

Technology Transfer as the Process of Pharmaceutical Quality System: Modelling Technology Transfer as a Process Strategy

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Abstract: The recent GMP (good medical practice) rules actualisation and its requirements introduction widened the GMP guidelines for every life cycle of medicinal products, including the stage of processes scaling and technology transfer. This requires the technology transfer process to be regulated as the part of pharmaceutical quality system and the following development of corresponding written procedures. The following publication is dedicated to the development of TTP (technology transfer process) and its accessible graphic formalisation alongside the definition of main stages and possible procedures limited by the offered model. According to the actualized GMP rules, the technology transfer is an essential part of pharmaceutical quality system at a modern pharmaceutical company.

Key words: Medicine, life cycle, technology transfer, process scaling, pharmaceutical quality system, quality system procedures.

1. Introduction

The modern quality assurance system for medicinal products is based on PQS (the Pharmaceutical Quality System), which was formed by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [1] and afterwards added as a required part of the GMP rules [2]. According to the PQS principles, GMP includes every stage of drug life cycle, starting from its pharmaceutical development, technology transfer, commercial manufacturing and product discontinuation.

Modern business strategies, committed by the pharmaceutical companies at different countries, require constant expanding of product nomenclature. This requires to involve more procedures of pharmaceutical development and technology transfer into the manufacturing control both for the original/innovational and generic drugs. Those

processes highly determine the production quality at the further commercial series production.

GMP rules and PQS requirements [1, 2] set only the main principles of quality assurance system and the need of quality system widening for the pharmaceutical development and technology transfer stages, but has almost no corresponding detailed control standards. Some recommendations about the technology transfer process can be found in the manuals of international organisations, which activity is connected to the regulation of drugs circulation (especially, ICH, WHO) [3, 4] and some professional associations (e. g. ISPE, the International Society for Pharmaceutical Engineering) [5]. To comply with GMP requirements and PQS principles, every company needs:

(a) To develop its own strategy of technology transfer control;

(b) To define its operational tactics by development, activation and usage of corresponding procedures in a form of written Standard Operating Procedures.

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The goal of our scientific and practical investigations was to develop a strategy and standardized approach to technology transfer as to the one of the main basic processes of pharmaceutical quality system. The main objective for achieving this goal is to develop a model of this process, that is to be practically applied (technology transfer process strategy development) and to define the key procedures of this process (the determination of strategic tasks realization tactics). Every procedure must be subsequently formalized in a form of SOPs. The GMP requirements, PQS principles well as recommendations about the technology transfer process, offered by the various international organisations and associations of medicines circulation (ICH, WHO and ISPE), mentioned above, have to be considered.

2. Materials and Methods

The main tasks for reaching the given goal and forming the detailed and unified model of technology transfer process which should be considered are following:

(a) the process start and end need to be clearly determined;

(b) according to the existing definitions [1, 4, 5], the technology transfer can be committed by two main ways: scaling, which is usually a logic extension of pharmaceutical development, or implementation of technology, copied from another production area. It is a principally important element, which has to be shown in the general process model (at least due to its requirement of separate procedures formation);

(c) to recommend an algorithm, helping the pharmaceutical company to introduce the technology transfer process into the general quality system. It is vital to formation and further proper functioning of the pharmaceutical quality system, which may and has to be formalized and visually demonstrated at the audits and official inspections);

(d) it is important to define and regulate the

connection of technology transfer process with other pharmaceutical quality system processes. We need to emphasize that the connections between any quality system processes are those “weak links” which can be easily broken and therefore are unable to provide and demonstrate the proper and bound quality system work;

(e) the proper functioning of any company quality system is sufficiently dependent on the interaction between structural units and personnel. This interaction is also one of the “weak links”, which can be “torn”. Understanding the relationship (“docking”) between units (departments) and between personnel within any process is also critical to the proper functioning of the quality system as a whole, which can also be ensured by the appropriate detailing of the process model schema;

(f) if relevant, consider the documented (formalized) interaction between different companies, which can be potentially involved into the technology transfer process, because each company may have its unique and different quality system;

(g) as far as maintaining the proper functioning of pharmaceutical company quality system is also the task of company’s top management, it is also important to determine its responsibility area in technology transfer introduction and functioning during the company development process.

Developing the equable (standardized) procedures in the overall technology transfer process allows their regulation and unifying in acceptance to every product and also really provide the practical drug quality at the stage of it commercial manufacturing. We need to consider, that those procedures development for the process scaling and technology transfer is possible, when the procedures of quality integration into the drug are executed at the previous life cycle (pharmaceutical development) [3]. But, considering the given publication topic, the questions and procedures, connected to the pharmaceutical development process, will be left beyond.

According to the WHO definition, the technology transfer is “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” [4]. An equal definition is given in the ICH Q10 manual and is transferred into the actualized ISPE manual [5]: “The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement”. First, the technology transfer is a system of procedures for the transfer of documented knowledge and experience, gained during the pharmaceutical development or commercial product production to the area of product’s commercial release. This requires providing of precise interaction between the pharmaceutical company units or the companies themselves. And secondly, the process should be based on the single principle for two scenarios: new product implementation to the production area using the technology scaling from R&D laboratory to the production area or the manufactured product technology transfer between the production areas. It is vital to consider this in the strategy of technology transfer works, which were also brought to the attention.

