WHO GUIDELINES ON THE TRANSFER OF TECHNOLOGY
IN PHARMACEUTICAL MANUFACTURING

DRAFT FOR COMMENTS

Please send your comments to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 20 February 2021. Please use the attached “Table of Comments” document for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the “Working documents in public consultation” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
WHO GUIDELINES ON THE TRANSFER OF TECHNOLOGY
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1. Introduction

1.1. Production and control procedures, validation and other related activities may be transferred from one site to another site prior to obtaining a marketing authorization. In some cases, this transfer takes place after the approval of, for example, a product, by a regulatory authority. This transfer can be, for example, from drug discovery to product development; to clinical trials; or to full-scale commercialization and commercial batch manufacturing; cleaning and validation.

1.2. A technology transfer, particularly one between different companies, has legal and economic implications. If such issues, which may include intellectual property rights, royalties, pricing, conflicts of interest and confidentiality agreements, are expected to impact on the open communication of technical matters in any way, they should therefore be addressed before and during the planning and execution of the transfer.

1.3. A technology transfer requires a planned approach by trained, knowledgeable personnel working within a quality system, with documentation, data and information covering all aspects of development, production and quality control (QC), as applicable.

1.4. A technology transfer takes place between a sending unit (SU) and a receiving unit (RU). In some cases, there may be a separate unit managing the project.

1.5. The technology transfer project should fulfil the following general principles and requirements. There should be:
   • a documented project plan covering the relevant aspects of the project;
   • a detailed risk management plan;
   • a comprehensive technical gap analysis, including due diligence performed covering technical and regulatory aspects;
   • similar capabilities between the SU and RU, including but not limited to, facilities and equipment;
   • an adequate number of adequately trained personnel with suitable qualifications and experience; and
   • effective process and product knowledge management.
1.6. A technology transfer should include relevant documentation, data, information and knowledge from the SU in order to enable the RU to effectively perform the specified process or procedure in, for example, production and QC. A successful transfer of technology should result in proof that the RU can routinely reproduce the transferred product, process or procedure against a predefined set of specifications as agreed between the SU and RU.

1.7. This document should be read in conjunction with other WHO guidelines as referenced below (2-14), as well as other regulatory guidelines which include The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q7, Q8, Q9, Q10 and Q11. This guideline does not intend to replace any of these guidelines.

1.8. This version of the guideline provides updated requirements and expectations reflecting current good practices (GxP) in the transfer of technology and replaces the previous version published (1).

2. **Scope**

2.1. This document provides guiding principles on technology transfer.

2.2. This guideline should be applied when transferring the technology of processes and procedures relating to active pharmaceutical ingredients (APIs), in-process bulk materials, finished pharmaceutical products (FPPs), process validation, cleaning procedure development and validation and analytical procedures.

2.3. The guideline applies to all pharmaceutical dosage forms and may be adapted on a case-by-case basis by using risk management principles. Particular attention should be given to certain complex formulations such as, for example, sterile products and metered dose aerosols.

2.4. Although this document focuses on pharmaceutical products, the principles can also be applied to the transfer of production, related processes and controls for other products such as biopharmaceutical products, vaccines, medical devices and vector control products.

2.5. Because each transfer project is unique, the provision of a comprehensive set of guidelines specific to a product or process is beyond the scope of this document.

2.6. This document does not provide guidance on any legal, financial or commercial considerations associated with technology transfer projects.
2.7. This document addresses the following principal areas:

- organization and management of the transfer;
- transfer of development information in production, including but not limited to processing and packaging;
- transfer of development information and analytical procedures;
- documentation, premises, equipment;
- personnel qualification and training;
- quality management and risk management;
- life cycle approach;
- control strategy; and
- qualification and validation.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They have been aligned as far as possible with the terminology in related WHO guidelines and Good Practices and included in the WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guideline [https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cf6_5], but may have different meanings in other contexts.

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

**active pharmaceutical ingredient (API).** Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

**ALCOA+.** A commonly used acronym for “attributable, legible, contemporaneous, original and accurate that puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit basic ALCOA principles.

**bracketing.** An experimental design to test 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. 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.

control strategy. A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to API and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

corrective action. 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 on product quality or performance in a significant way.

