GMP Series

A Successful Concept for Technology Transfer in Drug Manufacturing

Excerpt from the GMP Compliance Adviser
## Contents

1 Technology transfer

1.1 Transfer of information 3
1.2 Organisation 4
1.3 Risk management 5
1.4 Technology transfer phases 5
1.5 Product transfer challenges 10
1.6 Areas of conflict during transfer 12
1.7 Quality of the product transfer 12
1.8 Example of a transfer plan 13

Index 29

Contributors 30
1Technology transfer

Dr. Christian Gausepohl

Here you will find answers to the following questions:
• What are the legal requirements for contract manufacturing?
• What has to be observed when selecting a contract manufacturer?
• What can be the scope of contracted work?
• What are the respective responsibilities of the contract giver and contract manufacturer?
• What must be observed when preparing and carrying out the product or technology transfer?

There are currently very few mandatory requirements for transferring products to another manufacturing location, e.g. of a contract manufacturer. The WHO describes this transfer of technology as “a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacturing sites”.

The WHO guidelines represent an advancement of the corresponding ISPE Guide and a draft text of the Japanese authorities on technology transfer. The ICH guideline Q10 states: “The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation.”

This knowledge forms the basis for the
• manufacturing process
• control strategy
• process validation approach
• and the ongoing continual improvement.

Figure 1 summarises the main aspects of a technology transfer in accordance with the WHO guidelines.

Important aims and content of the technology transfer

- Successful transfer of information and experience
- Reproducible manufacture within predefined limits
- Acceptance of results by both partners and the authorities
- Comprehensible documentation of the transfer process
- Project planning that takes quality and risk management into account
- Similar (not necessarily identical) premises and facilities
- Technical GAP analysis for identifying and evaluating differences
- Trained and competent personnel for the transfer
- Communication of difficulties with regard to the ongoing transfer of knowledge
- Resolution of possible conflicts before the start of or during the transfer, e.g. IP rights, prices, conflicts of interest, confidentiality

Figure 1 Aspects of technology transfer in accordance with WHO guidelines

The implementation of a product transfer is a complex project that is characterised by some of the factors for success described below.

### 1.1 Transfer of information

A product transfer is first and foremost a transfer of knowledge. The larger the volume of data and information provided to the contract manufacturer, the smaller the risk of unsuccessful attempts or failure of the transfer. This also corresponds to the expectations of Chapter 7 in the EU GMP Guidelines. When sending, sharing and receiving data, it must be taken into account that not all of the available product knowledge can be transferred between the two transfer partners.

A differentiation must be made between
- conscious knowledge
- unconscious knowledge

**Conscious knowledge** refers to the simplest part of the information. This is documented information that can be retrieved and made available. Figure 2 shows a number of typical documents that can be used during the transfer of information. Confidentiality, privacy and IP protection must be safeguarded during transfers to other companies such as contract manufacturers. The contract giver is generally responsible for sharing conscious knowledge. The contract manufacturer can support the contract giver by making requests in a systematic and targeted way.

On the other hand, **unconscious knowledge** can be of great importance for the robustness of the transferred processes. This involves undocumented systematic basic knowledge that informs the current approach to manufacturing, e.g. shift models or the test frequencies of in-process controls. These internal company time patterns can influence many process steps to such a degree that they cannot be easily reproduced without this knowledge (e.g. stress relaxation of tablets during the period prior to further processing).

To improve the transfer of knowledge during internal company transfers, training in the manufacturing processes is frequently carried out; first on site at the sending unit followed by coaching by experts from the sending unit at the receiving unit. During the transfer of products to the contract manufacturer, this approach is often limited to support for the transfer batches by the contract giver.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Documentation of the sending unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project definition</td>
<td>• project plan&lt;br&gt;• risk analyses&lt;br&gt;• GAP analyses</td>
</tr>
<tr>
<td>Starting materials</td>
<td>• specifications&lt;br&gt;• additional information on active ingredients and excipients, e.g. material safety data sheets, material characteristics (that are not part of the specifications)</td>
</tr>
<tr>
<td>Equipment</td>
<td>• list of the facilities and systems used including type designation&lt;br&gt;• special installations and features (e.g. system controllers)&lt;br&gt;• qualification documentation&lt;br&gt;• drawings&lt;br&gt;• operating instructions&lt;br&gt;• SOPs (e.g. preparation, operation, cleaning, maintenance/calibration)</td>
</tr>
</tbody>
</table>