3. Results and Discussion

3.1 Progress of Analysis and Research

The fundamental PQS principle is that the quality of every drug can only be guaranteed to the consumer, when it is introduced and maintained on every life cycle of a product. Conceptually, every drug life cycle has 5 stages: stage start decision → stage preparation → stage implementation → stage results evaluation → stage finishing (with the transition to the next product’s life cycle or its whole life cycle ending). This

concept of standard drug life cycle stages contain is formulated by the authors in the form of scheme given on the Table 1.

This concept realization by any pharmaceutical company, constantly willing to improve its quality system and provide the compliance of production quality and technology to the modern knowledge level, has the following requirements:

- the expansion of whole quality system usage, in compliance to which the commercial series production procedures are given on all of the company units, incl. the units (labs), is responsible for the pharmaceutical development (R & D labs/depts) alongside the trade licensing (product state registration);
- expansion of the existing SOPs on the processes of pharmaceutical development, register dossier formation and registration (trade license receiving) and also on a process of drug technology transfer on the production area.
- development and introduction of separate SOPs on the processes of pharmaceutical development, register dossier formation and registration (trade license receiving) and also on a process of drug technology transfer. The technology transfer is considered to be one of the drug life cycle stages, which precedes the drug appearance on the market.

The ISPE *Good Practice Guide. Technology Transfer*, Last Accessed manual offers the simple TTP model, including the 6 subsequences (stages). This model scheme is represented on Fig. 1.

According to the given ISPE explanations, the process model consists 4 main stages (and absorb the following 6 steps): Project Initiation → Project Delivery Planning → Project Implementation → Project Close Out. Every stage includes one or more components. The scheme of this model is represented in modernized by authors form on Fig. 2. It is essentially close to the concept of standard drug life cycle components, which is formulated and represented by the authors on Table 1.

Table 1 The concept of standard drug life cycle stage contains.

	Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Decision making	The decision of product development	The decision of product involvement (transfer)	The decision of product commercial manufacturing	The decision of product discontinuation and its remnants utilizing on the market
Stage preparation	Information gathering, its analysis, raw materials ordering, development preparation activities	Transfer preparation activities, programme/plan forming	The commercial series plot post-licensing inclusion into the production plan	Activities planning for the product discontinuation and its remnants on the market
Stage holding	Direct product development	Direct technology transfer (incl. the scaling process)	Routine commercial series manufacturing	Product discontinuation measures taking
Results analysis and evaluation	Development report evaluation. The expertise of corresponding parts of Marketing authorisation dossier	Technology transfer evaluation – process validation results	Regular quality reviews and stream process verification	Evaluation of the product discontinuation plan completion results
Stage finishing	Development materials transferring (the parts of Marketing authorisation dossier, TTP, process validation programme)	Evaluation of process validation results. The main production documentation transferring. Product industrial introduction act.	Production cancelling at the industrial plot. Last series realization	The in-market remnants removal and utilization OR the last in-market series expiration

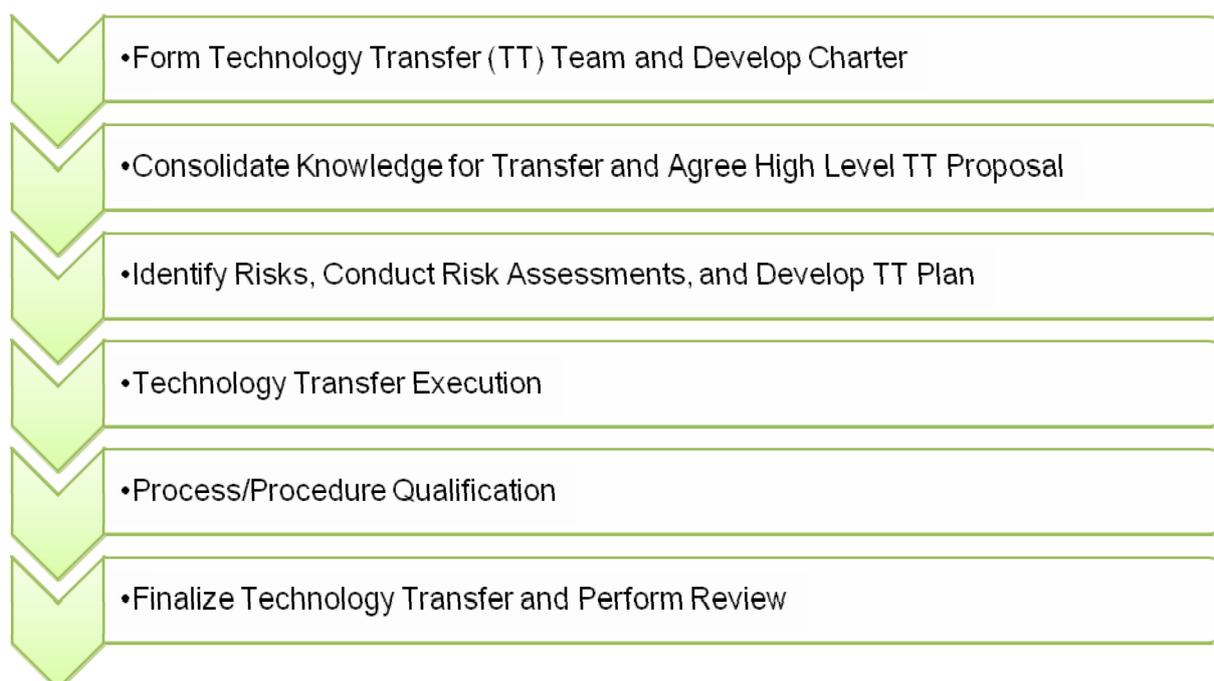


Fig. 1 Technology transfer project phases (ISPE model).

