



Regulatory and Scientific Considerations for API Drug Development

August 26, 2009



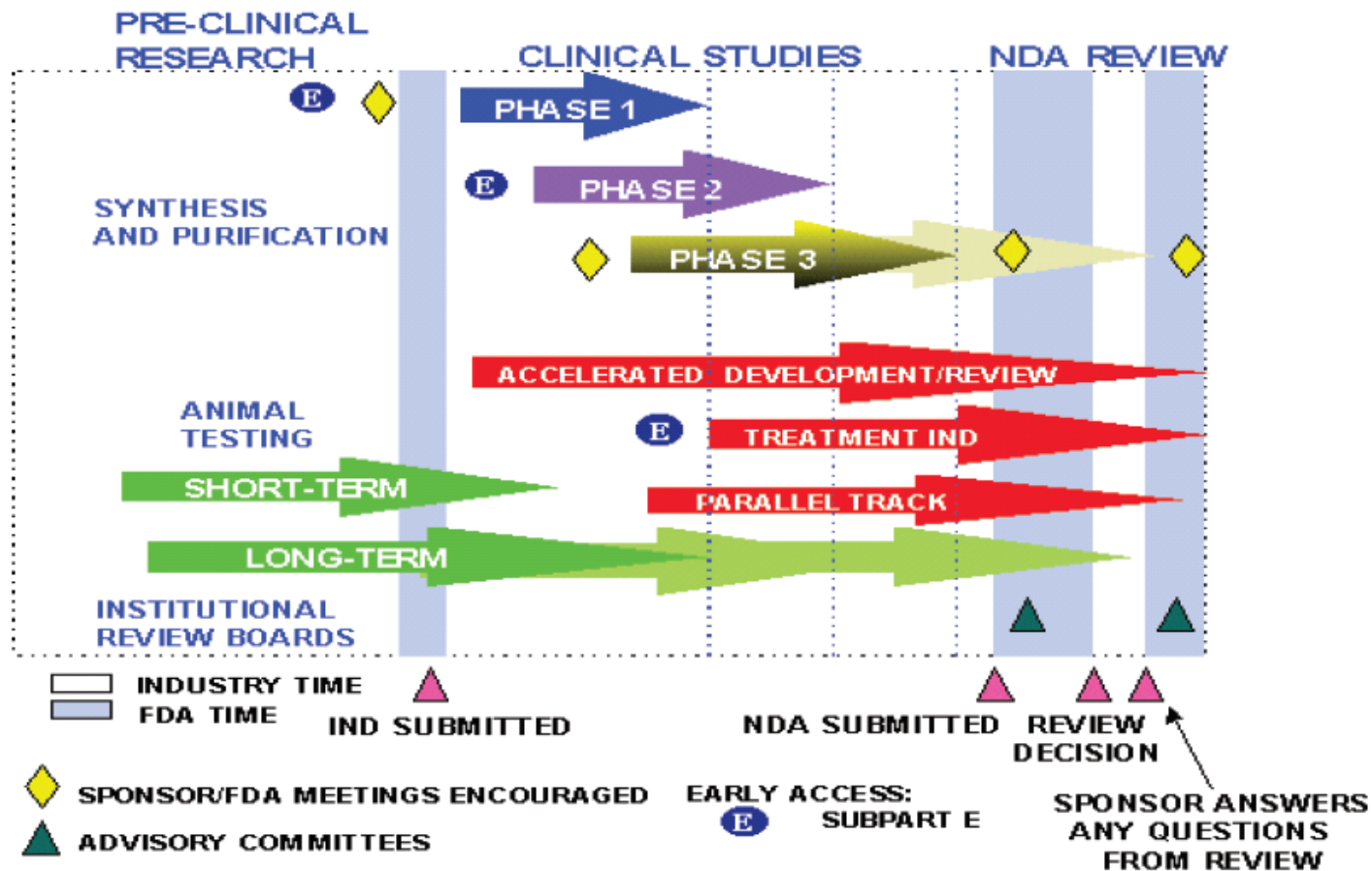
Objectives

- ◆ Overview of API activities during drug development
- ◆ Overview of API requirements for marketing applications
- ◆ Considerations for use of DMFs for APIs
- ◆ Considerations for manufacturing of APIs at a CMO
- ◆ Considerations for APIs manufactured from biologic sources
- ◆ Overview of post-approval requirements
- ◆ Recap of Major Points - Conclusions
- ◆ Questions and Answers

