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19 Feb 2021

Dr. Sabine Kopp
Team Lead, Norms and Standards for Pharmaceuticals
Department of Health Products Policy and Standards
World Health Organization
CH-1211 Geneva 27
Switzerland

Re: Working document QAS/20.869 *WHO guidelines on the transfer of technology in pharmaceutical manufacturing*

Dear Dr. Kopp:

PDA appreciates the opportunity to comment on WHO's draft revision of its guidelines on the transfer of technology in pharmaceutical manufacturing. PDA supports WHO's efforts to update this guideline, as technology transfer is a complex but increasingly prevalent tool in pharmaceutical manufacturing globally.

In the attached comment table, PDA offers specific suggestions that may provide clarity for those engaging in technology transfer activities. In addition, PDA offers general suggestions for the document, as more fully described in the attached table:

- PDA strongly suggests that WHO add discussion of the role of the marketing authorization holder (MAH), along with the roles of the sending unit (SU) and receiving unit (RU). It is increasingly common that the MAH will be neither SU nor RU. Even in this circumstance, the MAH retains responsibility for compliance with regulatory expectations and commitments, as well as for updating of regulatory documentation. Thus, it would be helpful to discuss the role of the MAH in this document.
- PDA suggests that WHO clarify the scope of the document and applicability of language throughout. While in some respects the document mainly seems to refer to technology transfers of drug products, at points it also appears to include active pharmaceutical ingredients, excipients, in-process bulk materials, and packaging. PDA is concerned that the differences in technology transfers of these items, as compared to drug products, will not be clear to readers.
- WHO may wish to consider the level of detail that is most appropriate for this document. While many sections of this document provide a general overview of the technology transfer process, other sections provide significantly more detail. If WHO chooses to provide detailed, bulleted lists (as in section 12), it is important that those lists be comprehensive. High-level or general considerations, along with references to other document that provide more complete discussion of associated topics, may better fit WHO's intent.
- It may be helpful to provide additional clarity about the documents that the parties will create to guide the technology transfer. While the guideline mentions that certain documents are necessary (e.g., in sections 5.3, 5.10, 5.11, 7.1, 12.9, and 12.30), it

may be helpful to provide a clear definition or description of at least the (1) technology transfer plan or change control, (2) protocols, and (3) summary report.

In addition, as we note in the attached comment table, a revision to PDA's Technical Report 65 on Technology Transfer has recently been peer reviewed in preparation for publication. This revised Technical Report will touch on many of the same topics, but with more detail. We hope that the revised Technical Report will be useful to WHO and to those involved in technology transfer globally, and that WHO will consider including it in the Further Reading list that begins at line 1004.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments have been prepared by a committee of global experts in technology transfer and pharmaceutical and biopharmaceutical manufacturing on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,

Richard Johnson
President and CEO

cc: Glenn Wright, PDA; Ruth Miller, PDA

**COMMENTS ON WHO WORKING DOCUMENT:** QAS/20.869
**TITLE OF THE DOCUMENT: WHO GUIDELINES ON THE TRANSFER OF TECHNOLOGY IN PHARMACEUTICAL MANUFACTURING**

Name: Parenteral Drug Association
Employer:
Position, Title:
City, Country: Bethesda, Maryland, USA and Berlin, Germany

*Kindly complete the table **without modifying the format** of the document - thank you.*

| **Comments** | | | |
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| **Line number(s)** | **Comments** | **Suggested text** | **Justification** |
| | PDA suggests that WHO may wish to consider the level of detail that is most appropriate for this document and make revisions accordingly. While many sections of this document provide a general overview of the technology transfer process, other sections provide significantly more detail.<br><br>In particular, subsections of section 12 provide detailed, bulleted lists. If WHO wishes to provide detailed lists, it must take special care to ensure that those lists are complete and comprehensive. High-level or general considerations may better fit WHO's intent and be more consistent with the remainder of the document. For instance, where WHO specifies that the materials to be provided should be assessed using the principles of quality risk management, as discussed in line 616 and 653, PDA is uncertain that it is useful to provide a list of approximately 20 considerations.<br><br>If WHO does decide to take a more detailed approach throughout the document, WHO might provide a list of documents (or examples of documents) in the text in line 366. Likewise, WHO might include "sampling plans" in line | | |

