Chemistry and Manufacturing Data Requirements for Early Clinical Development

What's in there? Prove it.

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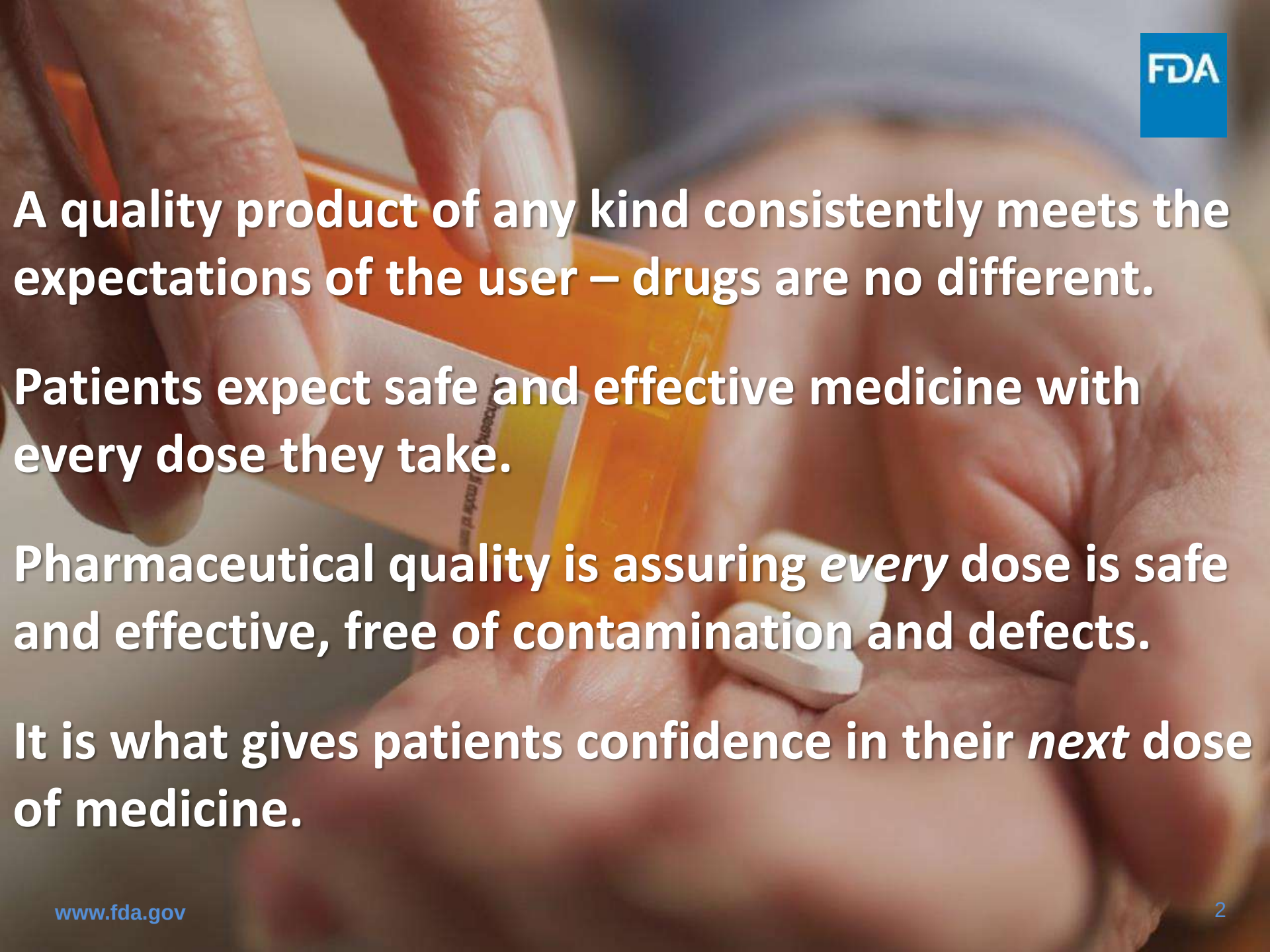
SBIA/OCE Meeting March 30-31, 2021



A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

What this talk will address

- We will not:
  - Design your product. We are not consultants
  - Limit your product design
- We will:
  - Be a resource for all published guidance
  - Provide our expectations for future interactions
  - Provide general advice for avoiding common pitfalls

What CMC information is required by law in an IND?

