WHO GUIDELINE ON TRANSFER OF TECHNOLOGY

DRAFT DOCUMENT FOR COMMENT

The need for new WHO guidance for transfer of technology was discussed at the forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2007. Colleagues from the WHO Prequalification Programme shared their experience of recently submitted dossiers by, and inspections carried out in, plants that had undergone technology transfer. Technology transfer is happening worldwide both within and between companies, and within the same country as well as between countries. The Expert Committee, therefore, recommended that WHO guidelines on transfer of technology be developed. This draft text was subsequently prepared by Mr John Startup, United Kingdom and by Dr Monika Zweygarth, South Africa.

Please address comments on this proposal, by 30 September 2008, to Dr S. Kopp, Manager, Quality Assurance, Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int with a copy to rwakisetaa@who.int.
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QAS/08.259:

**WHO GUIDELINE ON TRANSFER OF TECHNOLOGY**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation made by WHO Expert Committee on Specifications for Pharmaceutical Preparations to prepare the guideline</td>
<td>15-19 October 2007</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
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</tr>
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<td>November 2008 - ...</td>
</tr>
<tr>
<td>Mailing of revised, second draft for comments</td>
<td></td>
</tr>
</tbody>
</table>
CONTENTS

1. INTRODUCTION ............................................................................................................4
2. SCOPE ..........................................................................................................................5
3. GLOSSARY ....................................................................................................................5
4. PRODUCTION: TRANSFER (PROCESSING, PACKAGING AND CLEANING) ..........8
5. QUALITY CONTROL: ANALYTICAL METHOD TRANSFER ......................................13
6. ORGANIZATION AND MANAGEMENT .................................................................17
7. PERSONNEL ..................................................................................................................20
8. PREMISES AND EQUIPMENT ....................................................................................20
9. DOCUMENTATION ....................................................................................................22
10. QUALIFICATION AND VALIDATION .......................................................................24
11. BIBLIOGRAPHY .........................................................................................................27
1. INTRODUCTION

1.1 Transfer of processes to an alternative site occur at some stage in the life-cycle of most products, from preclinical development through clinical studies, scale-up and launch, to the post-approval phase. The processes usually transferred are those of manufacturing investigational pharmaceutical products for clinical trials as part of research and development, manufacturing active pharmaceutical ingredients (APIs), manufacturing and packaging established finished pharmaceutical products (FPPs) and/or performing analytical testing.

1.2 Transfer of technology is defined as “a logical procedure that controls the transfer of an established process together with its documentation and professional expertise to a site capable of reproducing the process and its support functions to a predetermined level of performance”.

1.3 Literature searches revealed little information on the subject from national or regional regulatory bodies. Guidance on intra-company transfers was prepared by the International Society for Pharmaceutical Engineering (ISPE) (1).

1.4 The ever-changing business strategies of pharmaceutical companies increasingly involve intra- and inter-company transfers of technology for reasons such as the need for additional capacity, relocation of operations or consolidations and mergers. The WHO Expert Committee on Specifications for Pharmaceutical Preparations, therefore, recommended in its forty-second report that WHO address this issue through preparation of WHO guidelines in this area (2).

1.5 Transfer of technology requires a planned approach using trained and knowledgeable personnel working within a robust quality system, with documentation of data covering all aspects of production and quality control.

1.6 In order for the transfer to be successful, the following requirements should be met:
   • the faculties and equipment at the sending unit (SU) and at the receiving unit (RU) should be equivalent;
   • adequate trained staff should be available at the RU; and
   • SOPs, protocols and reports, specifications, critical process parameters and supportive data should be transferred from the SU to the RU.

1.7 A time frame should be defined for the transfer project.

1.8 Regulatory requirements in the countries of the SU and the RU should be taken into account and interpreted consistently throughout any transfer programme project.

1.9 Technology transfer can be considered successful if there is documented evidence that the RU can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with the SU.

1.10 Technology transfer projects, particularly those between different companies, have legal and economic implications. If such issues, which may include intellectual property rights, royalties, pricing, conflict of interest and confidentiality, are expected to impact on technical matters in any way, they should be considered before and during planning and execution of the transfer.
2. SCOPE

2.1 This document gives guidance in principle and provides general recommendations on the necessary activities that should be addressed to conduct a successful intra- or inter-site transfer of technology as described in the Introduction to this guideline. The intention is to address the basic requirements needed for a successful transfer in order to satisfy any regulatory authority.

2.2 The guideline addresses following areas at the sending unit (SU) and the receiving unit (RU):

- transfer of production (processing, packaging and cleaning);
- transfer of analytical methods for quality assurance and quality control;
- skills assessment and training;
- organization and management of the transfer;
- assessment of premises and equipment;
- documentation; and
- qualification and validation.

2.3 The recommendations provided in this guideline apply to all dosage forms. Particularly close control of certain aspects will be required for complex formulations such as sterile products, metered-dose aerosols and clinical trials supplies. WHO guidance on manufacture of specific pharmaceutical products (4d,4e) will be useful in this regard.

2.4 Because each transfer project is unique, the provision of a comprehensive set of guidelines is beyond the scope of this document.

2.5 This guideline does not provide guidance on any legal, financial or commercial considerations associated with technology transfer projects.

