CMC 101: Introduction to the Chemistry, Manufacturing, and Controls Sections of a Regulatory Dossier

Dr. RS Robin Robinett
Merck & Co., Inc.
So…. What is my background?

• Education
  – Biochemistry – BS
  – Chemical Engineering – BS, MS, PhD

• AMWA Certifications
  – Editing & Writing Certification
  – Pharmaceutical Certification
  – Regulatory & Research Advance Certification

• Areas of Experience
  – Medical Devices (i.e., diagnostic testing)
  – Pharmaceutical (i.e., assay development, assay validation, & clinical trial sample testing)
  – Vaccine (i.e., assay development, assay validation, process development, process validation, CMC)
  – Biologics (i.e., CMC)

• CMC Experience
  – Clinical Trial Applications (>300 submission in >15 vaccine/biological products)
  – Marketing Applications (9 major market, submissions in >10 MOW in 6 vaccine/biological products)
  – Post-Market Applications (5 major market submissions in 3 vaccine/biological products)
So…. What is my background?

- **Writing**
  - Journal articles (14)
  - Abstracts/posters (18)
  - Presentations at major meetings (9)
  - Book chapters (2)

- CMC is very exciting and challenging
- Learning about CMC is not so exciting
Chocolate is fun!!!! So we will learn about CMC by working with examining how CMC would be prepared for a D-ration bar.
Assignment: Create Module 3 for D-Ration Bar

• Colonel Logan had four requirements for the D ration Bar.
  – Weigh 4 ounces (112 g)
  – Be high in food energy value (1800 calories or minimum sustenance recommended each day)
  – Be able to withstand high temperatures (heat-resistant up to 120 °F or 49 °C)
  – Taste "a little better than a boiled potato"

• Ingredients
  – Chocolate (API or NCE or active)
  – Sugar
  – Oat flour
  – Cacao fat
  – Skim milk powder
  – Artificial flavoring

• Packaging
  – The 4-ounce (112 g) bars' boxes were covered with an anti-gas coating and were
  – packed 12 to a cardboard carton, which was also coated
  – cartons were packed 12 to a wooden crate for a total of 144 bars to a crate.
What We Will Cover

- CTD Pyramid
  - Module 2.3
  - Module 3

- Nomenclature
  - Drug Substance – active pharmaceutical/biological ingredient
  - Drug Product – product that is marketed
  - Appendix
    - Facilities Information
    - Adventitious Agents
    - Excipients
  - Regional

- Module 3 CMC Sections
  - Chemistry
  - Manufacturing
  - Controls

- Typical Module 3 Submission Timeline
CTD Pyramid
The Common Technical Document is organized into five modules.

- Module 1 has region-specific information and is intended only for that region.
- Module 2 is a summary of quality (CMC), safety (nonclinical), and efficacy (clinical) information.
- Modules 3, 4, and 5 have the details for quality, safety, and clinical, respectively.
Guidance on CMC Content

• ICH harmonized Table of Content, not content
• ICH guidance document gives general guidelines but there is no specific good source for exact content
• Content varies widely due to product type
  – Pharmaceutical
  – Biologics
  – Vaccine
  – Biosimilars
  – Generics
Guidance on Content

• Level of detail is dependent upon
  – Type of Product
    • Well characterized (pharms) – least content
    • Somewhat characterized (biologics)
    • Not characterized (vaccines) – most content
  – Country and Their Specific Requirements
  – Stage of the Program
    • FIH IND – (least content)
    • Phase 2B/Phase 3 IND
    • Marketing Application – (most content)
    • Post-Marketing – (depends upon topics)
# CMC Section Reference Sheet