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

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

design space. The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

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

finished pharmaceutical product (FPP). A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more active pharmaceutical ingredients (APIs).

gap analysis. The identification of the critical elements of a process which are available at the sending unit (SU) but are missing from the receiving unit (RU).
**good manufacturing practices (GMP).** That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

**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).** Documented verification that the installations (such as machines equipment and instruments, computer system components, measuring devices, utilities and manufacturing) used in a processor system are appropriately selected and correctly installed, in accordance with established specifications.

**intercompany transfer.** A transfer of technology between the sites of different companies.

**intracompany transfer.** A transfer of technology between sites of the same group of companies.

**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 performs consistently and reproducibly within defined specifications and parameters in its normal operating environment (i.e. in the production environment).

**process validation.** The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of continuously delivering the finished pharmaceutical product meeting its predetermined specifications and quality attributes.

**qualification.** Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications when properly installed, and/or work correctly and lead to the expected results.

**qualification batches.** Those batches produced by the receiving unit (RU) to demonstrate its ability to reproduce the product.
**quality assurance (QA)**. “Quality assurance” is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is 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)**. 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 (FPP) conform with established specifications for identity, strength, purity and other characteristics.

**quality planning**. Part of quality management, focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives.

**quality policy**. A brief statement that describes the organization’s purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

**quality risk management (QRM)**. A systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product throughout the product’s 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 from where a designated product, process or method is expected to be transferred.

**standard operating procedure (SOP)**. An authorized written procedure giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (for example, operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master and batch production documentation.

**transfer of technology**. A logical procedure that controls the transfer of any process, together with its documentation and professional expertise between development and manufacture or between manufacture sites. It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and/or commercialization to an appropriate, responsible and authorized party.

**technology transfer report**. A documented summary of a specific technology transfer project listing procedures, acceptance criteria, results achieved and conclusions.
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 summarizes the manufacturer’s overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer’s qualification and validation work programme and defines details of and timelines for the work to be performed, including a statement of the responsibilities of those implementing the plan.

validation protocol (VP). A document describing the activities to be performed during validation, including the acceptance criteria.

validation report (VR). A document in which the records, results and evaluation of validation are documented and summarized. It should also contain a conclusion of the outcome of the validation.

4. **Due diligence and gap assessments**

4.1. A process of due diligence, gap assessment or audits of the SU and RU should be one of the first steps when considering a technology transfer project.

4.2. The suitability and degree of preparedness of the RU should be assessed prior to the start of the transfer. The procedure to be followed should be documented.

4.3. The assessment should be done by a team of appropriately qualified persons with knowledge and experience in the field of GxP and the activity to be transferred.

4.4. The assessment should further cover resources including personnel, premises, equipment and instruments, utilities, QC, documentation, computerized systems, qualification and validation and waste management.

4.5. The assessment to determine feasibility and readiness for technology transfer may include technical, business, regulatory and legal aspects.
5. **Organization and management**

5.1. All technology transfer activities should be organized and planned.

5.2. There should be a formal agreement between the parties which specifies the responsibilities of each party before, during and after transfer. The agreement should cover, for example, data management, data integrity, documentation and validation.

5.3. All the necessary activities to be executed during the technology transfer project should be identified, organized and documented at the start of the project. Responsibilities should be defined.

5.4. The SU should provide the necessary documentation relating to the process, product or procedure to be transferred.

5.5. The SU should provide criteria and information on inherent risks, hazards and critical steps associated with the process, product or procedure to be transferred. This may serve as a basis for the risk assessment exercise.

5.6. The technology transfer should be managed by responsible persons from the SU and RU. A technology transfer team may be appointed with identified and documented responsibilities.

5.7. The team members should have the necessary qualifications and experience to manage the particular aspects of the transfer.

5.8. The SU should make all the necessary information and knowledge with regard to the product, process or procedure available in relevant documents in order to ensure a successful transfer.

5.9. A training programme should be implemented specific to the process, product or procedure to be transferred.

5.10. Any changes and adaptations made during the course of the project should be fully documented and agreed to by both parties.

5.11. The execution of the technology transfer project should be documented in a report which is supported by the relevant data.

5.12. Data should meet ALCOA+ principles.
6. Quality management and quality risk management

6.1. The SU and RU should each have an appropriately designed, clearly defined and documented quality system.

6.2. The quality system should be adequately resourced, implemented and maintained.

6.3. The quality system should incorporate GxP which should be applied to the life cycle stages of the products and processes, including the technology transfer.