3. GLOSSARY

Acceptance criteria
Measurable terms under which a test result will be considered acceptable.

Bracketing
An experimental design to test only the extremes of, for example, dosage strength. The design assumes that the extremes will be representative of all the samples between the extremes.

Change control (C/C)
A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

Commissioning
The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.
Corrective action (C/A)
Any action to be taken when the results of monitoring at a critical control point indicate a loss of control.

Critical
Having the potential to impact product quality or performance in a significant way.

Critical control point (CCP)
A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

Design qualification (DQ)
Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of good manufacturing practices (GMP).

Drug master file (DMF)
Detailed information concerning a specific facility, process or product submitted to the drug regulatory authority, intended for the incorporation into the application for marketing authorization.

Gap analysis
Identification of critical elements of a process which are available at the SU but are missing from the RU.

Good Manufacturing Practices (GMP)(4)
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Inter-company transfer
A transfer of technology between sites of different companies.

Intra-company transfer
A transfer of technology between sites of the same group of companies.

In-process control (IPC)
Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Installation qualification (IQ)
The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

Operational qualification (OQ)
Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

Performance qualification (PQ)
Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. (In the context of systems, the term “process validation” may also be used.)
Process validation
Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

Quality assurance (QA)
Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. The totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

Quality control (QC)
Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

Qualification
Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

Quality risk management (QRM)
Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product across the product life-cycle.

Receiving unit (RU)
The involved disciplines at an organization where a designated product, process or method is expected to be transferred.

Sending unit (SU)
The involved disciplines at an organization where a designated product, process or method is expected to be transferred from.

Spiking
The addition of a known amount of a compound to a standard, sample or placebo, typically for the purpose of confirming the performance of an analytical procedure.

Standard operating procedure (SOP)
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Transfer of technology (TOT)
A logical procedure that controls the transfer of an established process together with its documentation and professional expertise to a site capable of reproducing the process and its support functions to a predetermined level of performance.
Validation
Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

Validation master plan (VMP)
A high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer’s overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer’s validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

Validation protocol (or plan) (VP)
A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process – or a part thereof – for routine use.

Validation report (VR)
A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and/or equipment.

4. PRODUCTION: TRANSFER (PROCESSING, PACKAGING AND CLEANING)

4.1 It should be established at the outset whether the intention is to perform single-batch manufacture, continuous production or campaigns, and whether the RU can accommodate the intended production capacity.

4.2 Consideration should be given to the level and depth of detail to be transferred to support production and any further development or process optimization at the RU as intended under the transfer project plan.

4.3 The SU and the RU should jointly develop a protocol for the transfer of relevant information related to the manufacturing process under consideration from the SU to the RU, as well as the development of an equivalent process at the RU.

Starting materials
4.4 The specifications of the starting materials (APIs and excipients) to be used at the RU should be consistent with reference batches (development batches, biobatches or batches manufactured at the SU). Any properties which are likely to influence the process or product should be identified and characterized. For example, an API having the correct purity and potency may have physical characteristics which make formulation to a registered specification impossible.

Active Pharmaceutical Ingredients (API)
4.5 The SU should provide the drug master file (DMF) and any relevant additional information on the API to the RU to be checked against the specifications of the API. The following information should be provided:

- manufacturer;
- flow chart of synthetic pathway, outlining the process, including entry points for raw materials, critical steps, process controls and intermediates;
• definitive form of the API (including photomicrographs and other relevant data) and any polymorphic and solvate forms;
• solubility profile;
• partition coefficient (including the method of determination);
• intrinsic dissolution rate (including the method of determination);
• particle size and distribution (including the method of determination);
• bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate;
• water content and determination of hygroscopicity, including water activity data and special handling requirements;
• microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the API supports microbiological growth) in accordance with regional pharmacopoeial requirements;
• specifications and justification for release and end-of-life limits;
• summary of stability studies conducted in conformity with current guidelines, including conclusions and recommendations on retest date;
• listing of potential and observed synthetic impurities, with data to support proposed specifications and typically observed levels;
• information on degradants, with a listing of potential and observed degradation products and data to support proposed specifications and typically observed levels;
• potency factor, indicating observed purity and justification for any recommended adjustment to the input quantity of API for product manufacturing, providing example calculations; and
• special considerations with implications for storage and/or handling, e.g. safety and environmental factors and sensitivity to heat, light or moisture.

Excipients

4.6 The excipients (4c) to be used have a potential impact on the final product. Their specifications as well as the DMF should, therefore, be made available by the SU for transfer to the RU site. The following information should be provided for all types of excipients:

• description of functionality, with justification for inclusion of any antioxidant, preservative or any excipient above recommended guidelines;
• manufacturer;
• specifications, i.e. monographs and additional information that may affect product processing or quality for compendia excipients, or a complete listing of specifications, including analytical methods and justification for release limits for non-compendial excipients. For excipients used for the first time in a human drug product or by a new route of administration, the same level of detail as for a drug substance should be provided;
special considerations with implications for storage and/or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets) and sensitivity to heat, light or moisture solubility; and

regulatory considerations, i.e. compendial status and appropriate regulatory information for non-compendial excipients; information on residual solvents or organic volatile impurities; and documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements (where applicable).

