



The Evaluation of Impurities in Investigational New Drug and New Drug Applications

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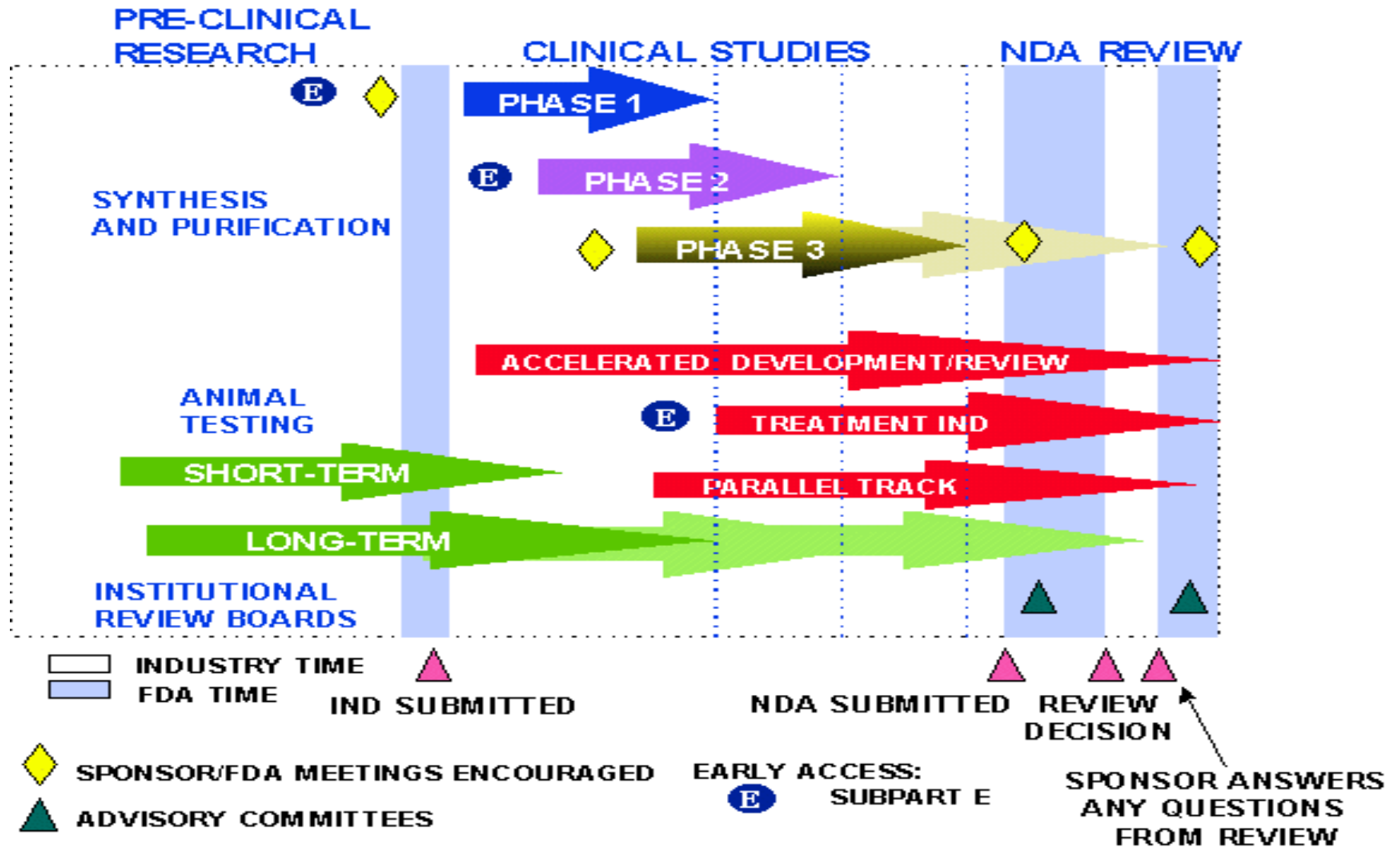
Branch 5/Division of Pre-Marketing Assessment 3

Office of New Drug Quality Assessment



Presentation Overview

- Introduction
 - Drug development overview
 - Key Agency interactions
- Definition of Quality
- CDER regulatory applications
 - INDs, DMFs
 - NDAs
- Evaluation of impurities in regulatory applications
- Current guidances
- Summary





Agency Interactions

- PreIND meetings
- IND submissions
- EOP1 meetings
- EOP2 meetings
- preNDA meetings
- Other meetings as appropriate
 - Quality By Design
 - As requested by Agency



What is Quality?

