



Optimizing Your Chemistry, Manufacturing, and Controls Program



June 10, 2009

Objectives/Overview

- ◆ High-level Overview
- ◆ Components of CMC Programs
- ◆ CMC Activities at Various Phases of Development
- ◆ General CMC Activities for Drug Substances
- ◆ General CMC Activities for Drug Products
- ◆ Compliance Activities for CMC Programs
- ◆ Recap of Major Points
- ◆ Questions and Answers

Common Abbreviations Used in this Presentation

<i>API</i>	Active Pharmaceutical Ingredient; a.k.a. drug substance
<i>CMC</i>	Chemistry, Manufacturing, and Control
<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, injections, etc.)
<i>Final Product</i>	API or drug substance resulting from a specific manufacturing process

Common Abbreviations Used in this Presentation *(continued)*

<i>Finished Product</i>	Formulated pharmaceutical product (e.g. tablets, injections, etc.); a.k.a. drug product
<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

Assumptions

- ◆ Drug substance is a small molecule produced by chemical synthesis
- ◆ Drug product is a solid dosage form (simple tablet or capsule)
- ◆ No last-minute changes of suppliers, contract manufacturers, and contract laboratories (if applicable) during Phase 3 or immediately before NDA submission
- ◆ Scope of presentation covers up to NDA submission. Post-approval changes are not covered.

Major Components of CMC Programs (as applicable)

- ◆ Development Plan and Target Dates
- ◆ Selection of Suppliers, Contract Manufacturers, and Contract Laboratories
- ◆ Drug Substance

- Structure and Characterization
- Physicochemical Properties
- Manufacture
- Impurities

- Controls
- Reference Standards
- Containers and Closures
- Stability

Major Components of CMC Programs (as applicable) *(continued)*

- ◆ Drug Product
 - Dosage Form and Composition
 - Manufacture
 - Impurities
 - Controls
 - Container Closures
 - Stability
- ◆ Toxicology Studies
 - Drug substance
 - Dosing solutions (vehicles)
 - Controls
- ◆ Compliance
 - GLP
 - GMP



Major Phases of Development of a Pharmaceutical Product

◆ Preclinical

- Drug discovery
- Drug screening
- Designation of drug as clinical candidate

◆ Clinical/Nonclinical

- Phase 1 (safety)
- Phase 2 (safety, efficacy)
- Phase 3 (efficacy, long-term safety, and proposed commercial dose)

Development Plan and Target Dates

◆ Regulatory Milestones

- Pre-IND Meeting
- Submission of DMF (if applicable)
- Submission of IND
- Phase 1 clinical trial(s)
- DMF Amendment (if applicable)
- IND Amendment (as necessary)
- Phase 2 clinical trials
- End-of Phase 2 Meeting

Development Plan and Target Dates

(continued)

◆ Regulatory Milestones

- DMF Amendment (if applicable)
- IND Amendment (as necessary)
- Phase 3 clinical trials
- Pre-NDA Meeting
- DMF Amendment (if applicable)
- Submission of NDA
- Approval of NDA

Development Plan and Target Dates

(continued)

◆ CMC Milestones

- Selection of suppliers, contract manufacturer(s) and contract laboratories
- Technology transfer
- Development and validation of analytical and (if necessary) microbiological tests methods
- Establishment of impurity profile
- Manufacture of drug substance and drug product

Development Plan and Target Dates

(continued)

◆ CMC Milestones

- Establishment of specifications
- Evaluation of batches
- Selection of container/closure systems for drug substance and drug product
- Stability studies
- Process validation

Development Plan and Target Dates

(continued)

◆ Compliance Milestones

- Quality agreements with key suppliers, contract manufacturers, and contract laboratories
- Letters of authorization to reference DMFs *(if applicable)*
- Qualification of key suppliers, contract manufacturers, and contract laboratories

Development Plan and Target Dates

(continued)

◆ Compliance Milestones

- Monitoring of quality activities (batch release, investigations, reprocessing, etc.)
- Audits of key suppliers, contract manufacturers, and contract laboratories
- PAI readiness

CMC/Compliance Activities During Preclinical Stage

◆ Drug Substance

- Preparation of batches at laboratory scale
- No requirement for GMP controls
- Manufacturing instructions recorded, at a minimum, in controlled laboratory notebooks
- Initial development of analytical methods
- No requirement for method validation
- Preliminary specification (wide acceptance criteria)



