World Health Organization

WHO guidelines on technology transfer in pharmaceutical manufacturing

INTERIM VERSION FOR SUBMISSION TO THE EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/20.869:

WHO guidelines on technology transfer in pharmaceutical manufacturing

Description of Activity	Date
Following a recommendation by the WHO Local Production & Assistance Unit, the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat enquire if the ***WHO guidelines on technology transfer in pharmaceutical manufacturing*** should be updated in order to support inspections for COVID-19 therapeutics.	October 2020
Preparation of first draft working document.	November 2020
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation	December 2020
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	February 2021
Discussion of the feedback received on the working document in a virtual meeting with an expert working group	February-March 2021
Preparation of working document for next round of public consultation.	April 2021
Mailing of revised working document inviting comments, including to the EAP, and posting of the working document on the WHO website for a second round of public consultation.	April 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	June 2021
Discussion of comments in the virtual meeting on *Good practices for health product manufacture and inspection*.	28 June – 2 July 2021
Preparation of working document for discussion in the ECSPP.	July – August 2021
Presentation to the Fifty-sixth meeting of the ECSPP.	TBD
Any other follow-up action as required.	

WHO guidelines on technology transfer in pharmaceutical manufacturing

Background

During the Fifty-fifth World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) meeting, Expert Committee members were updated on the annual consultation of Good Practices for Health Products and Inspection which took place in July 2020 over a series of virtual meetings (due to the COVID-19 pandemic). During these virtual meetings, a group of experts made a series of proposals for future activities, one of which was how to determine whether or not the *WHO guidelines on the transfer of technology in pharmaceutical manufacturing (1)* should be updated. This original document was published in 2011. Numerous regulatory changes have been made since then. Transfer of technology is considered an integral part of the product life cycle management and is subject to regulatory expectations. This includes a risk-based and science-based process and method design (such as a quality by design approach), achieving a "state of control" and data governance. The original document therefore requires updating, not least to support the consistent supply of therapies for critical needs, including public health emergencies.

The Expert Committee asked the WHO Secretariat to explore this proposal.

1. Introduction

1.1. Technology transfer is a logical procedure that controls the transfer of products, processes and knowledge together with its documentation and professional expertise. Technology transfers may involve development, manufacturing and testing sites.

1.2. The transfer of production and control procedures of pharmaceutical products from one site to another may take place before or after obtaining regulatory marketing authorization. Product transfer may therefore occur during development, full-scale commercialization and commercial batch manufacturing. The level of rigor applied in the technology transfer should be commensurate with the respective product life cycle phase.

1.3. A technology transfer, particularly one between different companies, has legal and economic implications which may include intellectual property rights, royalties, pricing, conflicts of interest and confidentiality agreements. Such matters should therefore be addressed.

1.4. A technology transfer requires a planned approach by trained, knowledgeable personnel working within a quality system with the appropriate documentation, data and information covering all aspects of development, production and quality control (QC), as applicable, and considering the stage of the product life cycle and the regulatory requirements.

1.5. A technology transfer takes place between a sending unit (SU) and a receiving unit (RU). In some cases, it may be advantageous to establish a separate unit to manage the project.

1.6. 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 quality risk management plan;
- a comprehensive gap analysis, including due diligence performed covering technical, quality and regulatory aspects;
- similar capabilities between the SU and RU, including but not limited to, facilities and equipment where appropriate;

- knowledge of the differences in process ability between the SU and RU, including the impact, risk and control strategies to overcome any differences;
- an adequate number of adequately trained personnel with suitable qualifications and experience;
- effective process and product knowledge management; and
- effective communication and transparency between the SU and RU.

1.7. A technology transfer should include relevant documentation, data, information and knowledge from the SU in order to enable the RU to effectively execute the specified process or procedure in, for example, production and QC. A successful technology transfer should result in documented evidence 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.

1.8. This document should be read in conjunction with other WHO guidelines as referenced below *(2-15)*, 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, Q11 and Q12. This guideline does not intend to replace any of these guidelines.

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

1.10. The 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.)

1.11. This version of the document provides guiding principles reflecting current good practices (GxP) in technology transfer and replaces the previous version published by WHO *(1)*.

2. Scope

2.1. This document provides guiding principles on technology transfer including transfer from research and development to production sites, and between two production sites. The principles therefore apply to newly commercialized products as well as to marketed products. The principles may also be applied to investigational products.