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| | 745, and "evaluation of scale-up volume impact" in the list that begins at line 763.<br><br>Additionally, section 7.1 (line 428 et seq.) provides detail that may not be necessary in lines 430-434, but then also appears to conflate aspects of the TT protocol with aspects of the corresponding TT report that is developed once the transfer is complete. If WHO wishes to attempt to provide a detailed list of "phases and activities" here, it may wish to include in the bulleted list additional items such as:<br>business and regulatory strategies which should address stability requirements, samples, and expected use of the validation/qualification batches. | | |
| | In the Glossary and throughout the document, WHO does not acknowledge the role of the marketing authorisation holder (MAH). This role could be different from that of the SU, especially with the increased usage of contract development and manufacturing organizations throughout the product lifecycle.<br><br>PDA suggests that WHO consider referring to the role of the MAH throughout the document. Two such locations are lines 371 and 576, for which we provide suggested text in the next column. Additional suggestions are included below.<br><br>Further, WHO might consider more clearly specifying the "owner" of responsibilities (SU, RU, and MAH) for the activities described. In particular, some users may appreciate additional detail in section 9 to more clearly describe the roles. Likewise, in lines 507-511, specific check points or clear descriptions of the responsible party could be helpful. | Add the underlined text:<br>The marketing authorisation holder (MAH) has the overall responsibility of defining the technology transfer between the SU and the RU and has to ensure the regulatory aspects of technology transfer.<br><br>The technology transfer should be managed by responsible persons from the SU and RU, and at times, the MAH when performing outsourced production.<br><br>The SU, RU, and MAH (if separate from the SU and RU) ~~and RU~~ should jointly establish a team that will coordinate activities and execute the technology transfer exercise. | With the growth of contract manufacturing, more parties than the SU and RU may be involved. This adds complexity to the technology transfer. Each party involved should have a designated contact person and defined teams of personnel assigned to assist. |
| | It may be helpful to include schemes, illustrations, and/or tables in this document. | We would suggest including in the document some high-level schemes, for example:<br>- Timeline scheme for project<br>- Table of documents (e.g., technology transfer plan; specific technology transfer reports such as analytical transfer and process validation transfer; technology transfer overall summary report, etc.) | Some readers may appreciate visual representations of the text for greater clarity and understanding. |

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| | PDA is now completing the peer review of a revision to PDA Technical Report 65 Technology Transfer, which will be a longer and more comprehensive document touching on some of the same topics as this guideline. WHO might wish to consider reviewing that updated Technical Report. PDA hopes that the revised Technical Report will be useful to WHO and to those involved in technology transfer globally. | Please consider including the updated PDA Technical Report 65 Technology Transfer in the Further Reading list that begins at line 1004. | |
| 62 | PDA suggests that updating the document is worthwhile in general, and may be especially useful to those working to ensure the supply of therapeutics for critical needs in these challenging times. We find WHO's specific reference to inspections slightly confusing and therefore suggest making this sentence slightly more general. | This document was published in 2011 and it was considered that it should require updating, not least to support ~~the inspections for COVID-19 therapeutics~~ consistent supply of therapies for critical needs. | |
| 104 | PDA suggests revising this paragraph for clarity and consistency. While the first sentence refers to validation, validation is not required for drug products that are not being commercially marketed. PDA also suggests revising a later sentence to refer to process validation rather than simply validation. | Revise this paragraph:<br>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.<br><br>To read:<br>The transfer of production of pharmaceutical products from one site to another may take place before or after obtaining authorization to commercially market a drug product. A product transfer therefore may occur during development; during clinical trials; or for full-scale commercialization and commercial batch manufacturing, cleaning and process validation. The level of rigor in the transfer should be commensurate with the phase of a development program. | |
| 119 | PDA suggests adding text to clarify that requirements may differ based on the product lifecycle phase. | 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 considering the stage of the product lifecycle. | |
| 134 | PDA suggests adding text. | Effective process and product knowledge management, including evaluation of impact of RU planned differences on product and process. | It is not enough that the SU know how. Technology transfer also requires evaluation of the impact of the changes required for the activity to occur at the RU. |