6.4. The quality system should ensure that:
   - responsibilities are clearly specified in writing;
   - operations are clearly defined in writing;
   - there is a system for quality risk management; and
   - arrangements are made for the documented technology transfer.

6.5. Quality risk management should be implemented as a systematic process for the assessment, control, communication and review of risks.

6.6. The system for quality risk management should be described in writing and cover appropriate areas such as, but not limited to, premises, equipment, materials, products, production, processes, QC, qualification, validation and the process of technology transfer.

6.7. The evaluation of the risk should be based on scientific knowledge and experience including that of the process and product.

6.8. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

6.9. The procedures and records for quality risk management should be retained.
7. **Documentation**

*Note: A list with examples of documents commonly required in technology transfer is presented in Appendix 1.*

7.1. An authorized technology transfer document should list the intended sequential phases and activities of the transfer. The document should include, for example, the following:
- title;
- objective;
- scope;
- name and addresses of the SU and RU;
- names of key personnel and their responsibilities;
- phases of the project and actions;
- a parallel comparison of premises, equipment, instruments, materials, procedures, and methods;
- experimental design, quality attributes, process parameters and acceptance criteria;
- information on trial production batches, qualification batches and process validation;
- change and deviation management;
- arrangements for keeping retention samples of active ingredients, intermediates and finished products, and information on reference substances where applicable; and
- review of the transfer, outcome, signature(s) and date of conclusion of the transfer.

7.2. Standard operating procedures (SOPs) should be followed, describing actions to be taken during the technology transfer process.

7.3. Records should be maintained for the activities performed during the technology transfer process (e.g. a technology transfer report). The report content should reflect the protocol and SOPs that were followed. The report should summarize the scope of the transfer, the critical parameters as obtained in the SU and RU, and the final conclusions of the transfer. The discrepancies and appropriate actions taken to resolve them should be recorded. Supportive documents with data, results and other relevant information should be referenced in the report and be readily available.
8. **Premises**

8.1. The RU should have appropriate premises with the layout, construction and finishing to suit the intended operations. Utilities such as heating, ventilation and air conditioning, as well as gas and water systems, should be appropriate for the intended process, product or procedure to be transferred.

8.2. The SU should provide the RU with 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.

9. **Equipment and instruments**

9.1. The SU should provide a list of equipment and instruments involved in the production, filling, packing and QC testing. The list should include the makes and models of the relevant equipment and instruments.

9.2. Other relevant documentation may include, on a case-by-case basis as required, drawings; manuals; maintenance procedures and records; calibration procedures and records; as well as procedures such as equipment set-up, operation and cleaning.

9.3. A review and a side-by-side comparison of equipment and instruments of the SU and RU should be carried out in terms of their working principle, make and models.

9.4. Where the review and comparison identify any gaps or differences, appropriate action should be taken. This may include the adaptation of existing equipment or acquisition of new equipment. Such action should be taken by following a change management procedure which should be documented.
9.5. Production volumes and batch sizes at the SU and RU should be compared. Where batch sizes are different, the impact should be assessed and the appropriate action planned and taken. Other factors relating to equipment to be reviewed may include:
  • minimum and maximum capacity;
  • material of construction of contact surfaces;
  • critical operating parameters;
  • components (e.g. filters, screens, and temperature/pressure sensors); and
  • range of intended use.

9.6. The impact of the potential product to be transferred, on existing products manufactured on site, should be assessed.

10. **Qualification and validation**

10.1. The extent of qualification and validation to be performed should be determined on the basis of risk management principles.

10.2. The qualification of premises, utilities and equipment should be done in accordance with a qualification master plan and protocols.

10.3. Validation, such as process validation, should be done in accordance with a validation master plan and protocols.

10.4. Where technology is transferred to commercial sites, the qualification of equipment and instruments should be completed prior to the actual technology transfer.

10.5. Process validation usually starts in research and development facilities either as prospective validation (traditional approach) or as stage I process validation (see references regarding the new approaches in process validation; and the life cycle approach). *Note: Process validation should be done according to current guidelines as published in current WHO Technical Report Series (3).*

10.6. Procedures including processing and analytical procedures, should be appropriately validated at the SU and transferred to the RU following documented procedures. Verification and validation, as appropriate, should be continued at the RU as identified and documented in the technology transfer protocol.
10.7. For cleaning procedures, development and validation should be done in accordance with the guidelines as published in current WHO Technical Report Series (6). Points to consider when using HBEL in cleaning validation (14) should be taken into account in establishing cleaning procedures, cleanability studies and setting acceptance limits.