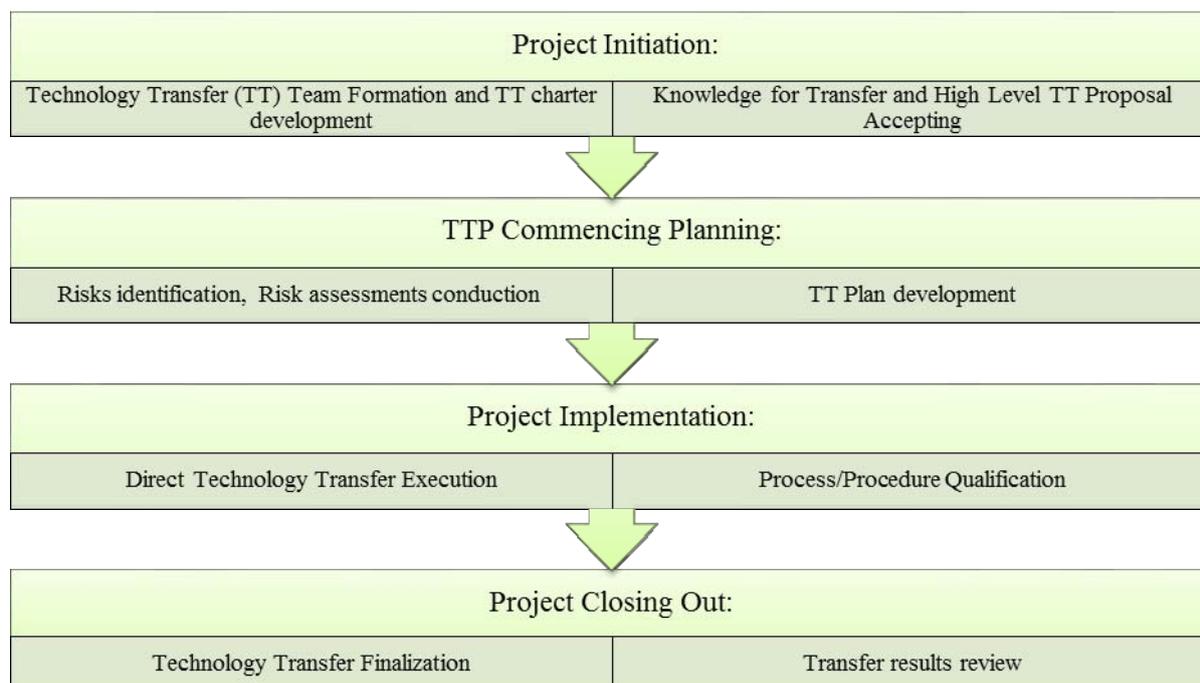


Fig. 2 The author-modernized TTP SPE model.

However the authors think that the suggested technology transfer model, needs further development in details. Such detalisation is principally important for:

- the convenience of process model understanding

and practical usage by the pharmaceutical companies (both at expanding of existing and mandatory SOPs for production area quality and at the definition of separate SOPs for the given process);

- the demonstration and formalization of

technology transfer links (as of the separate quality system process) with other processes in the solid pharmaceutical quality system functioning.

A good pattern of the given process model building, compliant with the given requirements, is a principle of model building, offered by the ICH for the QRM process [6] and which was considered by the authors to be the basic one for the development of technology transfer process model. Besides that, it also considered ISPE-offered TTP, modernized by the authors (Fig. 2) and also the concept of standard drug life cycle components (Table 1). According to the given concept, the main stages of technology transfer process, as one of the drug life cycle stages, are the next: decision taking about the stage start (e. g. about the new product implementation to the production area) → the preparing of technology scaling or transfer stage by the formation of a Programme/Plan, the definition and implementation of required preparational measures → the direct holding of technology transfer stage (incl. the process scaling or copied process transfer) → transfer results evaluation (as an analysis of process validation results) → and, finally, the technology transfer stage finishing (including the transfer of main production documentation, the composition of the Act of Product Industrial Introduction) followed by the next cycle, the *Commercial Manufacturing*, which requires the *continuous or ongoing process verification* [7, 8].

It is vital for the TTP model and procedures to be linked between the sending/receiving units or production areas to form and practically realize the technology transfer strategy, considering the specifics of every company and possible variations of the transfer itself, e. g:

- for different units/areas at one company and country, participating in the procedure of scaling or/and product technology transfer at its introduction;
- for the different company/corporation units, located in different countries and participating in the procedure of new or existing technology transfer from

one area to another (incl. the production areas in different countries);

- for the different companies, which production areas are used for technology transfer in one country;
- for the different companies in different countries, which production areas have the technology transfer committed.

A schematic pattern of technology transfer possible variation with a consideration of company specific is represented on the Fig. 3.

The mentioned samples evidence the technology transfer to be committed both inside the company, with compliance with the rules, set by it (incl. the law specifics of different countries, where can the company production areas and units be located) and based on the outsourcing works (e. g. between the independent production areas of one company, between different companies, between the manufacturer and trade license owner etc). Those factors must also be considered and included into the technology transfer model and procedures.

According to the mentioned information, we formed the technology transfer model as the qualitative process, which is one of the basics of pharmaceutical quality system at the modern pharmaceutical company and its production areas. The offered model is represented on Fig. 4. It “connects” to the concept of standard drug life cycle contents (Table 1) and includes 5 main stages:

- (1) stage start decision = technology transfer process start,
- (2) stage preparation = technology transfer process preparation,
- (3) stage implementation = a technology transfer process itself,
- (4) stage results evaluation and analysis = a technology transfer finishing (analysis) and process validation (evaluation),
- (5) stage finishing = technology transfer finishing = product implementation.