2.2. Throughout life cycle stages, transfers should be appropriate and proportionate to the phase of the product life cycle in order to ensure that product knowledge is maintained and that processes are appropriately controlled. This guideline should be applied when transferring the technology of manufacturing processes and analytical procedures relating to active pharmaceutical ingredients (APIs), isolated API intermediates, bulk drug products and finished pharmaceutical products (FPPs). While medical devices, as part of the finished pharmaceutical product of a combination medicinal product, would be considered under this guidance, the specific regulatory and quality requirements for medical device manufacturing are covered under separate medical device regulations and quality management systems.

2.3. The guideline applies to all pharmaceutical dosage forms, including biological products and vaccines, 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 sterile products and metered dose inhalers.

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, advanced therapy medicinal products/cellular and gene therapy 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 intellectual property, legal, financial or commercial considerations associated with technology transfer projects. These are prerequisites for a successful transfer that need to be defined and controlled prior to the

transfer because of due diligence. Examples include Health, Safety and Environmental (HSE) Aspects and a Confidentiality Disclosure Agreement which should exist prior to the start of the transfer.

2.7. This document addresses the following principal areas:

- organization and management of the transfer;
- transfer of relevant information in production, including but not limited to processing, packaging and analytical procedures;
- documentation, premises and equipment;
- personnel qualification and training;
- quality management and risk management;
- change management and 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 much as possible with the terminology in related WHO guidelines and GxP and included in the WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guidelines *https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_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 the registration and validated status. The intent is to determine the need for action that would ensure that the system is maintained in a regulatory compliant and validated state.

confirmation testing. An execution of tests that confirm and validate the results obtained by another.

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 active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) 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 process parameter (CPP). A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and/or controlled to ensure the process produces the desired quality.

critical quality attribute (CQA). A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

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, packaging material 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). In some cases, it may be in combination with a medical device.

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) with the objective to assess which gaps have potential impact on the process or method and to mitigate those gaps, as appropriate.

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.

good practices (GxP). A collection of quality guidelines and regulations in order to ensure that products are safe, effective and of required quality; meet their intended use and adhere to quality processes during production, control, storage and distribution.

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.

marketing authorisation holder (MAH). An individual or a corporate entity being in possession of a marketing authorization of a pharmaceutical product.

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

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 consistently delivering the active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) 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.

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 (e.g. 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.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

technology transfer / transfer of technology. A logical procedure that controls the transfer of any product and process, including product and process knowledge, together with its documentation and professional expertise. Technology transfers may involve development, manufacture and/or testing sites.

technology transfer protocol (master plan). A document that describes the intended sequential phases and activities of the transfer, and serves as a plan for the execution and management of the transfer.

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 batches. Those batches produced by the receiving unit (RU) to demonstrate its ability to manufacture the transferred product which complies with its predetermined specifications, or as part of process performance qualification.

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 analysis

4.1. A process of due diligence and gap analysis visits of the SU and RU should be some 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 and the results and conclusions should thereafter be documented.

4.3. The gap analysis should be performed by a team of appropriately qualified persons with knowledge and experience in the field of GxP and the activity to be transferred. It is recommended that the quality units of the SU and RU participate in this activity. The team should be involved throughout each phase of the project as appropriate. (See Section 12 on phases of a technology transfer project.)

4.4. The gap analysis should further cover the capabilities and resources related to personnel, premises, equipment and instruments, utilities, cleaning, QC, documentation, computerized

systems, qualification, validation and further HSE-related considerations including waste management.

4.5. The gap analysis to determine the feasibility for technology transfer may include technical, engineering, business, quality, regulatory, supply and legal aspects.

5. Organization and management

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

5.2. There should be formal written agreements, signed between the parties involved in technology transfer, which specify 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. The responsibilities of the SU, RU, sponsor and Marketing Authorization Holder (MAH) should be defined in writing.

5.4. Where applicable, the MAH should coordinate the transfer of the necessary documentation related to the technology transfer from the SU to the RU, including the relevant regulatory documents. The product dossier, production and control documentation should be assessed for compliance with regulatory requirements before the transfer of the documentation.

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

5.6. The technology transfer should be managed by responsible persons from each site (the SU and RU) and any other units with the appropriate technical and quality oversight. 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 available in relevant documents all the necessary information and knowledge with regard to the product, process or procedure in order to ensure a successful transfer.

5.9. The RU should be able to accommodate the intended production capacity. If possible, it should be established at the outset whether or not the intention is to perform single-batch manufacture, continuous production or campaigns.

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

5.11. Consideration should be given to the technical expertise, site technology and site capabilities for the RU. Any product and process robustness issues should be identified upfront by the SU so that plans may be put in place at the RU.