10.8. Analytical procedures should be validated according to the guidelines as published in current WHO Technical Report Series (7).

10.9. Qualification and validation procedures, protocols, data and results should be appropriately recorded. The documents should be retained as defined in procedures.

11. **Product life cycle and project management principles**

11.1. The relevant stage of the life cycle of the facility, equipment, instrument, utility, product, process or procedure to be transferred should be taken into consideration when the transfer is planned and executed.

12. **Phases of a technology transfer project**

12.1. The technology transfer project plan may be divided into different phases. These may include, for example:

- Phase I: Project initiation;
- Phase II: Project proposal;
- establishing a team;
- risk assessment;
- project plan;
- control strategy;
- Phase III: Project transfer; and
- Phase IV: Project review.

**Phase I: Project initiation**

12.2. During the initiation phase of the project, a unit should normally identify the need for the technology transfer. This may be because of lack of capacity, transfer from development to commercial site or transfer from one company to another.

12.3. The units should establish initial discussion and identify whether or not there is any interest for such a project. (See also section on due diligence above).

12.4. The RU should be able to accommodate the intended activity.
12.5. The RU should have the necessary technical expertise, technology and capability.

12.6. A sufficient level and depth of detail to support the activity, and any further development and optimization at the RU, should be transferred.

**Phase II: Project proposal**

12.7. The SU and RU should jointly establish a team that will coordinate activities and execute the technology transfer exercise.

12.8. The team should perform a risk assessment based on the available data, information and knowledge of the premises, materials, products, procedures and other related information.

12.9. The team should prepare the technology transfer document.

12.10. The team should develop a control strategy which includes, for example:

- risks;
- material attributes;
- processing steps and stages in production;
- testing steps in QC;
- equipment working principles and their impact on the process;
- critical quality attributes (CQAs), critical process parameters (CPPs) and in-process controls;
- QC instruments;
- acceptance criteria and limits;
- alarms and trends;
- personnel requirements, such as qualification and training; and
- qualification and validation.

**Phase III: Project transfer**

12.11. The team should execute the project in accordance with the procedures and agreed plan.

**Production:**

**Starting materials**

12.12. The specifications and relevant functional characteristics of the starting materials (APIs and excipients) to be used at the RU should be consistent with those materials used at the SU. Any properties which are likely to influence the process or product should be identified and/or characterized.
Active pharmaceutical ingredients

12.13. The SU should provide the RU with the open part of the Drug Master File (API master file), or equivalent information, as well as any relevant additional information on the API of importance for the manufacture of the pharmaceutical product. The following are examples of the information which may typically be provided; however the information needed in each specific case should be assessed using the principles of QRM:

- manufacturer and associated supply chain;
- step of the API to be transferred;
- flow chart of synthesis pathway outlining the process, including entry points for raw materials, critical steps, process controls and intermediates;
- where relevant, definitive physical form of the API (including photomicrographs and other relevant data) and any polymorphic and solvate forms;
- solubility profile;
- if relevant, pH in solution;
- 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 national, regional or international pharmacopoeia 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;
- list of potential and observed synthetic impurities, with data to support proposed specifications and typically observed levels;
- information on degradants, with a list 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, 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.
Excipients

12.14. The specifications and relevant functional characteristics of excipients should be made available by the SU for transfer to the RU site. The following are examples of the information which may typically be provided; however, the information needed in each specific case should be assessed using the principles of QRM:

- manufacturer and associated supply chain;
- description of functionality, with justification for inclusion of any antioxidant, preservative or any excipient;
- definitive form (particularly for solid and inhaled dosage forms);
- solubility profile (particularly for 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 or topical dosage forms);
- pH range (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- ionic strength (for parenteral dosage forms);
- specific density or gravity (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- viscosity and or viscoelasticity (for parenteral, semi-solid or 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, semisolid or topical, liquid and transdermal dosage forms);
- microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the excipient supports microbiological growth) in accordance with national, regional or international pharmacopoeia requirements, as applicable (for general and specific monographs);
- specifications and justification for release and end-of-life limits;
- information on adhesives supporting compliance with peel, sheer and adhesion design criteria (for transdermal dosage forms);
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 (MSDS)) and sensitivity to heat, light or moisture; and

regulatory considerations (e.g. documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements, where applicable).