CMC/Compliance Activities During Preclinical Stage

◆ Drug Substance *(continued)*

- Testing and release
- No requirement for formal COA as results may be recorded in controlled notebooks
- Preliminary (prototype) stability studies
- No requirement for preliminary stability studies to be performed in accordance with ICH guidelines



CMC/Compliance Activities During Preclinical Stage

◆ Drug Product (Dosing Vehicle)

- Preparation of dosing vehicles under laboratory conditions
- No requirement for GMP controls
- Partial requirements for GLP controls (e.g., records and approvals)
- Manufacturing instructions recorded, at a minimum, in controlled laboratory notebooks
- Initial development of analytical methods
- No requirement for method validation
- Preliminary specification (wide acceptance criteria)



CMC/Compliance Activities During Preclinical Stage

◆ Drug Product (Dosing Vehicle) *(continued)*

- Testing and release
- No requirement for formal COA as results may be recorded in controlled notebooks
- Preliminary (prototype) stability studies
- No requirement for preliminary stability studies to be performed in accordance with ICH guidelines



CMC/Compliance Activities During Phase 1

◆ Drug Substance

- Characterization of drug substance and elucidation of its structure
- Establishment of limited physicochemical properties (e.g., solubility, appearance, chirality, isomerism, pH properties, crystallinity, potential for polymorphism, etc.)
- Selection of suppliers, contract manufacturer, and contract laboratory
- Qualification and audits of key suppliers, contract manufacturer, and contract laboratory



CMC/Compliance Activities During Phase 1

◆ Drug Substance *(continued)*

- Preparation of batches at laboratory or pilot scale
- Requirement for GMP controls applicable to Phase 1 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



CMC/Compliance Activities During Phase 1

◆ Drug Substance *(continued)*

- Initial characterization of impurity profiles (i.e., inorganic, organic, and organic volatile impurities)
- Development and partial validation of analytical methods (accuracy, precision, linearity, stability-indicating properties)
- Initial preparation and characterization of primary reference standard for drug substance
- Establishment of approved preliminary specification (wide acceptance criteria; avoid “report results” or “for information only”)



CMC/Compliance Activities During Phase 1

◆ Drug Substance *(continued)*

- Testing and release
- Testing results may be recorded in controlled notebooks or data sheets
- Formal COA issued by Quality Unit
- Stability studies performed in accordance with approved protocols and in keeping with ICH guidelines
- Establishment of preliminary retest date
- Preparation and submission of initial DMF, if applicable
- Preparation and submission of IND
- Continued development and optimization of manufacturing process and scale
- Continued characterization of impurity profiles



Sample Release Specification for API During Phase 1

Test	Acceptance Criteria	Analytical Procedure
Appearance	White to off-white powder	Visual observation
Identification:	Matches spectrum of reference standard	FTIR
a. IR Spectrum		
b. Retention Time Comparison	Matches retention time of reference standard	HPLC
Assay (on dried basis)	97.0 – 103.0%	HPLC
Related Substances :	NMT 0.5%	HPLC
a. Related Substance A		
b. Related Substance B	NMT 0.5%	
c. Other Related Substances	NMT 2.0%	
d. Total Related Substances	NMT 3.0%	
Residual Solvents	NMT 1000 ppm	GC
a. Solvent A		
b. Solvent B	NMT 500 ppm	
Water Content	2.0 – 3.0%	KF
Residue on Ignition	NMT 0.2%	USP
Heavy Metals	NMT 20 ppm	USP

CMC/Compliance Activities During Phase 1

◆ Drug Product

- Selection of suppliers, contract manufacturer, and contract laboratory
- Qualification and audits of key suppliers, contract manufacturer, and contract laboratory
- Excipient compatibility studies
- Selection of prototype formulation
- Preparation of batches at laboratory or pilot scale
- Requirement for GMP controls applicable to Phase 1 drugs

CMC/Compliance Activities During Phase 1

◆ Drug Product *(continued)*

- Manufacturing instructions recorded, at a minimum, in controlled laboratory notebooks but preferably in an approved batch record
- Cleaning verification, if shared equipment is used
- Development and partial validation of analytical methods (accuracy, precision, linearity, stability-indicating properties)
- Establishment of approved preliminary specification (wide acceptance criteria; avoid “report results” or “for information only”)
- Testing and release
- Testing results may be recorded in controlled notebooks or data sheets