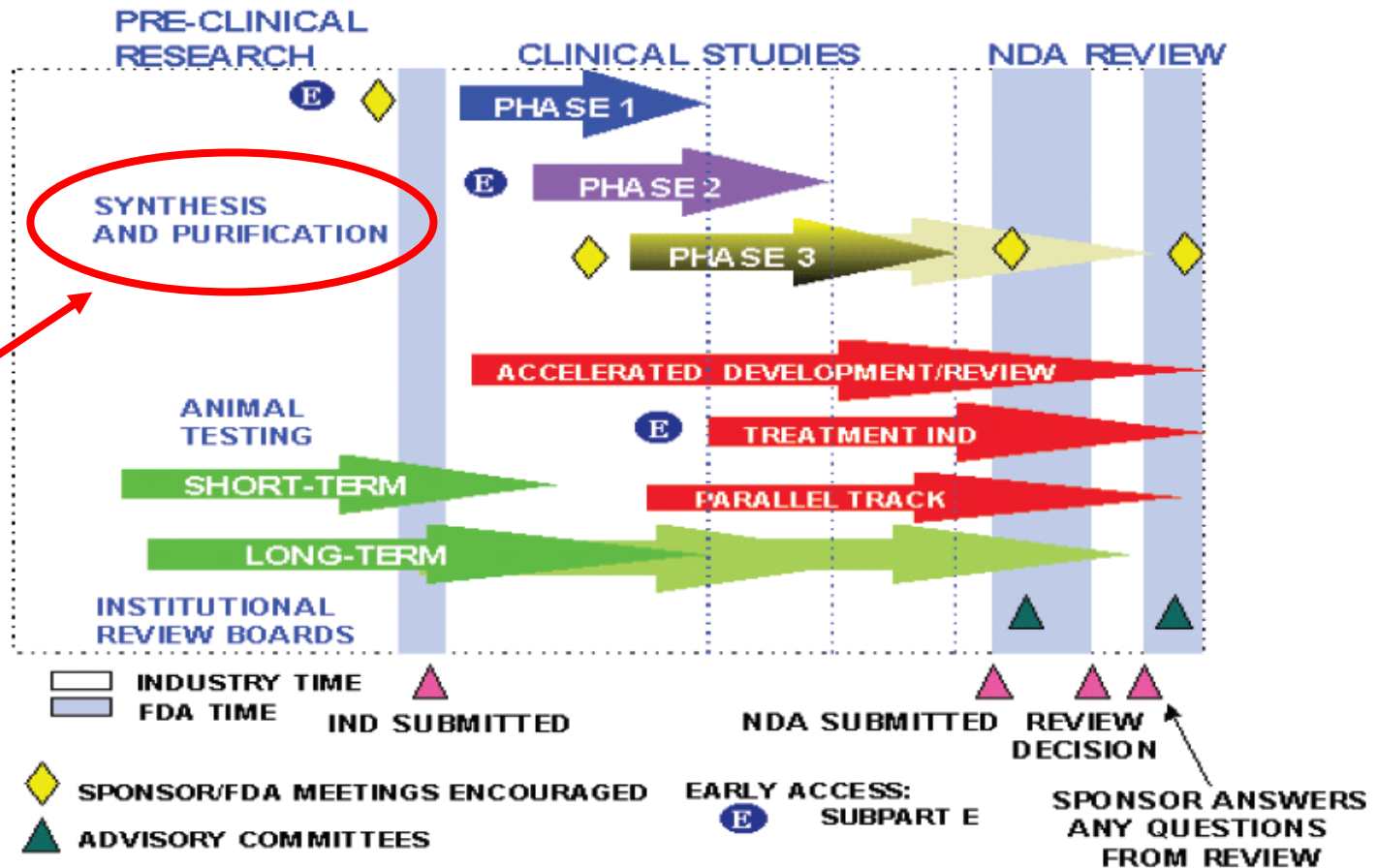
Common Abbreviations Used in this Presentation

| | |
|---------------------|---|
| <i>API</i> | Active Pharmaceutical Ingredient (drug substance) |
| <i>CMC</i> | Chemistry, Manufacturing, and Control |
| <i>CMO</i> | Contract Manufacturing Organization |
| <i>COA</i> | Certificate of Analysis |
| <i>CPP</i> | Critical process parameter |
| <i>DMF</i> | Drug Master File |
| <i>Drug Product</i> | Formulated pharmaceutical product (e.g., tablets) |
| <i>GLP</i> | Good Laboratory Practice |
| <i>GMP</i> | Good Manufacturing Practice |
| <i>ICH</i> | International Conference on Harmonisation |
| <i>IND</i> | Investigational New Drug Application |
| <i>NDA</i> | New Drug Application |
| <i>PAI</i> | Pre-Approval Inspection |

