Chemistry, Manufacturing, and Controls of Drug Candidates for Dummies

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Topics

- Discovery to IND
- Requirements for the CMC Section of the FTIH IND
- Impurities, stability, dosage forms and methods – The KISS Principle

Discovery and development viewpoints often differ

Discovery view (preclinical experiment)	**Development view** (candidate selection experiment)
Get it into solution any way you can to enable the experiment	Solubilization options are constrained. Unrealistically solubilized systems can be misleading.
Metastable systems are okay.	Equilibrium (thermodynamic) solubility is all that matters.
Isn't DMSO a marvelous solvent?	*Never* use DMSO.
First add cosolvent.	First adjust pH (if there is an ionizable group).
Reasonably pure is sufficient	Methods in place to separate impurities and assess purity a must
Stability requirement is measured in hours or days.	Stability is measured in months or years.

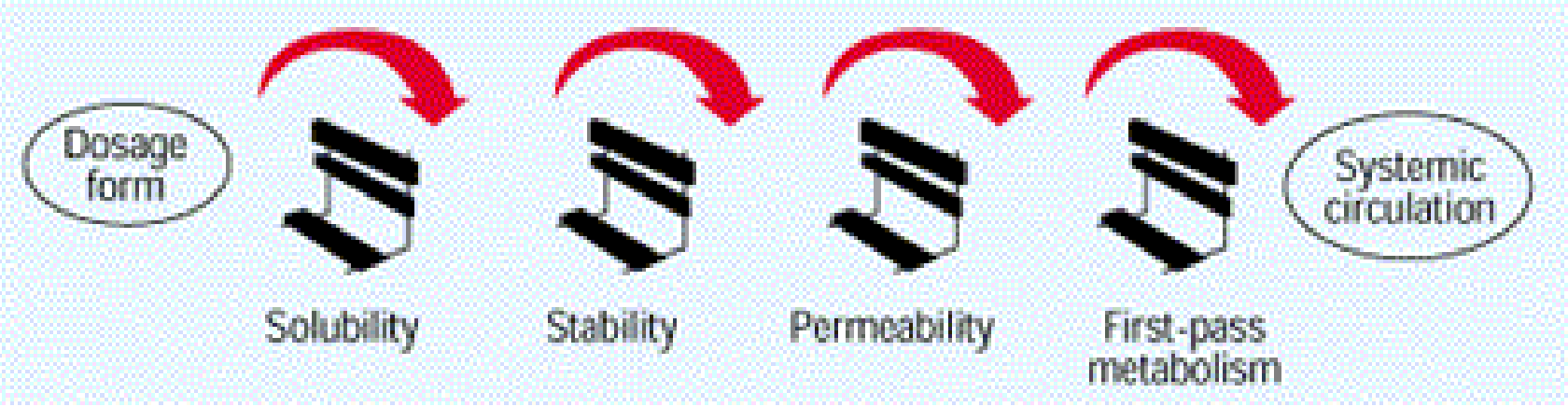

Figure 2. Key biopharmaceutical properties affecting developability of a drug for enteral delivery. The properties are shown as hurdles to be surmounted if a dosage form is to achieve effective systemic delivery. Poor biopharmaceutical properties may sometimes be corrected by formulation, but at a cost in time and resources. Poor solubility and stability may be amenable to being fixed by formulation. Poor permeability is difficult to correct by formulation. First-pass metabolism problems are difficult to fix by oral formulation.

The Rule of Five

An awareness tool for discovery chemists:
Compounds with two or more of the following characteristics are flagged as likely to have poor oral absorption.

- More than 5 H-bond donors
- Molecular weight >500
- *c* log *P*>5
- Sum of N's and O's (a rough measure of H-bond acceptors) > 10

Preparing for the IND

Foolish Assumptions
“True or False”

- A single investigator IND is simpler than a commercial IND

The IND Application Must Contain….

- “Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.”

From www.fda.gov/cder

Can I fully Characterize my Drug?