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| 138 | PDA suggests noting that these requirements are specific to the transfer of marketed products. PDA also suggests referring to "documented evidence" rather than "proof." | Transfer of technology for marketed products should result in ~~proof~~ documented evidence that the RU can routinely reproduce the transferred product, process, or procedure… | Evidence to routinely produce (i.e., validation) is usually only required for transfers of product from clinical phase 3 to commercial manufacturing, or the transfer of a product that is already in commercial production. Typically, clinical phase production is a very limited number of batches. |
| 143 | PDA suggests including references to ICH Q2 and Q12 as well. | The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q2, Q7, Q8, Q9, Q10, ~~and~~ Q11, and Q12. | These guidance documents also apply to technology transfer. |
| 155-166 | PDA suggests revising this text in the Scope for clarity, as the intended scope of the document is not entirely clear from this and following text. The reference to "pharmaceutical manufacturing" in the title of the document and the index appear to mainly refer to drug product, but this text appears also to include biochemical manufacturing and in-process bulk materials. The following paragraphs confirm special attention to sterile products and metered aerosols, but lines 164-166 appear to exclude vaccines and biopharmaceutical products.<br><br>For instance, we suggest:<br>• Explicitly describing whether drug substance or API TTs are covered by this document.<br>• Clarifying which drug products (FPP) are not included. For example, are combination products included? Medical devices are not considered a product.<br>• Including phase-appropriate language in the Scope section, in addition to the Introduction. | In addition to the clarifications provided in the comment to the left, WHO could consider the following changes:<br><br>This document provides guiding principles on technology transfer. The principles apply to marketed products as well as investigational products.<br><br>Throughout development lifecycle stages, transfers should be appropriate and proportionate to the phase of the development program to ensure product development knowledge is maintained and processes are appropriately controlled.<br><br>This guideline should be applied when transferring the technology of processes and procedures relating to active pharmaceutical ingredients (APIs), ~~in-process bulk materials,~~ isolated API intermediates, bulk drug products, finished pharmaceutical products (FPPs), including product specification, process validation … | |
| 158, 178 | Add "test methods" | …and analytical procedures/test methods. | Methods used at the bench, also referred to later in the document. |
| 162 | PDA suggests adding modified release solid oral dosage forms as an additional example. | …such as, for example, sterile products, modified release solid oral dosage forms, and metered dose aerosols. | |
| 166 | PDA suggests adding advanced therapy medicinal products as an additional example. | …medical devices, advanced therapy medicinal products, and vector control products. | |
| 171 | PDA suggests adding intellectual property as an additional consideration. | … on any legal, intellectual property, financial or commercial considerations… | |
| 202 | PDA suggests adding a reference to Good Documentation Practices in the definition of ALCOA+ | ALCOA+. A commonly used acronym for the Good Documentation Practice expectations for GXP documentation to be ~~for~~ attributable, legible, contemporaneous … | |
| 219 | PDA suggests revising the definition of "corrective action." | corrective action. Corrective action is an action taken to eliminate the root cause of identified non-conformity so that it | |

