Multipurpose Prevention Technology (MPT) for Reproductive Health

Manufacturing Issues

Live Webinar

CAMI
Multipurpose Prevention Technology (MPT) Manufacturing Issues

Featuring:
Dr. Joseph Romano (NWJ Group LLC)
Dr. Kenneth Stockholm (Q Pharma)
Dr. Robert Russell (RJR Consulting)
Introductory Remarks

Dr. Joseph Romano
President of NWJ Group LLC
Background for Today’s Webinar

- Quality elements of new products are critical from the earliest stages of development.

- Early stage design decisions must be informed by later stage quality requirements and consequences.

- Inadequacies in the CMC package can prevent product approval despite clinical demonstration of safety and efficacy.

- Are MPT funders and developers adequately informed of CMC requirements and risk?
Today’s CMC Topics

Consideration of late stage manufacturing requirements in early stage product design
Kenneth Stockholm
Q Pharma

A review of the FDA guidance for Scale Up and Post-Approval Changes (SUPAC)
Robert Russell
RJR Consulting
MPT Manufacturing
- The CMO Perspectives

Mr. Kenneth Stokholm
Managing Director at QPharma
Agenda

- Introduction

- CMO perspectives
  - Challenges
  - Our involvement across the development phases
  - Design path and space

- Cost of goods
  - Components and drivers
  - Scale up
Who we are

Contract Development and Manufacturing Organisation
- Solid pharmaceutical history since 1975
- Private company

Employs 134 people

Turn-over 26 million USD (167 MSEK) in 2013
- AAA Financial rating

Compliance with US FDA & EMEA regulations

Competencies
- Solid dosage forms
- Vaginal rings, IUD's and implants
The common ground

Indications
- HRT
- STD, HIV
- Infertility
- Contraception
- Urinary incontinence
- Reproductive cancers
- Oncology
- Pain

Formulations

Clients

Pfizer

NORDIC PHARMA

Actavis

FERRING PHARMACEUTICALS

International Partnership for Microbicides

Population Council

IMPT for Reproductive Health

MPT Manufacturing Issues
Live Webinar – 26 September 2014
Challenges

Split between pharmaceutical clients and non-profit organizations (and their donors)

- Understanding pharmaceutical development
  - Design path and space
  - Clinical trials
  - Cost of goods

Defining finished product properties in early development

- Early involvement of CMO
  - Regulatory approval
  - Robust, cost effective process
CMO involvement across phases

- Feasibility studies (Proof of Concept)
- Design development
- Clinical trial supplies I-II, based on lab scale
- Scale up of manufacturing process (QbD and DoE)
- Clinical supplies III, based on pilot/commercial scale
- Launch
- Post approval changes (SUPAC)
Do process development properly before Clinical Phase III trials.
Design parameters 1

- Polymeric formulation (IVR, IUD, Implant)
- Design (reservoir, matrix)
- Release profile (rate, duration, burst)
- Raw materials (Silicone type, thermoplastic (EVA, PU, other))
  - Cross linking
  - Curing system
- API (grade, particle size, SSA, etc.)
- Manufacturing process (mixing, extrusion/injection molding)
- Scale (laboratory, pilot, commercial)
- Cost of goods
- IP
Design path 2

- Duration – short or long term?
- Formulation
  - Tablets, gels
- Polymeric formulation (IVR, IUD, Implant)
  - Release profile, rate – burst?
  - Design
  - Reservoir
    - Matrix
    - Extrusion
      - Silicone, API
        - Membrane, enhancer
          - Scale
          - Design/manufacturing process 2
            - IP protection / license opportunity?
              - Design/manufacturing process 1
                - Cost of goods?
                  - Raw materials
        - Membrane, enhancer
          - Scale
          - Design/manufacturing process 1
            - IP protection / license opportunity?
              - Design/manufacturing process 1
                - Cost of goods?
                  - Raw materials
          - Membrane, enhancer
            - Scale
            - Design/manufacturing process 1
              - IP protection / license opportunity?
                - Design/manufacturing process 2
                  - Which development process?
Design space 3

Polymeric formulation

Silicone, API
Release profile
MPT
Final Design Space
Cost of Goods components

- Direct material
- Direct labor
- Production
- Quality
- Overhead

Cost components:

- Direct Material 12%
- Direct Labour 27%
- Production 28%
- Quality 9%
- Overhead 24%
Cost of Goods dependencies 2

- Manufacturing scale (Laboratory, pilot and commercial)
  - Batch size
    - Direct costs
    - Fixed costs
  - Automation versus labor
Cost of Goods comparison 3

- Price development through clinical supply phases into commercial supply
- At larger volumes, fixed costs will be insignificant
- Price per unit, per day of treatment or total cost of treatment?