- Do I have a reliable synthetic route that is reproducible?
- Do I have a reliable, specific and sensitive analytical method?
- What are the physical chemical properties of the drug substance? Can it be readily formulated/delivered and maintain stability?
- How do I want to (need to) deliver the drug?
- What, if any, are the key properties of the drug that could confound clinical results?
- Can I produce a compliant and convincing CMC package?

Objectives and CMC Requirements of the IND

Primary Objectives of IND

- Phase 1: Safety
  - Initial introduction of a new drug into humans
  - Closely monitored, patients or normal volunteers
    - Metabolism and pharmacological actions of drug in humans
    - Side effects associated with increasing doses
    - Early evidence of effectiveness
    - Design of well-controlled, scientifically valid phase 2 studies
- Phase 2: Limited well controlled clinical studies
- Phase 3: Expanded well controlled and uncontrolled clinical trials

Moheb Nasr, Ph.D., ONDC, FDA 2004

IND Content and Format

- 21 CFR 312
  - 21 CFR 312.21: Phases of an Investigation
    - Phase I, II, and III
  - 21 CFR 312.22: General Principles
  - 21 CFR 312.23: Content
    - Drug Substance
    - Drug Product
    - Placebo
    - Labeling
    - Environmental Analysis

IND Phase 1 – CMC Requirements

- The amount of information needed depends on:
  - Phase of the investigation
  - Novelty of the drug
  - Previous studies
  - Dosage form/Route of administration
  - Duration of the Study
  - Patient population
  - Known or suspected risks

Drug Substance	FDA Expectation (● = Expected; — = Not Required)				
Description:	**Phase 1**	**Phase 2**	**Phase 3**	**NDA**	**Comments**
Code Number	●	●	●	●	
Chemical Name(s)	●	●	●	●	
Common (or other) Name(s)	—	—	●	●	
Molecular Formula	●	●	●	●	
Molecular Weight	●	●	●	●	
Chemical Structure, Including Stereochemistry	●	●	●	●	
Appearance	●	●	●	●	
Physicochemical Properties:					
Solubility (e.g., water, ethanol, ether)	●	●	●	●	
pH Solubility Profile	—	●	●	●	
pKa	●	●	●	●	
Partition Coefficient	—	—	●	●	
Hygroscopicity	—	●	●	●	
Melting Point/Boiling Point	●	●	●	●	
X-Ray Diffraction/Single Crystal	—	●	●	●	
Chirality/Optical Rotation	●	●	●	●	
Refractive Index	—	—	●	●	
Polymorph Screen	●	●	●	●	Needed for solid dosage forms
Particle Size	●	●	●	●	Needed for solid dosage forms
pH of Aqueous Solution	●	●	●	●	Needed for liquid dosage forms
Structure Elucidation:					
Elemental Analysis	—	●	●	●	
UV Spectroscopy	●	●	●	●	
IR Spectroscopy	●	●	●	●	

IND Phase 1 – CMC Requirements

Drug Substance

- Description (physical, chemical, biological)
- Manufacturer (name and address)
- Method of Preparation (brief description/ flow diagram, reagents, solvents, catalysts)
- Analytical Methods (brief description, proposed criteria, certificates of analysis)
- Stability (brief description of study/test methods, preliminary tabular data)

IND Phase 1 – CMC Requirements

Drug Product

- Components (grade; *e.g. USP/ NF, ACS,* novel excipients, etc.)
- Quantitative composition
- Manufacturer (name and address)
- Method of Manufacture (narrative *and/or* flow diagrams, sterilization process for sterile products)
- Analytical Methods
  - brief description of test methods and limits *(dosage form dependent)*
- Stability of Drug product
  - Information to assure the product's stability during the planned clinical studies

FTIH Dosage Forms

- The simpler, the better hierarchy
- For Oral Dosage forms:
  - Powder in a capsule (PIC) or Powder in a bottle (PIB)
  - Aqueous solutions or suspensions
  - Formulated tablet or capsule
- For Parenteral Dosage Forms
  - Terminally sterilized (glass ampoules, vials)
  - Aseptic Processing – solutions
  - Aseptic processing - lyophilized