Major Components of API Development Programs



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Major Components of API Development Programs

- ◆ API Development Plan
- ◆ Selection of Resources including Suppliers and Contract Facilities
- ◆ Drug Substance Development – key technical aspects



- Structure and Characterization
- Physicochemical Properties
- Manufacture
- Impurities

- Controls
- Reference Standards
- Containers and Closures
- Stability

Major Components of API Development Programs

- ◆ Phase 0 (drug discovery)
 - lead compound
- ◆ Phase 0 (Nonclinical) – safety
- ◆ **Investigational application**
- ◆ API Development (API and process optimization and characterization)
 - Phase 1 Clinical Trials (safety)
 - Phase 2 Clinical Trials (safety and efficacy)
 - Phase 3 Clinical Trials (safety and efficacy)
- ◆ **Marketing application**
- ◆ Process validation and **commercialization**
- ◆ Postapproval activities



API Development – Question

- ◆ What is the most critical aspect of API development?

API Development – Question

- ◆ What is the most critical aspect of API development?
- ◆ **SUPPLIES FOR STUDIES**
- ◆ NO API = NO CTM = NO CLINICAL STUDIES
- ◆ Close interaction with nonclinical and clinical colleagues
 - Extension or extra arm to studies
 - New toxicology study needs to be completed

API Development – Phase 0

- ◆ Phase 0 - Drug Discovery
 - Search for lead compounds
 - Synthesize in sufficient purity for in vitro screening

- ◆ Phase 0 - Nonclinical
 - Selection of lead compound
 - Manufacture of supplies for toxicology studies
 - ◆ GMP not-required
 - ◆ Manufacturing instructions recorded, at a minimum, in controlled laboratory notebooks
 - Initial determination of API's safety (toxicity)



API Development – Phase 0 (continued)

◆ Phase 0 – Nonclinical (continued)

- Synthesis is based on development process (medicinal chemistry)
 - ◆ Often not appropriate for large scale manufacture
 - Equipment, Reagents and Solvents, Thermodynamic Considerations, Impurities
 - ◆ Initial feasibility evaluation of scale up
- Development of initial analytical methods (assay and purity)
 - ◆ Often simple HPLC area % (Impurity assessment is still key)
- Testing and release to preliminary specification
- No requirement for formal COA as results may be recorded in controlled notebooks
- Preliminary (prototype) stability studies

◆ Pre-IND meeting

API Development – Meetings with FDA

- ◆ Take advantage of all FDA feedback
- ◆ Standard FDA/Sponsor meetings are not just for clinical questions
 - Pre-IND, End of Phase 2/Pre-Phase 3, Pre-NDA
 - May 2009 *FDA Guidance for Industry* “Formal Meeting Between the FDA and Sponsors or Applicants”
 - May 2001 *FDA Guidance for Industry* “IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information”
- ◆ Excellent time to discuss key API issues
 - Physical properties (polymorphism and particle size)
 - Elucidation of structure
 - Control of stereochemical purity
 - Control and qualification of impurities
 - API Starting materials
 - Changes, changes, changes (it’s normal for development)

API Development – Phase 1 (Continued)

◆ Regulations

- November 1995, 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”

◆ Drug Substance Manufacturing

- Scale-up and Preparation of clinical trial material (small [lab or pilot] scale)
 - ◆ GMPs for manufacture: July 2008, FDA *Guidance for Industry* “CGMP for Phase 1 Investigational Drugs”
 - ◆ Manufacturing instructions recorded, at a minimum, in controlled laboratory notebooks but preferably in an approved batch record
 - ◆ Cleaning verification, if shared equipment is used

API Development – Phase 1 (Continued)

