

Dr. Christian Gausepohl

# GMP Series

**A Successful Concept  
for Technology Transfer  
in Drug Manufacturing**



*Maas & Peither*  
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# 1 Technology 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".<sup>1</sup> The documented knowledge and experience gained during development and manufacture should be passed on in a systematic way. In addition to the transfer of documentation, the **aim** of the transfer process is to show that the receiving unit can effectively carry out the critical steps of the transferred process to the satisfaction of both parties and the authorities.

The WHO guidelines represent an advancement of the corresponding ISPE Guide<sup>2</sup> 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

1. WHO Technical Report Series, No. 961, 2011, Annex 7, WHO guidelines on transfer of technology in pharmaceutical manufacturing
2. ISPE Good practice guide Technology transfer. Tampa, FL, International, Society for Pharmaceutical Engineering, 2003.

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.

Issue	Documentation of the sending unit
Project definition	<ul style="list-style-type: none"> <li>• project plan</li> <li>• risk analyses</li> <li>• GAP analyses</li> </ul>
Starting materials	<ul style="list-style-type: none"> <li>• specifications</li> <li>• additional information on active ingredients and excipients, e.g. material safety data sheets, material characteristics (that are not part of the specifications)</li> </ul>
Equipment	<ul style="list-style-type: none"> <li>• list of the facilities and systems used including type designation</li> <li>• special installations and features (e.g. system controllers)</li> <li>• qualification documentation</li> <li>• drawings</li> <li>• operating instructions</li> <li>• SOPs (e.g. preparation, operation, cleaning, maintenance/calibration)</li> </ul>

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

Issue	Documentation of the sending unit
Process	<ul style="list-style-type: none"> <li>• comparative or reference batches (e.g. clinical batches)</li> <li>• development report</li> <li>• process specifications and their rationale</li> <li>• critical manufacturing parameters</li> <li>• process validation reports</li> <li>• current manufacturing and packaging instructions</li> <li>• deviation reports, investigations or complaints</li> <li>• PQR, APR</li> </ul>
Cleaning	<ul style="list-style-type: none"> <li>• information about solubility, therapeutic dose and toxicological data</li> <li>• current cleaning instructions</li> <li>• cleaning validation reports</li> </ul>

Figure 2 Example: Documents used during transfer (without analytical methods transfer) (cont.)

## 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.

Team member	Function
Project manager	<ul style="list-style-type: none"> <li>• project management with responsibility for the budget and schedule</li> <li>• central communication point</li> </ul>
Process engineer	<ul style="list-style-type: none"> <li>• central point of contact for technological issues during the project</li> <li>• compilation of information and evaluations</li> <li>• initial feasibility evaluation of transfer project from a technical point of view</li> <li>• creation of plans and reports</li> </ul>
Quality Assurance	<ul style="list-style-type: none"> <li>• checking documents and processes for compliance</li> <li>• adherence to project phases, e.g. completion of reports before the start of the subsequent phase</li> <li>• evaluation of analytical procedures (with Quality Control), systems and equipment, personnel training status</li> <li>• monitoring of authorisation status</li> </ul>