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| | | does not recur. ~~Any action to be taken when the results of monitoring at a critical control point indicate a loss of control.~~ | |
| 271 | Because process validation also may apply to active pharmaceutical ingredients, we suggest expanding the definition. | …which establishes scientific evidence that a process is capable of continuously delivering the active pharmaceutical ingredient or finished pharmaceutical product meeting its predetermined specifications and quality attributes. | |
| 278 | PDA suggests omitting the reference to the RU in this sentence. | Qualification batches. Those batches produced ~~by the receiving unit (RU) to demonstrate its ability to reproduce the product~~ as part of process performance qualification. | While PDA understands that this document is focused on technology transfer, qualification batches can be executed in other settings as well. In order to avoid confusion, PDA suggests that the definitions used here should be appropriate for use in other settings, as well, when relevant. |
| 312 | PDA suggests that WHO define the term "technology transfer," which is used throughout the document, rather than "transfer of technology." In addition, PDA suggests broadening the definition to include references to transfers between development sites and to testing sites. | Technology transfer~~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~~. Technology transfers may involve development, manufacture, and/or testing sites. | Technology transfer includes analytical transfer too. |
| 338 | The use of the word "audits" at the due diligence phase might be too stringent, but visits are usually a must. | …. Gap assessment ~~or audits~~ and due diligence visits of the SU… | Less stringent language is appropriate because, at this point, no agreements between the parties are in place. |
| 345 | PDA suggests adding a sentence recommending that the Quality units be involved in the gap assessment. | It is recommended that the Quality units of both the SU and the RU participate in this activity. | Too often Quality is not included in the team, leading to change control, documentation and approval issues. |
| 351 | PDA suggests omitting the discussion of readiness at this point. | The assessment to determine feasibility ~~and readiness~~ for technology transfer may include technical, business, regulatory and legal aspects. | This discussion is for feasibility and whether to proceed with a TT. Readiness is evaluated at a later point in the process. |
| 358 | PDA suggests allowing greater flexibility by referencing that there may be more than one formal agreement governing the TT. At the same time, however, a technology transfer that involves two sites of the same organization may not require a formal agreement. | There should be ~~a~~ formal agreement or agreements between ~~the~~any external parties involved in the technology transfer. | Adding more flexibility in this sentence will be useful in reflecting the wide range of technology transfer situations. |
| 363 | PDA suggests adding text to emphasize that the responsibilities are shared by the RU, SU, and MAH and that the responsibilities should be documented in a technology transfer plan. | Responsibilities across the SU, RU, and MAH should be defined in a technology transfer plan. | |
| 366 | Include the role of the MAH in the discussion of documentation to be provided. | Revise this sentence:<br>The SU should provide the necessary documentation relating to the process, product or procedure to be transferred.<br><br>To read:<br>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. | |

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| 367 | PDA suggests noting that the level of information required will vary by lifecycle phase. | The SU should provide the necessary documentation relating to the process, product or procedure to be transferred, appropriate to the requirements for the product's lifecycle phase. | It would be helpful for users to understand that the information needed for a product in later clinical phases will be greater than the information required for products in clinical phase 1, and even more information will be required for a product that is in commercial production. |
| 373 | When the authorization holder is neither the SU nor the RU, the technology transfer may be managed by a third party. | Revise this sentence:<br>The technology transfer should be managed by responsible persons from the SU and RU.<br><br>To read:<br>Responsible persons from the SU and RU should be assigned to manage the project at each site. The overall management of the technology transfer could be done by the SU, the RU, or the MAH. | The revised language specifies the need to set a responsible person at each site, and also considers the role of the MAH. |
| 374 | PDA recommends that WHO add a sentence that clearly identifies some of the necessary members of the technology transfer team. | It is recommended that the SU and RU ensure participation by, for instance, their regulatory, quality, engineering, process, and analytical units or functions on the technology transfer team. | Many companies do not employ cross-functional team for TTs effectively. Any additional guidance that WHO can provide may assist companies in understanding that a successful technology transfer must be cross-functional. For instance, if the quality unit is not included on the team, there may be change control, documentation, and approval issues. |
| 382 | PDA suggests adding more detail regarding the training program to be developed. | Revise this text:<br>A training programme should be implemented specific to the process, product or procedure to be transferred.<br><br>To read:<br>Based on the specific product, process documentation and activities to be carried out, the training curricula for RU personnel should be evaluated and integrated with appropriate elements, such as technical seminars led by SU experts related to product-specific aspects and lesson learnt. | |
| 386 | PDA suggests adding additional detail. | Any changes and adaptations made during the course of the project should be fully documented and agreed to by both parties. Technical, Quality, and Regulatory functions are key to assessing the risks to the technology transfer from the proposed change(s). The project manager should evaluate the impact to the project cost, schedule, and resourcing based on an updated risk assessment. | PDA recommends including more details about changes to the initial scope, goals, and boundaries of a TT. These types of changes are a significant factor in technology transfers not adhering to the initial budget and timeframe. |
| 387 | PDA suggests adding a sentence suggesting that the SU should have an on-site presence at the RU at critical phases. | Whenever possible, it is recommended that SU send personnel to the RU site at critical phases of the project to assist with the transfer of knowledge. | Knowledge transfer is critical to the success of the technology transfer, and on-site presence by experienced SU personnel |