<table>
<thead>
<tr>
<th>Section</th>
<th>Drug Substance (3.2.S)</th>
<th>Drug Product (3.2.P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General Information</td>
<td>Description/Composition</td>
</tr>
<tr>
<td>2</td>
<td>Manufacturing</td>
<td>Pharmaceutical Development</td>
</tr>
<tr>
<td></td>
<td>2.6  DS Development</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Characterization/Impurities</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>4</td>
<td>Control of Drug Substance</td>
<td>Control of Excipients</td>
</tr>
<tr>
<td></td>
<td>• Specifications</td>
<td>• Specifications</td>
</tr>
<tr>
<td></td>
<td>• Assay Descriptions</td>
<td>• Assay Descriptions</td>
</tr>
<tr>
<td></td>
<td>• Assay Validation</td>
<td>• Assay Validation</td>
</tr>
<tr>
<td></td>
<td>• Batch Analysis</td>
<td>• Batch Analysis</td>
</tr>
<tr>
<td></td>
<td>• Justification of Specs</td>
<td>• Justification of Specs</td>
</tr>
<tr>
<td>5</td>
<td>Reference Standards or Materials</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Container Closure System</td>
<td>Reference Standards or Materials</td>
</tr>
<tr>
<td>7</td>
<td>Stability</td>
<td>Container Closure System</td>
</tr>
<tr>
<td></td>
<td>• Stability Summary</td>
<td>• Stability Summary</td>
</tr>
<tr>
<td></td>
<td>• Commitments</td>
<td>• Commitments</td>
</tr>
<tr>
<td></td>
<td>• Stability Data</td>
<td>• Stability Data</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Stability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stability Summary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Commitments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stability Data</td>
</tr>
</tbody>
</table>
Nomenclature
Nomenclature: API/NCE/Active

- **API**: active pharmaceutical ingredient
- **NCE**: new chemical entity
- **Active**: biological material that elicits a response in the body
  - Peptide – two or more amino acids
  - Protein – complex combination of amino acids
  - Recombinant Protein – genetically engineered protein commonly grown in *E. coli* or *S. aureus*
  - Nucleic Acid – DNA or RNA
  - Virus – disease causing agent made up DNA or RNA surrounded by a protein coat

⇒ Theobroma cacao
Drug Substance vs Drug Product

**Drug Substance**

- Active ingredient intended to furnish pharmacologic 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 body
  - Liquid
  - Powder

**Drug Product**

- Dosage form that contains an active drug ingredient or placebo.
Drug Substance vs Drug Product

Drug Substance

- Active ingredient intended to furnish pharmacologic 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 body
  - Liquid or powder containing
    - Chemical entity
    - Virus particles
    - Proteins
    - Nucleic acids

Drug Product

- Dosage form that contains an active drug ingredient or placebo.
  - Liquid
    - Elixir
    - Injectable
    - Drops
    - Gel caps
  - Powder
    - Tablet
    - Capsule
    - Lyophilized powder
  - Ointment
  - Suppository
Appendix – Facilities Information (A1)

For Biotech

- Diagrams provided illustrating the flow in and out of manufacturing areas
  - Raw materials, personnel, waste, intermediate(s)
- Information on other products manufactured in the area
  - List of products, type, manufacturing schedules
- Description of product-contact equipment including cleaning information (single/multi-use)
  - Tanks, lines, fermenters, bottles
- Information on design features
  - Area classifications (Class 100/Class A), features to prevent cross contamination
Appendix – Adventitious Agents (A2)

- **Non-Viral - Information about the avoidance of**
  - TSE/BSE (spongiform encephalopathy agents)
  - Bacteria
  - Mycoplasma
  - Fungi

- **Viral**
  - Viral Evaluation Studies
    - Materials of Animal Origin (e.g., milk, hair, hooves, bones, BSA)
    - Materials of Human Origin (e.g., blood, organs)
  - Viral Clearance Studies
Appendix – Novel Excipients (A3)

• A common is a novel adjuvant (material not currently licensed as an adjuvant)

• Or maybe Oatmeal???
Regional Section

• **US**
  - Environmental exemptions (IND)
  - Executed batch records (BLA)

• **EU**
  - Viral safety dossier, TSE/BSE Declaration, GMP certificates (CTA)
  - Materials of Animal Origin Tables, Table A and Table B (MAA)

• **Canada**
  - Executed batch records (MAA)
Module 3 CMC Sections
CMC or Quality Sections

• **C: Chemistry** – Composition of product

• **M: Manufacturing** – How we make it

• **C: Controls** – How we ensure it is what we say it is
C: Chemistry

- General Information (S1)
- Characterization (S3)
- Composition (P1)
• S1.1: Nomenclature
  – Compendial names, chemical names, laboratory names, other nonproprietary names

• S1.2: Structure
  – NCE: stereochemistry, molecular formula, and molecular mass
  – Biotech: amino acid sequence, protein structure, post-translational modification, nucleic acid sequence

• S1.3: General Properties of Drug Substance
  – NCE: physicochemical and other relevant properties
  – Biotech: Biological activity
The nomenclature that has been used for D Ration drug substance is provided in Table 1.