5.12. The SU should assess the suitability and degree of preparedness of the RU before transfer with regard to, for example, personnel, premises, equipment, materials, suppliers and support services (i.e. purchasing and inventory control mechanisms and pharmaceutical quality system - QC procedures, documentation, computer validation, site validation, equipment qualification, water for pharmaceutical production and waste management).

5.13. The SU and the RU should jointly verify that the following, satisfactorily completed, qualification and validation protocols and/or reports are available:

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

5.14. A training programme should be implemented covering various topics, including those specific to the process, product or procedure to be transferred. The effectiveness of training should be evaluated and records should be maintained.

5.15. Any changes and adaptations made during the course of the project should be carried out in accordance with a standard procedure. Risk assessment, where appropriate, should cover technical, quality, regulatory and other aspects. The project manager should evaluate the impact to the project cost, schedule and resourcing based on an updated risk assessment.

5.16. The execution of the technology transfer project should be documented, for example, in a report which is supported by the relevant data. The overall technology transfer strategy and acceptance criteria to confirm a successful transfer should be documented a priori in the technology transfer protocol. These should consider the stage of development, that is, for clinical or for commercial stages (including the fulfilment of relevant regulatory country requirements).

5.17. Whenever possible, targeted on site or virtual visits between the SU and RU at critical phases of the project should be allowed to assist with the transfer of knowledge.

5.18. 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 management system.

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

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

6.4. The quality management system should ensure that, for example:

- responsibilities are clearly specified in writing;
- operations are clearly defined in writing;
- there is a system for change management;
- 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 and microbiology, 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

7.1. An authorized technology transfer document, such as a Master Plan (or Technology Transfer Protocol), should list the intended sequential phases and activities of the transfer, where appropriate. The document should include, for example, the following:

- title;
- objective;
- scope;
- names and addresses of the SU and RU;

- technology transfer team including key personnel and their responsibilities from SU and RU;
- phases of the project including key activities, deliverables and the associated accountabilities;
- approximate timing of key activities/deliverables including the timing of trial production batches and validation batches;
- reference to other transfer plan documents relevant to the process being transferred;
- reference to validation master plans relevant to the process being transferred: equipment/facilities/utilities qualification project plan, site-independent/site-dependent process validation master plan(s), method validation master plan;
- reference to gap analysis and risk assessments;
- acceptance criteria for a successful transfer; and
- a parallel comparison of premises, equipment, instruments, materials, procedures, and methods for the transfer under consideration.

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

7.2. Standard operating procedures (SOPs) should be followed describing the 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. Changes, deviations, investigations and the relevant appropriate actions taken should be recorded. The SU should provide all the relevant supportive documents with data, results and other relevant information in order to facilitate a successful technology transfer .

8. Premises

8.1. The RU should have appropriate premises with a layout, construction and finishing suitable for the intended operations. Utilities such as heating, ventilation and air conditioning, as well as gas and water systems, should have sufficient capacity and 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:

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

9. Equipment and instruments

9.1. The SU should provide a list (or similar document) of equipment and instruments involved in the production, filling, packing, QC and microbiological testing. It should include the makes and models of the relevant equipment and instruments, including automated systems and those of single-use, in order to ensure the evaluation of similar principles of operation.

9.2. A review and side-by-side comparison of the equipment and instruments, as well as process steps and parameters of the SU and RU, should be carried out in terms of their working principle, capacity, make and model in order to ensure that they are capable of appropriately performing the required processes and methods.

9.3. 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 the flow of personnel and the flow and intermediate storage of materials.

9.4. Where the review and comparison identify any gaps or differences, the appropriate action should be taken. This may include the adaptation of existing equipment or the acquisition of new equipment. Any modification or adaptation of existing equipment to become capable of reproducing the process being transferred should be documented.

9.5. The production volumes and batch sizes at the SU and RU should be compared. Where batch sizes are different, the impact should be assessed as part of risk assessment 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 (and vice versa), 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, taking into account the product's life cycle phase.

10.2. The equipment and instruments should be qualified and calibrated before use in order to support the technology transfer activities.

10.3. Process validation should be carried out according to guidelines as published in the current WHO Technical Report Series *(3)*.

10.4. Production processes and analytical procedures should be appropriately transferred to the RU following documented procedures. Where validation data exist, these should be included in the transfer.

10.5. For cleaning procedures, development and validation should be performed in accordance with the guidelines as published in the 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 in setting acceptance limits.

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

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

11. Life cycle approach

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. This also applies to the control strategy and process validation.

11.2. The responsible entities should monitor the progress of the project at each applicable stage of the life cycle aspect of the transfer in order to ensure a successful completion of the transfer.

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 planning;
- Phase III: Project transfer execution; and

- Phase IV: Project review and closeout.