◆ Development Activities

- Initial Process Development
 - ◆ Scale-up
 - ◆ Evaluation of impurities
- Initial assessment of physiochemical properties and structural elucidation
- Selection (and initial audits) of suppliers and contract facilities
- Analytical Methods development (evaluation - stability indicating nature) – document development and changes (history)
- Start to know your impurities and impurity profile
 - ◆ Retain samples (as much as possible) – assess future changes
- Start to know your design space (changes which effect quality)
- Start development report (document changes with data)
- Stability of Clinical Batches

API Development – Phase 1 (Continued)

- ◆ Regulatory (DMF/IND) Submission Requirements
 - Description, Physical, Chemical, or Biological Characteristics
 - Name and Full Street Address of Manufacturer
 - General Method of Preparation of Drug Substance
 - Acceptance Limits and Analytical Methods Used to Assure the Identity, Strength, Quality, and Purity
 - Certificate of Analysis (Quality Unit released) [suggested]
 - Information to Support Drug Substance Stability During Toxicology Studies and Proposed Clinical Study(ies)

API Development – GMP Manufacture

- ◆ Drugs intended for human administration are required to be produced under current Good Manufacturing Practices (cGMP)
 - Modified Phase I requirements
- ◆ 21 CFR 210 and 21 CFR 211
- ◆ ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- ◆ Will discuss general requirements (when applied) today. Detailed discussion of GMP requirements part of subsequent teleconference.

API Development – Phase 2

◆ Regulations

- May 2003, FDA *Guidance for Industry* “INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information”

◆ Drug Substance Manufacturing

- Preparation of clinical trial material supplies (larger scale)
 - ◆ GMP control
 - ◆ Manufacturing instructions in an approved batch record
 - ◆ Formal COAs issued by Quality Unit
 - ◆ Cleaning verification, if shared equipment is used
 - ◆ Assessment of changes in sites and manufacturing process
 - ◆ Establishment of chemical equivalency of drug substances manufactured by revised or completely new processes

API Development – Phase 2 (Continued)

- ◆ Development activities
 - Continued process development (scale-up and optimization) including selection of the “Phase 3 and proposed commercial manufacturer and synthetic route”
 - Assessment of critical process parameters (CPPs)
 - ◆ Refine your design space (changes which effect quality)
 - Continued evaluation of impurities (RRFs)
 - ◆ Have retain samples (as much as possible) – assess future changes
 - Continued development of analytical methods (especially for changes)
 - Establishment of additional physicochemical properties
 - Refinement of approved specification based on historical data
 - Establishment of primary reference standard
 - Continuation of stability studies
 - Periodic audits of suppliers and contract facilities
- ◆ Regulatory
 - End of Phase 2/Pre-Phase 3 FDA Meeting

API Development – Phase 2 (Continued)

- ◆ Regulatory (DMF/IND) Submission requirements
 - General information
 - Manufacturing (highlight changes from Phase 1)
 - ◆ Control of Materials
 - ◆ Control of Critical Steps and Intermediates
 - Characterization (support structure and physical properties)
 - Specification (test methods and acceptance criteria)
 - Impurities (know, track, and predict them...changes)
 - Reference Standard (Purchased standard or in-house qualified)
 - Container Closure
 - Stability (support CTM and evaluate degradation)

Comparability Study for API Manufactured at Original and Alternate Site

- ◆ Applicable for major changes in development
 - Preparation of comparability (equivalence) protocol
 - Manufacture of batches at least on pilot scale at both sites or with both routes
 - Comparability of physical properties
 - Comparability of impurities
 - ◆ Similar profiles
 - ◆ Any new impurities
 - Comparison of batch analysis results according to specifications
 - Comparison of stability results according to specifications

Considerations for Outsourcing Use of CMOs

- ◆ CMOs provide resources and expertise
- ◆ Visit and Audit them
 - The future of your drug is on the line
- ◆ SUPPLY AGREEMENTS
- ◆ QUALITY AGREEMENTS
- ◆ **Key to success: Communication**

API Development – Phase 3

◆ Regulations

- May 2003, FDA *Guidance for Industry* “INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information”