CMC/Compliance Activities During Phase 1

◆ Drug Product *(continued)*

- Formal COA issued by Quality Unit
- Stability studies performed in accordance with approved protocols and in keeping with ICH guidelines
- Establishment of preliminary expiration date (i.e., at least stable for duration of clinical trial)
- Preparation and submission of initial IND
- Continued development and optimization of manufacturing process and scale
- Consideration of alternate dosage forms for Phase 2 and Phase 3

CMC/Compliance Activities During Phase 2

◆ Drug Substance

- Establishment of additional physicochemical properties
- Selection of alternate suppliers, contract manufacturer, and contract laboratory (as applicable)
- Periodic audits of key suppliers, contract manufacturer, and contract laboratory
- Continued development and optimization of manufacturing process



CMC/Compliance Activities During Phase 2

◆ Drug Substance *(continued)*

- Continued preparation of batches at laboratory or pilot scale using most current manufacturing process
- Requirement for GMP controls
- Manufacturing instructions in an approved batch record
- Cleaning verification, if shared equipment is used
- Establishment of chemical equivalency of drug substances manufactured by revised or completely new processes

CMC/Compliance Activities During Phase 2

◆ Drug Substance *(continued)*

- Continued characterization of impurity profiles (especially new impurities as a result of changes to manufacturing process)
- Development and validation of analytical methods based on changes to manufacturing processes
- Preparation and characterization of primary reference standard for drug substance
- Establishment of approved specification based on manufacturing history and batch analysis data
- Testing and release
- Testing results may be recorded in controlled notebooks or data sheets
- Formal COA issued by Quality Unit

CMC/Compliance Activities During Phase 2

◆ Drug Substance *(continued)*

- Continuation of stability studies performed in accordance with approved protocols and in keeping with ICH guidelines
- Revision and establishment of retest date based on available stability data
- Preparation and submission of DMF Amendment, if applicable
- Preparation and submission of IND Amendment for any changes made

CMC/Compliance Activities During Phase 2

◆ Drug Substance *(continued)*

- Continued development and optimization of manufacturing process and scale
- Continued characterization of impurity profiles
- Consideration of alternate suppliers and/or manufacturing processes for Phase 3 and commercialization

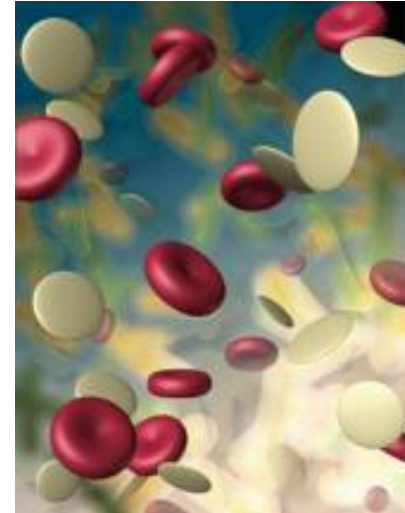
Comparability Study for API Manufactured at Original and Alternate Site

- ◆ Preparation of protocol
- ◆ Manufacture of batches at least on pilot scale at both sites
- ◆ Comparison of impurity profiles: similar; no new impurities
- ◆ Comparison of release results according to specifications
- ◆ Comparison with historical batches
- ◆ Performance of stability studies
- ◆ Comparison of stability results

CMC/Compliance Activities During Phase 2

◆ Drug Product

- Selection of alternate suppliers, contract manufacturer, and contract laboratory
- Periodic audits of key suppliers, contract manufacturer, and contract laboratory
- Continued development and optimization of manufacturing process



CMC/Compliance Activities During Phase 2

◆ Drug Product *(continued)*

- Selection of Phase 2 formulation
- Preparation of batches at laboratory or pilot scale using most current formulation and manufacturing processes
- Requirement for GMP controls
- Manufacturing instructions in an approved batch record
- Cleaning verification, if shared equipment is used
- Establishment of chemical equivalence of same drug product formulation manufactured by revised or completely new processes

CMC/Compliance Activities During Phase 2

◆ Drug Product *(continued)*

- If a different formulation or a different contract manufacturer has been used, comparison of dissolution and impurity profiles
- Development and validation of analytical methods based on changes to manufacturing processes
- Establishment of approved specification based on manufacturing history and batch analysis data
- Testing and release
- Testing results may be recorded in controlled notebooks or data sheets
- Formal COA issued by Quality Unit

CMC/Compliance Activities During Phase 2

◆ Drug Product *(continued)*

- Continuation of stability studies performed in accordance with approved protocols and in keeping with ICH guidelines
- Revision and establishment of expiration date based on available stability data
- Preparation and submission of IND Amendment for any changes made
- Continued development and optimization of manufacturing process and scale
- Consideration of alternate suppliers and/dosage forms for Phase 3 and commercialization