**Information on process and finished pharmaceutical product information**

**Processing, packaging**

12.15. Product, process and procedure knowledge should be an essential part of the transfer process from SU to RU.

12.16. The quality target product profile, critical quality attributes, critical process parameters, material attributes, control strategy and any other impacting elements on the quality of the product should be available. (See also ICH guidelines.)

12.17. The SU should provide the total product quality profile with its qualitative and quantitative composition, physical description, method of manufacture, in-process controls, control method and specifications, packaging components and configurations, and any safety and handling considerations to the RU.

12.18. 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 after successful transfer.

12.19. 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, critical quality attributes, pilot report and/or information on pilot-scale development activities indicating the number and disposition of batches manufactured;
- information or report on full-scale development activities, indicating the number and disposition of batches manufactured, and deviation and change control (sometimes referred to as change management) reports which led to the current manufacturing process;
- the change history and reasons (e.g. a change control log, indicating any changes to the process or primary packaging or analytical methods as a part of process optimization or improvement); and
- information on investigations of problems and the outcomes of the investigations.
12.20. The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and the implications thereof (e.g. need for gowning or protective clothing).

12.21. 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;
- information on starting materials, applicable MSDS and storage requirements for raw materials and finished products;
- description of manufacturing steps (narrative and process maps or flow charts, and/or master batch records), 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;
- identification and justification of control strategy (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);
- design space, in cases where this has been defined;
- validation information (e.g. validation plans and reports);
- annual product quality reviews;
- stability information;
- an authorized set of protocols and work instructions for manufacturing; and
- environmental conditions or any special requirement needed for the facility or equipment depending on the nature of the product to be transferred.

12.22. During the transfer process, the RU should identify any differences in facilities, systems and capabilities and discuss these with the SU. The potential impact should be understood and satisfactorily addressed in order to assure equivalent product quality. 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 the relevant site operating procedures and documentation before the start of routine production.
12.23. Process development at the RU should address the following tasks:

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

Packaging

12.24. The transfer of packaging operations should follow the same procedural principles as those of the product processing.

12.25. Information on packaging to be transferred from the SU to the RU should include specifications for a suitable container and closure system, as well as any relevant additional information on design, packing, processing or labelling requirements and tamper-evident and anti-counterfeiting measures.

12.26. For QC testing of packaging components, specifications should be provided including drawings, artwork and material.

12.27. Based on the information provided, the RU should perform a suitability study for the initial qualification of the packaging components.

12.28. Packaging is considered suitable if it provides adequate protection (preventing degradation of the medicine due to environmental influences), safety (absence of undesirable substances released into the product), compatibility (absence of interaction possibly affecting medicine quality) and performance (functionality in terms of drug delivery).
Quality control: analytical method transfer

12.29. Analytical methods used to test pharmaceutical products, starting materials, packaging components and cleaning (residue) samples, if applicable, should be implemented at the testing laboratory before the testing of samples for process validation studies is performed by the RU.

12.30. A protocol defining the steps should be prepared for transfer of analytical methods. The analytical methods transfer protocol should include:
- a description of the objective, scope and responsibilities of the SU and the RU;
- a specification of materials and methods;
- the experimental design and acceptance criteria;
- documentation (including information to be supplied with the results, and report forms to be used, if any);
- procedure for the handling of deviations; and
- details of reference samples (starting materials, intermediates and finished products).

12.31. The SU’s responsibilities for the transfer of analytical procedures are to:
- provide method-specific training for analysts and other QC staff, if required;
- assist in analysis of QC testing results;
- define all methods to be transferred for testing a given product, starting material or cleaning sample;
- define experimental design, sampling methods and acceptance criteria;
- provide any validation reports for methods under transfer and demonstrate their robustness;
- provide details of the equipment used, as necessary (part of validation report, if available) and any standard reference samples;
- provide approved procedures used in testing; and
- review and approve transfer reports.

12.32. The RU should exercise its responsibility 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 QC is available and qualified at the RU site. The equipment used by the RU during the analytical transfer should meet the appropriate specifications in order to ensure the requirements of the method or specification are met;
- ensure that adequately trained and experienced personnel are 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);
• execute the transfer protocol;
• perform the appropriate level of validation to support the implementation of the methods; and
• generate and obtain approval of transfer reports.