IND Phase 1 – CMC Requirements

- **Placebo**
  - Description
  - Composition and Controls
  - Control

IND Phase 1 – CMC Requirements

Sponsor Agency Interactions

- Pre-IND Meetings: Generally to focus on ***safety issues*** related to the identification, strength, quality, purity of the investigational drug and to identify any ***potential clinical hold issues***
- EOP2 Meetings: Generally to focus on CMC specific issues for the planned phase 3 studies
- Pre-NDA Meetings: Generally to focus on filing and format issues
- Follow-up teleconferences and other meetings, as warranted

Moheb Nasr, Ph.D., ONDC, FDA 2004

Safety Concerns

- In general, Phase 1 review of the CMC sections to ensure the identity, strength, quality, and purity of the investigational new drugs as they relate to safety
- Examples:
  - Product made with unknown or impure components
  - Sterility and/or apyrogenicity not assured (i.e., injectables)
  - Product not stable through clinical study duration
  - Strength or impurity profile insufficiently defined
  - Product possessing structures of known or likely toxicity
  - Impurity profile indicates health hazard
  - Poorly characterized master or working cell bank

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Assembling the CMC Section of the IND

7	Chemistry, Manufacturing and Controls (CMC)
7.A	**Drug Substance**
7.A.1	Physical and Chemical Characteristics
7.A.2	Manufacturer’s Name and Address
7.A.3	Raw Materials List and Specifications
7.A.4	Method of Manufacture
7.A.5	Process Controls
7.A.6	Drug Substance Controls
7.A.6.a	Release Controls and Test Methods
7.A.6.b	Reference Material
7.A.6.c	Impurities
7.A.6.d	Analytical Results
7.A.7	Drug Substance Stability
7.A.7.a	Stability Protocol and Test Methods
7.A.7.b	Analytical Results

7.B	**Drug Product**
7.B.1	Description
7.B.2	Components, Specifications, and Quantitative Composition
7.B.3	Method of Manufacture and Packaging
7.B.4	Container-Closure Information
7.B.5	Drug Product Controls
7.B.5.a	Release Controls and Test Methods
7.B.5.b	Analytical Results
7.B.6	Drug Product Stability
7.B.6.a	Stability Protocol and Test Methods
7.B.6.b	Analytical Results
7.C	Placebo
7.C.1	Description
7.C.2	Components, Specifications, and Quantitative Composition
7.C.3	Method of Manufacture and Packaging
7.C.4	Container-Closure Information
7.C.5	Placebo Controls
7.C.5.a	Release Controls and Test Methods
7.C.5.b	Analytical Results
7.C.6	Placebo Stability
7.C.6.a	Stability Protocol and Test Methods
7.C.6.b	Analytical Results
7.D	Labeling
7.E	Environmental Assessment

Impurities and Stability

Foolish Assumptions
“True or False”

- A single investigator IND is simpler than a commercial IND
- The IND must comply with ICH Guidelines

Impurities

- Two kinds of impurities are distinguished in the ICH Guidelines:
  - Drug substance impurities that do not change in the drug product
  - Drug degradation products that can increase over time in both drug substance and drug product

ICH Q3(R) – Impurities in Drug Substance

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

ICH Q3B(R2) – Impurites in Drug Product

THRESHOLDS FOR DEGRADATION PRODUCTS IN NEW DRUG PRODUCTS

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Genotox Impurities*

- “exposure to the potentially genotoxic impurities can not exceed 60 micrograms per day. For longer duration clinical trials the levels would have to be further reduced; for clinical trials of greater than one year duration, the daily exposure to these impurities should not exceed 1.5 micrograms.”
  - “You will therefore need to address the potential for carry-over of genotoxic impurities to the drug substance as development proceeds.”

