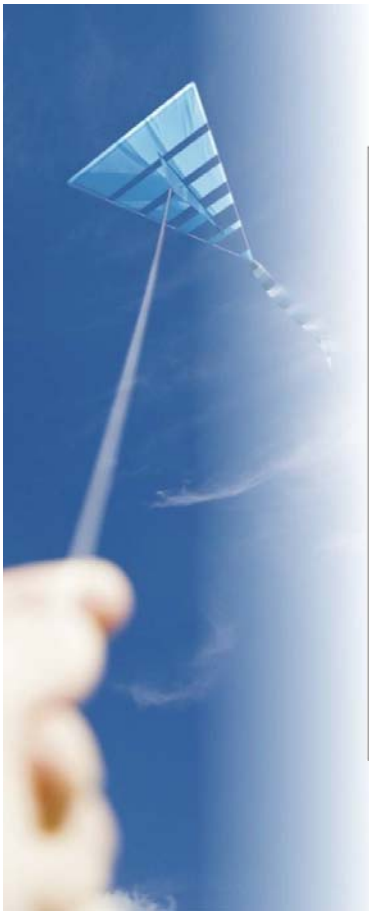
- If any part of the trial is to be conducted by a CRO, attach statement
- Name and title of person responsible for evaluating the safety of the drug

### • CTA

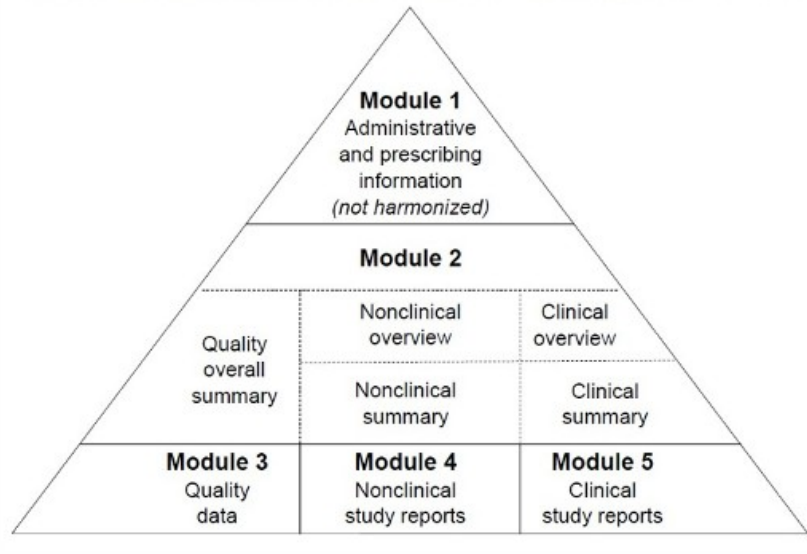
- If any part of the trial is to be conducted by CRO, attach statement and mention in cover letter; CRO representatives can sign on behalf of sponsors
- A simplified IMPD may be submitted in certain instances (e.g., when a CTA has been approved by the respective regulatory authority)
- Additional items required by some MS: subject-related; protocol related; IMP related; Facilities and staff related; Finance related

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## Modular Structure of Common Technical Document



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## US IND CMC vs. EU CTA IMPD

- The science is the same
- CTA and IND documentation requirements are mostly the same; some minor differences
- Summaries expected early in development
- CTD format accepted worldwide

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## The IMPD

- Clinical protocol, toxicology studies and CMC – but only need summaries
- Follows CTD format
- Separate 3.2.P sections for investigational drug (all strengths), placebo and comparator

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## IMPD in CTA or CMC section of IND 3.2.S Drug Substance

- General Information
- Manufacturer
- Control of Drug Substance
- Reference Standards
- Container Closure System
- Stability

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## IMPD in CTA or CMC section of IND 3.2.S Drug Substance

