



# What Clinical Investigators Should Know About Chemistry, Manufacturing and Controls (Quality)

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U.S. Department of Health and Human Services

Food and Drug Administration



# ■ ■ ■ Outline

- IND guidance
- CMC safety concerns
- Impurities
- CMC efficacy concerns
- Stability and shelf life
- Specifications
- Overview of drug patents

## ■■■ IND Guidance Sources

- Food Drug and Cosmetic Act
- Code of Federal Regulations (Title 21)
- Guidance
  - FDA
  - ICH  
International Conference on  
Harmonisation



# International Conference on Harmonisation\*

- Regulatory Authorities
  - US, FDA
  - Japan, Ministry of Health and Welfare
  - European Union, EMEA
- Industry
  - US, PhRMA
  - Japan, JPMA
  - European Union, EFPIA
- Observers

\*International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use  
<http://www.ich.org>

# ■ ■ ■ CMC IND Requirements

- 21 CFR\* 312
  - Format and content
- 21 CFR 211
  - Expiry date for reconstituted products

## ■■■ Investigator Brochure CMC

21 CFR 312.23(a)(5) Investigator's brochure.

If required under § 312.55, a copy of the investigator's brochure, containing the following information:

- (i) A brief description of the drug substance and the formulation, including the structural formula, if known.

## ■ ■ ■ FDA IND Guidance

- Phase 1 (<http://bit.ly/IND-Phase-1>)
- Phase 2 & 3 (<http://bit.ly/IND-Phase2-3>)
- Meetings (<http://bit.ly/IND-meetings>)
- MaPP 6030.1 (<http://bit.ly/IND-MaPP>)
- GMP for Phase 1 (<http://bit.ly/IND-cGMP>)
- Exploratory IND (<http://bit.ly/Expl-IND>)
- Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects  
FDA October 2009 (<http://bit.ly/1VFjV8>)

## ■ ■ ■ ICH IND Guidance

- E6 Good Clinical Practice  
<http://bit.ly/E6-GCPs>
- Many of the “E” Guidances  
<http://bit.ly/1g4oWz>



# Drug Substance Drug Product

- Drug Substance (Active Pharm Ingredient, API)
  - An active ingredient, intended for incorporation into a finished dosage form, that meets the statutory definition of a drug (i.e., that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body)
- Drug Product
  - A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally but not necessarily in association with one or more other ingredients