- 21 CFR 312.23(a)(7)
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- (7) *Chemistry, manufacturing, and control information.* (i) ***As appropriate for the particular investigations*** covered by the IND, a section describing the ***composition, manufacture, and control of the drug substance and the drug product.*** Although in each phase of the investigation sufficient information is required to be submitted to assure the proper ***identification, quality, purity, and strength*** of the investigational drug, the ***amount of information*** needed to make that assurance ***will vary with the phase of the investigation***, the proposed ***duration of the investigation***, the ***dosage form***, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the ***emphasis in an initial Phase 1 submission*** should generally be placed on the ***identification and control of the raw materials and the new drug substance***. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.
- As appropriate for the particular investigations
- Composition, manufacture, and control of the drug substance and the drug product
- Identification, quality, purity, and strength
- Amount of information will vary with the phase of the investigation
- Investigation, …duration of the investigation, … dosage form,
- Emphasis in an initial Phase 1 submission
- Identification and control of the raw materials and the new drug substance
- Stability data

What CMC information is required by law in an IND?

21 CFR 312.23(a)(7)

- (iv)(*a*) *Drug substance.* A description of the drug substance, including its ***physical, chemical, or biological characteristics***; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the ***identity, strength, quality, and purity*** of the drug substance; and information sufficient to support ***stability*** of the drug substance during the toxicological studies and the planned clinical studies.

21 CFR 312.23(a)(7)

- (iv)(a) Drug substance
- Physical, chemical, or biological characteristics;
- Manufacturer
- Method of preparation
- Identity, strength, quality, and purity
- Stability

What CMC information is required by law in an IND?

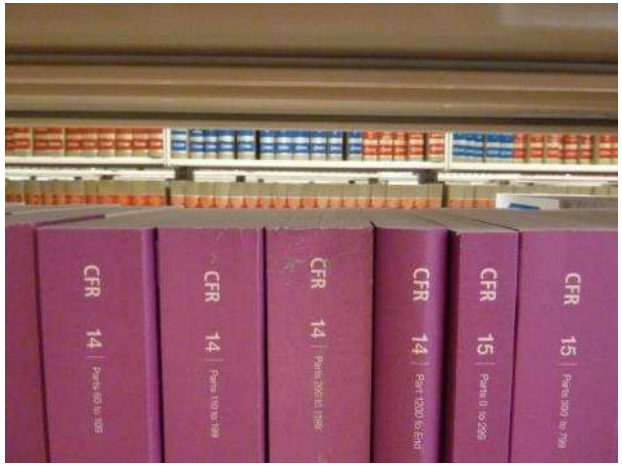
21 CFR 312.23(a)(7)(iv)