- The degree to which a set of inherent properties of a product, system, or process fulfills requirements (ICH Q9)
- The suitability of either a drug substance or drug product for its intended use. Includes such attributes as the identity, strength, and purity (ICH Q6A)

ICH Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

ICH Q9 Quality Risk Management



Pharmaceutical Quality

Identity

Strength

Purity

Quality

Potency



Availability

Affordability



Why is Quality Important?

- Ties product performance to label claim
- Applies to design, manufacture and clinical use of product
- Relates critical attributes of the drug to patient safety and fitness for use
- Necessary for product availability to patient (i.e., poor quality often results in recalls and shortages)



CDER Regulatory Submissions

Investigational New Drugs (INDs)

- Initial INDs (Research/commercial)
- Amendments
- Special Protocol Assessments (SPAs)

New Drug Applications (NDAs)

- Original NDA submissions
- Commitments/protocols
- Supplements
- Annual Reports

Drug Master Files (Types I, II, III, IV, and V)



Impurities – Investigational New Drug (IND) Applications



IND Submissions

Initial INDs

- 30 day evaluation period
- Focus on safety
- Safe to proceed or clinical hold.
- Some Sponsors elect to withdraw or inactivate rather than be placed on clinical hold.

Single patient use (Compassionate use) - ASAP

Treatment INDs and Treatment Protocols

- cGMP evaluation requests submitted
- cGMP recommendation issued within a 30-day clock

Exemptions



The IND Review Team

- Primary Clinical reviewer
- Primary Chemistry reviewer
- Primary PharmTox reviewer
- Sometimes consulted: Clinical Pharm.
- Project manager (aligned with the clinical division)
- Supervisory/secondary signoffs



IND Guidances

- INDs for Phase 2 and Phase 3 Studies
Chemistry, Manufacturing, and Controls
Information
- Content and Format of Investigational New Drug
Applications (INDs) for Phase 1 Studies of Drugs
- Apply to both research and commercial
sponsors of INDs.



Examples of IND Safety Issues (CMC)

- **Lack of batch analysis (preclinical and/or clinical)**
- **Insufficient or missing compatibility data for injectable formulations**
- Inconsistent or deficient CMC information
- Lack of detail regarding manufacturing process, including compounding process
- Lack of proper authorization for cross-referenced information
- **Deficiencies in impurity profile**
- Omission of CMC items required by regulations (labeling, categorical exclusion, etc)



Impurities (INDs) - Considerations

- Are impurity profiles of preclinical and proposed clinical batches comparable?
- If an injectable (or solution) product, have potential leachables and extractables been addressed?
- If an injectable or solution product, are in-use stability and compatibility data provided?
- Is manufacturing process description adequate?
- Are all impurities in proposed clinical batch adequately qualified? (PharmTox)
- Are analytical methods adequate?
- Are there any trends on stability that may significantly alter the impurity profile of the clinical batch?



Impurities (INDs) – General Assessment

- Impurities need not be identified at this stage, but need to be characterized sufficiently for comparison between preclinical and proposed clinical supplies.
- However, in cases where an impurity (or impurities) are present at relatively high levels, structural identification can assist in determining safety.
- Initial INDs include proposed specifications, including criteria for impurities.
- Focus on qualification of impurities; negotiation of specifications is reserved for later in development.



Drug Master Files (DMFs)

- Covered under 21CFR 314.420
- Mechanism to preserve confidentiality of proprietary information
- FDA neither independently reviews nor approves or disapproves DMFs
- Types of DMFs:
 - **Type 1** [Reserved] Formerly facility descriptions
 - **Type 2**: Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
 - **Type 3**: Packaging materials
 - **Type 4**: Excipient, colorant, flavor, essence, or materials used in their preparation
 - **Type 5**: FDA-accepted reference information (pre-arranged via letter of intent with FDA).