◆ Drug Substance Manufacturing

- Preparation of clinical trial material supplies and registration stability batches (proposed commercial / pilot scale)
 - ◆ Full GMP controls
 - ◆ Manufacturing instructions in an approved batch record
 - ◆ Cleaning verification, if shared equipment is used
 - ◆ Assessment of changes in sites and manufacturing process
 - ◆ Establishment of chemical equivalency of drug substances manufactured by revised or completely new processes

API Development – Phase 3 (Continued)

- ◆ Development activities
 - Selection of proposed commercial manufacturing and testing facilities
 - Finalization of manufacturing process, in-process controls, and CPPs
 - Finalization and understanding of all API physicochemical properties
 - Final evaluation of impurities (characterization of profiles)
 - Full validation of analytical methods, including those used for in-process controls
 - Preparation and characterization of sufficient supplies of reference standards for drug substance, specified impurities, and major degradation product(s)
 - Establishment of final specification based on manufacturing history and batch analysis data
 - Continuation of stability studies, including those for registration batches, performed in accordance with approved protocols and in keeping with ICH guidelines
 - Audits of contract facilities including Mock PAI
- ◆ Regulatory
 - Pre-NDA FDA Meeting

API Development – Phase 3 (Continued)

- ◆ Regulatory (DMF/IND) Submission requirements
 - Complete API information (proposed commercial)
 - Manufacturing (highlight changes from Phase 2)
 - ◆ Control of Materials
 - ◆ Control of Critical Steps, CPPs, and Intermediates
 - Full API Characterization
 - Specification (test methods and acceptance criteria)
 - ◆ Impurities (know them, predict them, control them)
 - Reference Standard (Purchased standard or in-house qualified)
 - Container Closure
 - Stability (support CTM and registration [retest date])

API Development – Marketing Application

- ◆ The ultimate goal – Marketed product
 - API development should focus on marketing application (reverse engineering)
 - Full information on the API
 - The API information provided to US regulatory reviewers can be in the form of DMF (Type II – API) or marketing application (NDA/ANDA)
 - There are some typical differences between API development focused on a NDA vs ANDA
 - There are regional differences in CMC content within the CTD

API Development (NDA vs. ANDA)

◆ NDA

- Often de novo development in house

◆ ANDA

- Often drug substance purchased from CMO
- Often API is under DMF with restricted access to purchaser
- Same API regulatory and scientific requirements with respect to CMC
- Managing CMO is critical
 - ◆ Quality
 - ◆ Supply chain

API Development (to DMF or not to DMF)

- ◆ A Type II DMF and the NDA Drug Substance section are very similar (if not identical). The same format is used in both documents.
- ◆ The DMF is used for business/confidentiality reasons
- ◆ Confidentiality:
 - DMF provides clear ownership of the information
 - If the product is licensed and the API information can be kept confidential even when the IND is transferred.
 - If desired, a DMF may only include part of the process (proprietary).
- ◆ Business:
 - The DMF holder is responsible for regulatory submission maintenance.
 - Multiple application will reference the DMF.

API Development (CMC and the CTD)

◆ Can the Same Quality Sections be Submitted to Multiple Regions?

- Short answer: Essentially!
- But beware:
 - ◆ FDA requests a Methods Validation Section and Executed Batch Records; EU does not
 - ◆ EU requests an Expert Report for Module 2; FDA requests
 - ◆ QbR format for ANDAs
- Therefore, they are not all the same!

API Development Marketing Application – General Information

- ◆ **Focus on Module 3, but summary (or QbR) information related to API will be provided in Module 2 (Quality Overall Summary)**
- ◆ **3.2.S Drug Substance**
 - **3.2.S.1 General Information**
 - ◆ **3.2.S.1.1 Nomenclature**
 - ◆ **3.2.S.1.2 Structure**
 - ◆ **3.2.S.1.3 General Properties**

API Development Marketing Application - Manufacturing

◆ 3.2.S.2 Manufacture

– 3.2.S.2.1 Manufacturers

- ◆ *Full contact information for any company involved with manufacture and testing of the drug substance, including contractors.*

– 3.2.S.2.2 Description of Manufacturing Process and Process Controls

- ◆ *Provide a description of the manufacturing process and process controls, including the following:*
 - *A detailed flow diagram and narrative description of the process.*
 - *Any alternative processes should also be described.*
 - *In-process controls.*
 - *Reprocessing and/or reworking steps, if applicable.*