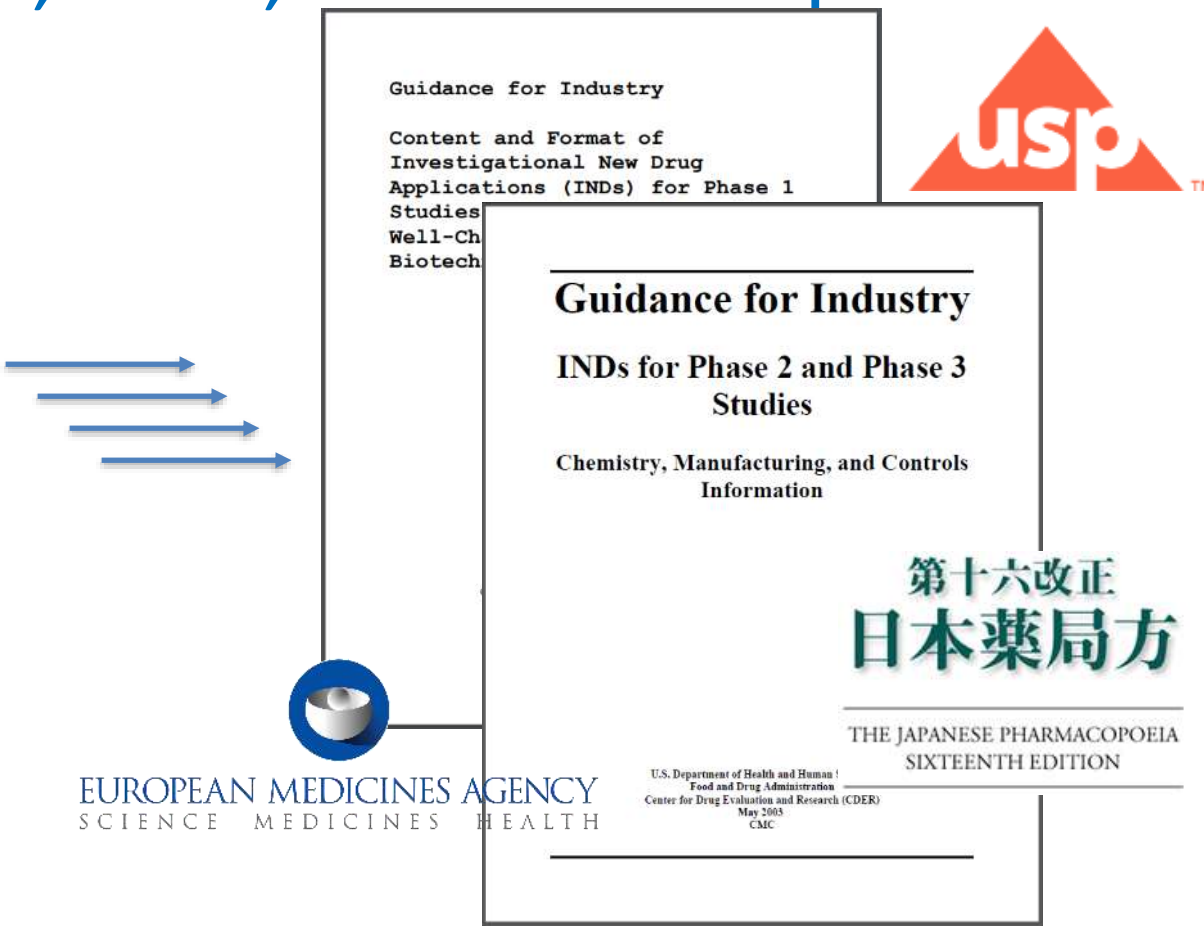
- (b) Drug product.
- List of all components
- Quantitative composition of the investigational drug product
- Drug product manufacturer
- Description of the manufacturing and packaging procedure
- The identity, strength, quality, and purity of the drug product
- Stability

21 CFR 312.23(a)(7)(iv)

(*b*) ***list of all components***, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the ***quantitative composition of the investigational drug product***, including any reasonable variations that may be expected during the investigational stage; the name and address of the ***drug product manufacturer***; a brief general ***description of the manufacturing and packaging procedure*** as appropriate for the product; the acceptable limits and analytical methods used to assure ***the identity, strength, quality, and purity of the drug product***; and information sufficient to assure the product's ***stability*** during the planned clinical studies.

The CFR is dense and vague; other literature is more prescriptive: FDA Guidance, USP, EMA, JP Pharmacopeia





- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-and-format-investigational-new-drug-applications-inds-phase-1-studies-drugs-including-well
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inds-phase-2-and-phase-3-studies-chemistry-manufacturing-and-controls-information

CFR and guidance documents paint the picture of risk/benefit analysis

Product design reflects study's purpose

- Learn objectives from your study?
- Critical physical and chemical attributes of your drug substance?
- Clinical supply characterized, controlled, and stable?
- *Knowledge gaps:* how are you mitigating residual risk?

Drug Substance CMC Information

- Manufacture Process
- Characterization Data
  - Structural Characterization
  - Physicochemical Properties
- Impurities
- Specification for Release
- Stability

Drug Substance: Manufacture Process

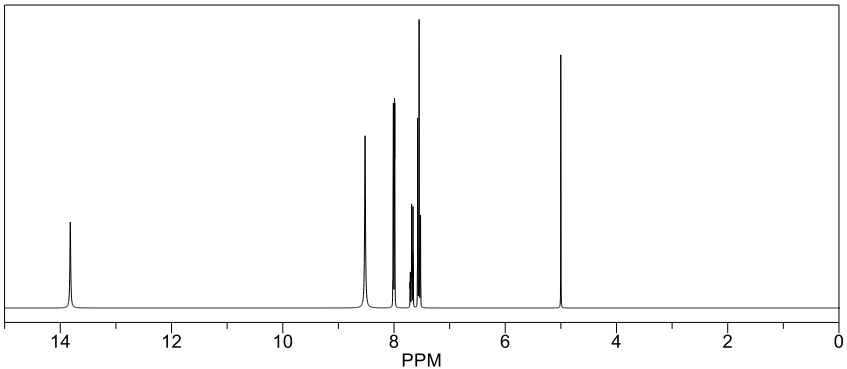
- Synthesis is likely at an early stage for an NME
  - Brief Description
    - Written and detailed flow diagram
    - Include all reagents, solvents, catalysts, etc.
  - In-process Controls (e.g. tests for reaction completion)
  - Manufacture of “starting materials” and controls (if available)
  - Isolated intermediates and controls (if available)
  - Controls for raw materials (e.g. solvents, reagents, catalysts)