Drug Master Files (Cont.)

- Can be cross-referenced for either INDs or NDAs
- Letter of Authorization required for cross-reference
- Manufacturing sites included in EES request for NDAs and supplements
- Separate review conducted for each cross-referenced DMF
- Status of DMF (adequate or inadequate) referenced in NDA or IND review document
- DMF deficiencies not specifically conveyed to Applicant!



Impurities – New Drug Applications (NDAs)



The NDA Primary Review Team

- Medical Officer
- CMC Reviewer
 - Biopharmaceutics Reviewer as needed
 - Use of team review
- Statistics Reviewer
- Clinical Pharmacology Reviewer
- Pharmacology/Toxicology Reviewer
- Project Manager (aligned with clinical division)
- Supervisory signoffs for all disciplines
- Consults: Microbiology, DMEPA, Compliance (EES), others as needed



The NDA Review

- The review clock
 - NDA submission - clock starts (S or P)
 - FDA review team assigned
 - Review initiated to determine filability
 - Day 60 filing decision
 - If not filable, application is “Refuse to File (RTF)”
 - FDA refusal to file if:
 - Incomplete application
 - Improper format (see 21 CFR § 314.50)
 - Absence of environmental assessment
 - Absence of English translation



Examples of Potential CMC RTF Issues

- Undefined manufacturing facilities and/or lack of confirmation of facility information
- Insufficient stability data to support a commercially viable expiration dating period
- Significant changes to the commercial formulation following clinical trials
- Insufficient parallel between preclinical supplies, primary stability batches and proposed commercial formulation(s)



Impurities (NDAs) - Considerations

- CMC review of impurities follows ICH Q3A and Q3B guidances
- During review, absolute determination (PharmTox) of impurity qualification status
- If not appropriately qualified, can be either an approvability issue or can be handled post-approval
- CMC reviewer(s) confirm validity of analytical methodology, batch data, justification of specifications, and ability of process to control impurities.



ICH Q3A: Impurities in New Drug Substances

- Finalized June/2008
- Does not cover certain drug substances: e.g. radiopharmaceuticals, herbal products, peptides.
- Impurities classified into:
 - Organic impurities (process- and drug-related)
 - Inorganic impurities
 - Residual solvents
- Organic impurities subdivided into:
 - Identified, unidentified, volatile, nonvolatile



ICH Q3A: Impurities in New Drug Substances

- “Specified impurities” have a single proposed acceptance criterion in DS specification.
 - Can be either identified or unidentified
- Overall specification should include:
 - Each specified identified impurity
 - Each specified unidentified impurity
 - Any unspecified impurity proposed at a level higher than the identification threshold.
 - Total impurities
 - Residual solvents
 - Inorganic impurities