### Table 1  Nomenclature for D Ration Drug Substance

<table>
<thead>
<tr>
<th>Name Classification</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code Name</td>
<td>HC-1234</td>
</tr>
<tr>
<td>CAS Name</td>
<td>83-67-0</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Theobromine cacao</td>
</tr>
<tr>
<td>Trade Name</td>
<td>D Ration Bar</td>
</tr>
<tr>
<td>ATC Code</td>
<td>C03BD01 R03DA07</td>
</tr>
<tr>
<td>Drug Bank</td>
<td>DB01412</td>
</tr>
<tr>
<td>IUPAC Name</td>
<td>3,7-dimethyl-1H-purine-2,6-dione</td>
</tr>
</tbody>
</table>
NCE: stereochemistry, molecular formula, and molecular mass

<table>
<thead>
<tr>
<th>Chemical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
</tr>
<tr>
<td>Molecular Mass</td>
</tr>
</tbody>
</table>

Source: Wikipedia - Theobromine
S1.3 General Properties

• Cocoa Butter
  • Brittle fracture below 20 °C
  • A melting point about 35 °C
  • Softening around 30–32 °C

Source: International Cocoa Organization; http://www.icco.org/
Characterization (S3)

- **S3.1: Elucidation of Structure and other Characteristics**
  - NCE: confirmation of structure, stereochemistry, potential polymorphs
  - Biotech: primary, secondary, and higher-order structure, post-translational forms, purity, bioactivity, immunochemical properties

- **S3.2: Impurities**
  - Anything that is not intentionally added
Elucidation of Structure and other Characteristics

• Characterization Studies (example methods)
  – CD: circular dichroism
  – FRET: fluorescence resonance energy transfer
  – FTIR: Fourier-transform infrared spectroscopy
  – GC-MS: gas chromatography-mass spectrometry
  – ICP: inductively coupled plasma
  – LC-MS: liquid chromatography-mass spectrometry
  – MFI: micro-flow imaging
  – NMR: nuclear magnetic resonance
  – SEM: scanning electron microscopy
  – TEM: transmission electron microscopy
Impurities

• Anything that is brought into the process with a raw material or excipient that was not intentional

Oat Husks
Description and Composition of Drug Product (P1)

- Description of the Dosage Form
- Composition
- Description of Accompanying Reconstitution Diluents
- Type of Container and Closure
  - Used for the dosage form
  - Used for accompanying reconstitution diluent, if applicable
HC-1234 drug product (DP) is a nonsterile heavy paste formed into bars by pressing into molds. Bars contain 4 oz of chocolate paste. Route of administration is primarily oral with an alternate route of melting the bar in hot water prior to drinking. The composition of the DP is presented in Table 1.

Table 1 Composition of HC-1234 Drug Product

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Compendial Grade</th>
<th>Target Amount (parts)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chocolate Liquor (&gt; 54% cocoa fat)</td>
<td></td>
<td>160</td>
<td>It’s a chocolate bar</td>
</tr>
<tr>
<td>Sugar</td>
<td>USP, Ph. Eur.</td>
<td>Just enough</td>
<td>Make it palatable</td>
</tr>
<tr>
<td>Oat Flour</td>
<td></td>
<td>30</td>
<td>Increase melting temperature</td>
</tr>
<tr>
<td>Cacao Butter</td>
<td></td>
<td>160</td>
<td>Add calories</td>
</tr>
<tr>
<td>Skim Milk Powder</td>
<td>USP, Ph. Eur.</td>
<td>20</td>
<td>Make taste better</td>
</tr>
<tr>
<td>Vanillin Crystals</td>
<td>USP, Ph. Eur.</td>
<td>70</td>
<td>Make taste better</td>
</tr>
<tr>
<td>Thiamine Hydrochloride</td>
<td>USP, Ph. Eur.</td>
<td>1/6</td>
<td>Prevent beriberi</td>
</tr>
</tbody>
</table>
CMC or Quality Sections

- **C**: Chemistry – Composition of product
- **M**: Manufacturing – How we make it
- **C**: Controls – How we ensure it is what we say it is
M: Manufacturing

- Manufacturing: S2 and P3
  - Materials (S2.3 and P4)
  - Manufacturer (S2.1 and P3.1)
  - Manufacturing Process (S2.2 and P3.3)
  - Manufacturing Process Validation (S2.5 and P3.5)
  - Manufacturing Process Controls (S2.4 and P3.4)
- Development: S2.6 and P2
- Container Closure: S6 and P7
Manufacturing Process (S2.2 and P3.3)