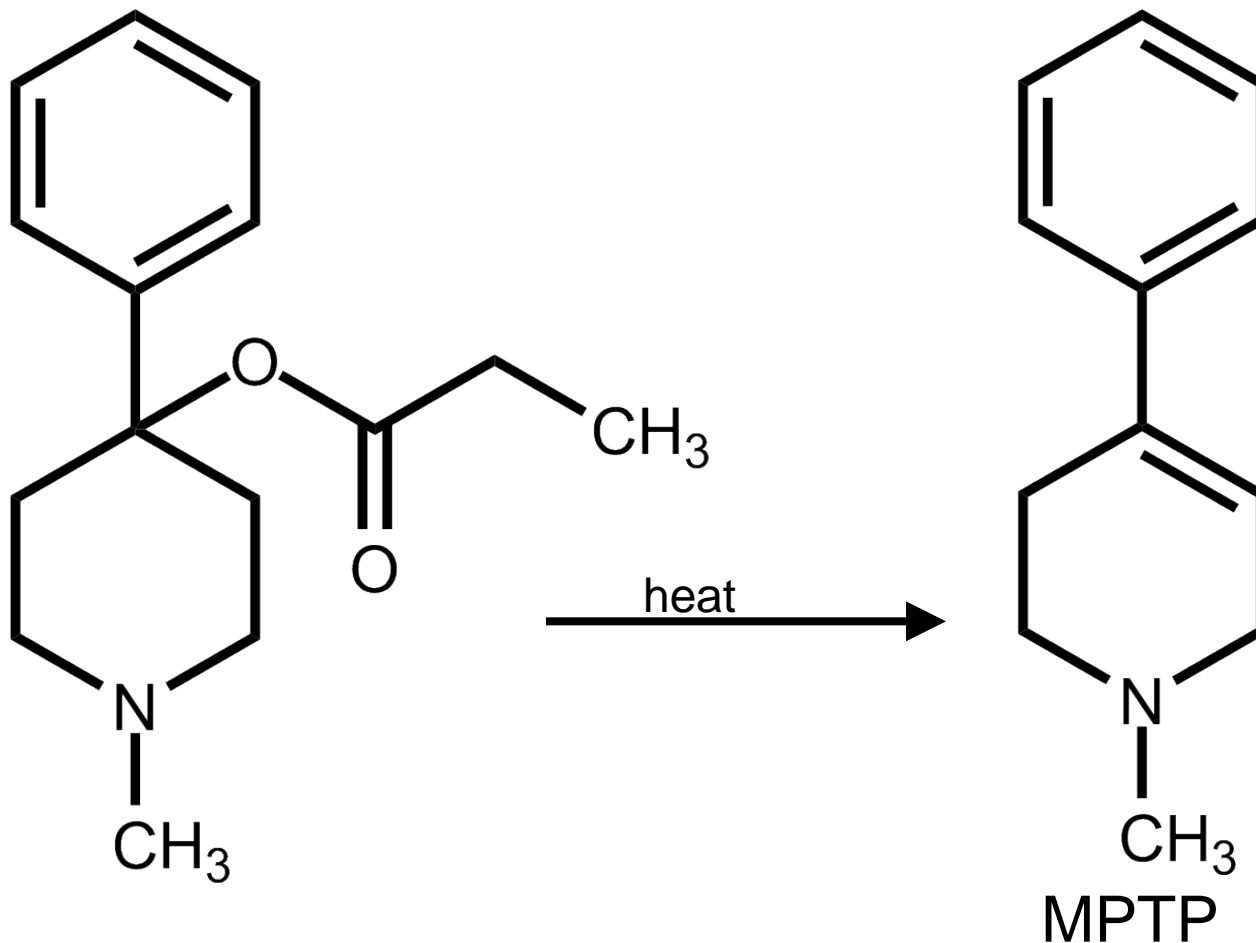
# ■ ■ ■ CMC Safety Concerns

- Generally
  - Impurities
  - Overdose
- For parenteral products
  - Sterility
  - Endotoxins
  - Particulates

## ■■■ Impurities

- Generally limits are based on levels qualified in non-clinical testing
- Specification should include impurity test and acceptance criteria for
  - Individually specified if above the identification threshold
  - General threshold limit for those impurities *not* individually specified
  - Total impurities
- Special considerations for potential or known genotoxic impurities

# ■■■ Impurities More Toxic than Drug



Desmethyprodine  
an opioid analgesic

MPTP  
causes chronic irreversible  
Parkinsonian symptoms

Markey SP, Schmuff NR, Med Res Rev. 1986, 6(4):389-429

## ■■■ Impurities

“In addition, for pre-clinical studies to be useful in assuring the safety of human studies, sponsors should be able to relate the drug product being proposed for use in a clinical study to the drug product used in the animal toxicology studies that support the safety of the proposed human study.”

# ■■■ Pre-30 Day Impurity Request

Sample text for impurity information request:

As stated in our Phase 1 IND Guidance:

“In addition, for pre-clinical studies to be useful in assuring the safety of human studies, sponsors should be able to relate the drug product being proposed for use in a clinical study to the drug product used in the animal toxicology studies that support the safety of the proposed human study.”

We are unable to determine whether the impurities present in your proposed clinical trial lot has been adequately qualified. Consequently you must provide the following information as soon as possible or your study may be placed on clinical hold.

- Lot number proposed for clinical trials
- Certificate of Analysis for the clinical trial lot or a comparable listing of measured impurity/degradation product levels.
- Study number and location in your application in which all impurities were qualified

## ■■■ CMC Efficacy Concerns

- Not a reason for a “clinical hold”
- Assay uncertainty
- Uniformity of content
- Bioavailability

# ■ ■ ■ What Controls Product Quality

- GMPs
- Component quality
- Processes
- ~~• Specifications~~

## ■ ■ ■ What is Quality by Design (QbD)?

- Systematic approach to development
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