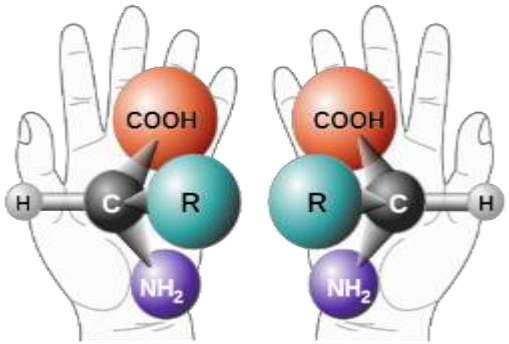
Drug Substance: Manufacture Process

- Differences in synthesis of toxicology and clinical batches
- Use of the same batch for toxicology and clinical batches
- Regulatory starting materials
  - Initiate a CMC Type C meeting, typically end-of-phase 2
  - ICH Q11 – *Development and Manufacture of Drug Substances*
  - ICH Q11 Q&A – *Development and Manufacturing of Drug Substances – Questions & Answers*

Drug Substance: Structural Characterization

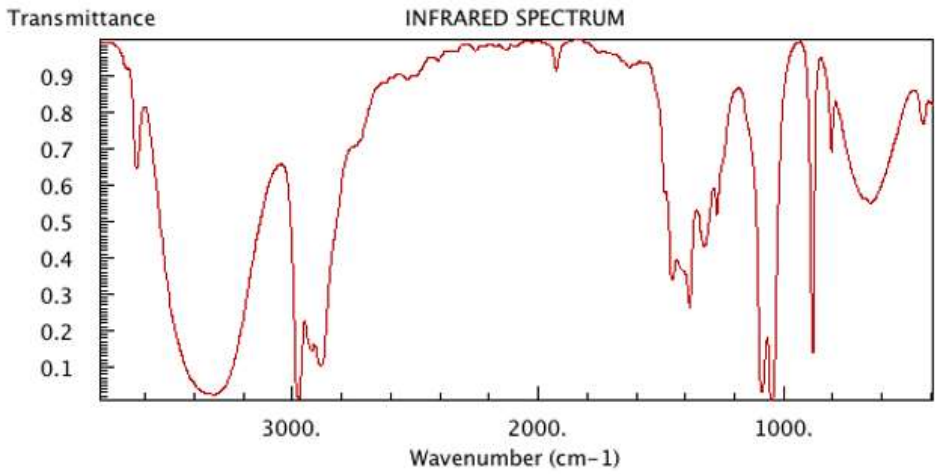
- Data to support the proposed structure
- Structural data may be limited at early stages of development
  - Nuclear Magnetic Resonance (NMR)
  - UV-Vis Spectroscopy
  - Infrared Spectroscopy (IR)
  - Elemental Analysis
  - High Performance Liquid Chromatography (HPLC)
  - Mass Spectrometry (MS)
  - Chirality/Optical Rotation
  - Single-crystal X-ray





Drug Substance: Structural Characterization

- Raw spectral data alone is not sufficient
- Your interpretation (e.g. peak assignments) is expected
- We will evaluate interpretation of spectral and other characterization data
- Some ambiguity can be justified for impurities present at low levels