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| | | | can facilitate information sharing, issue-spotting, and rapid resolution of potential issues. |
| 388 | PDA suggests discussing the several types of documents needed, rather than simply the report. | Replace this sentence:<br>The execution of the technology transfer project should be documented in a report which is supported by the relevant data.<br><br>To read:<br>The technology transfer should be documented with a plan, associated protocol(s), and a report. | Documentation of the technology transfer throughout the project is essential to its organization and management. Therefore, a more complete listing of the documentation needed would be appropriate in this section. WHO could consider moving this text into section 5.3, above. |
| 401 | PDA suggests referring to technology transfers in the plural form. | The quality system should incorporate GxP which should be applied to the life cycle stages of the products and processes, including ~~the~~ technology transfers. | TT is not a single activity. It may occur multiple times across a product lifecycle. Product manufacturing often changes sites and with significant scaleup. |
| 413 | PDA suggests adding a reference to regulatory strategy in this discussion of the system for quality risk management. | The system for quality risk management should be described in writing and cover appropriate areas such as, but not limited to, regulatory strategy, premises, … | The regulatory strategy needs to be considered as part of quality risk management to determine any impact on the ability to implement the technology transfer. |
| 434 | PDA notes that it may not be useful to include staff names at this stage of the technology transfer. | … ~~names~~ functional area role of key personnel and their responsibilities … | Given staff mobility, and the potential that personnel will change roles and/or companies, it be more useful to describe the functional areas at this stage, rather than names. |
| 441 | It is not necessary to discuss the retention of samples in the transfer document as this is covered by GMP requirements. | Omit this text:<br>• arrangements for keeping retention samples of active ingredients, intermediates and finished products, and information on reference substances where applicable; | |
| 443 | WHO might consider transferring the following text to section 7.3, as it appears to relate to the summary report:<br>• Review of the transfer, outcome, signature(s) and date of conclusion of the transfer | Move the text without revision. | |
| 457 | PDA suggests using a different word than “finishing,” as it may not be clear to all readers. Does WHO refer to equipment polish, floor and wall construction, etc? PDA also suggests using the word “suitable.” | …and finishing suitable for ~~to suit~~ the intended operations. | Different wording would improve clarity. |
| 474 | Where WHO suggests providing a list of equipment and instruments, PDA suggests also allowing for documents that provide similar information. | The SU should provide a list of equipment and instruments involved in the production, filling, packing and QC testing or documents containing similar information. | It should suffice to provide documents which contain similar information, to reduce redundancy. For example, if the analytical method is provided, it should not be necessary to also provide a list with equipment for performing the analytical method. A gap assessment for the analytical method between the SU and the RU will be performed as well. |
| 478 | PDA suggests removing the additional examples provided, as they are rarely relevant in technology transfer. Each site has their own procedures for these purposes. | Omit this text:<br>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. | |