API Development Marketing Application - Control

- **3.2.S.2.3 Control of Materials**
 - ◆ *Starting materials, reagents, solvents, and auxiliary materials*
 - *Specification (tests and criteria) and justification*
 - ◆ *For biologically sourced materials, the source, manufacture, and characterization details should be included in Section 3.2.A.2.*
- **3.2.S.2.4 Control of Critical Steps and Intermediates**
 - ◆ *Isolated intermediates: specifications (tests and criteria).*
 - ◆ *Justification of critical in-process controls and operating parameters*
 - ◆ *Critical controls for reprocessing and reworking*

API Development

Marketing Application – Validation / Development

◆ **3.2.S.2.5 Process Validation and/or Evaluation**

- *Provide if process validation is required*
 - ◆ *Aseptic processing and sterilization*
- *Reprocessing or reworking procedures = validation*

◆ **3.2.S.2.6 Manufacturing Process Development**

- *The manufacturing process development*
- *Postapproval process changes (cross reference to clinical data)*

API Development

Marketing Application - Characterization

◆ 3.2.S.3 Characterization

– 3.2.S.3.1 *Elucidation of Structure and Other Characteristics*

- ◆ *Data to support general properties, absolute stereochemical configuration and physiochemical properties (polymorphism and particle size).*

– 3.2.S.3.2 *Impurities*

- ◆ *Inorganic (e.g., catalysts, heavy metals)*
- ◆ *Organic (e.g., intermediates, byproducts, degradation products, and residual solvents [USP <467>])*
 - *Cross-reference supporting nonclinical/clinical studies*
 - *Impurity identification studies including synthesis*
 - *Synthesis and characterization may be placed in Section 3.2.S.5 for reference standards of impurities*
 - *Attempts to identify unknowns*

API Development Marketing Application – Control

- ◆ **3.2.S.4 Control of Drug Substance**

- **3.2.S.4.1 Specifications**

- ◆ *Provide the tests, acceptance criteria, and a reference to the location of the analytical procedures that the drug substance must meet for release.*
- ◆ *Based on historical data, process capability and regulatory requirements*

- **3.2.S.4.2 Analytical Procedures**

- ◆ *Provide detailed analytical procedures for all tests used for the release of the drug substance.*

- **3.2.S.4.3 Validation of Analytical Procedures**

- ◆ *Validation - noncompendial procedures*
- ◆ *Include relevant chromatograms or spectra for the validations*
- ◆ *Copies of validation reports or summary information*
- ◆ *Transfer reports*

API Development Marketing Application - Control

◆ 3.2.S.4.4 Batch Analyses

- *Results from all relevant batches (e.g., clinical, nonclinical, and stability), including batches used to justify the specification*
- *References to developmental manufacturing processes (Section 3.2.S.2.6)*
- *References to or provision of historical analytical procedures*

◆ 3.2.S.4.5 Justification of Specification

- *Provide a summary of data from other sections.*
- *Specific topics to be addressed may include:*
 - ◆ *Justification of specification methods and acceptance criteria*
 - ◆ *Justification of any test not performed which would normally be expected for this type of drug substance*
 - ◆ *Justification of periodic quality indicator tests or in-process tests performed in lieu of drug substance tests*

API Development Marketing Application – Standards / Containers

- ◆ **3.2.S.5 Reference Standards or Materials**

- *Provide the preparation and characterization of reference standards used for testing the drug substance.*

- ◆ **3.2.S.6 Container Closure System**

- *Provide a detailed description of the packaging for the drug substance, including the identity of the materials of construction for each primary packaging component and a specification. Include bags, liners, drums, desiccants, etc.*

API Development Marketing Application - Stability

- ◆ **3.2.S.7 Stability**
 - **3.2.S.7.1 Stability Summary and Conclusions**
 - ◆ *Description of the stability protocol including photostability*
 - ◆ *Stability specification (acceptance criteria, and analytical procedures)*
 - ◆ *Summary of the data and conclusions (e.g., retest period)*
 - ◆ **3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment**
 - *Postapproval stability protocol and stability commitment*
 - ◆ **3.2.S.7.3 Stability Data**
 - *Provide a brief description of the test results obtained to date on primary and supporting batches.*
 - *Provide data and chromatograms from stress studies (e.g., forced degradation study). Information on analytical procedures (including historical) that are used only for stability studies should be included in this section.*
 - *Representative chromatograms following storage at long term conditions.*