* FDA response to pre-IND question asking about suitability of impurity specifications

Drug Product Stability

- IND regulations require that the product remains within specification for the life of the clinical trial; i.e., from first patient first dose to last patient last dose.
- Accelerated stability testing can be used to support stability

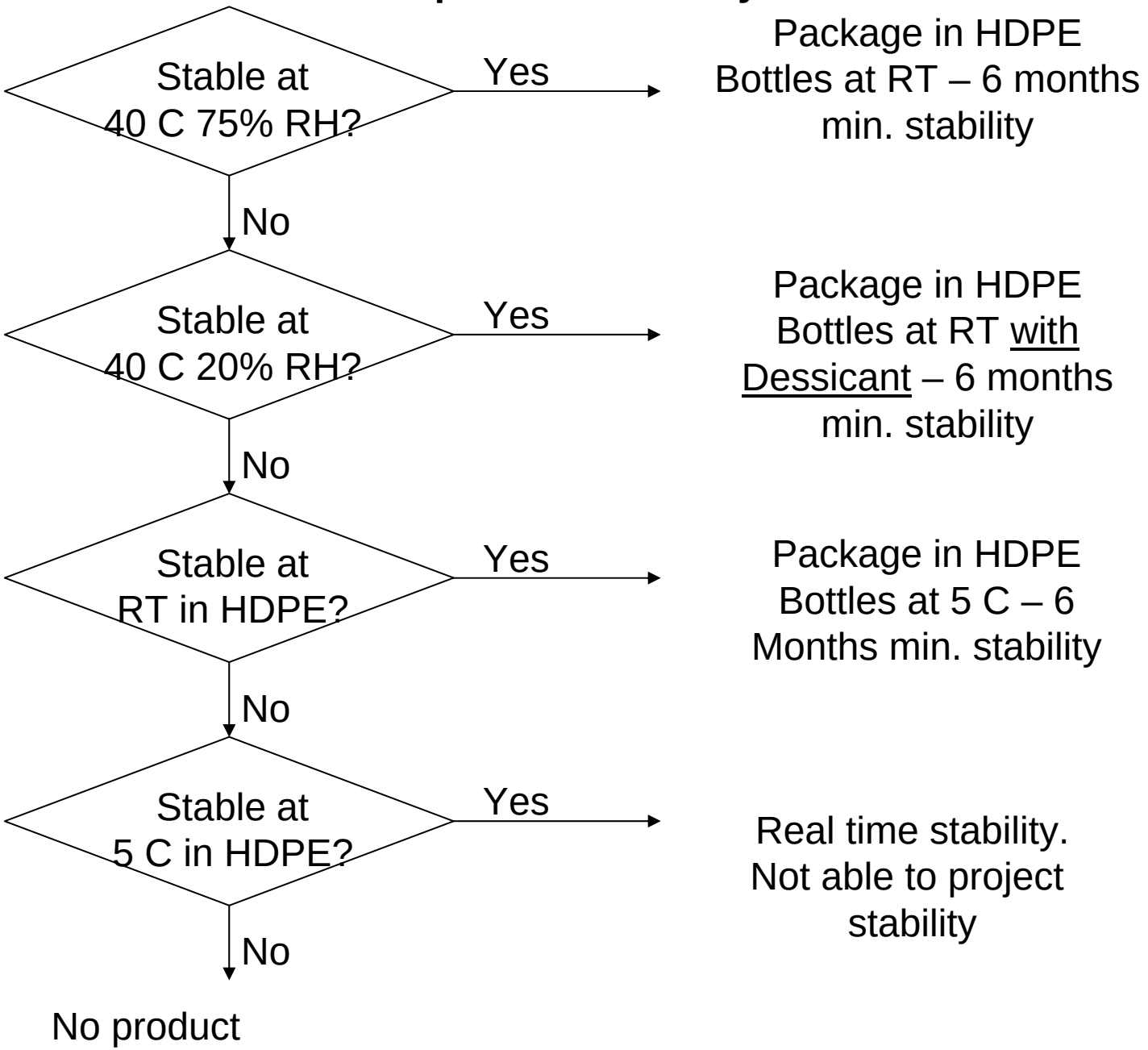
Guidelines for Stability Data for IND Filing (Target IND Stability)

For a first in human (FIH) IND, stability data for drug product should include either:

1. in house “open dish” stability (3M minimum) plus statement that clinical trial material (CTM) is on stability, or
2. 1M stability data (all ICH conditions) on CTM.