Phase I: Project initiation

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

12.3. During an initial discussion, it should be identified whether or not a RU has any interest in such a project. (See also the 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 in order to support the activity, and any further development and optimization at the RU, should be transferred.

Phase II: Project planning

12.7. The marketing authorization holder and the SU and RU should jointly establish a team in order to coordinate activities and execute the technology transfer exercise. Where the technology transfer involves a site that has limited manufacturing experience or if the process being transferred is complicated, the SU should consider providing extensive training and onsite support before the project execution phase begins.

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

12.9. The team should prepare the technology transfer document such as the Master Plan (or Technology Transfer Protocol).

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

- risks;
- raw, starting and packaging material attributes;
- analytical and microbiological test procedures;
- sampling plans, and release and stability specifications;
- critical quality attributes (CQAs), critical process parameters (CPPs) and in-process controls; and
- acceptance criteria and limits

12.11. The specifications and critical material attributes of the starting materials (APIs and excipients) to be used at the RU should be consistent with those materials used at the SU, unless there is a planned change associated with these materials as part of the transfer and regulatory approval is obtained as applicable. Documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements or other regulatory requirements should be available at the RU, where applicable.

12.12. The SU should provide the RU with the open part of the Drug Master File (DMF), API Master File (APIMF), as applicable, or equivalent information, as well as any relevant additional information on the API of importance for the manufacture of the pharmaceutical product.

12.13. The SU should provide the product information including 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.

12.14. The marketing authorization holder or SU should provide any information on the history of process development, as well as any historical process changes which may be required to enable the RU to perform any further development and/or process optimization after a successful transfer.

12.15. 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 (i.e. a need for gowning or protective clothing).

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

- a detailed description of facility requirements and equipment;
- information on starting materials, applicable Material Safety Data Sheet (MSDS) where required, storage and distribution requirements for raw materials, intermediates and finished products;
- a description of manufacturing steps (narrative and process maps or flow charts, and/or master batch records), including the qualification of in-processing hold times and conditions, the order and method of raw material addition and bulk transfers between processing steps;
- a description of analytical procedures;
- the 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, sampling plans, 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.

12.17. 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.

12.18. For QC and microbiological testing of packaging components, specifications should be provided, including drawings, artwork and material and reference to relevant pharmacopoeias, where applicable.

Phase III: Project transfer execution

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

Production (example: finished pharmaceutical product)

12.20. During the transfer process, the RU should identify any differences in facilities, systems and capabilities and discuss these with the SU. The SU should cooperate with the RU in order to understand the potential impact and satisfactorily address this to assure an equivalent product quality. Based upon 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 prior to the start of routine production.

12.21. The RU should address the following tasks:

- the comparison and assessment of suitability and qualification of facility and equipment;
- a description of the manufacturing process and flow of personnel and/of materials at the RU (a narrative and/or process map or flow chart);
- the determination of critical manufacturing steps, including hold times, endpoints, sampling points and sampling techniques;
- the writing and approval of a training plan, 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 and microbiology), packaging, cleaning, testing and storage;
- the 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).

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

12.23. The RU should determine the need for qualification and validation for the packaging process.

Quality control: analytical procedure transfer

12.24. Analytical procedures 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. The transfer of the analytical procedure may be accomplished by several approaches such as confirmation testing, comparability testing between SU and RU results, co-validation between laboratories, or through a "paper-based knowledge" transfer. The chosen strategy should be risk-based and scientifically justifiable.

12.25. A protocol and Test Transfer Plan defining the steps should be prepared for transfer of analytical procedures. The analytical procedures transfer protocol should include:

- a description of the objective, scope and respective responsibilities of the SU and 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);
- the procedure for the handling of deviations; and
- details of test samples (i.e. starting materials, intermediates and finished products).

12.26. The SU's responsibilities for the transfer of analytical procedures are typically to:

- provide method-specific training for analysts and other QC and microbiology staff, if required;
- assist in the analysis of QC and microbiology testing results;
- define all procedures 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 procedures under transfer, including proof of their robustness;
- provide details of the equipment used, as necessary (part of validation report, if available) and any standard test samples;

- provide approved procedures used in testing; and
- review and approve transfer reports.

12.27. The RU should exercise its responsibility to:

- review analytical procedures 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 procedure or specification are met;
- ensure that adequately trained and experienced personnel are in place for analytical testing;
- provide a documentation system capable of recording the receipt and testing of samples to the required specification using approved test procedures, and reporting, recording and collating data and designation of status (i.e. approved, rejected, quarantine);
- execute the transfer protocol;
- perform the appropriate level of validation or verification to support the implementation of the procedures; and
- generate and obtain the approval of transfer reports.