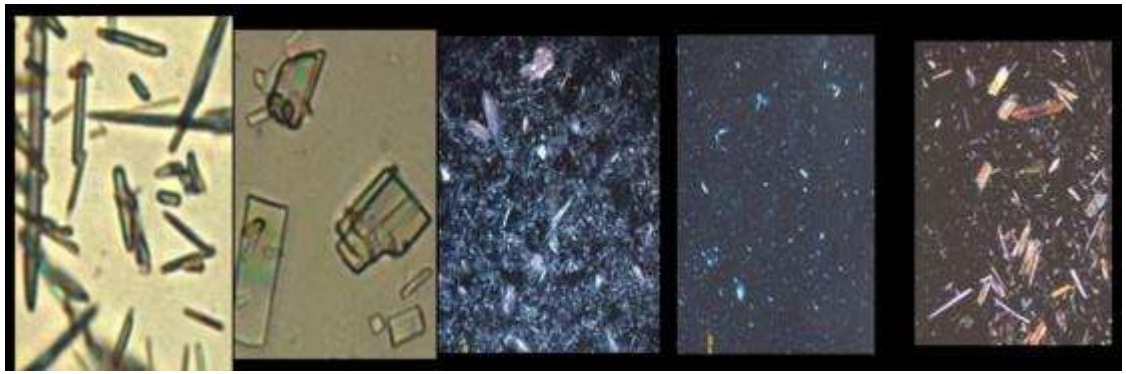
Drug Substance: Physicochemical Characterization

- Understand Criticality to Drug Product
  - Appearance and Physical Form (e.g. solid, oil, etc.)
  - Solubility (aqueous and in organic solvents)
  - Particle Size Distribution
  - Hygroscopicity
    - Is your drug substance hygroscopic?
    - Implications for stability, polymorphic form, dissolution, and bioavailability?




Drug Substance: Physicochemical Characterization

– Polymorphic Forms
  - Have you screened for different forms?
  - Do different forms exist and controlled at release and stability?
  - Impact of polymorphic form on dissolution, bioavailability, stability?



Impurities

Any *component* of the drug substance that is *not the chemical entity*

- **Organic impurities**
  - ICH Q3A(R2) – Impurities in New Drug Substance
  - Reporting, identification and qualifications thresholds
- **Mutagenic Impurities**
  - ICH M7(R1) – Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk
- **Residual solvents**
  - ICH Q3C(R6) – Impurities: Residual Solvents
- **Elemental impurities**
  - USP<232>, <233>, and ICH Q3D(R2) – Elemental Impurities
- **Microbial contaminants**
  - USP<61> Microbial limits; USP<85> Bacterial endotoxins

Impurities

- Control strategy for potential impurities
- Address differences in impurities between toxicology and clinical batches
- List of process impurities and potentially mutagenic impurities
  - Include reference to nonclinical data (e.g. AMES or QSAR)
  - Address risk of potentially mutagenic impurities based on manufacture process

Drug Substance Specification

- Test methods and limits to assure identity, strength, quality and purity
- Description of analytical test methods or reference to compendial tests
- Proposed limits based on available analytical testing, toxicology, and clinical batch data
- Batch data for proposed clinical batches with data on purity level and impurity profile

Drug Substance Specification

- Specification tests and limits are likely to change as development proceeds
  - Methods are being developed and validated
  - Manufacture process is being optimized (removal of toxic/dangerous reagents, solvents etc.)
  - Commercial process and scale is being developed

Drug Substance Stability

- How much data?
  - Preliminary data on representative material (e.g. technical batches, nonclinical batches)
  - Submit available data on clinical batches
- Provide information on the tests used to monitor stability
- Stability commitment

Drug Substance Concerns

- Drug substance manufactured with impure/unknown materials
- Impurity profile insufficiently characterized
- Impurities of known or potentially high toxicity
- Stability issues (significant changes in assay)

Develop with an eye to bridging to the future

- Critical quality attributes (solubility, polymorphic form, drug substance particle size, salt form, stability)
- Retain Samples for bridging
- Monitor and characterize even if not controlled (dissolution, disintegration, polydispersity index, particle size, water content)

Early Formulation Development

- Exposure and Safety Study?
  - Complex formulation or powder in capsule?
  - Commercially available solubilizing agents?
  - Oral formulation or sterile injection with added endotoxin and sterility concerns
- Efficacy Study?
  - Bridged to early safety studies?
  - Adequate characterization to bridge to commercial product?