Cost comparison

USD per ring vs. Rings per year
Conclusions

Early CMO involvement will secure

- Right priority of the final product properties
- Scalability
- Less regulatory impact
- Robust, cost effective commercial process
- Shorter time to market
Thank you & Questions
Scale-Up Post-Approval Changes (SUPAC) with FDA

Robert Russell
President and CEO RJR Consulting
Scale-Up and Post-Approval Changes (SUPAC)

- Initial batch sizes to supply early Phase trials are small and are increased for trial size and commercial production.

- This increase is called “scale up”.

- These scale-up changes made after drug product approval in components, composition, manufacturing process, manufacturing equipment and/or manufacturing site are SUPAC.

- SUPAC guidelines are published by FDA and are based on dosage type form.
FDA Published Guidelines Include:

- SUPAC-IR: Questions and Answers about SUPAC-IR Guidance
- SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum
- SUPAC-SS: Non-sterile Semisolid Dosage Forms: Scale Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
- SUPAC-SS: Non-sterile Semisolid Dosage Forms Manufacturing Equipment Addendum
  - Tables provided at the end of all guidance documents that list the change type, level, documentation and filing type for easy reference (example on next slide)
## Extended Release Solid Oral Dosage Forms
### Non-Release Controlling Components and Composition

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>CLASSIFICATION</th>
<th>THERAPEUTIC RANGE</th>
<th>TEST DOCUMENTATION</th>
<th>FILING DOCUMENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>- Complete or partial deletion of color/flavor&lt;br&gt;- Change in inks, imprints&lt;br&gt;- Upto Supac-IR Level 1&lt;br&gt;- No other changes</td>
<td>ALL DRUGS</td>
<td>- Stability&lt;br&gt;- Application/Compendial requirements&lt;br&gt;- No Biostudy</td>
<td>- Annual Report</td>
</tr>
<tr>
<td>II</td>
<td>- Change in technical grade and/or specifications&lt;br&gt;- Higher than Supac-IR Level 1 but less than Level 2 excipient ranges&lt;br&gt;- No other changes</td>
<td>ALL DRUGS</td>
<td>- Notification &amp; updated batch record&lt;br&gt;- Stability&lt;br&gt;- Application/Compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1% HCl, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached ¹&lt;br&gt;- Apply some statistical test (F2 test) for comparing dissolution profiles ²&lt;br&gt;- No Biostudy</td>
<td>- Prior Approval Supplement</td>
</tr>
<tr>
<td>III</td>
<td>- Higher than Supac-IR Level 2 excipient ranges</td>
<td>ALL DRUGS</td>
<td>- Updated batch record&lt;br&gt;- Stability&lt;br&gt;- Application/Compendial (profile) requirements&lt;br&gt;- Biostudy or IVIVC ³</td>
<td>- Prior Approval Supplement</td>
</tr>
</tbody>
</table>

¹ In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
² In the absence of an established in vitro/in vivo correlation.
SUPAC-IR, SUPAC-MR and SUPAC-SS Change Types
Level of Changes for Components and Composition

- Components and composition changes are focused on the changes of excipients in a drug product and not in the change of the amount of drug substance.

- Three levels:
  - Minor (Level 1 change)
    - Changes that are unlikely to have an impact on formulation quality and performance ex. Change in color or flavor
    - Changes filed in the annual report (including long term stability)
  - Moderate (Level 2 change)
    - Changes that could have a significant impact on the formulation quality and performance ex. Change in technical grade of an excipient
      - Tests and filing requirements vary based on therapeutic range, solubility and permeability
    - Changes filed as a prior approval supplement (all info including accelerated data and in the annual report (long term stability data)
Level of Changes for Components and Composition Cont’d

- **Major (Level 3 change)**
  - Changes that will likely have a significant impact on formulation quality and performance ex. A qualitative or quantitative excipient change to a narrow therapeutic drug
    - Tests and filing requirements vary based on therapeutic range, solubility and permeability
  - Changes filed as a prior approval supplement (all info including accelerated data and in the annual report (long term stability data)

- **Preservative change (4th option) only for SUPAC-SS**
  - Any change in the preservative of a semisolid product that may affect the quality of the product
  - No in vitro release or in vivo bioequivalence needed for preservative changes
    - Level 1 – quantitatively 10% or less change in approved amount of preservative
    - Level 2 - quantitatively 10% - 20% change in approved amount of preservative
    - Level 3 - quantitatively more than 20% in approved amount of preservative
  - See guidance for any additional chemistry documentation for a preservative change and filing type
Level of Changes for Site Changes