- **General Information**  
[nomenclature, structure, general properties]
- **Manufacturer**  
[name, process, control of materials, critical process, process validation, manufacturing process development]
- **Characterization**  
[proof of structure, impurities]
- **Controls**  
[specification, analytical methods, validation, batch analysis, justification of specs]
- **Reference Standards**
- **Container Closure System**
- **Stability**

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## FDA - CMC section for IND

Same basic information – slight difference in format \*

- Drug substance
- Drug product
- Placebo
- Labeling
- Environmental assessment

\* Can use CTD or IND format

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## IMPD in CTA or CMC section of IND 3.2.P Drug Product

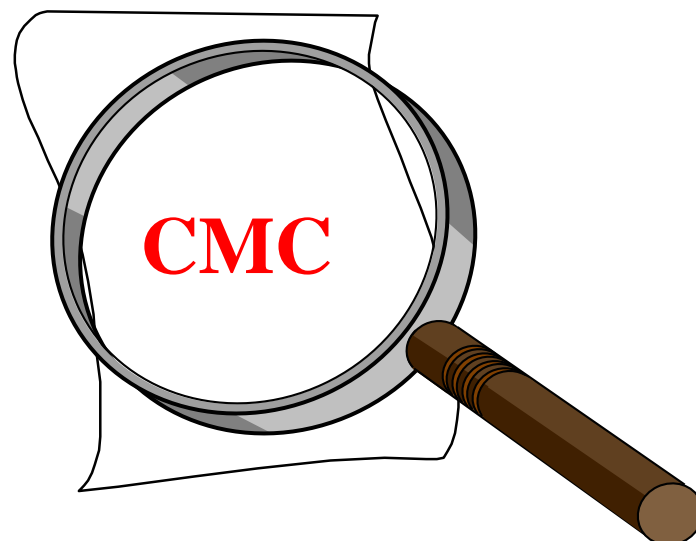
- Description and Composition
- Pharmaceutical Development
- Manufacturer
- Control of Excipients
- Control of Drug Product
- Reference Standards
- Container Closure System
- Stability

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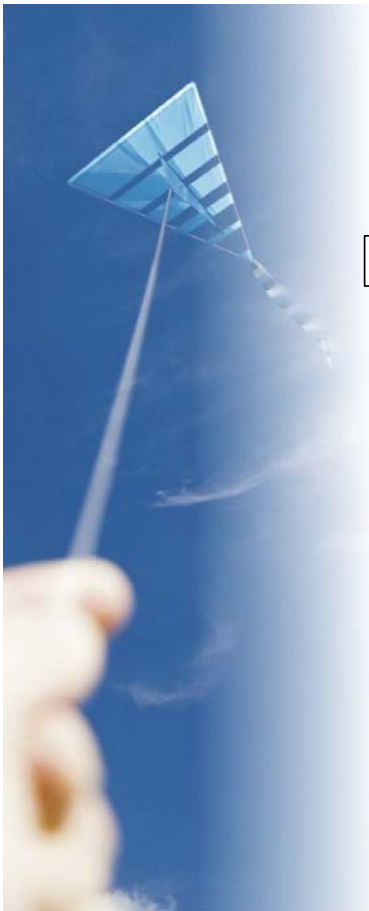