*from ICH Q8(R)*

# What are the elements of QbD?



## Product & process design and development

Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

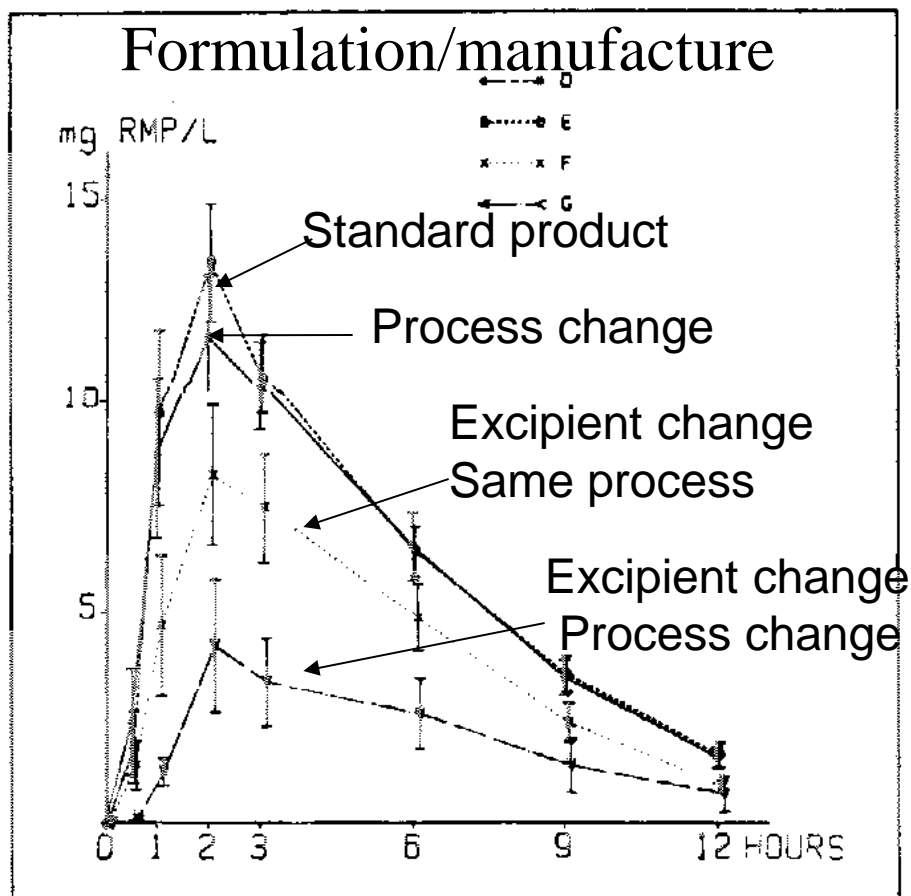
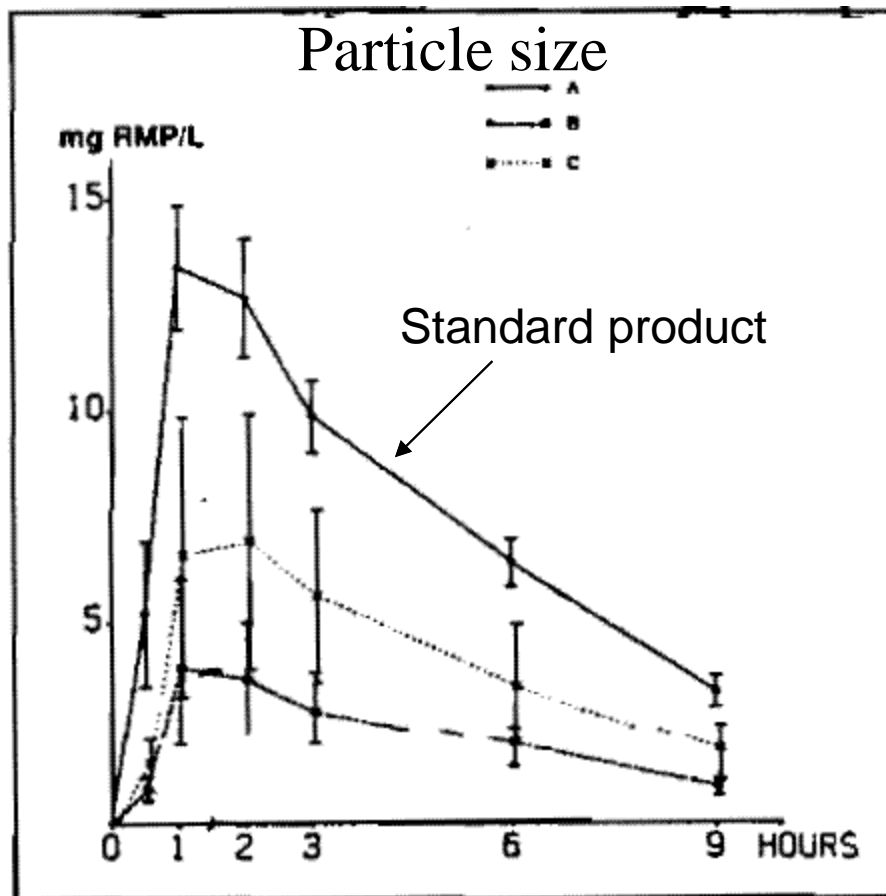
Continually monitor and update process to assure consistent quality