- Site changes include changes in location of the site of manufacturer for both company owned facilities or contract manufacturers.
- Does not include scale-up
- Three levels:
  - Minor (Level 1 change)
    - Site change in a single facility where the same equipment, SOP’s, environment conditions and controls, and the same personnel are used. No additional changes are made to the batch records except for admin information and location of the facility.
    - Changes filed in the annual report
  - Moderate (Level 2 change)
    - Site change with in a contiguous campus or between facilities in adjacent blocks where the same equipment, SOP’s, environment conditions and controls, and the same personnel are used. No additional changes are made to the batch records except for admin information and location of the facility.
    - Changes filed as changes being effected supplement and in the annual report (long term stability data)
Level Changes for Site Changes
Cont’d

- Major (Level 3 change)
  - Site change to a different campus where the same equipment, SOP’s, environment conditions and controls, and the same personnel are used. No additional changes are made to the batch records except for admin information and location of the facility.
  - Changes filed as changes being effected supplement and in the annual report (long term stability data)
Level Changes in Batch Size

- Includes post approval changes of the batch size from pilot scale to full scale
- A scale down is possible, but cannot be scaled down below 100,000 dosage units.
- All scale-up changes must be validated and if needed, inspected by appropriate agency personnel.

Two levels:
- Minor (Level 1 change)
  - Change in batch size up to 10x the size of pilot batch where the equipment used to produce the test batches is the same design and operating principles and the batches are manufacturing in full compliance with cGMP’s. Additionally the same SOP’s and controls as well as the same formulation and manufacturing procedures are used on the test and full scale product batches
  - Changes filed in the annual report (including long term stability)
- Moderate (Level 2 change)
  - Change in batch size greater than 10x the size of pilot batch where the equipment used for the test batches is of the same design and operating principles and the batches are in full compliance with cGMP’s
    - The same SOP’s and controls, formulation and manufacturing procedures are used on the test and full scale product batches
  - Changes filed in a changes being effected supplement and in the annual report (long term stability)
Level Changes in Manufacturing

- Manufacturing changes can effect both equipment and the actual process.
- Equipment change has two levels:
  - Minor (level 1 change) - Equipment can be a change from non-automated to automated or vice versa to move ingredients or a change to alternative equipment of same design and the operating principles of the same or of a different capacity.
    - Changes filed in the annual report (including long term stability)
  - Moderate (Level 2 changes) – change in equipment to a different design or different operating principles or a change in type of mixing equipment.
    - Changes filed as prior approval supplement with justification for change and in the annual report (long term stability data)
Level Changes in Manufacturing Cont’d

- Process change has three levels:
  - Level 1 – Process changes like mixing times and operating speeds within application/validation ranges
    - Changes filed in the annual report
  - Level 2 – Process changes like mixing times and operating speeds outside of application/validation ranges
    - Changes filed as changes being effected supplement and in the annual report (long term stability data)
  - Level 3 – Change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder
    - Changes filed in a prior approval supplement with justification and as the annual report (long term stability)
SUPAC-IR/MR

- To be used in conjunction with SUPAC-IR and SUPAC-MR to determine which documentation should be submitted to FDA when there is a change in equipment

- Only covers manufacturing equipment
  - Subsections include:
    - Particle size reduction/separation
    - Blending and mixing
    - Granulation
    - Drying
    - Unit dosing
    - Soft gelatin capsules
    - Coating/printing/drilling
SUPAC-SS Manufacturing Equipment Addendum

- To be used in conjunction with SUPAC-SS to determine which documentation should be submitted to FDA when there is a change in equipment
  - Only covers manufacturing equipment
    - Subsections include:
      - Particle size reduction/separation
      - Mixing
      - Emulsification
      - Deaeration
      - Transfer
      - Packaging
SUPAC-IR, SUPAC-MR and SUPAC-SS Documentation Required
SUPAC-IR, SUPAC-MR, and SUPAC-SS

- Have the same template and same levels of change per topic
- Stability and dissolution document requirements are the main things that varies between SUPAC-IR and SUPAC-MR
- SUPAC-SS has an in vitro release document instead of a dissolution document
- Recommendation are provided for all changes relating to:
  - Component or composition
  - Manufacturing site
  - Scale up or scale down of manufacture
  - Manufacturing process and equipment
- Guidance defines the:
  - Levels of change
  - Recommended chemistry, manufacturing and controls for each level of change
  - In vitro dissolution test and/or in vivo bioequivalence tests for each change
  - Documentation needed to support the change
Documentation Required