### Let's take a closer look!

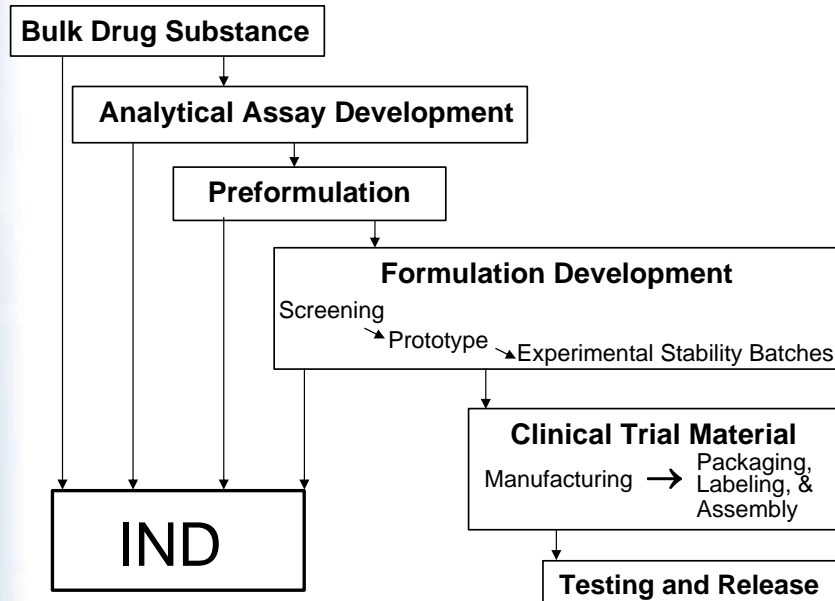


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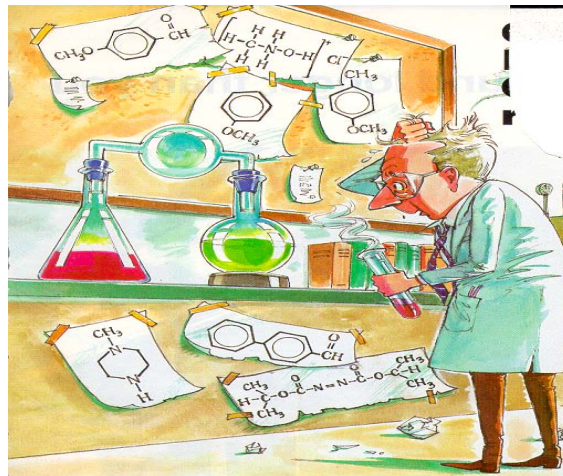


# CMC Activities Required for IMPD and IND Submission



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For API's, there are two important items:

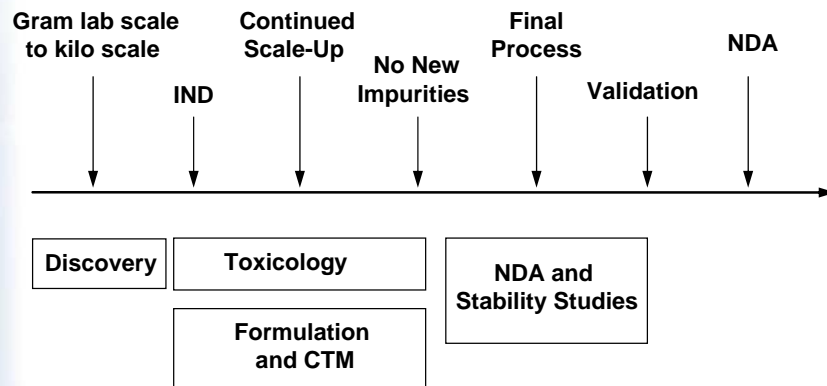
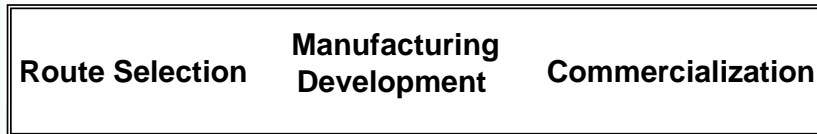
- 1) Impurity profile
- 2) Impact of drug substance characteristics on drug product performance

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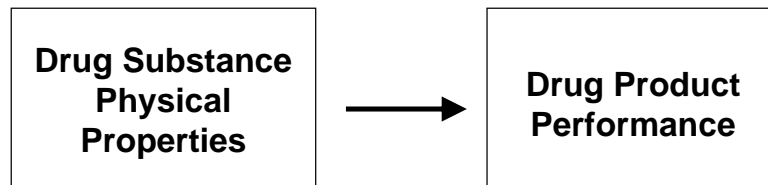