Figure 3 Example: Interdisciplinary project team for the product transfer

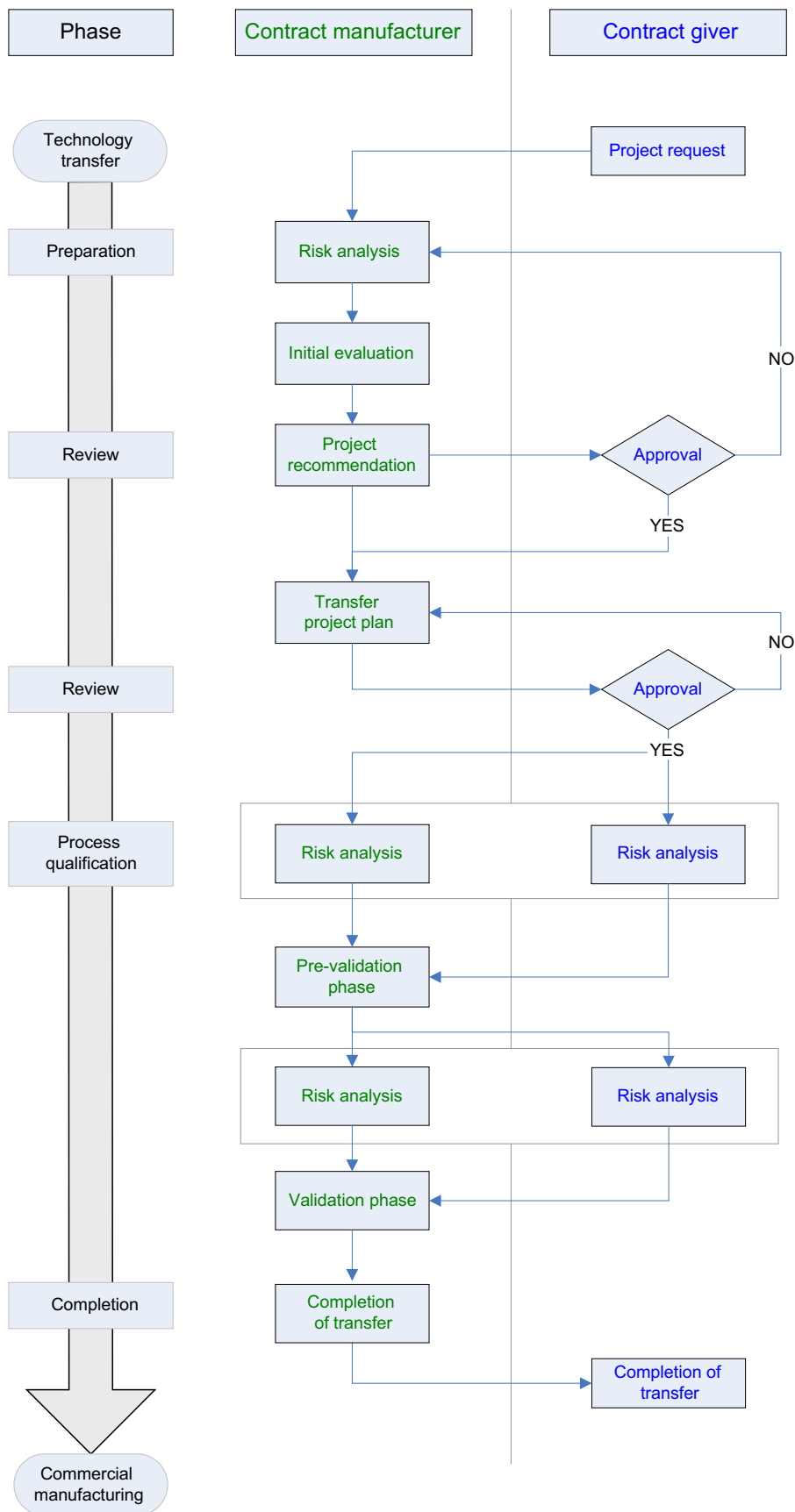


Figure 4 Examples of technology transfer phases

Content of a product transfer plan	
•	Aim and scope of the transfer
•	Key players and their responsibilities
•	Comparison and evaluation of differences in starting materials, manufacturing processes and equipment/machinery (GAP analysis)
•	Identification of critical issues
•	Specification of acceptance criteria for the individual phases of the transfer
•	Type of evaluation of the manufactured batches
•	Aspects of the analytical method transfer
•	Planned strategy for test batches, qualification batches and process validation
•	Handling of deviations in the individual phases
•	Acceptance criteria for the final conclusion on the transfer

Figure 6 Standard content of any technology transfer plan

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.

CQA	Process steps					
	Granulation	Drying	Milling	Mixing	Tabletting	Film-coating
Appearance	low	low	low	low	medium	high
Content	low	low	low	low	low	low
Purity	low	low	low	medium	low	low
Homogeneity	low	low	medium	high	high	low
Release	medium	low	high	medium	low	medium
Particle size distribution	medium	low	high	low	low	low
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.	Tabletting 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.

Figure 7 Evaluation of process steps

<b>Transfer plan Fantasin 10 mg film-coated tablets</b>		
<b>Document no.</b>	<b>PTF-10000</b>	
<b>Version</b>	<b>01</b>	<b>Number of appendices: 6</b>
<b>Replaces version</b>	<b>n/a</b>	<b>Page 1 of 14</b>

**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*

Figure 9



<b>Transfer plan Fantasin 10 mg film-coated tablets</b>		
<b>Document no.</b>	<b>PTF-10000</b>	
<b>Version</b>	<b>01</b>	<b>Number of appendices: 6</b>
<b>Replaces version</b>	<b>n/a</b>	<b>Page 7 of 14</b>

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2	Document transfer
3	Document transfer
4	System comparison
5	Regulatory affairs activities
6	Stability studies

Figure 9 (cont.)

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### **Activities:**

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