*Figure 2  Example: Documents used during transfer (without analytical methods transfer)*
1.2 Organisation

As a rule, a transfer is carried out between two production locations or between a development department and a commercial production location. The WHO guidelines use the terms sending unit and receiving unit. The organisation or project management of the transfer project is frequently covered by one of the two units. However, other units in the same company or their contracted partners can also take over the overall management of the project. A project management plan is then needed for monitoring the individual activities. The precise set-up and all responsibilities must be defined and contractually agreed for the phases before, during and after the transfer. The overall responsibility during commercial manufacture is often defined in quality agreements or technical agreements. Specific responsibilities during the transfer phase are normally described in the transfer documents.

Project team

In practice, the transfer is carried out by an interdisciplinary project team which is made up of representatives from both parties (the sending and receiving units). It is important that the transfer team members are experienced and competent. Functions from Production, QC and QA are included in the team so that different perspectives are represented. Figure 3 shows an example of a mixed project team and the individual tasks in a transfer project. In the case of complex transfer projects, a joint steering committee should be set up at managerial level to compliment the project team and solve any problems that may occur during the project at either of the transfer partners.

<table>
<thead>
<tr>
<th>Team member</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project manager</td>
<td>• project management with responsibility for the budget and schedule</td>
</tr>
<tr>
<td></td>
<td>• central communication point</td>
</tr>
<tr>
<td>Process engineer</td>
<td>• central point of contact for technological issues during the project</td>
</tr>
<tr>
<td></td>
<td>• compilation of information and evaluations</td>
</tr>
<tr>
<td></td>
<td>• initial feasibility evaluation of transfer project from a technical</td>
</tr>
<tr>
<td></td>
<td>point of view</td>
</tr>
<tr>
<td></td>
<td>• creation of plans and reports</td>
</tr>
<tr>
<td>Quality Assurance</td>
<td>• checking documents and processes for compliance</td>
</tr>
<tr>
<td></td>
<td>• adherence to project phases, e.g. completion of reports before the</td>
</tr>
<tr>
<td></td>
<td>start of the subsequent phase</td>
</tr>
<tr>
<td></td>
<td>• evaluation of analytical procedures (with Quality Control), systems</td>
</tr>
<tr>
<td></td>
<td>and equipment, personnel training status</td>
</tr>
<tr>
<td></td>
<td>• monitoring of authorisation status</td>
</tr>
</tbody>
</table>

Figure 3 Example: Interdisciplinary project team for the product transfer

Figure 2 Example: Documents used during transfer (without analytical methods transfer) (cont.)
**Figure 4**  Examples of technology transfer phases
schedule. The bilateral approval of the transfer plan reflects mutual expectations and represents the beginning of the active transfer phase.

**Risk analyses**

As a part of risk management, new information and insight must undergo risk assessment on an ongoing basis during the transfer project. Ideally, the assessment should be carried out by both transfer partners. This simplifies the transfer of knowledge on the basis of specific product knowledge, experience gained by the contract giver during product manufacture, as well as general experience with technological processes and other products at the contract manufacturer.

A systematic evaluation of the process steps allows risk prioritisation. Figure 7 gives an example of a simplified representation.

<table>
<thead>
<tr>
<th>CQA</th>
<th>Granulation</th>
<th>Drying</th>
<th>Milling</th>
<th>Mixing</th>
<th>Tabletting</th>
<th>Film-coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>medium</td>
<td>high</td>
</tr>
<tr>
<td>Content</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Purity</td>
<td>low</td>
<td>low</td>
<td>medium</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>low</td>
<td>low</td>
<td>medium</td>
<td>high</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Release</td>
<td>medium</td>
<td>low</td>
<td>high</td>
<td>medium</td>
<td>low</td>
<td>medium</td>
</tr>
<tr>
<td>Particle size distribution</td>
<td>medium</td>
<td>low</td>
<td>high</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

| Justification for „high“ | n/a         | n/a    |         |        |            |              |

The diameter of the sieve opening and velocity can impact particle size distribution, and as a result the flow properties of the material and the filling control of the tablet press.