# Bulk Drug Timeline



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## Characteristics that Impact Drug Product Performance

Particle size distribution	Impurity profile
Bulk and tap density	Moisture
Crystal habit	Flow properties
Polymorphism	Compaction
Dissolution rate	Hygroscopicity
Melting point	Color

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## Key Physical/Chemical Characteristics of Early API

For oral dosage form:

- pH – solubility profile
- Permeability

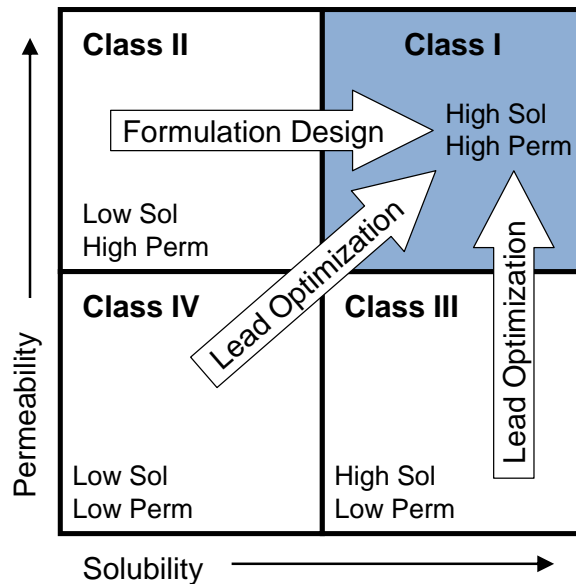
These define the Biopharmaceutical Classification System (BPCS) Class I, II, III, IV

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## BPCS



Pouton CW EJPS 29 (2006) 278–287

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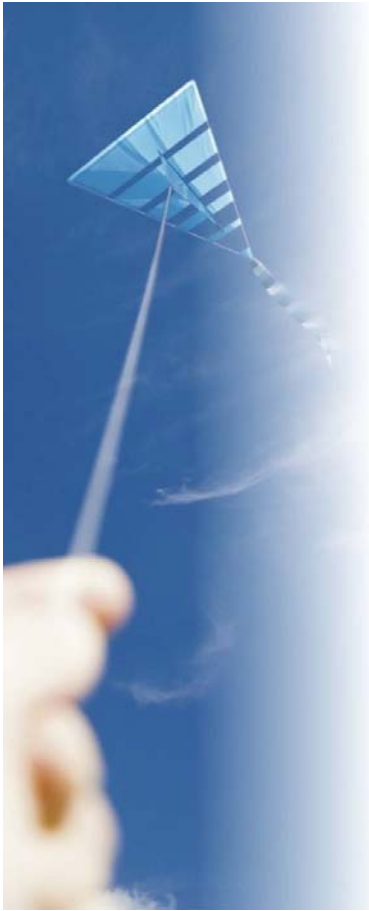


## Drug Master Files

- Often used in US for API information, especially for generic drugs
- Not reviewed by FDA unless specifically mentioned in an IND, ANDA or NDA and then only with a letter of authorization
- Potential risk if YOU reference a DMF without due diligence of the manufacturer

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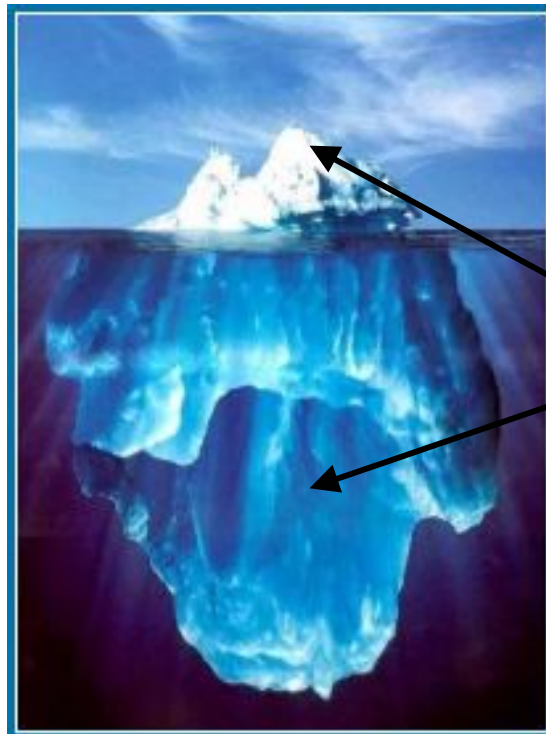