1M stability data on CTM should be considered the target stability data for a FIH IND. However, an IND may be filed with 3M in house open dish stability data and a statement that CTM has been placed on stability. The goal should be to put product on stability 1 week post manufacture.

DS/DP Stability/Packaging Decision Analysis
Three Month Open Dish Stability



Common CMC Delays in Drug Development

- Interruption of drug substance supply
  - A new polymorph or impurity shows up, lost batches
- Unavailable validated analytical methods
- Inadequate clinical formulation
  - Lost batches, failure to meet specifications, limited quantities
- Problematic stability data
  - More commonly, dissolution failures, sterility failures, media failures
- Non-GMP compliance – usually paperwork problems
- Being put on clinical hold for CMC reasons

FDA PLACES CLINICAL HOLD ON VAXGEN'S ANTHRAX VACCINE TRIAL

VaxGen announced it has received a clinical hold notification from the FDA that will postpone the initiation of the company's second Phase II trial for its investigational anthrax vaccine, rPA102.

The FDA's Center for Biologics Evaluation and Research (CBER) said the hold notice was issued because data submitted by the company are insufficient to determine that the product is stable enough to resume clinical testing.

November 3, 2006

Foolish Assumptions
“True or False”

- A single investigator IND is simpler than a commercial IND
- The IND must comply with ICH Guidelines
- FTIM clinical trial materials should be “GMP-like” but not necessarily full GMP
- Experienced contractors know what to do
- INDs do not get put on “clinical hold” for CMC reasons

Early Development Case Study – Polymorphic form and impact on safety

- A new lot of drug substance tested in a 4 week tox study was more toxic than previously demonstrated with earlier lots.
- Company decides to put ongoing clinical trial on hold
- What Happened? Impurity profile change? Animals dosed incorrectly?
- Finding: All previous toxicology done with crystalline form of the drug. New batch was amorphous. Hypothesis tested and confirmed in repeat tox studies
- Time lost in the clinic = 1 year