The mixing process can impact the homogeneity, the purity and the release characteristics. Tableting can impact the homogeneity of the tablets due to fluctuations in particle size distribution and flow behaviour. The final appearance and the release rate can be affected by the quality of the coating.
## Transfer plan

### Fantasin 10 mg film-coated tablets

<table>
<thead>
<tr>
<th>Document no.</th>
<th>PTF-10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version</td>
<td>01</td>
</tr>
<tr>
<td>Replaces version</td>
<td>n/a</td>
</tr>
<tr>
<td>Number of appendices:</td>
<td>6</td>
</tr>
</tbody>
</table>

### Authorised copies:
- Head of Regulatory Affairs
- Head of Production
- Head of Quality Control
- Head of Quality Assurance
- Head of Contract Administration
- Head of Contract Manufacturing

### Approval and release of the transfer plan:

#### Contract giver

- Created by: NN
- Checked/approved by: NN (Head of Contract Manufacturing)
- Checked/approved by: NN (Head of QA)
- Checked/approved by: NN (Head of Quality Control)
- Checked/approved by: NN (Head of Regulatory Affairs)

#### Contract manufacturer

- Checked/approved by: NN (Head of Product Transfer)
- Checked/approved by: NN (Head of Production)
- Checked/approved by: NN (Head of QA)
- Checked/approved by: NN (Head of Quality Control)
- Checked/approved by: NN (Head of Regulatory Affairs)
### Transfer plan
**Fantasin 10 mg film-coated tablets**

<table>
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</tbody>
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### Appendices

<table>
<thead>
<tr>
<th>Appendix no.</th>
<th>Transfer plan appendix</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Project plan</td>
</tr>
<tr>
<td>2</td>
<td>Document transfer</td>
</tr>
<tr>
<td>3</td>
<td>Document transfer</td>
</tr>
<tr>
<td>4</td>
<td>System comparison</td>
</tr>
<tr>
<td>5</td>
<td>Regulatory affairs activities</td>
</tr>
<tr>
<td>6</td>
<td>Stability studies</td>
</tr>
</tbody>
</table>

**Figure 9** (cont.)
Index

C
contract manufacturing
  - technology transfer 2

P
product transfer
  - see technology transfer 2

T
technology transfer 2
  - aim 2
  - areas of conflict 12
  - batch usage 11
  - bulk hold times 11
  - documents 3
  - information 3
  - marketing authorisation issues 11
  - measuring devices 11
  - organisation 4
  - phases 5
  - pre-validation 9
  - process control 10
  - process issues 11
  - project plan 7
  - project request 5
  - project team 4
  - quality 12
  - risk analysis 8
  - risk management 5
  - starting materials 10
  - systems 10, 11
  - transfer plan 7, 13
  - transport validation 11
  - validation 10
transfer plan
  - content 7
  - example 13
**Contributors**

Dr. Christian Gausepohl  
Rottendorf Pharma GmbH, Germany

Pharmacist  
1994–1997 Institute for Pharmaceutical Chemistry, Münster  
1998–1999 Galenical Dept., Rottendorf Pharma GmbH:  
responsible for coordination of technology transfers, process optimisation  
1999–2002 Production, Rottendorf Pharma GmbH  
Head of Dosage Forming, Production manager  
2002–2006 Pharmaceutical Technology, Rottendorf Pharma GmbH:  
Head of Product Transfer, Process Validation  
since 2006 Quality Assurance, Rottendorf Pharma GmbH:  
Head of Quality Assurance, Qualified Person

**Activities:**  
Course Instructor for hygiene, QM-systems, supplier qualification, CAPA, auditing and inspections, change control, PQR, documentation, technology transfer, process validation, manufacturing technologies, packaging process, training systems