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| 483 | PDA suggests expanding on this sentence with additional explanatory text, and also adding a reference to the capacity of the equipment.<br><br>With this in mind, points 9.3 and 9.5 also could be combined. | 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, capacity, make and models to ensure that they are capable of properly performing the required processes and methods. | These changes will add clarity. In addition, capacity is equally important as the other points when assessing scale effect. |
| 491 | PDA suggests clarifying that the assessment to be made is a part of the risk assessment. | Where batch sizes are different, the impact should be assessed as part of the risk assessment and the appropriate action planned and taken. | This change will add clarity. |
| 505 | PDA suggests adding language to help readers understand that the lifecycle phase of the product will have a significant impact on the qualification and validation requirements | 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 lifecycle phase. | Clinical phases do not require full validation and development progresses with each clinical phase. |
| 514 | PDA suggests using more specific language than "actual technology transfer." That phrase is confusing, as a technology transfer includes all of the stages of the project, including the qualification phase. | WHO might delete section 10.4. In the alternative, revise the text to say:<br><br>Where technology is transferred to commercial sites, the qualification of equipment and instruments should be completed prior to ~~the actual technology transfer~~ Phase III, as defined below. | The "actual technology transfer" includes the qualification of equipment and instruments at the RU. |
| 516 | In PDA's view, it is adequate to refer to the process validation guidelines, as they provide a complete overview. | Remove the first sentence to simply contain the note:<br><br>~~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).* | |
| 522 | PDA suggests redrafting the sentence to make it more objective and purpose-driven. | Revise the text to read:<br><br>The Process and Analytical team responsible for the technology transfer at the RU should support in appropriately validating the processes and analytical procedures with a well-documented knowledge transfer from research and development or SU. ~~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. | The focus of WHO's text seems to divert to validation at SU, which might not be in the scope of TT. Some regulatory agencies insist that the validation must be done at the actual testing site. Also, as initially written, the text does not consider transfers from research and development to RU. Hence, PDA suggests redrafting the sentence to better serve the purpose of this process. |

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| 551-554 | PDA suggests omitting the bullets in lines 551-554 and providing instead a list of the four suggested phases. In addition, we suggest including the word "execution" in the title of phase III (in this location and also in line 597).<br><br>WHO also might consider changing the four phase names to match typical project management terms that are widely understood, e.g., Initiation, Planning, Execution, Monitoring, Closeout. This would require corresponding changes later in the document as well. | The technology transfer project plan may be divided into different phases. These may include, for example:<br>• Phase I: Project initiation;<br>• Phase II: Project ~~proposal~~planning;<br>• ~~Establishing a team;~~<br>• ~~Risk assessment;~~<br>• ~~Project plan;~~<br>• ~~Control strategy;~~<br>• Phase III: Project transfer execution; and<br>• Phase IV: Project ~~review~~closeout. | The ideas contained in the bullets in question are provided in later text, so omitting them here will reduce confusion without eliminating important ideas. |
| 573 | PDA suggests adding a section 12.7 raising the need for extensive training and on-site support in some circumstances. | 12.7 If the technology transfer involves a site that has limited manufacturing experience, or the process being transferred is complex, the SU should consider providing extensive training and on-site support before the project execution phase begins. | |
| 582 | PDA suggests that the term "technology transfer document" is vague. If WHO is referring to a document referenced earlier in the guideline, a cross reference may be helpful. | The team should prepare the technology transfer ~~document~~ project plan. | |
| 584-595 | PDA suggests that WHO carefully review the list provided in section 12.10. Several items on this list may not be aspects of a control strategy. A control strategy includes specifications for CMAs, controls on CPPs, controls during storage, in-process controls etc.<br><br>Perhaps WHO would consider referencing a different document with detailed discussion of control strategies instead of including this list.<br><br>In line 585, please clarify what WHO refers to in terms of "materials." If WHO is referring to raw materials/excipients, please indicate this explicitly.<br>In line 587, PDA is uncertain what WHO means by "testing steps in QC." If WHO refers to methods, PDA agrees that these impact the control strategy. | If WHO chooses to retain this list, revise it to, at a minimum, omit the items that are not part of the control strategy:<br><br>The team should develop a control strategy which includes, for example:<br>• risks;<br>• material attributes;<br>• ~~processing steps and stages in production;~~<br>• testing steps in QC;<br>• ~~equipment working principles and their impact on the process;~~<br>• critical quality attributes (CQAs), critical process parameters (CPPs) and in-process controls;<br>• ~~QC instruments;~~<br>• acceptance criteria and limits;<br>• ~~alarms and trends;~~<br>• ~~personnel requirements, such as qualification and training; and~~<br>• ~~qualification and validation.~~ | |
| 603-699 | While PDA appreciates that WHO attempted to separately describe the differences for active pharmaceutical ingredients, packaging, and excipients, we are concerned that the text may be too vague to meaningfully guide users | | |