Comparability Study for Drug Product Manufactured at Original and Alternate Site

- ◆ Preparation of protocol
- ◆ Manufacture of batches at least on pilot scale at both sites
- ◆ Comparison of impurity profiles: similar; no new impurities
- ◆ Comparison of release results according to specifications
- ◆ Comparison with historical batches
- ◆ Performance of stability studies
- ◆ Comparison of stability results

CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Substance

- Finalization and understanding of all physicochemical properties
- Appointment of primary and alternate suppliers, contract manufacturers, and contract laboratories (as applicable)
- Audits of key suppliers, contract manufacturers, and contract laboratories in preparation for PAIs
- Finalization of manufacturing process and in-process controls
- Establishment of CPPs
- Preparation of registration batches using final manufacturing process
- Requirement for full GMP controls



CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Substance *(continued)*

- Manufacturing instructions in an approved batch record
- Finalization of characterization of impurity 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

CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Substance *(continued)*

- Testing and release
- Testing results may be recorded in controlled notebooks or data sheets
- Formal COA issued by Quality Unit
- Continuation of stability studies, including those for registration batches, performed in accordance with approved protocols and in keeping with ICH guidelines

CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Substance *(continued)*

- Revision and establishment of expiration date based on available stability data
- Preparation and submission of DMF Amendment, if applicable
- Preparation and submission of NDA
- Validation of manufacturing process (not required during Phase 3 or at the time of submission)
- Cleaning validation, if shared equipment is used
- Mock PAI
- PAI

CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Product

- Appointment of primary and alternate suppliers, contract manufacturers, and contract laboratories (if applicable)
- Audits of key suppliers, contract manufacturers, and contract laboratories in preparation for PAIs
- Finalization of manufacturing process and in-process controls
- Establishment of CPPs
- Preparation of registration batches at a suitable scale using final manufacturing processes
- Requirement for full GMP controls



CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Product *(continued)*

- Manufacturing instructions in an approved batch record
- Full validation of analytical methods, including those for in-process controls
- Preparation and characterization of sufficient supply of reference standard for at least the major degradation product
- Establishment of final specification based on manufacturing history and batch analysis data
- Testing and release

CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Product *(continued)*

- Testing results may be recorded in controlled notebooks or data sheets
- Formal COA issued by Quality Unit
- Continuation of stability studies, including those for registration batches, performed in accordance with approved protocols and in keeping with ICH guidelines
- Revision and establishment of expiration date based on available stability data

CMC/Compliance Activities During Phase 3 and NDA

◆ Drug Product *(continued)*

- Validation of manufacturing process (not required during Phase 3 or at the time of submission)
- Cleaning validation, if shared equipment is used
- Mock PAI
- PAI

Scope of Typical Mock PAI

- ◆ Review all documentation in support of data submitted in NDA
 - Batch records for registration batches (and validation batches, if submitted)
 - In-process testing results and comparison with raw data for registration batches (and validation batches, if submitted)
 - Release testing results and comparison with raw data for registration batches (and validation batches, if submitted)
 - Stability testing results for registration batches
 - Review of deviations, OOS investigations, reprocessed and/or reworked batches, and so forth



Scope of Typical Mock PAI *(continued)*

- ◆ Review of process validation protocol and results
 - Development reports
 - Critical process parameters and justifications for these

Scope of Typical Mock PAI *(continued)*

- ◆ Review of systems at site(s)
 - Quality system
 - ◆ Quality Unit responsibilities
 - ◆ SOPs
 - ◆ Training programs and training records
 - Building and Facilities system
 - Materials system
 - Production system
 - Packaging and Labeling system
 - Laboratory Control system

Scope of Typical Mock PAI *(continued)*

- ◆ Miscellaneous reviews

Recap of Major Points

- ◆ This has been a high-level overview of CMC activities
- ◆ CMC activities include compliance activities
- ◆ Level and depth of activities depend on the stage of development
- ◆ As the development moves from Phase 1 to Phase 3 the controls need to be tightened



Recap of Major Points *(continued)*

- ◆ Changes in manufacturing processes or sites are not recommended during Phase 3
- ◆ Specifications should reflect not only commonly accepted levels (e.g., per ICH guidelines) but also manufacturing capabilities and batch history



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THANK YOU!