4.7 Depending on the type of dosage form, the SU should provide relevant information on physical properties of excipients to the RU, including:

- definitive form (for solid and inhaled dosage forms);
- solubility profile (for solid, inhaled and transdermal dosage forms);
- partition coefficient, including the method of determination (for transdermal dosage forms);
- intrinsic dissolution rate, including the method of determination (for transdermal dosage forms);
- particle size and distribution, including the method of determination (for solid, inhaled and transdermal dosage forms);
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate (for solid and inhaled dosage forms);
- compaction properties (for solid dosage forms);
- melting point range (for semi-solid/topical dosage forms);
- pH range (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- ionic strength (for parenteral dosage forms);
- specific density/gravity (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- viscosity and/or viscoelasticity (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- osmolarity (for parenteral dosage forms);
- water content and determination of hygroscopicity, including water activity data and special handling requirements (for solid and inhaled dosage forms);
- moisture content range (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- microbiological considerations in accordance with regional pharmacopoeial requirements (for parenteral, semi-solid/topical, liquid, inhaled and transdermal dosage forms); and
- information on adhesives supporting compliance with peel, sheer and adhesion design criteria (for transdermal dosage forms).
Process information

4.8 The SU should provide a detailed characterization of the product, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls and specifications, packaging components and configurations, and any special safety and handling considerations.

4.9 The SU should provide any information on the history of process development which may be required to enable the RU to perform any further development and/or process optimization intended after successful transfer. Such information may include the following:

- information on clinical development, e.g. information on the rationale for the synthesis, route and form selection, technology selection, equipment, clinical tests, and product composition;
- information on scale-up activities: process optimization, statistical optimization of critical process parameters, pilot report and/or information on pilot-scale development activities indicating the number and disposition of batches manufactured; and
- information or report on full-scale development activities, indicating the number and disposition of batches manufactured, and deviation and change control reports which led to the current manufacturing.

4.10 The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and resulting implications, e.g. need for gowning or protective clothing (see also Section 8).

4.11 The SU should provide to the RU information on current processing and testing, including but not limited to:

- a detailed description of facility requirements and equipment (see Section 8);
- process technology selection;
- information on starting materials (see Points 4.5-4.7 above), applicable MSDs and storage requirements for raw materials and finished products;
- description of manufacturing steps (narrative and process maps or flow charts), including qualification of in-processing hold times and conditions, order and method of raw material addition and bulk transfers between processing steps;
- description of analytical methods (see Section 5);
- in-process controls, including, e.g. identification of critical performance aspects for specific dosage forms, identification of process control points, product quality attributes and qualification of critical processing parameter ranges, statistical process control (SPC) charts;
- validation information, e.g. validation plans and reports, and annual product reviews;
- stability information; and
- an authorized set of SOPs and work instructions for manufacturing.

4.12 Based on the information received from the SU, the RU should consider its own capability to manufacture and pack the product to the required standards, and should develop
relevant plant operating procedures and documentation before the start of the transfer. Process development at the SU should address the following tasks:

- comparison and assessment of suitability and qualification of facility and equipment (see Section 8);
- description of manufacturing process and movement of man and material at RU (narrative and/or process maps or flow charts);
- determination of critical steps in manufacture, including hold times, end-points, sampling points and sampling techniques (4f);
- writing and approval of SOPs for all production operations (e.g. dispensing, granulation/blending/solution preparation, tablet compression, tablet coating, encapsulation, liquid filling, primary and secondary packaging and in-process quality control), packaging, cleaning, testing and storage;
- evaluation of stability information, with generation of site-specific stability data if required (5); and
- compliance with regulatory requirements for any changes made, e.g. in terms of batch size.

Packaging

4.13  The transfer of packaging operations should follow the same procedural patterns as those of the production transfer.

4.14  Information on packaging to be transferred from the SU to the RU include specifications for a suitable container/closure system, as well as any relevant additional information on design, packing, processing or labelling requirements needed for qualification of packaging components at the RU.

4.15  For quality control testing of packaging components, specifications should be provided for drawings, artwork, material (glass, card, fibre board, etc.).

4.16  Based on the information provided, the RU should perform a suitability study for initial qualification of the packaging components. Packaging is considered suitable if it provides adequate protection (preventing degradation of the drug due to environmental influences), safety (absence of undesirable substances released into the product), compatibility (absence of interaction possibly affecting drug quality) and performance (functionality in terms of drug delivery).

Cleaning

4.17  During the manufacturing process, pharmaceutical products and APIs can be contaminated by other pharmaceutical products or APIs if processing different products. To minimize the risk of contamination and cross-contamination, operator exposure and environmental effects, adequate cleaning procedures are essential.

4.18  The SU should provide information on cleaning procedures in use at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including:

- solubility information of active ingredients, excipients and vehicles;
• minimum therapeutic doses of active ingredients;
• therapeutic category and toxicological assessment;
• existing validated cleaning procedures;
• cleaning validation reports (chemical and microbiological);
• information on cleaning agents used (efficacy, evidence that they do not interfere with analytical testing for residues of actives); and
• recovery studies to validate the sampling methodology.

4.19 Prior to the transfer the SU should provide information on limits for product residues, and the rationale for limit selection. Details on cleaning validation are given in Section 10.