12.33. The appropriate training should be provided and all training activities and outcomes should be documented.

12.34. Reference should be made to compendial monographs such as *The International Pharmacopoeia*, European Pharmacopoeia, British Pharmacopoeia and United States Pharmacopeia), where these are available.

12.35. An experimental design should be prepared which includes acceptance criteria for the main analytical testing procedures. (See Appendix 2.)

12.36. Where products are transferred from one unit to another, the applicable analytical procedures should also be transferred.

12.37. All relevant analytical procedure development and validation documentation should be made available by the SU to the RU.

12.38. The appropriate transfer protocols and procedures should be followed when analytical procedures are transferred.

12.39. The number of analysts involved in the transfer, from both SU and RU, should be defined and justified.

12.40. The parameters of the analytical procedure to be included in the validation should be defined and justified.

12.41. Acceptance criteria should be set to determine the success of the transfer. Statistical trending of results should be considered in order to show capability of the procedure.
Cleaning

12.42. To minimize the risk of contamination and cross-contamination, adequate cleaning procedures should be followed.

12.43. Cleaning procedures and their validation should normally be site-specific. In order for the RU to define its cleaning strategy, the SU should provide information on cleaning at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including:
   • information on solubility of active ingredients, excipients and vehicles;
   • minimum therapeutic doses of active ingredients;
   • therapeutic category and toxicological assessment; and
   • existing cleaning procedures.

12.44. Additional applicable information should be provided, such as:
   • cleaning validation reports (chemical and microbiological);
   • information on cleaning agents used (efficacy, evidence that they do not interfere with analytical testing for residues of APIs, removal of residual cleaning agents); and
   • recovery studies to validate the sampling methodology.

12.45. Before the transfer, the SU should provide information on limits for product residues and the rationale for limit selection.

12.46. 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 and temperature sensitivity), manufacturing equipment design and configuration, cleaning agent and product residue.

Phase IV: Project review

12.47. The progress and success of the transfer of technology should be monitored and reviewed during and after completion of the project.

12.48. Compliance with the procedures and protocols should be verified. Deviations and changes should be documented and investigated where appropriate.

12.49. Where possible, data and results should be subjected to appropriate statistical calculation and evaluation to determine trends, compliance with control limits and capability studies.

12.50. A technology transfer report should be prepared, based on the data and information obtained during the project. The supportive data should be kept and be accessible.

12.51. The report, which should include a conclusion, should be authorized by the persons responsible to do so.
References


Further reading


## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCOA+</td>
<td>“attributable, legible, contemporaneous, original and accurate”.</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>FPP</td>
<td>finished pharmaceutical product</td>
</tr>
<tr>
<td>GMP</td>
<td>good manufacturing practices</td>
</tr>
<tr>
<td>GxP</td>
<td>good practices</td>
</tr>
<tr>
<td>ICH</td>
<td>The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use</td>
</tr>
<tr>
<td>IPC</td>
<td>in-process control</td>
</tr>
<tr>
<td>IQ</td>
<td>installation qualification</td>
</tr>
<tr>
<td>OQ</td>
<td>operational qualification</td>
</tr>
<tr>
<td>PQ</td>
<td>performance qualification</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>quality control</td>
</tr>
<tr>
<td>QRM</td>
<td>quality risk management</td>
</tr>
<tr>
<td>RU</td>
<td>receiving unit</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
<tr>
<td>SU</td>
<td>sending unit</td>
</tr>
<tr>
<td>TRS</td>
<td>Technical Report Series</td>
</tr>
<tr>
<td>VMP</td>
<td>validation master plan</td>
</tr>
<tr>
<td>VP</td>
<td>validation protocol</td>
</tr>
<tr>
<td>VR</td>
<td>validation report</td>
</tr>
</tbody>
</table>
Appendix 1
Example of documentation commonly required for the transfer of technology*

The table below provides an example of documentation commonly required for the transfer of technology.