While forming the offered TTP model, we considered

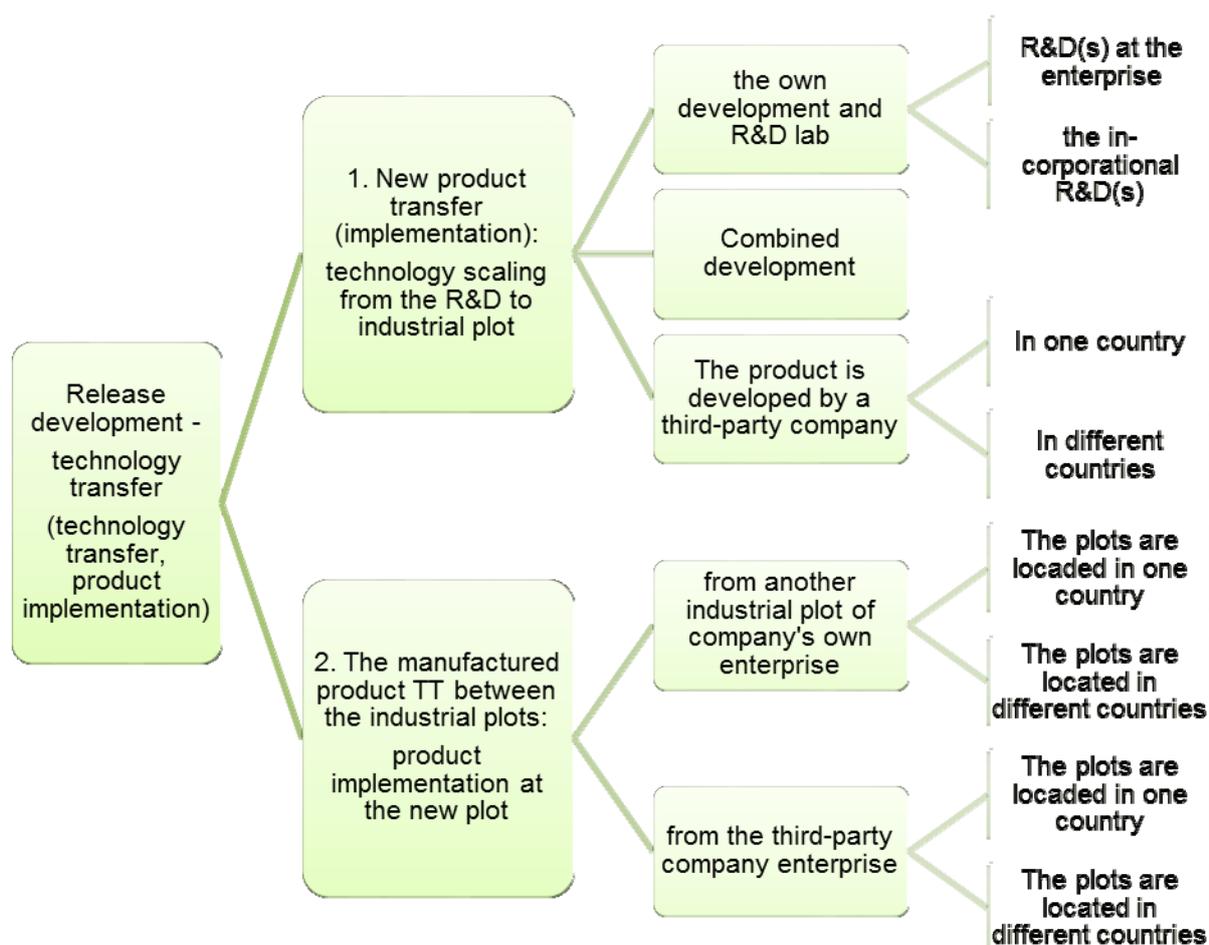


Fig. 3 The scheme of Technology Transfer Process variation patterns with a consideration of company specifics and the possible transfer variations itself.

and included the following components:

- defined the main process stages (every stage can be regulated by one or more SOPs);
- the process stages are divided in order to understand, when to make the proper decisions. The decisions itself can be regulated by PQS as an analysis or the review by the management;
- underlined the essence and need in the analysis inside the TTP (especially, we pointed out the knowledge and production area abilities analysis);
- defined the separate components, required to be included in the TTP and which absence disables the TTP from independent functioning (the process validation first, as the vadiatory process contains);
- the process model contains other separate

processes, which requirements must be followed during the whole TTP (quality risk management, knowledge control process). To connect those processes with the TTP, the special procedures must be developed, introduced and completed.

We gave the more detailed description of basic components, which need to be realized on every stage of given TTP model.