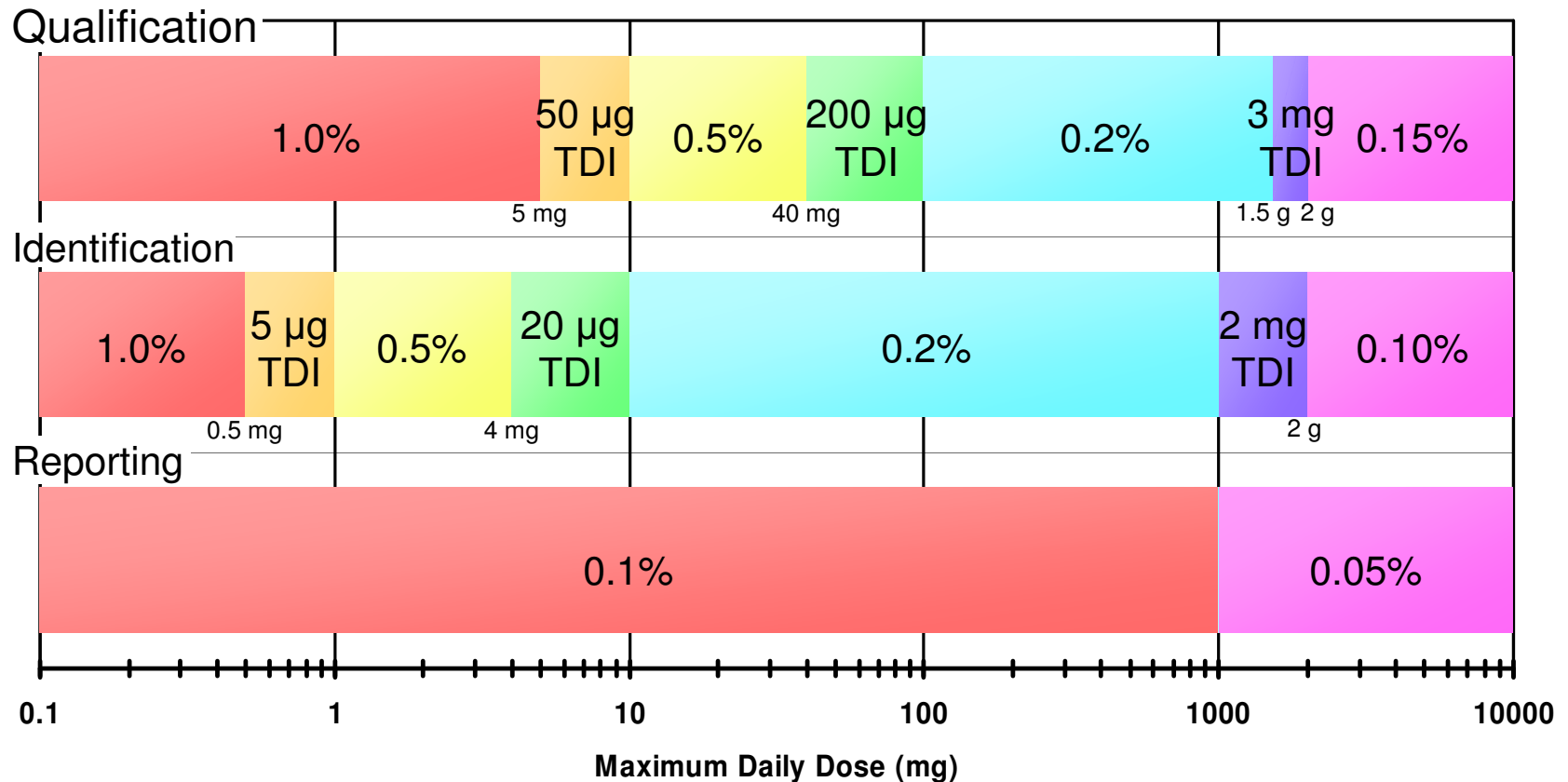


ICH Q3B(R): Impurities in New Drug Products

- Finalized July/2006
- Similar exclusions as ICH Q3A
- Process impurities not necessary in DP specification
- Overall specification should include:
 - Each specified identified degradation product
 - Each specified unidentified degradation product
 - Any unspecified degradation product proposed at a level higher than (or equal to) the identification threshold.
 - Total degradation products



ICH Q3B(R) Thresholds





ICH Q3C: Residual Solvents

- Finalized December/1997
- Residual solvents classified into three categories based on potential effect: Class 1, 2, and 3.
 - Class 1: solvents to be avoided
 - Class 2: solvents to be limited
 - Class 3: solvents with low toxic potential



ICH Q3C: Residual Solvents

- Class 1: restrict levels to ICH Q3C levels, but only if use is unavoidable.
- Class 2: restrict levels to ICH Q3C levels (Option 1) **OR** calculate allowable mg/day to determine allowable level in DP (Option 2)
- Class 3: generally acceptable if levels are below those stated in ICH Q3C



Summary

- Drug development – preIND through NDA
- CDER Regulatory Applications
 - INDs, DMFs, NDAs
- Impurities in INDs
- Impurities in NDAs
- Residual Solvents
- Increased product knowledge in early development can facilitate future development (e.g. Quality by Design)



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