Early Formulation Development

- Use conventional excipients within demonstrated level[1]
- Novel excipients and human/animal excipients require evaluation
- Dose according to the active moiety[2]
- Justify novel technology (e.g. nanotechnology, device combinations)

[1]https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
[2]https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf

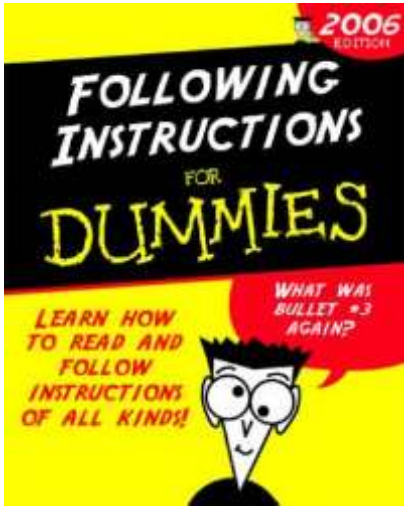
Stability: Ensuring Identity, Potency, and Purity During Dose Administration

- At least a month of long-term and accelerated data
- Commitment to follow prescribed protocol
- Consider an Accelerated Stability Assessment Program (ASAP)
- *Demonstrate you understand your product:*
  - *What is critical for it to perform,*
  - *How to maintain its integrity.*

Q. Chan et. al. J. Pharm. Innov. 2012, 7:214-224.
K. Waterman et. al. *Pharmacetucial Research* 2007, 24:780-790.
K. Waterman *Pharmaceutical Outsourcing* 2012,

Investigational Label

- Product label required as per 21 CFR 312.23(a)(7)(iv)(*d*)
  - Product/container label
    - Product name, Dosage form, Strength, Storage conditions
    - Statement of “Caution: New Drug Limited by Federal Law to Investigational Use”
    - Manufacturer and Lot number
  - Investigational brochure
    - In-use stability data and in-use conditions
    - Extemporaneous preparations
    - Hold times after dose preparation



Environmental Analysis Exemption Request

- 21 CFR 312.23(a)(7)(iv)(*e*) *Environmental analysis requirements.*
  - Claim for categorical exclusion under 25.30 or **25.31(e)**

Placebo or Active Control

- Active control commercially sourced or cross referenced?
- Placebo:
  - Description of composition, manufacture, batch data, and test for confirmation of absence of active
  - Differences in the placebo and the drug product?
    - Quantitative composition of placebo or commercially available (e.g. saline)
    - Demonstrate blinding by taste masking and appearance

pIND Meetings are a gift

Best, free advice; don't waste it.

- FDA is not a developing your product
- Seek to reach agreements
  - Impurity limits and justifications
  - Data necessary to launch a clinical study
  - Mitigation strategy for known residual risks
  - Link study objective to product design
  - Demonstrate rational design
  - Current and future data package

To err is human, but it slows clinical development

- Sponsor meetings take enormous resources from FDA
  - Words like ‘must’, ‘required’, and ‘include’ are definitive necessities
  - Words like ‘should’, ‘can’, and ‘justify’ indicate concern
- Ignoring advice from FDA leads to
  - Diminished trust
  - Loss of confidence in sponsor
  - More scrutiny

Documentation vs. Data Dump?

- Synthesize the data into a coherent narrative
- Provide representative spectra
- Organize data sets into tables
- Organize data according to eCTD

Odds and Ends for CMC Review

- If purchasing or licensing drug substance, obtain:
  - LoA's to historical INDs or DMFs
  - CoA's for toxicology and clinical batches
  - Bridging data of the drug product

GMP Requirements

- Good manufacturing practices are part of your control strategy
- **Sponsor and manufacturer** are responsible to use methods, facilities, and manufacturing controls to ensure the investigational drug's **safety, identity, strength, quality, and purity**[1]

[1]http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf

Mis-steps at early stage development

- Poor characterization data of impurities
- Insufficient nonclinical data to support proposed impurity limits
- Unreliable analytical methods undermine confidence in data
- Insufficient microbiological controls during in use period

How should we formulate?
Should we contract a CRO?
How much will this cost?
Who is a good CRO?

- Get thee to a consultant.
  - FDA does not direct product development
  - FDA **evaluates** development and makes **agreements** on data packages
  - FDA will identify data gaps and risks
  - Business operations are your responsibility

References

1. FDA guidance on the “Preparation of Investigational New Drug Products (Human and Animal)” 1991 (reprinted November 1992).
2. FDA “Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies.”
3. FDA “Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,” Section 19.
4. FDA “Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.”
5. FDA “Draft Guidance for Industry: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs),” August 2003.
6. FDA “Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs),” November 2004.
7. FDA “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices.”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