The TTP start (1) begins from the decision making by the company management. This decision, made using the properly functioning PQS, must be made inside the management review. It's important to keenly define the possible scenarios of transfer:

- Scenario 1: the new product implementation at the production area using the technology scaling. It can

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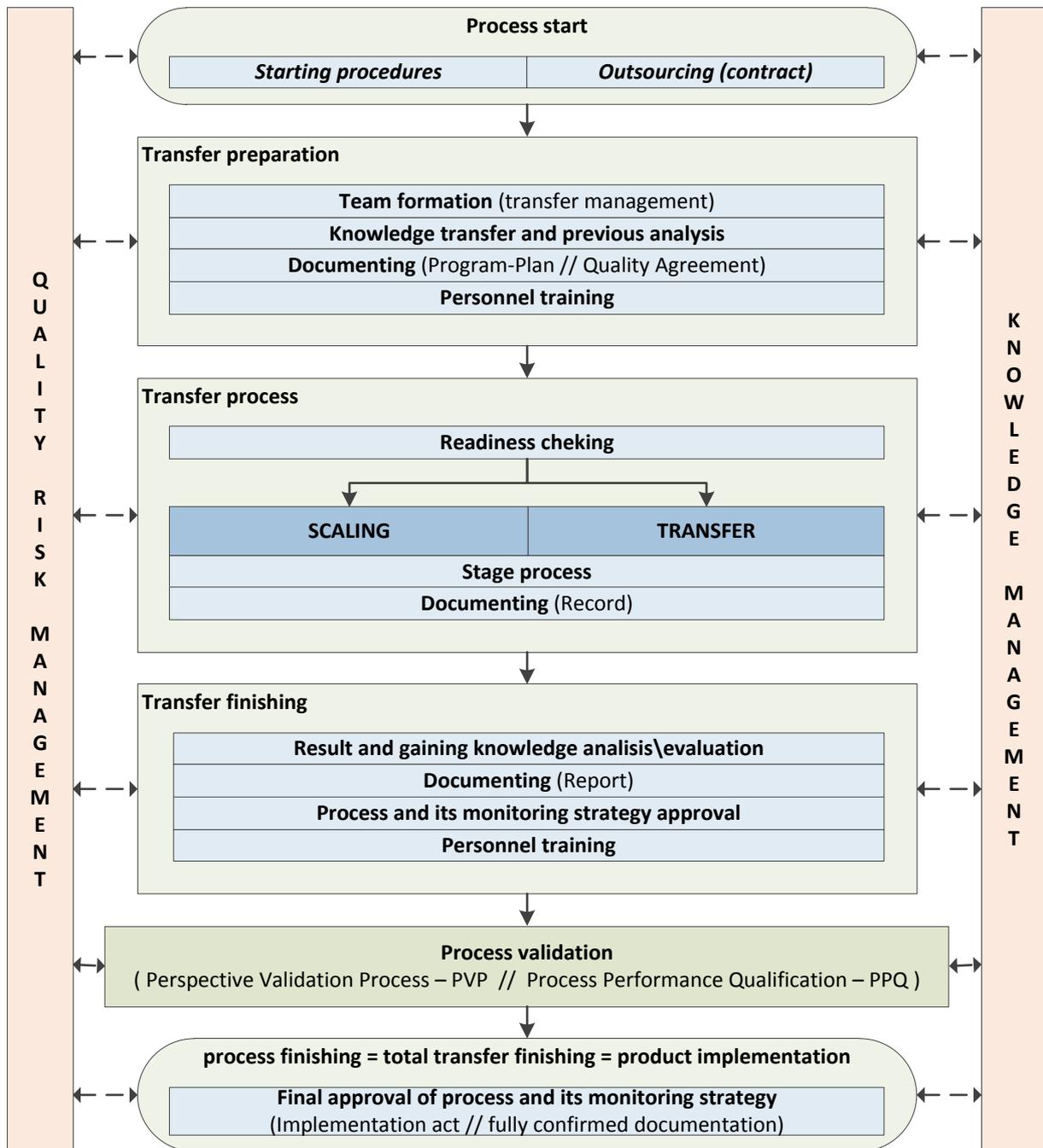


Fig. 4 TTP (technology transfer process) model.

be commenced from R & D to the industrial area (sc. 1.1) or from the lesser series production area to the area with the series growing (sc. 1.2)

- Scenario 2: the transfer of manufactured product technology between the production sites. For example, it can be executed between the production sites of one corporation/company (sc. 2.1) or between the

production sites of two different companies (sc. 2.2). The advanced approaches classifying can be defined by the areas location or the difference/similarity of drug production laws at those countries.

If the TTP is executed using the process copying and process copy transfer from other company’s production sites or between two different companies,

the works must also comply with the Outsourced Activities Management requirements alongside the chapter 7 of GMP EU rules and PQS corresponding theses.

TTP preparation (2) covers a number of contents, and each of them can be regulated by the separate SOPs: transfer team formation (**2.1**); pre-analysis and knowledge transfer (**2.2**); personnel training (**2.3**), and the corresponding documentation (**2.4**).

A transfer team formation (**2.1**) is one of the basic contains for quality, optimal and short-term transfer with the minimal changes and faults. To do this, it requires the qualified and responsible personnel from the receiving, sending and, sometimes, process managing units, which can be a trade marketing authorization owner. One of the most important questions in transfer team formation is the definition of team members' functions, responsibilities and duties. It can be realized in the most convenient way, when the responsibilities matrix is used. The approach to the transfer team formation, qualification requirements, responsibilities matrix and other aspects must be regulated by the corresponding SOPs.

The knowledge transfer and pre-analysis procedures (**2.2**) depend on the following transfer scenario: whether it is executed using the scaling or the manufactured product technology transfer between the production areas (sc. 2). When the TTP is executed inside the one IA or one company's IAs in one country, it can be held basing on the quality system procedures. But when it is committed between different companies or production areas in different countries, it can be performed not only inside the internal procedures of both IAs, but within the contracts between them, considering the Outsourced Activities Management work process and also in compliance with the Technical or Quality Agreement between the companies or production areas.