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| | in the differences and nuances of TT requirements for each. As noted in our first comment in this table, it may be necessary to provide either more detail or less, in order to give users appropriate information.<br><br>As one specific point, in section 12.13 (line 612), PDA suggests that WHO clarify whether this section is intended to apply to the transfer of API manufacturing process or drug product manufacturing process, as it refers to both.<br><br>Additionally, the content of section 12.13 (line 616) appears to be more related to the API specification for use in a DP. If it is intended to apply only in that case, and not to the transfer of an API is the intended scope, alone, we suggest clarifying that.<br><br>We further inquire whether section 12.16 (line 701) and the following subsections are intended to apply only to processing and packing, as the formatting leaves this unclear. | | |
| 605 | PDA suggests revising the reference to "relevant functional characteristics" to use instead standard and well-understood terminology. | The specifications and ~~relevant functional characteristics~~ critical material attributes of the starting materials (APIs and excipients) … | |
| 616 | If, as noted in our initial comment above, WHO wishes to provide detailed checklists, PDA recommends adding content to ensure completeness. | Add bullets:<br>• Safety and environmental assessments and control;<br>• Process specific equipment requirements including materials of construction for a technology transfer;<br>• Sensitivity to light, oxygen, temperature for a technology transfer;<br>• Process and Analytical development reports;<br>• Technology transfer report for the transfer to the SU initially including all validation/qualification reports. | |
| 645 | PDA suggests adding bullets for completeness. | • Mass transfer, heat transfer and mixing information that could impact scale-up,<br>• Packaging configuration, and | These items often are not discussed, which can lead to production problems upon scale-up, or even preclude specific equipment form being capable for the process. |
| 756 | From the document, it is not clear how to investigate issues. | PDA suggests adding a section in Phase III describing that, in case of failed process validation or significant deviations, the SU must commit to work with the RU to understand the impact and to decide next steps. | |



| **Comments** | | | |
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| 761 | PDA suggests adding “training plan” to the list of items to develop before the start of routine production. | …and should develop the relevant site operating procedures, training plan, and documentation before the start of routine production. | |
| 817 | PDA suggests adding a reference to methods. | …for the transfer of analytical procedures/test methods are to: | Methods used at the bench, also referred to later in the document. |
| 843 | PDA suggests adding a reference to demonstration of compendial methods. | perform the appropriate level of validation, including demonstration of compendial methods, to support the implementation of the methods; | While compendial methods are not required to be qualified on products new to a site, they do need to be evaluated and demonstrated to work for a new product. If this step is missed (as it often is, in practice), there may be issues during process validation. |
| 860 | PDA suggests specifying that only the applicable documentation should be provided. | ~~All~~ If applicable, analytical procedure development and validation documentation should be made available by the SU to the RU. | Analytical development data is provided as needed for execution, transfer, or investigation. However, upon initiation of method transfer typically the SU will only be expected to provide validation and/or execution information. Development data is only provided as applicable. |