- Includes:
  - Chemistry document for SUPAC-IR, SUPAC-MR and SUPAC-SS:
    - Must always follow application/compendial release requirements and batch records
    - Additional requirements based on level and type of change include:
      - 1 batch long term stability testing
      - 1 batch with 3 months accelerated stability reported in the supplement and 1 batch in long term stability reported in the annual report
      - For SUPAC-IR or SUPAC-SS level 2 or 3 change as required by change type:
        - Significant body of information available: 1 batch with 3 months accelerated stability reported in the supplement and 1 batch in long term stability reported in the annual report
        - Significant body of information not available: up to 3 batches with 3 months accelerated stability reported in the supplement and 1 batch in long term stability reported in the annual report
Documentation Cont’d

- For SUPAC-MR level 2 or 3 change as required by change type:
  - Non-narrow therapeutic range drugs: One batch with three months’ accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.
  - Narrow therapeutic range drugs: Three batches with three months’ accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.
- Location of new site and updated batch records
- Notification of change and submission of updated batch records
- Stability must be on production batches for SUPAC-MR
Documentation Required Cont’d

- Dissolution Documentation for SUPAC-IR:
  - Must always follow application/compendial requirements (pharmacopeia for general dissolution specifications)
  - Additional requirements based on case can be required based on level 2 or 3 change
    - Case A: High Permeability, High Solubility Drugs
      - Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C
    - Case B: Low Permeability, High Solubility Drugs
      - Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.
Case C: High Permeability, Low Solubility Drugs

Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

Dissolution documentation for SUPAC-MR beyond compendial requirements can be:

- Nonnarrow therapeutic range drugs (SUPAC-MR level 2 change):
  - Extended release: multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.
Documentation Required Cont’d

- Delayed release: dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).
All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing need be performed (i.e., only in vitro release data by the correlating method need to be submitted). The dissolution profiles of the changed drug product and the bio-batch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

Narrow therapeutic range drugs (SUPAC-MR level 3 change):

- Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained in application/compendial medium for the changed drug product and the bio-batch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

- Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial medium for the changed drug product and the bio-batch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.
Documentation Cont’d

- In Vivo Bioequivalence document (SUPAC-IR, SUPAC-MR and SUPAC-SS):
  - Not required unless stipulated based on level and type of change
    - Level 3 change can require bioequivalence studies
    - Full BE study for SUPAC-IR or SUPAC-SS
    - Single dose BE study for SUPAC-MR
      - The BE may be waived for both if a suitable in vivo / in vitro correlation has been verified
SUPAC-SS Documentation

- SUPAC-SS requires In vitro release documentation instead of the dissolution documentation that is required for SUPAC-IR and SUPAC-MR
  - In vitro tests are used to assure product quality and performance are maintained over time and in the presence of change as well as assure consistent delivery of the active component from semisolid products
  - In vitro release is not required for level 1 changes
  - Level 2 and 3 changes require:
    - Components and composition or batch size level 2 change - The in vitro release rate of a lot of the new/modified formulation or scale-up batch should be compared with that of a recent lot of comparable age of the pre-change formulation of the product. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the two formulations should be demonstrated to be within acceptable limits using the testing procedure described in section VII of the guidance.
SUPAC-SS Documentation Cont’d

- Components and Composition level 3 change - The in vitro release rate of the new/modified formulation should be established as a point of reference. Under this level 3 change, in vitro release documentation is not required, but sponsors are encouraged to develop this information for use in subsequent changes under this guidance.

- Equipment or process level 2 change - The in vitro release rate of a lot of the dosage form prepared in new equipment should be compared with the release rate of a recent lot of comparable age of the product prepared using original equipment. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the two formulations should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST).

- Manufacturing site level 2 change - The in vitro release rate of a lot of the dosage form prepared in a new manufacturing site should be compared with the release rate of a recent lot of comparable age of the product prepared at the prior site. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) from the two sites should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST).
Manufacturer Responsibilities

- Required to inform FDA of any changes made that fall under any of the SUPAC guidance's
- Based on the type of change, it may either be implemented first (notification) or may need prior approval
- Depending on the change and its level, it must be informed in one of 3 ways:
  - Annual report
  - Changes being affected supplement
  - Prior approval supplement
- Use the charts at the end of the guidance's for easy reference to determine the requirements
Thank You & Questions
Learn more about MPTs

www.CAMI-Health.org & www.MPTs101.org
Support for this project is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of the HealthTech Cooperative Agreement #AID-OAA-A-11-00051, managed by PATH. The contents are the responsibility of CAMI/PHI and its partners and do not necessarily reflect the views of USAID or the US Government.