API Development

Marketing Application – Appendices / Regional

◆ 3.2.A Appendices

– 3.2.A.1. Facilities and Equipment

- ◆ *For biotechnology or sterile drug substances, provide a facility diagram to illustrate the flow of materials during manufacture; a list of other products handled in the same areas; a summary of product-contact equipment and its use (i.e., dedicated or multiuse); information on preparation, cleaning, sterilization and storage of equipment and materials; and information on procedures and facility design to prevent cross-contamination.*
- ◆ *For nonsterile or nonbiotechnology drug substances, this section may be omitted.*

– 3.2.A.2. Adventitious Agents Safety Evaluation

- ◆ *Provide information assessing the risk of potential contamination with adventitious agents. For nonviral adventitious agents, provide information on avoidance and control of the agents such as BSE certification of raw materials. For viral adventitious agents, provide information from viral safety evaluation studies.*
- ◆ *If no adventitious agents are used, this section may be omitted.*

◆ 3.2.R Regional Information

- *Regional information such as executed batch records, comparability protocols, or method validation package for drug substance.*

API Development – Validation

◆ Process validation

- Required prior to commercial distribution
- Develop process validation protocol based on development activities and manufacturing design space (QbD principles) and continuous process verification/validation (lifecycle approach)

◆ Cleaning validation

- Dependant on use of dedicated equipment
- Other API's in your API
- Your API in other APIs

API Development – Postapproval

- ◆ April 2004 FDA *Guidance for Industry* “Changes to an Approved NDA or ANDA”
- ◆ **Major Change**
 - Has substantial potential to cause an adverse affect on a drug product’s identity, strength, quality, purity or potency.
 - Reporting category: **Prior Approval Supplement (PAS)**
- ◆ **Moderate Change**
 - Has moderate potential to cause an adverse affect on a drug product’s identity, strength, quality, purity or potency.
 - Reporting categories: there are two categories of moderate change:
 - ◆ **Changes Being Effected in 30 Days Supplement (CBE-30)**
 - ◆ **Changes Being Effected Supplement (CBE or CBE-0)**

API Development – Postapproval (continued)

◆ **Minor Change**

- Has minor potential to cause an adverse affect on the drug product's identity, strength, quality, purity or potency.
- Reporting category: **annual report**

◆ **Comparability Protocol**

- Used to reduce the reporting category for specified changes
- Includes tests, validation studies, and acceptable limits to demonstrate absence of adverse effect
- Submitted as a prior approval supplement or in an original application

API Development – Biological Products

- ◆ Biological APIs have inherently different properties
 - The steps of development and the analysis thereof are similar, but each class of biotechnology derived therapeutic agent has its own unique set of tests and criteria.
 - For example: The assay (content) measurement may require a measurement of activity when compared to a simple determination of how much material is present.
 - World wide regulatory authorities have provided class specific guidance for biotechnology APIs
 - ◆ **ICH Q5A(R1)** Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
 - ◆ **ICH Q5B** Quality of Biotechnological Products : Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
 - ◆ **ICH Q5C** Quality of Biotechnological Products : Stability Testing of Biotechnological/Biological Products
 - ◆ **ICH Q5D** Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
 - ◆ **ICH Q5E** Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

API Development – Biological Products

- ◆ FDA Guidance for Industry:
 - February 1999, For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma- Derived Biological Products, Animal Plasma or Serum-Derived Products
 - April 2008, Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
 - February 1996, Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
 - April 2008, FDA Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
 - August 1996, For The Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use
 - February 1997, Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use
 - September 2006, Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases
 - April 1995, Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology

API Development – Conclusions

- ◆ API development is an integral part of the overall drug development process
- ◆ Supply of API is critical to clinical trials
 - Interact with nonclinical and clinical teams (API necessary)
 - Retain samples for each batch (as much as possible)
 - ◆ There will be future changes
- ◆ Initiate API development with the NDA in mind (document)
 - Manage, assess, document and control changes
 - Development information should grow to be the marketing application
 - Watch impurities and physical properties closely
- ◆ DMFs can help protect confidentiality
- ◆ Communicate with your contractors
- ◆ Interact with FDA
- ◆ Biotechnology derived therapeutic agents have unique assessments required

Questions?

THANK YOU!

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