4.20 Based on the information provided by the SU, cleaning procedures should be designed at the RU, taking into account relevant characteristics of the starting materials (e.g. potency, toxicity, solubility, corrosiveness, temperature sensitivity), manufacturing equipment design and configuration, cleaning agent and residue, and disposal of rinsing process.

Commissioning of processing, packaging and cleaning systems

4.21 Once approved manufacturing, packaging, cleaning, testing and storage procedures have been designed at the RU, systems should be set up and commissioned, and initial trial batches should be produced. All processing parameters and finished product specifications should be challenged.

4.22 Once process capability has been demonstrated, assuring that the product, process or method at the new site meets predefined and justified specifications, process validation and cleaning validation can be carried out (see Section 10).

5. QUALITY CONTROL: ANALYTICAL METHOD TRANSFER

5.1 Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the registered specification (3).

5.2 Transfer of analytical methods used to test pharmaceutical products, their ingredients and cleaning (residue) samples, needs to be in place before process validation studies of manufacturing operations can be carried out.

5.3 The SU should prepare a protocol defining the steps to be undertaken for analytical method transfer. The analytical methods transfer protocol should describe the objective; scope; responsibilities of the SU and the RU; materials, methods and equipment; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used if any); deviations; references; signed approval; and details of reference samples (APIs, intermediates and finished products).

5.4 The SU's responsibilities for the transfer of analytical methods are to:
• provide method-specific training for analysts and other quality control staff;
• provide acceptance criteria and validation protocols for any RU training exercises;
• assist in analysis of quality control testing results;
• define and justify all methods to be transferred for testing a given product, ingredient or cleaning sample;
• define experimental design, sampling methods and acceptance criteria;
• provide any validation reports for methods under transfer, and demonstrate their robustness;
• provide data for the equipment used and any standard reference samples; and
• provide approved SOPs used in testing.

5.5 The RU's responsibilities are to:
• review analytical methods provided by the SU, and formally agree on acceptance criteria before execution of the transfer protocol;
• ensure that the necessary equipment for quality control is available and qualified at the RU site. Equipment should be replicated where possible, but it is accepted that different models, e.g. spectrometers and chromatographs, could already be in place;
• ensure that adequately trained and experienced personnel is in place for analytical testing;
• provide a documentation system capable of recording receipt and testing of samples to the required specification using approved test methods, and of reporting, recording and collating data and designation of status (approved, rejected, quarantine); and
• execute the transfer protocol.

5.6 A suggested analytical training protocol would be as follows:
• SU and RU analysts assay two retained samples from SU;
• SU and RU analysts then assay two sub-potent samples (available from SU or spiked);
• SU and RU analysts assay samples taken from RU production;
• RU analyst provides sufficient replicate analyses to enable a significance test (e.g. student’s t) against the established method at the SU site; and
• a similar exercise should be undertaken for analysis of low levels of APIs in rinse waters for equipment cleaning validation.

5.7 All training activities and outcomes should be documented.

5.8 Relevant tests applicable to APIs and finished pharmaceutical products include:
• identity;
• assay for potency;
• uniformity of content (finished pharmaceutical products);
• impurities and degradation products;
• physical criteria (see Point 5.9 below);
• cleaning verification to assure that residues and viable organisms on equipment and critical areas of the work environment are below specified limits; and
• microbiological testing (for APIs which promote biological growth).

5.9 Physical properties applicable to different dosage forms are reflected in the specifications for excipients to be transferred (see Point 4.7). Relevant tests for physical criteria include, but are not limited to:

• disintegration, in vitro dissolution, moisture, average weight, thickness, friability and hardness for solid dosage forms;
• factors affecting filling such as specific density/gravity, viscosity for liquid dosage forms;
• pH for parenteral, semi-solid/topical, liquid and transdermal dosage forms; and
• particle size for inhaled dosage forms.

5.10 Where a sterile manufacturing process is involved, a comprehensive, fully validated system of control should be in place to minimize the risks of microbiological, particulate and pyrogen contamination. Specific points for the manufacture of sterile preparations are outlined in relevant WHO guidance (4d).

5.11 Reference to compendial monographs (e.g. The International Pharmacopoeia (3), European Pharmacopoeia, British Pharmacopoeia and United States Pharmacopeia), where available, is expected. Typically, transfer of compendial methods is only necessary if additional detail needs to be described or if critical parameters need to be specified to obtain accurate results.