The knowledge is transferred using the transfer of corresponding documentation, corresponding unit's interaction, management and specialist meetings with

the involvement of qualified persons and personnel training.

The pre-analysis can contain:

- The product knowledge analysis can include the overall product knowledge gathering and analysis at the moment of transfer, incl. the information about the active, additional substances, primary package materials, intermediate products and the finished product. This knowledge must contain the whole information from the registration dossier and the information about qualitative features (incl. the pharmaco-technological tests), analysis methods, manufacturers, delivery chains, incl. product history, etc.

- Process knowledge analyse = RU (receiving unit) area ability analysis (Capabilities Assessment), which provides: the analysis of knowledge about the process execution conditions, (the tech abilities analysis); production technology knowledge analysis (technological abilities analysis) and the analysis of product production control knowledge (analytical abilities analysis);

- The analysis of the resources required for the transfer successful holding. Primarily, those resources are the qualified personnel resource, the time resource, transfer procedure logistic supply resource, etc.

- The analysis of other information, sufficient for the technology transfer, e. g. the law specifics (incl. the necessity of the investigated drugs production licensing, marketing authorization and certification), other specifics.

The pre-transfer PT (personnel training) (**2.3**) must be directed onto the new knowledge about the new product, processes and controls, connected to it. This training must be hold according to the PT process, based on the corresponding training plans and programmes with the following making of required training protocols and the mandatory evaluation of training efficiency.

The corresponding documentation on the TTP preparation stage (**2.4**) must not be considered as the

separate procedure. The documentation relates to every quality system process. That's why every written procedure and transfer process recordings must comply with the requirements, set in the process of good documentation control. At the same time, the TTP requires the specific documents, having the requirements, in equality to other documentation (e.g. for the SOPs). This document on the TTP preparation stage can be the programme/plan of transfer holding with the corresponding transfer protocol form, special Tech instructions for the transfer process. If the product, gained during the scaling or process transfer, is considered to be used for the clinical testing, it is required to prepare the specifications dossier for the tested drug. Besides that, before the TTP holding there must be formed the projects of the corresponding registration dossier parts and the pharmaceutical engineering reports.

The direct TTP (3), as we mentioned above, can be committed within two main scenarios: the process scaling or the copied process transfer from another active area. Herewith, the direct TTP includes the transfer readiness checking (3.1), the staged transfer process (3.2), and also the corresponding documentation (3.3).

The readiness for the transfer (3.1) is directed to the resources presence and readiness evaluation and, finally, getting the approval for the direct staged transfer process start. The check is needed for:

- The presence of needed quality staple and materials amount (incl. the additional substance marks);
- the accessibility, operability and good condition of all the tech systems (chambers, items, equipment, good production area functioning supply systems) and also the transfer process providing with the good ("clean") technological environments;
- the availability of the required approved documentation (both for the procedures regulation and logging);
- the personnel readiness (technology transfer

group, manufacturing, QC, R & D personnel and other specialists);

- the QC readiness (both from the QC service, R&D labs and the third-party labs, if required), including the availability and accessibility of methodological, tech equipment, personnel qualification for the work with new test objects, the required time resource availability (e. g. including the QC servicemen involvement in the routine tests) and also the possibility of proper representative samples picking for their following control and other aspects;
- the possibility of technology transfer in the scheduled time and the production area readiness for that period of time;
- the readiness of other services, required for the good TTP holding (e. g. the engineering services, validation unit, supply service, other units).

The staged technology transfer process (3.2) must be committed according to the programme/plan, including the acceptable scenario, the possible variations of the production process itself and also the selected technology transfer methodology. The technology transfer is formed beforehand and must be approved on the technology transfer process preparation stage. The possible scenario patterns were represented above in the *TTP start* stage description.

When we talk about the variations of the production process, we can base it on the following approaches:

- there is one hardware scheme, which provides the industrial production of the one-size series;
- or we got one hardware scheme of the industrial production of two or more series sizes;
- or there is assumed a production of different size series number, using the different hardware schemes or/and their variations.

The transfer methodology must include the direct technology transfer principle and sequence, e. g. the approbation of separate stage technology or technological process operation → gained results evaluation and analysis → transition to other stage/operation. When the separate stage or operation

transfer is unacceptable, the proper CAPA plan must be accepted, the needed changes must be made (when it is appropriate) and then the unaccepted stage or operation process can be held. Herewith, when the next stages technology transfer is evaluated, there can be accepted the CAPA, which require the recurrence of earlier stages/process operations approved earlier. Such procedure block chart is represented on Fig. 5.

During the technology transfer, the technological process itself must be completed according to the corresponding manufacturing documentation (Manufacturing Formula, Processing Instruction, Packaging Instruction, Batch Record form, if needed) and include every tech process stage and operation. The special requirements can be regulated for:

- the production and results processing controls (incl. the in line, at line and on line controls);
- the fixing and evaluation of intermediate and unpacked product outcome on the process stages and

operations alongside the time of every process stage and operation;

- the samples picking procedures and plans (incl. the samples picking before the finishing of corresponding operations or tech process steps for the tendencies definition at the product features, if required);
- for the process monitoring (e. g. the process environment, tech environment monitoring and its other means, if needed);
- when the processed results of process parameters control and the test results are regulated (incl. the usage of graphics, control maps, standard deviation, control limit calculations, C_{PK} estimations, etc., if needed);
- for other factors, influencing the reproducibility, precision and variability of the analytical methods and process with any tendencies.