- **RAW MATERIALS**
  - DS Process with Many Steps
  - Excipients
- Drug Substance (active)
- DP Process with Many Steps
- Drug Product (marketed material)
Materials (S2.3 and P4)

- **Raw Materials (bought from a vendor or made in-house)**
  - Cocoa Beans

- **Drug Substance**
  - Chocolate Liquor (> 54% cocoa fat)

- **Excipients**
  - Sugar
  - Oat Flour
  - Skim Milk Powder
  - Vanillin Crystals
  - Thiamine Hydrochloride
Raw Materials (S2.3)

- S2.3 Control of Materials
- List of materials used in the manufacture of the drug substance and where each is used
  - Raw Materials (materials bought from a vendor)
  - Starting Materials (materials made in house)
    - Cell Banks
    - Master Seeds
  - Solvents (material that substance that dissolves a solute)
  - Reagents (a substance or mixture for use in chemical analysis or other reactions)
  - Catalysts (a substance that increases the rate of a chemical reaction without itself undergoing any permanent chemical change)
Excipients (P4)

• P4 Control of Excipients
  – Natural or synthetic substance formulated with the active ingredient
    • Bulking up formulations that contain potent active
    • Confer a therapeutic enhancement (e.g., facilitating drug absorption or solubility.
    • Aid in the manufacturing process (e.g., make powder flow-ability, create nonstick properties, allow lyophilization)
    • Improve stability over the expected shelf life
The site responsible for manufacturing, testing, packaging, and releasing D Ration bars is:

The Hershey Company
100 Crystal A Drive
P.O. Box 810
Hershey, PA 17033

Note: manufacturing, testing, packaging, and release sites may be different.
Manufacturing Process (S2.2 and P3.3)

DRUG SUBSTANCE PROCESS

Drug Substance

Excipients
- Sugar
- Oat flour
- Milk
- Vanillin
- Cocoa Butter

DRUG PRODUCT PROCESS

Drug Product

D-ration bar
Cocoa Beans

Raw Material Processing, not Drug Substance Processing

1. cacao tree, ripe red pods
   - grown in S. America, Africa, Indonesia

2. pods harvested, white cocoa beans

3. beans fermented

4. spread in sun to dry

5. put in large sacks

6. transported by train or lorry

⇒ Not described in submission
Manufacturing Process Validation (S2.5 and P3.5)

• Process validation is defined as “the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product”.*

• Process performance qualification (PPQ) lots are prepared to confirm manufacturing process performance expectations and may include:
  – Filter qualifications
  – Critical equipment and component qualification
  – Process simulations (media challenges)
  – Shipping qualification

* FDA’s Guidance for Industry: Process Validation: General Principles and Practices
Manufacturing Process Controls (S2.4 and P3.4)

• CPP (Critical Processing Parameter)
  – Physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product.

• CQA (Critical Quality Attribute)
  – Process inputs that have a direct and significant influence on CQAs when they are varied within regular operation range.

• PAR (Proven Acceptable Range)
  – A CPP that has been determined to be achievable and appropriate for the process or processes with which it is associated.

• NOR (Normal Operating Range)
  – The target and range at which a process parameter is controlled.
• S2.6 Manufacturing Process Development
  – Changes made to drug substance during scale-up

• P2 Manufacturing Process Development
  – Changes made to drug product during scale-up
Development (S2.6 & P2)

- S2.6 Manufacturing Process Development
  - Changes made to drug substance during scale-up

- P2 Pharmaceutical Development
  - P2.1 Components of the Drug Product
    - Drug Substance
    - Excipients
  - P2.2 Drug Product
    - Formulation Development
    - Overages
    - Physiochemical and Biological Properties
    - Manufacturing Process Development
    - Container Closure System
    - Microbial Attributes
    - Compatibility
Pharmaceutical Development (P2)

- **P2.2 Drug Product**
  - **Formulation Development**
    - Original 12-ounce bar of equal parts of bitter chocolate, sugar, and peanut butter was palatable but had poor keeping qualities, was thirst-provoking, and had poor acceptance.
  - **Manufacturing Process Development**
    - Heavy paste could not flow at any temperature requiring the development of special processing methods and machinery where material was pressed into moulds.
    - Automated process was required due to imminent war.
  - **Container Closure System**
    - Three 4-ounce bars sealed in parchment paper.
    - Possible damage by poison gas required new specifications where bar was placed in a heavy cellophane bag and individual cardboard carton, 12 waxed cartons in a master carton, and 12 master cartons in a wooden case.
Container Closure