5.12 Suggested experimental designs and acceptance criteria for the main analytical testing methods are shown in Table 1.
Table 1. Suggested experimental designs and acceptance criteria for analytical testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Considerations for transfer</th>
<th>Replication of tests</th>
<th>Set-up</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>Transfer should focus on sample preparation, instruments, data interpretation. Acceptable to include in assay transfer where relevant</td>
<td>One determination usually sufficient to demonstrate equivalence</td>
<td>Different sets of instruments and columns</td>
<td>Comparison of mean and variability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Independent solution preparation</td>
<td>Two one-sided t-tests with inter-site differences &lt;=2% , 95% confidence</td>
</tr>
<tr>
<td>Assay for potency</td>
<td>- Non-specific assay should not be used for stability testing.</td>
<td>At each site: 2 analysts x 3 lots, in triplicate (=18 per site)</td>
<td>Different sets of instruments and columns</td>
<td>Comparison of mean and variability</td>
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<tr>
<td></td>
<td>- Bracketing may be appropriate for multiple strengths</td>
<td></td>
<td>Independent solution preparation</td>
<td>Two one-sided t-tests with inter-site differences &lt;=3% , 95% confidence</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>If method is equivalent to assay method, separate transfer is not usually required</td>
<td>At each site: 2 analysts, x 1 lot (=2 per site)</td>
<td>Different sets of instruments and columns</td>
<td>Mean at RU within +/-3% of mean at SU; comparison of relative st. dev.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Independent solution preparation</td>
<td>Two one-sided t-tests with inter-site differences &lt;=3% , 95% confidence</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Bracketing may be appropriate for multiple strengths</td>
<td>6 units (12 if not routine at RU, and for extended release products)</td>
<td>Mean at RU within +/-5% of mean at SU</td>
<td>Compare profile (e.g. $F^2$), or Compare data at Q time points as for assay</td>
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<tr>
<td>Cleaning verification (recovery of residues from surfaces)</td>
<td>Confirm that same swabbing material is used at SU and RU</td>
<td>Use spiked samples, with levels within 3x validated st. dev. or within +/-10% of specification (whichever is the greater)</td>
<td>- All samples spiked above specification should fail</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- 90% of samples spiked below specification should pass</td>
<td>Two one-sided t-tests with inter-site differences &lt;=3% , 95% confidence</td>
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<tr>
<td>Microbiological testing (qualitative and quantitative limit tests)</td>
<td>- Execute common on-site validation protocol: rationale; method identity; validation parameters; data summary; acceptance criteria; methods of compiling and analysing data; handling of out-of-specification results; follow-up requirements</td>
<td>Validation in triplicate</td>
<td>Use different lots for each validation exercise</td>
<td>- Qualitative: Demonstrate recovery of microorganisms</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Quantitative: Recovery levels within acceptance limits specified in protocol</td>
</tr>
<tr>
<td>Impurity, degradation, residual solvents</td>
<td>- Confirm response factors for calculation relative to drug peak; - Confirm limit of quantitation at RU; - Compare chromatograms - Compare accuracy and precision for spiking experiments</td>
<td>At each site: 2 analysts × 3 lots, in duplicate (in triplicate if done together with assay)</td>
<td>- Different days, different sets of instruments and columns - Use samples of similar age, homogeneity, packaging, storage - Use spiked samples if necessary</td>
<td>(For low levels:) Values at RU within +/-25% of values at SU, or Mean at RU within +/- 0.05% of mean at SU (5%?)</td>
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* [Note from WHO Secretariat: are these figures correct?]

5.13 The SU and the RU should execute the transfer protocol and jointly prepare a transfer report. The points to be addressed in the analytical methods transfer report are listed in Section 10.

6. ORGANIZATION AND MANAGEMENT

6.1 Organization and management of a successful technology transfer need to assure that the following four main steps have been executed and documented:

- presence of specifications and acceptance criteria of the product, process or method to be transferred;
- establishment of adequate facilities, equipment, systems and trained staff;
- establishment of protocols and SOPs for the transfer itself and for reproduction of the product, process or method to be transferred; and
- data supporting the successful reproduction of the product, process or method by the RU.

6.2 There should be a project management plan which identifies and controls all the necessary activities identified at the start of the undertaking.

6.3 Both the SU and the RU are responsible for specifically allotted tasks within their unit, with others being shared between them. The actual transfer should follow an authorized protocol, assuring that all tasks are executed and documented.

6.4 The transfer protocol should list the intended sequential stages of the transfer. The protocol should include:

- objective;
- scope;
- key personnel and their responsibilities;
- a side-by-side comparison of materials, methods and equipment;
- the transfer stages with documented evidence that each critical stage has been satisfactorily accomplished before the next commences;
- identification of critical control points;
• experimental design and acceptance criteria for analytical methods;
• information on trial production batches, qualification batches and process validation;
• change control for any process deviations encountered;
• references;
• assessment of end-product;
• reference samples of active ingredients, intermediates and finished products; and
• conclusion, including signed-off approval by project manager.

6.5 A time frame should be defined for execution of the transfer protocol.

6.6 The SU should provide the necessary validation documentation for the process and its support functions. In the majority of cases an established process is transferred, and such documentation is already available.

6.7 The SU should provide criteria and information on hazards and critical steps associated with the product, process or method to be transferred, to serve as a basis for a quality risk management exercise at the RU (6,7,4a).

6.8 The SU should assess the suitability and degree of preparedness of the RU before transfer in terms of premises, equipment and support services (e.g. purchasing and inventory control mechanisms, quality control procedures, documentation, computer validation, site validation, equipment qualification, water for pharmaceutical production, waste management).

6.9 The SU and the RU should jointly verify that the following, satisfactorily completed validation protocols are available:

• installation qualification (IQ) and operational qualification (OQ) data for manufacturing and packaging equipment at the RU site; and
• qualification of the rooms for both manufacture and packaging at the RU site.

6.10 The SU and the RU should jointly implement training programmes specific to the product, process or method to be transferred, e.g. on analytical methods or equipment usage, and assess training outcomes (see Section 7).