While finishing the process or its separate stages,

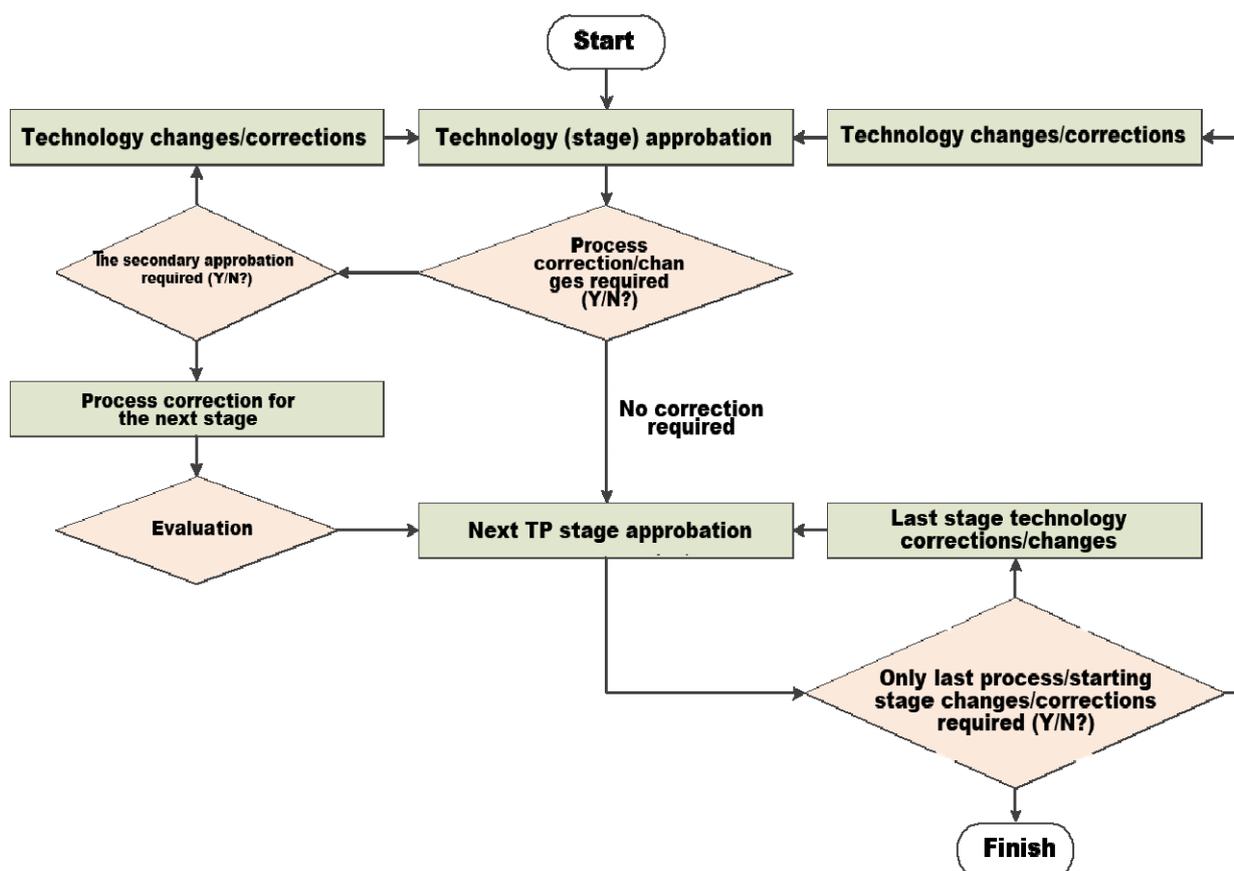


Fig. 5 A block-chart pattern for the methodology of technology transfer procedures.

the big attention must be paid to the cleaning (with the earlier setting of acceptance criteria), processing (disinfection, sterilisation, depyrogenisation, when usable), balance evaluation and calculation (including the primary package materials) and also the wastes handling.

During the process itself, the attention must be also paid to the ecology (incl. the different waste outcome), sanitary, Occupation Safety and Health, accident prevention and other requirements.

The appropriate documentation at the stage of direct TTP (3.3) must be made in compliance with these, mentioned above (par. 2.4. in the *description of transfer process preparation stage*). The main documentation task at the stage of *direct TTP* mainly touches the adherence to the registration rules. The specific TTP document type for this stage is the Transfer Protocol and the Product Series Scaled Manufacturing Protocols (both at the “pilot” and production areas) and/or at the technology transfer itself, including the Protocol of wholesale industrial series production. It’s natural, that every form of given protocols must base on the corresponding Manufacturing Formula, Processing Instructions, Package Instructions (not being confused with the Manufacturing Formula, Processing Instructions, Package Instructions to the Routine Production of Product commercial series/batches).

TTP Finishing (process analysis) (4.1) covers the following key contents: the transfer results and gained knowledge analysis and evaluation, process approval, the appropriate personnel training, and good documentation.

The transfer results and gained knowledge analysis (4.1.1) must include (with no limitation by mentioned below):

- the analysis of causal connections, which were theoretically determined during the pharmaceutical development and need to be approved during the technology transfer within the risk reviews (and quality risk-management);

- the analysis of imminent deviations during the technology transfer. They can be both planned (basing on the pre-transfer product knowledge) and unplanned. The corrections and planned/realized cautionary actions (within the CAPA process) must also be valued (incl. their sufficiency, fullness, absence of process/product status affection and other aspects);

- analysis of possible changes, resulted by technology transfer and the corresponding CAPA evaluation, which must be directed to confirm the stability of product quality characteristics and status alongside the process and control methods;

- process reproducibility evaluation, incl. the rightness evaluation of the set variable process parameters or their correction, analysis of every influence factor, based on the new knowledge about the process and product, rightness evaluation of process control and monitoring systems, its conditions or the corresponding corrections relevance.