Case Study: Inept Contractors

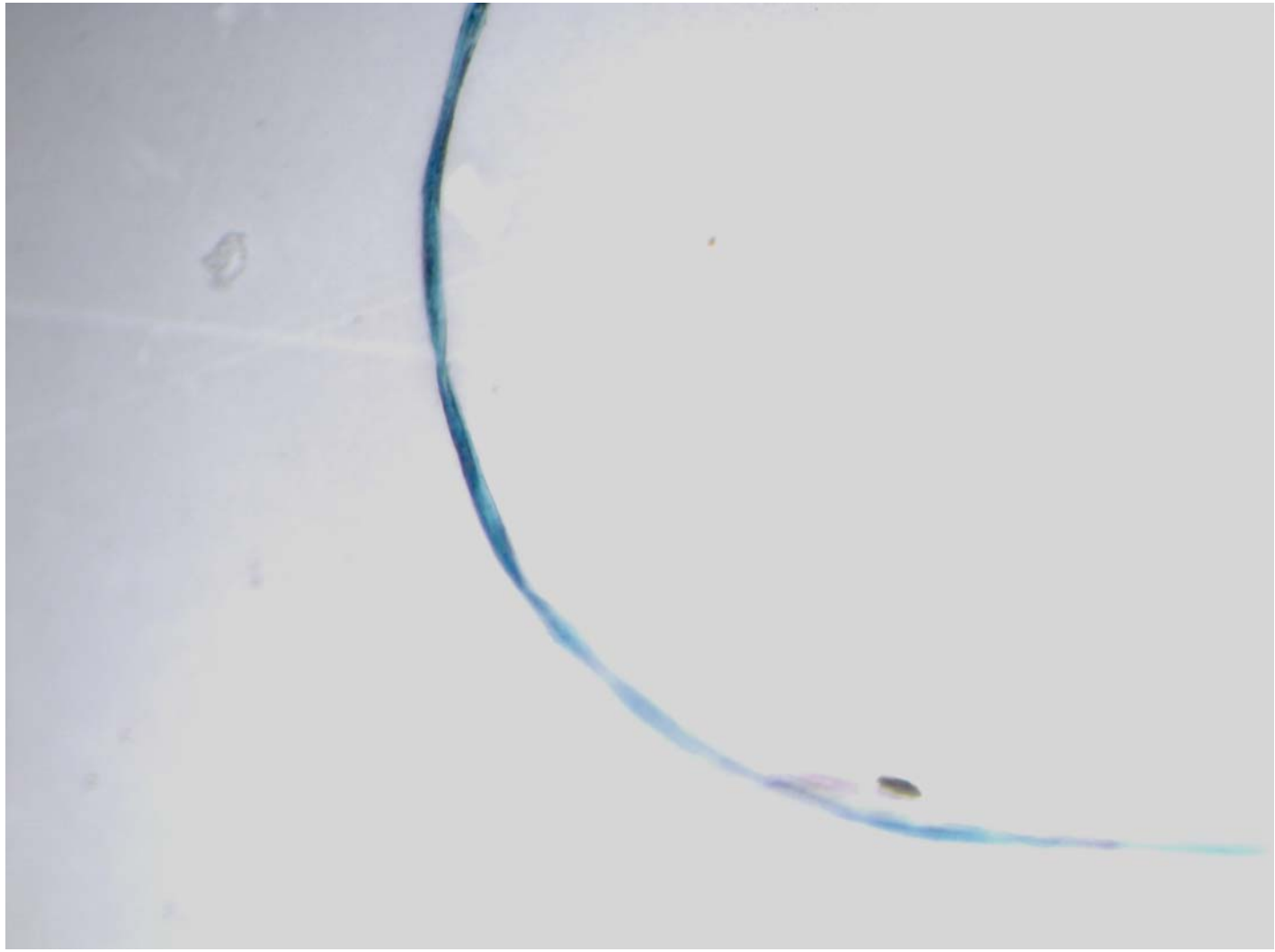
The case of the mottled tablets

- A simple tablet formulation was manufactured for a phase 1 study
- A slight amount of ferric oxide yellow was added to help in the blinding of the tablets
- After 3 months storage the tablets were reported to be “mottled” in appearance.
- The contractor was concerned that a new degradant had formed.
- Tablets were sent to SSCI for FTIR analysis

Second Lab investigates “blue fibers”

- Ten **10 mg.** sample of drug substance was dissolved in water and passed through a filter paper.
- Blue particles tended to be large and easily observed without the microscope
- Black particles also tended to be large and similar in appearance to blue particles under the microscope
- Red particles had a transparent appearance that was similar to the transparent part of the blue (black) particles

Sample of Fibers found on Filter paper



Mottled Tablets Outcome

- Two weeks after issuing the report detecting significant foreign particles in 10 mg. samples of drug substance, the company later found out that their glassware and laboratories were contaminated with blue and red fibers!
- The investigation continues. Clinical study delayed 6 months.

What you don’t know can hurt you….

“…there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say, we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don’t know.”

Former CEO G. D. Searle

Case study: Confusing and Inconsistent CMC submission

FDA Response to a new IND filing

- A qualification and quantification of the impurities identified in the batches of both drug substance and drug product used in the preclinical and/or clinical trials, and
- Updated information for drug substance batch (Lot No. XXXX) and drug product batch (Lot No. YYYY).
- ***The company was put on clinical hold due to inadequate responses to these requests***

Sample of problems with the IND

- Original IND analytical methods kept changing and were of questionable reliability as it relates to impurities qualification
- At least four lots of drug substance used in preclinical safety studies and two drug substance lots used to make clinical supplies. Different analytical methods used to test and release these lots
- Retention times of impurities varied somewhat across methods making it difficult to be sure which chromatographic peak represented which unknown impurity.

Sample of problems with the IND (cont)

- New analytical methods appear to be better and robust but require that glassware not be used as the drug adheres to glass.
- Apparently glassware was used both in the analytical methods as well as drug product storage and in the preclinical studies putting some doubt on the reliability of drug concentrations reported as part of those studies.
- The total impurity specification in the DS section of the original IND gives two different values: one was 4% and the other 6%

Conclusions