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Related documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting materials (API and excipients)</td>
<td>Material Safety Data Sheets</td>
</tr>
<tr>
<td></td>
<td>Product development report</td>
</tr>
<tr>
<td></td>
<td>Storage conditions</td>
</tr>
<tr>
<td></td>
<td>Stability data</td>
</tr>
<tr>
<td></td>
<td>Forced stability data</td>
</tr>
<tr>
<td></td>
<td>Specifications</td>
</tr>
<tr>
<td></td>
<td>Supplier qualification</td>
</tr>
<tr>
<td></td>
<td>References</td>
</tr>
<tr>
<td>Formulation</td>
<td>Formulation development reports</td>
</tr>
<tr>
<td></td>
<td>Master formula</td>
</tr>
<tr>
<td></td>
<td>Material compatibility/interaction studies</td>
</tr>
<tr>
<td>Batch manufacturing</td>
<td>Batch manufacturing document</td>
</tr>
<tr>
<td></td>
<td>Scale up information</td>
</tr>
<tr>
<td></td>
<td>Risk assessment</td>
</tr>
<tr>
<td></td>
<td>Critical process parameters</td>
</tr>
<tr>
<td></td>
<td>In-process control</td>
</tr>
<tr>
<td></td>
<td>Scale up protocol and report</td>
</tr>
<tr>
<td></td>
<td>Process validation</td>
</tr>
<tr>
<td>Batch packaging</td>
<td>Packaging material specification</td>
</tr>
<tr>
<td></td>
<td>Batch packaging document</td>
</tr>
<tr>
<td></td>
<td>Validation</td>
</tr>
<tr>
<td>Finished product</td>
<td>Specification</td>
</tr>
<tr>
<td>Analytical procedures</td>
<td>Analytical test procedures</td>
</tr>
<tr>
<td></td>
<td>Analytical method development</td>
</tr>
<tr>
<td></td>
<td>Analytical procedure validation</td>
</tr>
<tr>
<td></td>
<td>Standard test procedures</td>
</tr>
<tr>
<td></td>
<td>Instrument specifications</td>
</tr>
<tr>
<td>Quality control</td>
<td>Sampling procedures (e.g. in-process control)</td>
</tr>
<tr>
<td></td>
<td>Stability testing protocol and procedures</td>
</tr>
<tr>
<td>Equipment and instruments</td>
<td>List of equipment and instruments</td>
</tr>
<tr>
<td></td>
<td>Calibration information</td>
</tr>
<tr>
<td></td>
<td>Preventive maintenance information</td>
</tr>
<tr>
<td></td>
<td>Overview of qualification</td>
</tr>
</tbody>
</table>
| Cleaning | Overview of cleaning approach  
Cleaning procedure development and cleanability  
Cleaning procedures  
Health Based Exposure Level (Permitted daily exposure) information reports  
Analytical procedures validation for cleaning validation sample analysis |
|------------------|-----------------------------------------------------------------------------------|
| Other documents | Rejected batch information  
Bio-batch information  
Pilot batch information  
History of changes and change management  
Hold time protocols and reports |

*Note: These are examples. All the required documents should be identified for the different tasks.*
Appendix 2
Example of possible experimental designs and acceptance criteria for analytical testing

The table below provides an example of possible experimental designs and acceptance criteria for analytical testing. The numbers in the table are given as examples only and should not be considered as recommendations. Method transfers should account for the variability and sensitivity of the method and the specifications for the quality parameter. Alternative procedures and acceptance criteria may be applied based on science and the characteristics of the analytical method and the analyte.

<table>
<thead>
<tr>
<th>Test</th>
<th>Considerations for transfer</th>
<th>Replication of tests</th>
<th>Set-up</th>
<th>Acceptance criteria Direct</th>
<th>Statistically derived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay for potency</td>
<td>Specific methods where possible should be used</td>
<td>At each site: 2 analysts × 3 lots, in triplicate (= 18 per site)</td>
<td>Different sets of instruments and columns Independent solution preparation</td>
<td>Comparison of mean and variability</td>
<td>Two one-sided t-tests with inter-site differences ≤2%, 95% confidence</td>
</tr>
<tr>
<td></td>
<td>A bracketing approach may be used for multiple strengths</td>
<td></td>
<td></td>
<td></td>
<td></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, × 1 lot (= 2 per site)</td>
<td>Different sets of instruments and columns Independent solution preparation</td>
<td>Mean at RU within ±3% of mean at SU; comparison of relative standard deviation</td>
<td>Two one-sided t-tests with inter-site differences ≤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. F2), or compare data at Q time points, as for assay</td>
<td></td>
</tr>
</tbody>
</table>

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