## FDA Guidance - Phase I

- Amount of information depends on phase, duration of trial, dosage form
- Graded nature of information
- Changes are likely
- Relate toxicology dosing to clinical dosing
- “the sponsor does not believe that the chemistry or manufacturing of drug substance or drug product present any signals of risk to humans”

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## Transitioning to Development “Top 10” List

- Molecular weight? 850 – Is that a problem?
- Now that you mention it, the solutions were a little hazy
- Crystalline? No, all our work was with amorphous material...
- We didn't have any problems when we gave it in DMSO
- But, we lose activity without the twelve carbon side chain
- Toxicity? Can't be the drug; must be a metabolite
- Animal bioavailability range from 1% to 65% depending on species
- Drug X is a highly potent, selective inhibitor of (target) In preclinical models, the optimal dose was 200 mg/Kg
- We will need 8 different capsule strengths for phase 1
- It's a GREAT compound! But, it has formulation problems

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## The IMPD – CMC Differences between EU CTA and US IND

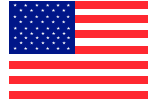
- EU expects analytical method validation early (US in Phase III)
- EU expects 3.2.P.2, Pharmaceutical Development (not addressed in US CMC, but is generally considered)
- EU and FDA emphasize discussion of tox coverage of API impurities for first-in-man studies

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## The IMPD – CMC Differences between EU CTA and US IND



- Environmental assessment
- IMP label text
- Placebo (separate)
- Debarment (NDA)
- Executed batch record (NDA)
- QP and GMP certification
- TSE/BSE certificates
- Appendices (facility summary)
- Different release and stability spec limits

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## CMC Safety Issues

- Impurity profile
- Stability
- Specifications
- Physical / Chemical Characterization
- Adventitious agents
- Sterility
- Pyrogenicity
- Bacterial / Viral / DNA contamination



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## CMC Safety Issues

- Factors which could influence the interpretation of all IMPD/IND data used to decide whether to dose in humans
- Toxicological implications are paramount
- Insufficient or missing CMC data which prevent the assessment of risks to subjects
- Can result in clinical hold in US

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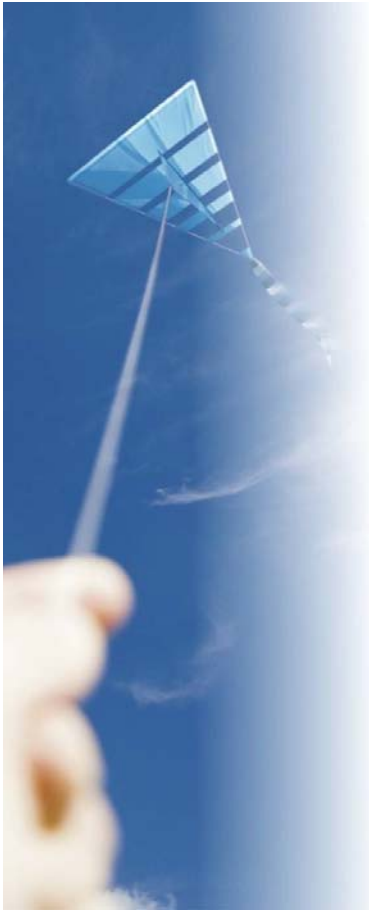