Drug Substance

Stainless Steel Tanks

Drug Product

Primary Packaging (paper)

Secondary Packaging (crate)
Container Closure – (S6)

• What touches the API/NCE/active
• Considerations
  – Liquid? Powder? Crystal?
  – Storage conditions – room temp, refrigerated, frozen?
• Typical Storage Systems
  – Stainless steel can
  – Bottle
  – Bags
  – Barrels
Container Closure – DP Primary (P7)

- Primary Packaging – what touches the product
  - Ampoules
  - Blister Packs
  - Bottles, Caps
  - Syringe, Plungers
  - Vials, Caps, Seals
Container Closure – DP Secondary (P7)

• Secondary Packaging – what the product or primary packaging is stored or shipped in
  – Trays
  – Cartons
  – Boxes
Container Closure (S6 & P7)

• Container Closure System Description
  – Identity of construction materials for each primary packaging component (e.g., Type-I borosilicate glass, DEHP plasticized PVC, polyolefin, HDPE, LDPE, MDPE, PET, PP, PS, stainless steel, etc.)
  – Specifications
    • Description (e.g., dimension, characteristics, compendial compliance (*USP, Ph. Eur., JP*))
    • Identification (e.g., name, manufacturer)
    • Critical dimensions with drawings (e.g., od, id height)
  – Noncompendial methods with validation (e.g., dye ingress, microbial ingress)
CMC or Quality Sections

- **C:** Chemistry – Composition of product
- **M:** Manufacturing – How we make it
- **C:** Controls – How we ensure it is what we say it is
C: Controls

• Specifications
  – Actual specification (S4.1 & P5.1)
  – Justification of specifications (S4.5 & P5.6)
• Assays
  – Description (S4.2 & P5.2)
  – Validations (S4.3 & P5.3)
• Reference Standards (S5 & P5)
• Batch Analysis (S4.4 & P5.4)
• Characterization of Impurities (P5.5)
• Stability Testing (S7 & P8)
Specifications

• Specification – list of drug substance/drug product requirements including
  – A list of tests
  – Reference to analytical procedures
  – Acceptance criteria (numerical limits, ranges or other criteria)

• Actual Specification (S4.1 & P5.1)
• Justification of Specifications (S4.5 & P5.6)
## Specifications

### Table 1: Specifications for Drug Product

<table>
<thead>
<tr>
<th>Components</th>
<th>Nib (%) Maximum</th>
<th>Shell (%) Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>3.2</td>
<td>6.6</td>
</tr>
<tr>
<td>Fat (cocoa butter, shell fat)</td>
<td>57</td>
<td>5.9</td>
</tr>
<tr>
<td>Ash</td>
<td>4.2</td>
<td>20.7</td>
</tr>
<tr>
<td>Total nitrogen</td>
<td>2.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Theobromine</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Starch</td>
<td>9</td>
<td>5.2</td>
</tr>
<tr>
<td>Crude fibre</td>
<td>3.2</td>
<td>19.2</td>
</tr>
</tbody>
</table>
### Justification of Specification – Table

<table>
<thead>
<tr>
<th>Assay</th>
<th>Specification</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Dark brown</td>
<td>It’s a chocolate bar!</td>
</tr>
<tr>
<td>Weight</td>
<td>4 oz</td>
<td>Light weight for shipping and for soldiers that needed to carrying them in their packs</td>
</tr>
<tr>
<td>Melting Temperature</td>
<td>&gt;120 °F</td>
<td>Be able to withstand high temperatures due to shipping and storage in tropical conditions and deserts</td>
</tr>
<tr>
<td>Calories</td>
<td>1800</td>
<td>Intended to furnish the individual combat soldier with the 1,800 calories (7,500 kJ) minimum sustenance recommended each day</td>
</tr>
<tr>
<td>Taste</td>
<td>Better than potato</td>
<td>Expectation that the bar is palatable and will be consumed by the intended recipients.</td>
</tr>
</tbody>
</table>
Rationale of the Specification

- **Test:** Melting temperature is tested using procedures described in *Ph. Eur. 1.2.34*, *USP <567>*, and *JP 8.90*.

- **Criterion:** Melting temperature must be $>120{°\text{F}}$.

