Transfer of a manufacturing process:
Case study ~ Solid dosage transfer within technical operations

Ian Flawn Orpana
QPharma AB, Sweden
Overview of Product

- Product fitted into "therapeutic area"
- Purchased from "big pharma"
- Product:
  - Highly potent
  - Explosive
  - Traditional production
Project history/setup

• Due diligence
  - 1 day to technically review process
    ○ Statistical process control (SPC) to determine variation
    ○ Robustness of process

• Clarification of scope
  - Bulk: Transferred CH to UK
  - Bulk: UK site produced small quantity of batches
  - Packaging outsourced to TPM
  - "Other” sites involved due to regulatory demands of certain countries
Selection of TPM

• Initial "overview" communication
  - Showing "show stopper" issues
  - No confidentiality agreement
  - Explosive, potent, volumes, major process/analytical equipment, bulk volumes & packaging forms & splits
  - Proof needed of EU GMP licence

• TPMs selected
  - Knowledge from RU’s people
  - Conferences
  - Web sites
Detailed scope for TPM

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Criteria for selection

- Decision making technique
  - Kepner Tragoe
  - *Musts*
    - EU GMP licence
  - *Wants*
    - Rank "wants" multiply by TPM’s response

- Criteria used
  - Commitment to quality
  - Flexibility
  - Reputation
  - Scope of resources (people, equipment, facility)
  - Price
  - Honesty
  - Financial standing
Experiences

😊 Spent 6 months finalising TPM selection process
😊 TPM pulled out from selection process on last day
😊 Serious GMP failure during selection process
😊 TPM’s pulled out immediately giving clear rationale of why
Project Team

• Makeup
  - Cross functional
  - Inter – company
  - Intra – company
  - Multi cultural
  - Multi experienced (high & low)

• Communication
  - High visibility with Sending & Receiving Units
  - Web/phone meetings
    ○ gotomeeting.com
  - Minutes of meeting & email confirmation
  - Central customer “electronic file directory”
Project Management tools

- Adopted structured approach to Project
Risks

- Regulatory approach PAT v's traditional approach
  - Traditional approach
- Process improvements
  - Minimise for reduction in regulatory effort
  - "Technical report" to support all changes
  - Changes made where "significant" cost saving could be realised
- Review of regulatory file
  - Identify discrepancies of SU procedures
- Timeline of transfer
  - Build up of safety stock from SU
- RU building new production area
  - Perform number of GMP audits
Process Understanding

• Historical review
  - Used during due diligence
  - Basis for writing Process Validation

• Statistical Process Control
  - Identify if the process is in control or not
    ○ In statistical control ~ repeatable & predictable
  - Determine capability of process
    ○ Process is centred of target ($C_p \approx C_{pk}$)
    ○ Robust or not ($C_p > 1.33$)
Examples of parameter assessment

Control Chart: Moving R
No special cases are present.

Issues:
The tablets are extremely hygroscopic, delays in performing the moisture analysis will result in tablets possessing a high moisture content, which is not a true reflection of the drying process.

Conclusions:
Perform the LOD test on the tablets during compression or as soon after compression as possible.

Chart: Capability
USL is below UCL, therefore there is a high degree of certainty that the upper specification limit shall be compromised.

Chart: Capability
The process is capable having a high Cpk (2.4). The process is relatively well-centred the Cpk (2.2) is similar to the Cp (2.3).

Issues:
The process demonstrates low variation and is well centred relative to the specification limits. The risk associated to the special causes is shown as LOW as the special causes are seen as border line occurrences.

Conclusions:
Process demonstrates good control.
## Conclusion & Recommendations

<table>
<thead>
<tr>
<th>Final product parameter</th>
<th>Strength (µg)</th>
<th>Risk</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss on drying</td>
<td></td>
<td>HIGH</td>
<td>Perform the LOD test on the tablets during compression or a soon after compression as possible.</td>
</tr>
<tr>
<td>Friability</td>
<td></td>
<td>LOW</td>
<td>Recommend that this parameter be kept as a in process control but is discarded as a final product release parameter</td>
</tr>
<tr>
<td>Mean weight</td>
<td></td>
<td>LOW</td>
<td>Process shows excellent control.</td>
</tr>
<tr>
<td>Dissolution</td>
<td></td>
<td>MEDIUM</td>
<td>The dissolution methodology has two additional steps if S1 fails, with S2 and then S3 (if S2 fails) tests becoming active. During the process validation attention should be made to distribution of active and the performance of the dissolution method. This should be cited within the process validation protocol.</td>
</tr>
<tr>
<td>Content of Uniformity</td>
<td></td>
<td>LOW</td>
<td>Process demonstrates good control.</td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td>LOW</td>
<td>Process demonstrates good control.</td>
</tr>
<tr>
<td>Degradation substances</td>
<td></td>
<td>HIGH</td>
<td>This is an observation only, it cannot be confirmed statistically due to low sample numbers. impurity a – no further action impurity b &amp; unknown substances - Contact with Novartis is recommended to determine any abnormal situations. This parameter should be evaluated further during process validation</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>✓</td>
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</tbody>
</table>

**Risk Levels**
- HIGH
- MEDIUM
- LOW
Process / Procedural changes (1/2)

- LOD tested during production
- Change of milling technology

Table 1  Unit Operation - Particle Size Reduction (cont.)