6.11 The SU and the RU should jointly execute the transfer protocol according to a checklist and/or flow diagram showing the sequence of steps to be carried out to effect an efficient transfer. A suggested simplified flow diagram is shown in Figure 1.

6.12 A documented history of process and method development and experiences encountered during the development work should be recorded during the course of the technology transfer to serve as a reference for any future projects.

6.13 The SU and the RU should jointly document the execution of the transfer protocol in a transfer report.
Figure 1: Suggested flow diagram

- Project definition
- Team development
- Process development
  - Starting materials assessment
  - Analytical method transfer (PQ)
  - Training
- Equipment selection and transfer (IQ, OQ)
  - Skills set assessment
  - Clinical performance (PQ)
- Process transfer: processing, packaging, cleaning
  - Trial batches (PQ: processing, packaging, cleaning)
  - Quality control
  - Stability testing
- Qualification batches
  - Authorized product
  - Registration
- Assessment: Facility (DQ, IQ, OQ)
  - Health, Safety & Environment
  - Supporting systems
  - Training
7. PERSONNEL

Project team

7.1 Any transfer project will be managed by a team comprised of members from both sites with clearly defined key responsibilities. The team shall be drawn from members of relevant disciplines from both the SU and RU sites.

7.2 The team members should have the necessary qualifications and experience to manage their particular aspect of the transfer.

7.3 The team should be headed by a senior manager with the responsibility of guiding the project and authorizing decisions made during the transfer operations. The disciplines involved include but are not limited to site engineering and maintenance, validation, manufacturing and quality control.

7.4 Quality assurance and regulatory affairs personnel should be available to monitor the project throughout.

Training

7.5 The RU should ensure that trained personnel is in place before validation of the process to be transferred.

7.6 The RU should perform a skills assessment and gap analysis to identify training needs associated with product-specific activities such as operation and maintenance of equipment, processing and testing. Existing training records should be reviewed and a programme drawn up based on discrepancies identified in the gap analysis exercise.

7.7 The RU should develop training protocols for any new procedures, describing the objective, methods of training and evidence of success of the training.

7.8 The SU should provide a training programme and assessment criteria for relevant personnel, e.g. engineers, production technicians, QC technicians.

7.9 After execution of the training protocols, the SU and the RU should jointly prepare a report confirming that all training has been successfully accomplished.

8. PREMISES AND EQUIPMENT

Premises

8.1 The SU should provide information to the RU on the layout, construction and finish of all buildings and services (4g, 4h) (heating, ventilation and air-conditioning (HVAC), temperature, relative humidity, water, power, compressed air) impacting the product, process or method to be transferred.

8.2 The SU should provide information on relevant health, safety and environmental issues, including:

- inherent risks of the manufacturing processes (e.g. reactive chemical hazards, exposure limits, fire and explosion risks);
• health and safety requirements to minimize operator exposure (e.g. atmospheric containment of pharmaceutical dust);
• emergency planning considerations (e.g. in case of gas or dust release, spillage, fire and firewater run-off); and
• identification of waste streams and provisions for re-use, recycling and/or disposal.

8.3 Differences in building, construction layout and services between the SU and the RU should be listed and compared in view of the following considerations:
• buildings and services at the RU should be capable of accommodating the product, process or method under transfer to the agreed quality standard and production volume in compliance with GMP;
• quality control laboratories should be equipped and capable of testing all APIs, excipients, intermediate and finished products, packaging components and cleaning validation samples;
• buildings intended for production of a highly sensitizing nature (e.g. penicillins and cytotoxic materials) should be dedicated for this purpose and located in a different facility from other production units; and
• health, safety and environmental issues, including waste management, emergency planning, minimization of operator exposure and environmental impact, should be addressed at the RU in compliance with any regulatory or company-developed rules, regulations and limits. Comparison with the most stringent global limits may be a useful indicator of potential future changes.

Equipment

8.4 The SU should provide a list of equipment, makes and models involved in the manufacture, filling, packing and/or control of the product, process or method to be transferred, together with existing qualification and validation documentation. Relevant documentation may include:
• drawings;
• manuals;
• maintenance logs;
• calibration logs; and
• SOPs (e.g. equipment set up, operation, cleaning, maintenance, calibration, storage).

8.5 The RU should review the information provided by the SU together with its own inventory list including the qualification status (IQ, OQ, PQ) of all equipment and systems, and perform a side-by-side comparison of equipment at the two sites in terms of their functionality, makes, models and qualification status.

8.6 Based on the side-by-side comparison, the RU should perform a gap analysis to identify requirements for adaptation of existing equipment, or acquisition of new equipment, to enable the RU to reproduce the process being transferred. GMP requirements should be satisfied, and intended production volumes and batch sizes (e.g. same, scaled-up or campaign) should be considered. Factors to be compared include:
• minimum and maximum capacity;
• material of construction;
• critical operating parameters;
• critical equipment components (e.g. filters, screens, temperature/pressure sensors); and
• range of intended use.

8.7 The facility- and building-specific location of all equipment at the RU should be considered at the time of drawing up process maps or flow charts of the manufacturing process to be transferred, including movement of personnel and material (see Point 4.12).

8.8 The impact of manufacturing new products on products currently manufactured with the same equipment should be determined.