- **Justification:** Bars must be able to withstand temperatures found during transportation and storage in all regions of the world without melting into a big mess prior to consumption. A minimum melting temperature of $120{°\text{F}}$ was found to be acceptable during shipping and storage studies.
Assays

- Assays – how materials are tested and how we know that the test is accurate
  - Description (S4.2 & P5.2) – information about how the actual testing is performed
  - Validations (S4.3 & P5.3) – information on what parameter were checked to make sure the information is accurate, repeatable, and reliable
Assay Description – Melting Temp

Melting point is determined by the capillary method. The point at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase is considered the melting point. A summary of the test method is provided in Table 1. This method was verified, and the verification summary is provided in Section 3.2.S.4.3.3.

Table 1: Summary of Melting Point Temperature Assay

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay Type</td>
<td>Capillary method, Class I, Apparatus 1</td>
</tr>
<tr>
<td>Test Samples</td>
<td>Drug product</td>
</tr>
<tr>
<td>Key Equipment</td>
<td>• Glass vessel containing a liquid bath</td>
</tr>
<tr>
<td></td>
<td>• Means of stirring</td>
</tr>
<tr>
<td></td>
<td>• Thermometer</td>
</tr>
<tr>
<td></td>
<td>• Alkali-free hard-glass capillary tubes with internal diameter of 0.9–0.1 mm, a wall of 0.10–0.15 mm, and sealed at one end</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>Benzophenone: melting point reference standards</td>
</tr>
<tr>
<td>Positive/Negative Controls</td>
<td>Regular Hershey bar (positive);</td>
</tr>
<tr>
<td>Critical Reagents</td>
<td>None</td>
</tr>
<tr>
<td>Sampling Plan</td>
<td>Samples, taken across the lot, are run in triplicate with reference standard panel and controls</td>
</tr>
<tr>
<td>Reportable Result</td>
<td>Report in °F to one decimal point.</td>
</tr>
<tr>
<td>Compendial Compliance</td>
<td>USP &lt;741&gt;, Ph. Eur. 2.2.14</td>
</tr>
</tbody>
</table>
**Assay Description - Details**

- **Sample Preparation**
  - Test sample is dried in vacuo at 105 °C for 5 hours.
  - Dried sample is reduced to a fine powder using a mortar and pestle.
  - Powder is packed tightly into a capillary glass tube to form a column 2.5 to 3.5 mm in height.

- **Test Procedure**
  - Bath temp is raised to ~10 °C less than melting temperature.
  - Heating rate is adjusted to 1 °C/min.
  - Capillary tube is immersed with the closed end near center of thermometer bulb.
  - Melting range is determined by observing the temperature at which the test sample begins to collapse and is completed at the temperature it becomes liquid throughout.
Assay Description – Other Parameters

• System Suitability
  – Coefficient of determination ($R^2$) of the standard curve
  – Percent spike recovery of spiked samples and spiked control
  – % coefficient of variation of spiked samples and spiked control

• Data Processing
  – Curve fit used for standard curve
  – Equations used to calculate values for both samples and controls
Validation vs Compendial vs Qualification/Verification

• Compendial – assay is performed using testing described in a pharmacopeia, considered validated if run as described

• Qualification/Verification
  – Compendial to confirm there are no components that would impact assay performance
  – Validated with another product to ensure assay performs as expected with the new matrix

• Validation – prove the assay performs reliably between people, labs, and material lots
Typical Assay Validation Parameters

- **Precision**: closeness of individual results when the same sample repeated several times
  - Within-run or intra-batch precision: **repeatability** during a single analytical run
  - Between-run or inter-batch precision: repeatability between 2+ analysts, 2+ laboratories, 2+ reagent lots, 2+ sample preparations, etc. (type of assay determines what is tested)
    - Intermediate precision – within a laboratory variation
    - Reproducibility – between laboratory variation

- **Accuracy**: closeness between accepted value and actual sample value

- **Sensitivity** or Limit of detection (LOD): lowest analyte concentration that can reliably differentiate from background noise

- **Specificity**: ability to detect a certain material within its matrix

- **Linearity**: ability (within a given range) to obtain test results directly proportional to analyte concentration (amount) in the sample.

- **Range**: interval between upper and lower concentration (amounts) where a suitable level of precision, accuracy, and linearity has been demonstrated

- **Robustness**: shows that method remains unaffected by small, but deliberate, variations in any of the method parameters
Assay Validation/Verification

- **Description**

Melting point in drug product samples is performed using a compendial capillary-based assay described in *USP <741>* and *Ph. Eur. 2.2.14 (Section 3.2.P.5.2.3)*. The method was verified using two lots of benzophenone reference standard and two lots of drug product. A summary of the verification results is shown in **Table 1**.