## CMC “Clinical Hold” Issues

- Unknown/impure components
- Known/highly likely toxicity of API
- Chemical instability during clinical trial
- Insufficient definition of impurity profile
- Impurity profile suggestive of potential health hazard
- Poorly characterized master cell (virus) bank
- Bridging pre-clinical materials and proposed CTM
- Clearly inadequate specifications

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## IND CMC API Section Low Risk Factors

- Proof of Structure
- Container – Closure
- Reference Standard



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## IND CMC API Section Medium Risk Factors

- Physical / Chemical Properties
- In-Process Controls
- Analytical Methods



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## IND CMC API Section High Risk Factors

- Impurity Profile
- Specifications
- Stability / Degradation



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## Recommendations

- Use CTD format for global submissions
- For CTA or IND, follow EU approach and list US required information [labeling, EA] in Regional Information Section
- For IND, when CTD headings are inappropriate, use “not applicable” or “information to be provided at later stage of development” (e.g. S.2.5 Process Validation, S.2.6 Process Development)

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## Recommendations

- Include a detailed Table of Contents
- Include a Guide to the Reviewer
- Brief narratives with salient points
- Flow charts for manufacturing processes
- Tables for stability data
- Take advantage of pre-IND meeting with FDA (they are free!)

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## Amendments to EU CTA and US IND

- Frequent CMC changes during development:
  - Formulation, strengths, process, methods, specifications, packaging and labeling, etc.
- Substantial differences between two regions in the way updates are handled:
  - US:** Safety implications best to get verbal or written confirmation that changes are acceptable
  - EU:** All classified as Major or Minor. Major require prior approval. Lack of agreement on what is Major.

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## FDA Guidance – cGMP Phase 1 Investigational Drugs (July 2008)

- Adherence to cGMP for Phase 1 through:
  - Well defined, written procedures
  - Adequately controlled equipment and manufacturing environment
  - Accurately and consistently recorded data from manufacturing (including testing)
- Manufacturer AND Sponsor are responsible for assuring cGMP compliance
  - Assurance is achieved, in part, by assessing and having effective quality control functions in place

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## Linking Regulation to Good Science

Several initiatives recently codified to link regulatory expectations to good science:

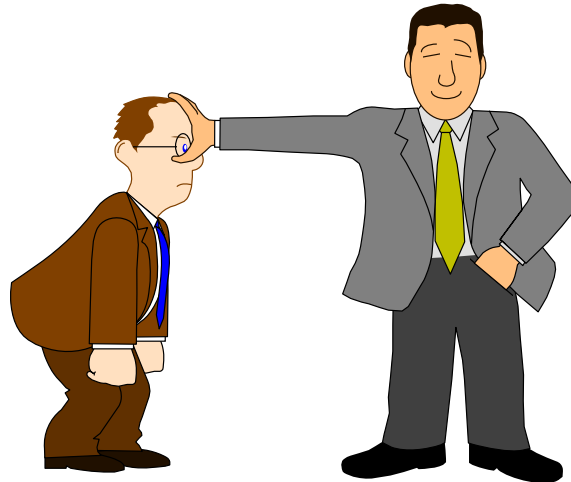
- *ICH Q8 (R1): Pharmaceutical Development*
  - Content of 3.2.P.2 and Quality by Design (QbD) concept
- *ICH Q9: Quality Risk Management*
  - Systematic approach: assessment, control, communication, and review
- *ICH Q10: Pharmaceutical Quality System*
  - Management responsibility and continuous improvement

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## Good Science Doesn't Slow Progress!



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## Guidances and Useful Web Links

- Directive 2003/94/EC (GMP Guidelines) [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-4/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-4/index_en.htm)
- ICH Guidelines <https://www.ich.org/cache/html/250-272-1.html>
- Timeline for initial CTA submission <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Currentissues/index.htm>
- CTA Format <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/MakingclinicaltrialstosubmissionstotheMHRA/index.htm>
- Mock applications and forms <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Mockapplications/CON024097>
- Annex 13 & 16 GMP and Role of QP [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index_en.htm)

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## Questions and Answers

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Global Submit



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