8.9 Where existing producing equipment needs to be adapted to be capable of reproducing the process being transferred, a detailed development project should be included in the transfer protocol.

8.10 New equipment should be designed and constructed to facilitate the process and ease cleaning and maintenance operations. Any newly acquired equipment should undergo a qualification protocol up to and including OQ level.

8.11 Applicable operating procedures for set-up, operation, cleaning, storage and maintenance should be developed by the conclusion of OQ. Supporting documents such as drawings of equipment and piping installations, manuals, maintenance logs and calibration logs should be retained.

**General**

8.12 The quality system at the RU should include validated cleaning and maintenance procedures for buildings, equipment services and support systems which impact the product, process or method under transfer.

8.13 A formal change control programme should be in place for equipment and utility systems.

8.14 The RU should integrate and commission the relevant systems and equipment before process validation is carried out (see Section 10).
9. DOCUMENTATION

9.1 The documentation required for the transfer project itself is wide ranging. Documentation commonly required is listed in Table 2.

Table 2. Documentation for transfer of technology

<table>
<thead>
<tr>
<th>Key task</th>
<th>Documentation provided by SU</th>
<th>Transfer documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project definition</td>
<td></td>
<td>Project implementation plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOT protocol</td>
</tr>
<tr>
<td>Team development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility assessment</td>
<td>Plans and layout of facility, buildings</td>
<td>Side-by-side comparison with RU facility and buildings; gap analysis</td>
</tr>
<tr>
<td></td>
<td>(construction, finish) Qualification status (DQ, IQ, OQ) and reports</td>
<td>Qualification protocol and report</td>
</tr>
<tr>
<td>HS&amp;E assessment</td>
<td>Product-specific waste management plans</td>
<td></td>
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<td></td>
<td>Contingency plans</td>
<td></td>
</tr>
<tr>
<td>Skill set analysis/training</td>
<td>SOPs and training records (product-specific operations, analysis, testing)</td>
<td>Training protocols, assessment results</td>
</tr>
<tr>
<td>Analytical method transfer</td>
<td>Analytical method specifications and validation, including in-process quality control</td>
<td>Analytical methods transfer protocol and report</td>
</tr>
<tr>
<td>Starting material evaluation</td>
<td>Specifications and additional information on APIs, excipients</td>
<td></td>
</tr>
<tr>
<td>Equipment selection and transfer</td>
<td>Inventory list of all equipment and systems, including makes, models, qualification status (IQ, OQ, PQ) Drawings, manuals, logs, SOPs (e.g. set-up, operation, cleaning, maintenance, calibration, storage)</td>
<td>Side-by-side comparison with RU equipment (makes, models, qualification status) Gap analysis Qualification and validation protocol and report</td>
</tr>
<tr>
<td>Process transfer: manufacturing and packaging</td>
<td>Reference batches (clinical, dossier, biobatches) Development report (manufacturing process rationale) History of critical analytical data Rationale for specifications Change control documentation Critical manufacturing process parameters Process validation reports</td>
<td>History of process development at RU Experiences at RU should be recorded for future reference</td>
</tr>
<tr>
<td></td>
<td>Drug master file API validation status/report(s) Product stability data Current master batch manufacturing and packaging records List of all batches produced List of pivotal batches Deviation reports Investigations, complaints, recalls Annual product review</td>
<td>Provisional batch manufacturing document (RU to develop) Provisional batch packaging document (RU to develop) Description of process at RU (narrative, process map, flow chart) Process validation protocol and report</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Cleaning validation, including: Solubility information; therapeutic doses; category (toxicology); existing cleaning SOPs; validation reports - chemical and micro; agents used; recovery study</td>
<td>Product- and site-specific cleaning SOPs at RU Cleaning validation protocol and report</td>
</tr>
<tr>
<td>Verification</td>
<td></td>
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<tr>
<td>Data review</td>
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<tr>
<td>Conclusion/Sign-off</td>
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<td>TOT report</td>
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</table>
10. QUALIFICATION AND VALIDATION

General

10.1 Qualification and validation (4i) of facilities, equipment, systems and procedures are essential to demonstrate that all critical stages of the transfer project have been completed successfully, enabling the RU to reproduce the product, process or method routinely to the specifications agreed with the SU.

10.2 Validation performed as part of the transfer project should be documented in a validation master plan (VMP). The VMP should identify the stages which need to be validated and define acceptance criteria.

10.3 For intra-company transfers, the RU should operate under the same VMP as the SU. For inter-company transfers, a VMP should be in place at the RU before the transfer.

10.4 The RU should prepare a validation protocol (VP) for each sequential step. Successful execution of each VP should be documented in a validation report (VR).

10.5 Setting up and commissioning of systems at the RU need to be completed before qualification and validation can be performed at the RU. The steps required for this purpose have been described in this guideline for buildings, services and equipment (see Section 8), manufacturing, packaging and cleaning (see Section 4) and analytical testing (see Section 5). In brief, the following basic steps apply equally to each of these areas:

- the SU should provide information on materials, systems and procedures involved in the manufacturing of the product, process or method to be transferred;
- the RU should review the information provided by the SU, and audit its current systems, equipment and processes, including non-process related practices and support services that impact the process;
- based on this review, the RU should either accept the information provided or develop it further to prepare site-specific procedures, SOPs, training programmes and protocols which will form the basis of the qualification and validation; and
- relevant staff, e.g. operators and analysts, should be trained in any new processes as required (see Section 7).