**Table 1: Summary of Verification Parameters for the Melting Point Temperature Assay**

<table>
<thead>
<tr>
<th>Verification Parameter</th>
<th>Acceptance Criterion</th>
<th>Verification Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melting Point Verification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzohenone</td>
<td>47–49 °C</td>
<td>Lot 1123A: 48.7 °C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lot 1569D: 47.3 °C</td>
</tr>
<tr>
<td>Drug Product</td>
<td>≥49 °C</td>
<td>Lot 42-11-43: ≥49 °C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lot 43-7-123: ≥49 °C</td>
</tr>
<tr>
<td><strong>Intermediate Precision</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzohenone</td>
<td>%CV between results is ≤20%</td>
<td>Lot 1123A: 15.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lot 1569D: 11.9%</td>
</tr>
<tr>
<td>Drug Product</td>
<td></td>
<td>Lot 42-11-43: 13.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lot 43-7-123: 17.2%</td>
</tr>
</tbody>
</table>
Assay Validation/Verification

• **Data**
  Tables and figures as appropriate

• **Discussion**
  All analyses were performed using the samples from drug product Lots 42-11-043 and 43-7-123.

• **Conclusion**
  All method verification acceptance criteria were met for the melting point method. The method is acceptable for use for drug product samples.
Reference Standards (S5 & P5)

• Reference Standards
  – Materials used in assay that have a known concentration
  – Results of known standards are used to calibrate equipment and predict values for unknown samples
Reference Standards

• Melting-point standard examples:

<table>
<thead>
<tr>
<th>Standard</th>
<th>Melting-Point Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzophenone</td>
<td>+47 to +49°C</td>
</tr>
<tr>
<td>p - Nitrotoluene</td>
<td>+52 to +54°C</td>
</tr>
<tr>
<td>Vanillin</td>
<td>+81 to +83°C</td>
</tr>
<tr>
<td>Benzoic Acid</td>
<td>+121 to +123°C</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>+133 to +135°C</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>+158 to +160°C</td>
</tr>
<tr>
<td>Sulphanilamide</td>
<td>+164 to +166°C</td>
</tr>
<tr>
<td>Caffeine</td>
<td>+235 to +237°C</td>
</tr>
<tr>
<td>Carbazole</td>
<td>+244 to 248°C</td>
</tr>
<tr>
<td>Anthraquinone</td>
<td>+283 to +286°C</td>
</tr>
</tbody>
</table>
Stability (S7 & P8)

• Stability information includes
  – Stability Summary and Conclusions (S7.1 & P8.1)
  – Post-Approval Stability Protocol and Stability Commitment (S7.2 & P8.2)
  – Stability Data (S7.3 & P8.3)
• Stability Summary and Conclusions
  – Types of studies conducted
  – Protocols used
  – Results of studies summarized with respect to storage conditions and retest or shelf-life (e.g., ICH studies including forced degradation and stress conditions)
Stability Summary and Conclusions

This section provides a summary of the stability studies performed to support the shelf life of the HC-1234. An initial shelf-life of 12 months at 120 °F is proposed based on real-time stability data from the formal stability study (FSS) lots. The shelf-life of the DP at 120 °F will be extended to a maximum of 24 months. Lots used for stability studies are summarized in Table 1.

Table 1: HC-1234 Lots Used in Stability Studies

<table>
<thead>
<tr>
<th>Lot Number</th>
<th>Date of Manufacture</th>
<th>Lot Size (bars)</th>
<th>Lot Purpose</th>
<th>Available Data at 120 °F</th>
</tr>
</thead>
<tbody>
<tr>
<td>42-11-043</td>
<td>17-Nov-1942</td>
<td>11,792</td>
<td>FSS</td>
<td>12 months</td>
</tr>
<tr>
<td>43-7-123</td>
<td>29-Jul-1943</td>
<td>567,987</td>
<td>PPQ</td>
<td>6 months</td>
</tr>
</tbody>
</table>

FSS: formal stability studies
PPQ: process performance qualification
Results of the stability studies
- List of testing
- Acceptance criteria
- Initial testing results (i.e., batch release)
- Testing times and data where available

Batches typically include
- Pivotal batches
  - Clinical trials – clinical lots, important safety assessment lots
  - Formal stability studies – lots to support shelf life
  - Marketing – process and clinical consistency lots; critical lots
  - Accelerated stability testing
- All batches that are included in the batch analysis
# Stability Data