Identify and control sources of variability in material and process

Understand impact of material attributes and process parameters on product CQAs

## Risk assessment and risk control

# ■ ■ ■ Rifampin Bioavailability



## ■ ■ ■ Specifications

- Includes attributes that serve as surrogates for performance
- Defined in ICH Q6A as:
  - “...a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.
- Universal tests described in Q6A for
  - Drug substance
  - Drug product

## ■■■ Universal Tests in a Specification

- Drug substance and drug product
  - Description
    - E.g. Physical state, color
  - Identification
    - By two independent tests (e.g. HPLC and IR)
  - Assay
    - E.g. HPLC
  - Impurities
    - E.g. HPLC, sometimes same as assay procedure

## ■■■ Blinding

- It is important to ensure that placebos are adequately blinded in terms of all sensory characteristics that might distinguish the active from the placebo. These include:
  - Appearance (e.g. color, shape, marking)
  - Feel (e.g. mass, mouth-feel of suspension)
  - Smell
  - Taste
  - Sound

## ■ ■ ■ Stability and Shelf-Life

- IND regs require that a drug be stable for the duration of the trial
- Expiry dating not required, except for reconstituted products
- Assay usually 90–110%
- Impurity totals usually <10%
- At the end of trial, impurities should be less than levels qualified

## ■■■ Clinical Trial Supplies\*

- Examine container integrity on receipt
- Confirm label's 21 CFR 312.6 compliance
- Store at recommended conditions
- Document:
  - Receipt and storage
  - Condition of product on receipt
  - Dosing (including e.g. date & time, lot#, etc)
  - Reconciliation of all product at study conclusion

\*See International Conference on Harmonisation of Technical Requirements for Registration Of Pharmaceuticals for Human Use Guidance E6, "Guideline for Good Clinical Practice"

<http://bit.ly/E6-GCPs> and 21 CFR 312.62

## ■ ■ ■ Labeling

- Immediate package must bear a statement
  - “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”
- Label or labeling shall NOT
  - “...bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.”



# Patents



U.S. Department of Health and Human Services

Food and Drug Administration



## ■ ■ ■ What are patents

- Government grant of a property right to the inventor
- NOT a grant to practice the invention
- A right to exclude others for a fixed period
- A quid-pro-quo for disclosure
- Rights apply only in country of issue

## ■■■ Rocephin (ceftriaxone)

- Composition of Matter US 4,327,210
  - 11/24/78 US application
  - 4/27/82 Issued
  - 4/27/99 Expired
- To practice US 4,327,210 Roche licensed 8 patents!
  - Process patents
  - Hoechst composition of matter patents

# ■ ■ ■ Drug Patents and Exclusivity

- Patent term
  - 20 years from filing date
  - Previously 17 years from grant
- FDA regulation of exclusivity
  - Like patents, intended to reward innovation
  - Exclusive marketing rights granted by the FDA
  - Runs concurrently with a patent life (i.e. not additive)
  - Can be for 180 days, 6 months, 3 years, 5 years, 7 years

## ■ ■ ■ Patent Terms

- Most industrialized countries — 20 years from application date in that country
- US Generally
  - Previously
    - 17 years from date of issue in US
  - Now (post-GATT/TRIPS/WTO)
    - 20 years from application date in the US
    - If issued or filed before 8 June 1995 either:
      - 17 years from issue OR
      - 20 years from application

# ■ ■ ■ Patent Extensions

- Hatch-Waxman
  - Restores life lost due to regulatory review
  - Maximum 5 years extension
  - Limited to 14 years after first product approval
- Private patent bills

# ■ ■ ■ Patent Requirements

- Novelty
- Utility
- Non-obviousness

# ■■■ Infringement

- Literal infringement
  - Practicing what is in the claims of another's patent which is still in effect
- Doctrine of Equivalents infringement
  - Doing substantially the same thing in substantially the same way

# ■ ■ ■ Infringement Exceptions

- Experimental use

(with some exceptions, see *Madey v. Duke University* <http://bit.ly/E7g15>)

- Generic drug development

- Roche v. Bolar (Valium®) 1984

Bolar found to infringe Roche patent by manufacturing for purposes of development of a generic product, and bioequivalence testing

- Overruled by “Safe Harbor” provision of Hatch-Waxman

“It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”

## ■ ■ ■ Acknowledgement

- Thank you Norman Schmuff, Ph.D.