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Mills</td>
<td>Rotating Impeller</td>
<td>Bepec (Hosokawa)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fitzpatrick</td>
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<tr>
<td></td>
<td></td>
<td>Fluid Air</td>
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<td>Jetpharma</td>
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<td>Kemutec</td>
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<td>Stokes-Merrill</td>
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<tr>
<td></td>
<td></td>
<td>Zaninetta (Romaco)</td>
</tr>
<tr>
<td>Rotating Screen</td>
<td>Clatt</td>
<td></td>
</tr>
<tr>
<td>Oscillating Bar</td>
<td></td>
<td>Bepec (Hosokawa)</td>
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<td>Fwediey</td>
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<td></td>
<td></td>
<td>Jackson-Crockatt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stokes-Merrill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vector</td>
</tr>
</tbody>
</table>
Process / Procedural changes (2/2)

- Removal of in process dissolution
  - SU performed IPC, x3 hardness & perform dissolution test
  - Historical review identified suitable hardness specification, with confidence that dissolution would pass

- Removal of Industrial Methlylated Spirits (IMS)
  - Under direction from regulatory authorities
  - IMS contains wood derivative
Transfer Process (1/3)

- Training from SU personnel
- Developed checklist based upon ISPE checklist ~ to ’gather’ all info
- Formal analytical method transfer
- Placebo batch
  - Trained operators/technical support & RU people
  - Review 1st BMR
Transfer Process (2/3)

• Bracketing review
  - Lower strength
    ○ Similar manufacturing process (1 part)
    ○ μg API quantities
  - Upper strength
    ○ Similar manufacturing process (2 part)
    ○ μg API quantities

• Historical review
  - Good degree of statistitical control
  - Robust

• Conclusion
  - Lower strength (x1 'a' µg & x2 'b' µg) = ∑ 3 batches
  - Upper strength (x1 'c' µg & x2 'd' µg) = ∑ 3 batches
Main events of transfer process (3/3)

1) Technical supporting activities & reports
2) Review of regulatory file v/s SU BMR & analytical methods
3) Draft BMR & analytical methods and specifications
4) Validation strategy
5) Placebo production
6) Demonstration batches
7) Cleaning validation
8) Process validation
9) Validation Report
10) Routine maintenance of product
Structure of transfer protocols (1/3)

~ Preliminary activities

- Review of historical data
  - BMR update ~ perform LOD testing during compression
- MISSED: Review of regulatory file against BMR and analytical methods
- Sampling plans
  - Rationale derived from SPC
  - 20 sampling occasions with no understanding of process, this may be reduced to 10 if good data exists
Structure of transfer protocols (2/3)

~Transfer tests acceptance criteria

RU ~ Process in statistical control
RU ~ Meeting release specifications
RU similar to SU process

Assess of pack performance
Structure of transfer protocols (3/3)

~ Non conformance & further actions

• BMR update ~ increase in frequency of hardness/thickness testing
• BMR update ~ reduction in frequency of friability testing
• Low assay ~ monitor future batches to determine if process is statistically different than SU
Validation Report

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People issues

- Language
- Cultural
- Experience
- Technical
- Communication
- High turnover of people
Responding & communication of changes

- Presentation to steering group each month
- Budget set following review of TPM’s
- Close and honest relationship with TPM
- Scope clearly identified in contracts
- Fact: No matter how well initial risks are envisaged, project will throw up unplanned events:
  - Project team needs to react professionally to minimise impact
Maintenance of product

- Routine management of TPM
- Customer & TPM
- All key functions represented
  - QC, QA, Logistics, TechOps, Srn Manager
- ‘Guest’ members
  - Regulatory, R&D
- Meetings
  - Customer ~ monthly
  - Customer/TPM ~ ¼ yrly (low)
- Fixed agenda
Issues

- Packaging
  - 😞 Yield ~ high # batch changes
  - 😞 Artwork ~ did not appreciate complexity
  - 😞 Scope poorly defined for TPM

- Analytical methods
  - 😞 Significant amount of variation associated to methods
  - 😞 Timelines and effort needed to perform testing
  - 😊 Excellent support from R&D Maintenance

- Marketing
  - 😊 Closer, better and flexible understanding of their needs

- Project Management
  - 😞 Late start to project

- Transfer strategy
  - 😊 Well defined and good use of SPC in understanding the process being transferred

- Project team
  - 😊 Well supported by management
  - 😊 Team worked well understanding each others roles and expertise

- Budget and timelines
  - 😊 Set with data not gut feeling

- Selection of TPM
  - 😊 TPM honest, ethical & trustworthy
References

<table>
<thead>
<tr>
<th>Article or book</th>
<th>Reference and/or Year</th>
<th>Author</th>
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<tbody>
<tr>
<td>Sampling procedures and charts for inspection by variables for percent nonconforming</td>
<td>ISO 3951:1989 (E)</td>
<td>International Standard</td>
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<td>Control charts - General guide and introduction</td>
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• Contact details
  - ifo@qpharma.se

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