## Table 1: Stability Results for Lot 42-11-043 at Room Temperature, Ambient Humidity

<table>
<thead>
<tr>
<th>Test</th>
<th>Acceptance Criteria</th>
<th>Stability Test Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>Appearance</td>
<td>Dark brown</td>
<td>Dark brown</td>
</tr>
<tr>
<td>Weight</td>
<td>4 oz</td>
<td>4.1 oz</td>
</tr>
<tr>
<td>Melting Temperature</td>
<td>&gt;120 °F</td>
<td>127 °F</td>
</tr>
<tr>
<td>Calories</td>
<td>1800</td>
<td>1820</td>
</tr>
<tr>
<td>Taste</td>
<td>Better than potato</td>
<td>yes</td>
</tr>
</tbody>
</table>

TBT: to be tested
Post-Approval Stability Protocol and Stability Commitment  (S7.2 & P8.2)

• Post-approval stability protocol and commitment
• A commitment to continue the ongoing stability studies to support the shelf-life
• Ongoing long-term stability studies
  – Information about test methods and specifications
• Post-approval stability studies
  – Intentions of lots to be put on stability
  – Protocol for studies
Stability Protocol and Commitment

This section provides the post-approval stability protocol, stability commitment, and ongoing stability studies (Section 3.2.S.7.1) for drug product manufactured at the commercial manufacturing site. These studies will support the shelf life of the K-rations stored in paper packaging stored at room temperature/ambient humidity. The data used to support the proposed expiry at the long-term storage condition were evaluated against the proposed commercial specifications (Section 3.2.S.4.1).

Table 1: Protocol for Annual Stability Studies on Commercial Batches Stored at Room Temperature/Ambient Humidity

<table>
<thead>
<tr>
<th>Test</th>
<th>Protocol</th>
<th>Stability Test Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>Appearance</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Scale</td>
<td>X</td>
</tr>
<tr>
<td>Melting Temperature</td>
<td>Class 1a melting point</td>
<td>X</td>
</tr>
<tr>
<td>Calories</td>
<td>Calorimeter</td>
<td>X</td>
</tr>
<tr>
<td>Taste</td>
<td>Better than potato</td>
<td>X</td>
</tr>
</tbody>
</table>
Typical Module 3 Submission Timeline
# Typical Timeline

<table>
<thead>
<tr>
<th>Step</th>
<th>Duration (weeks)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft Content</td>
<td>4-12</td>
<td>Create content</td>
</tr>
<tr>
<td>Team Review</td>
<td>2-4</td>
<td>Get content alignment within section</td>
</tr>
<tr>
<td>Update Sections/</td>
<td>4-8</td>
<td>Update sections based upon review</td>
</tr>
<tr>
<td>Comment Resolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management Review</td>
<td>2-4</td>
<td>Get content alignment between sections</td>
</tr>
<tr>
<td>Update Sections/</td>
<td>4-8</td>
<td>Update sections based upon review</td>
</tr>
<tr>
<td>Comment Resolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-to-End Review</td>
<td>2-4</td>
<td>High level consistency check &amp; approval</td>
</tr>
<tr>
<td>Comment Resolution</td>
<td>1-2</td>
<td>Resolve E2E comments</td>
</tr>
<tr>
<td>Quality Check</td>
<td>4-6</td>
<td>Ensure accuracy of content</td>
</tr>
<tr>
<td>Publishing</td>
<td>4-6</td>
<td>Create submission document</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27–54 weeks</strong></td>
<td></td>
</tr>
</tbody>
</table>

⇒ Realistically, 6 months maybe for a pharm product, 1.5 – 2 years for a vaccine or biological product
Factors Effecting Timing

• Team members
  – Number of dedicated people working on the submission
  – Experience of the team members

• In-house or CMO/CRO organizations
  – Manufacturing site
  – Packaging site
  – Analytical data
  – Stability data
Factors Driving (or delaying) Timeline

- Data availability from
  - Stability Studies
  - Process Performance Qualification Lots
  - Validation Studies (e.g., shipping, cleaning, etc.)
  - Adventitious Agent Testing
  - Characterization Work (e.g., leachables)
  - On and on and on and on
• Good references to explore more about CMC
  – *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, M4Q Implementation Working Group Questions & Answers (R1), 17-Jul-2003*
Questions?

KEEP CALM AND EAT CHOCOLATE
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