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

12.29. Reference should be made to recognized compendial monographs, where these are relevant.

12.30. An experimental design should be prepared which includes acceptance criteria for the analytical testing procedures.

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

12.32. Relevant analytical procedure development and validation documentation should be made available by the SU to the RU, if required.

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

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

12.35. The parameters to be included in the experimental evaluation of the transfer of the analytical procedure should be defined and justified.

12.36. Acceptance criteria should be set to determine the success of the transfer and capability of the process and procedures. Where appropriate, the statistical trending of results should be undertaken in order to demonstrate this.

Cleaning

12.37. In order to minimize the risk of contamination and cross-contamination, adequate cleaning procedures should be followed.

12.38. 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 cleanability;
- information on solubility of active ingredients, excipients and vehicles;
- toxicological assessment including Health Based Exposure Limits; and
- existing cleaning procedures.

12.39. Additional applicable information should be provided, such as:

- cleaning validation reports (chemical and microbiological);
- potential degradation products and impurities;

- risks of antimicrobial resistance;
- information on cleaning agents used (i.e. 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.

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

12.41. Based on the information provided by the SU, cleaning procedures should be designed at the RU, considering relevant characteristics of the residues to be cleaned (e.g. potency, toxicity, solubility), manufacturing equipment design and configuration; and cleaning agent to be used.

Phase IV: Project review and closeout

12.42. The progress and success of the technology transfer should be monitored and reviewed during and after completion of the project. The review should further ensure that, as appropriate, stability studies are started and continued; post-marketing commitments are monitored; and new material suppliers are integrated into the quality management system.

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

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

12.45. A document such as 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 at all times.

12.46. The document, which should include an assessment of the data and information and a conclusion, should be authorized by the appropriate, responsible person(s). It should further state whether or not the team has achieved the completion of the technical transfer. Any

deviations and changes from the Master Plan should additionally be assessed and evaluated before closeout of the project.

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12. WHO guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996).

13. WHO guideline on data integrity. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021: Annex 4, (WHO Technical Report Series, No. 1033, 2021).

14. WHO points to consider when including health based exposure limits in cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021: Annex 2, (WHO Technical Report Series, No. 1033, 2021).

15. WHO A risk-based identification of essential medicines for local manufacturing in low-and middle-income countries. Draft for comments. Geneva: World Health Organization; 2016 (working document QAS/16.682).

Further reading

- Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. EMA, 2014 (EMA/CHMP/ CVMP/ SWP/169430/2012).
- ISPE Baseline, Good Practice Guide. Technology Transfer. Third edition, 2018.
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- International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised guideline. Pharmaceutical development Q8(R2). Current step 4 version. August 2009.
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Abbreviations

ALCOA+	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
FPP	finished pharmaceutical product
GMP	good manufacturing practices
GxP	good practices
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use
IPC	in-process control
IQ	installation qualification
OQ	operational qualification
QA	quality assurance
QC	quality control
QRM	quality risk management
RU	receiving unit
SOP	standard operating procedure
SU	sending unit
TRS	Technical Report Series
VMP	validation master plan
VP	validation protocol
VR	validation report

Appendix 1

Example of documentation commonly required for the technology transfer*

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

Aspect	Related documentation
Regulatory	Regulatory process description Applicable regulatory documentation
Starting materials (active pharmaceutical ingredients {APIs}) and excipients)	Drug Master File (DMF), API Master File (APIMF), Active Substance Master File (ASMF) Material Safety Data Sheets Product development report Storage conditions Stability data Forced stability data Specifications Supplier qualification References
Formulation	Formulation development reports Master formula Material compatibility/interaction studies Specifications for delivery devices
Batch manufacturing	Master of executed batch record Scale up information Risk assessment Critical process parameters In-process control specification Scale up protocol and report Process validation
Packaging	Packaging material specification Master of executed packaging record Validation Sampling plan Acceptance Quality Level (AQL) for products and defects Packaging validation
Finished product	Specification Product Dossier
Analytical procedures	Analytical test procedures

	Analytical procedure development Analytical procedure validation Standard test procedures Instrument specifications
Quality control	Sampling procedures (e.g. in-process control) Stability testing protocol and procedures Release test analytical procedure validation
Equipment and instruments	List of equipment and instruments Preventive maintenance information Overview of qualification
Cleaning	Cleaning validation master plan Cleaning procedure development and cleanability Cleaning procedures Health Based Exposure Level (Permitted daily exposure) information reports Analytical procedures validation for cleaning Cleaning validation reports and recovery study reports
Other documents	Recalls and complaint reports 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.