10.6 Once the required systems and procedures have been commissioned at the RU, and successful training has been documented, qualification and validation of facility and equipment should be executed, followed by validation of analytical test methods, process validation for manufacturing and packaging, and cleaning validation.

Qualification of facility and equipment

10.7 The RU should review the gap analysis described in Section 8 and prepare, where appropriate, VPs for the facility, services and equipment (4i).

10.8 Both new and existing equipment should satisfy the VPs associated with purchase and design specifications, factory acceptance tests (FAT) if possible, IQ and OQ.
Performance qualification, including a further assessment of operating parameters with relation to product characteristics, should be established on commencement of trial batches.

Successful completion of qualification and validation should be documented in a report.

**Analytical methods validation**

Validation of analytical methods \((4i)\) should address the specificity, linearity of response, range, accuracy, precision, detection limit, quantitation limit and robustness of the analytical test method.

The analytical methods transfer protocol should cover the following sections:

- objective;
- scope;
- responsibilities of the SU and the RU;
- materials, methods and equipment;
- the experimental design and acceptance criteria;
- documentation (including information to be supplied with the results, and report forms to be used if any);
- deviations;
- references;
- signed approval; and
- details of reference samples (APIs, intermediates and finished products).

Successful transfer and validation of analytical methods should be documented in a report.

**Manufacturing process validation**

Based on process information and documentation described in Section 4, the RU should make preparations to conduct process validation studies \((4i)\) to ensure that the manufacturing process and associated testing are executed properly. For this purpose, the RU should prepare:

- a provisional batch manufacturing document; and
- a process validation protocol, based on the key steps and parameters as defined in the description of the manufacturing process, and specifying testing requirements based on the analytical methodology transferred (see Section 5).

The process validation protocol should include:

- a short description of the process;
- batch manufacturing record;
- key stages of production;
• finished product specification;
• analytical methodology;
• sample plan for intermediates (e.g. tests for blend homogeneity, moisture levels, bioburdens);
• in-process quality control and acceptance criteria;
• corrective action;
• change control;
• sign-off of authorized person;
• regulatory assessments; and
• conclusions and recommendations.

10.16 Upon approval of the batch documents, SOPs, test methods and the VP, and after successful training of operators and analysts, the RU should execute the process validation study. While it is useful to have SU personnel present to supervise the first batches manufactured, staff from the RU should execute all activities (i.e. operate the equipment, take samples, perform testing) so that the study is representative of manufacturing operations undertaken at the RU.

10.17 Statistical optimization of key processing parameters and prospective validation will be undertaken at the RU after initial implementation of the manufacturing process. Any deviations or incidents should be recorded and reviewed by quality assurance and regulatory affairs personnel, and a change control procedure invoked if it is deemed necessary.

10.18 Successful completion of manufacturing process validation should be documented in a process validation report.

Packaging
10.19 After reviewing of the information provided received from the SU and initial qualification of packing components, the RU should prepare protocols for qualification of packaging equipment, a provisional packaging record protocol and validation of packaging operations.

10.20 Critical packaging parameters to be included in the packaging VP and subsequent in-process quality control include, e.g.:
• thermo-sealing temperatures for blister packs;
• accuracy of fill volumes/weights/tablets;
• seal integrity;
• torque;
• correct printing of data (lot numbers and expiry dates); and
• correct bar code and pharmacode readings.

10.21 Successful packaging validation will be documented in a VR which will form part of the transfer documentation.
Cleaning validation

10.22 Cleaning procedures should strictly follow validated methods. The objective of the cleaning validation (4i) is to confirm the reliability of the cleaning procedure, so that the analytical monitoring may be omitted or reduced to a minimum in the routine phase.

10.23 Normally only cleaning procedures for product contact surfaces of the equipment need to be validated.

10.24 Analytical methods for testing of swab or rinse samples should be validated before the cleaning validation study is carried out.

10.25 Based on information on limits of product residues transferred from the SU, the RU should determine its own practical, achievable and verifiable limits for cleaning validation based on a consideration of the materials involved, their properties and their therapeutic dose.

10.26 At least three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated. It is usually not considered acceptable to "test until clean".

10.27 The analytical methods should be challenged in combination with the sampling methods used, to demonstrate both the levels of recovery from the equipment surface and the reproducibility of results.

11. BIBLIOGRAPHY


Note: This compendium contains WHO guidance provided by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The following WHO guidelines included in the compendium may be found useful for technology transfer projects:


Note 1: An amendment of WHO stability guidelines was adopted in 2006 to reflect conditions for Zone IV as follows:
— Zone IVa (30 degrees Celsius and 65% relative humidity); and
— Zone IVb (30 degrees Celsius and 75% relative humidity).

Note 2: Working document QAS/06.179/Rev.2 ("Draft stability testing of active pharmaceutical ingredients and pharmaceutical products") is currently under discussion for revision of the WHO stability guidelines.


[Note from Secretariat: As portions of the main text of the report have been shifted the references will be put in correct order in the final version of the document.]