- quality reproducibility evaluation, incl. intermediate, bulk and finished products. The tendencies evaluation is also highly important;

- the trending reproducibility in product stability during the whole shelf life and absence of unacceptable tendencies of product quality change need the separate evaluation;

- evaluation of the cleaning methods and their control and validation ways. It’s advisable to review the whole cleaning strategy during this evaluation, to detect the influence of new product implementation on it at the production area;

- the analysis and evaluation of all the possible factors is able to influence the product quality, stability and its production tech process reproducibility.

It’s advisable to involve the maximal quantity of different instruments (processes) of pharmaceutical quality system (Quality Risk Management, Deviation Control System, Change Control/Management System, Trending Control System, Knowledge Management, Management Review, Outsourced Activities

Management, CAPA System, Self Inspection System etc) within the evaluation of transfer results and knowledge about it. It must also be demonstrated the improvement of product processing and quality control, without the changes in its qualitative, safety and efficiency features (the reference product is a product, produced for the clinical or equal tests, e. g. the generic drug bioequivalence testing).

The process approval, based on the transfer results (4.1.2) provides the approval of technological process of product commercial series manufacturing and also the process monitoring strategy by the authorized personnel. The procedures and corresponding documents, reviewed at this stage are the main production documentation, which includes the control and monitoring procedures (incl. in process control, on process control, at process control), samples picking plans and procedures, cleaning and cleaning control methods (within the cleaning strategies at the area) etc.

The corresponding personnel post-transfer training (4.1.3) is directed to the information transfer and its assimilation by the personnel according to the competence of every employee. The training information must cover every factor critical for the product quality at its industrial production. This information must cover the product itself, its features, industrial production technological process, methods and strategies of control and monitoring and other factors. Every factor can be defined and demonstrated using the causal diagrams as the assisting tool of quality risk management process. The training must itself be hold in compliance to the personnel training process, basing on the corresponding training programmes and plans, with the forming of corresponding training protocols and training efficiency evaluation at its end.

The required documentation at the process analysis stage (4.1.4) must be committed according to the theses from above (par. 2.4 in the description of *technology transfer stage*). The main documentation

task at this stage ("*direct technology transfer stage*") mainly touches the documentation of the processing of measuring, spectating, test results, gained during the technology transfer and also making of the reports, protocols, plans, other documents for some procedures, requiring those reports, e. g. the risk analysis report, deviation, change protocols, CAPA plan, if needed, other documents for other processes. The specific form of TTP document at this stage is the Technology Transfer Report (other documents are also possible).

Technology transfer procedure finishes with: A process validation (4.2): This stage is a *transfer process evaluation* in the context of technology transfer process and is made in compliance to other process requirements (qualification and validation works control process or the technological process validation works control process, or the equal process, depending on the structure of pharmaceutical quality and proper documentation systems).

The special attention must be paid to the validation and its results evaluation, including the comparative evaluation of trendings and production processes stability at different areas, at the technology transfer between active industrial plots. It's also required to consider the validation tests connection and their results analysis at the situations of different cycles execution on different areas.

While the process validation is a part of separate process and the volume of process validation itself, the authors think that it'll be right to put the questions of process validation off this tofig. It's required to pay attention to the expectance of process validation, according to the actualized EMA and US FDA requirements, which will be hold as the process qualification before the marketing authorization obtaining.

The process finishing/The TTP full stop (5) is a product implementation into the manufacturing and transferring to the stage of its commercial series released for the end-user (patient) consuming, at least, for one market. The stage provides the total approval

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of all the production documentation, in compliance to which the commercial series manufacturing and control, total monitoring strategy approval (within the Monitoring System, required by the PQS theses) and the product manufacturing introduction act forming and approval must be made. The given stage procedures, alongside the process start, must be committed with the involvement of company or its production area top management within the *Management Review*. At this stage, it must also be finished the procedures within the *Outsourced Activities Management*, if the technology was transferred using the outsourcing. There must be finally approved the *Risk Assessment* reports within the *Quality Risk Management System* and *Knowledge Management* and also considered the other requirements of the pharmaceutical system contents.

Documentation. To provide the proper functioning of the overall transfer process itself and all of its contents, it's advisable to review the SOPs for the every process stage (considering the requirements of the company and its production areas good documentation system). The development, formation, matching, approval, involvement and work usage of the SOPs, connected to the TTP, must be made

according the separate process of documentation control.

The possible decisions in the forming of possible models of good pharmaceutical company documentation system were well-highlighted in the separate publication series [9].

It's herewith imagined, that the documentation system must be formed and structured by the pyramid principle with the definition of possible document levels and it's levelling principles. The TTP-based pattern of such documentation system structure is shown on Fig. 6.

Some of the specific documentation for the TTP were mentioned above. The main are the TTP manual, transfer programme/plan, transfer protocol, transfer report and separate SOPs, which is based by the offered TTP model.

The processes, involved in the TTP will naturally require the appropriate SOPs and documents. For example, the risk management requires special SOPs, worksheets or protocols; the outsourcing works control requires its own procedures (incl. the composition of Tech Agreements, contracts matching etc.), the Contracts, Tech Agreements (quality agreements) for the contracts etc. The validation works

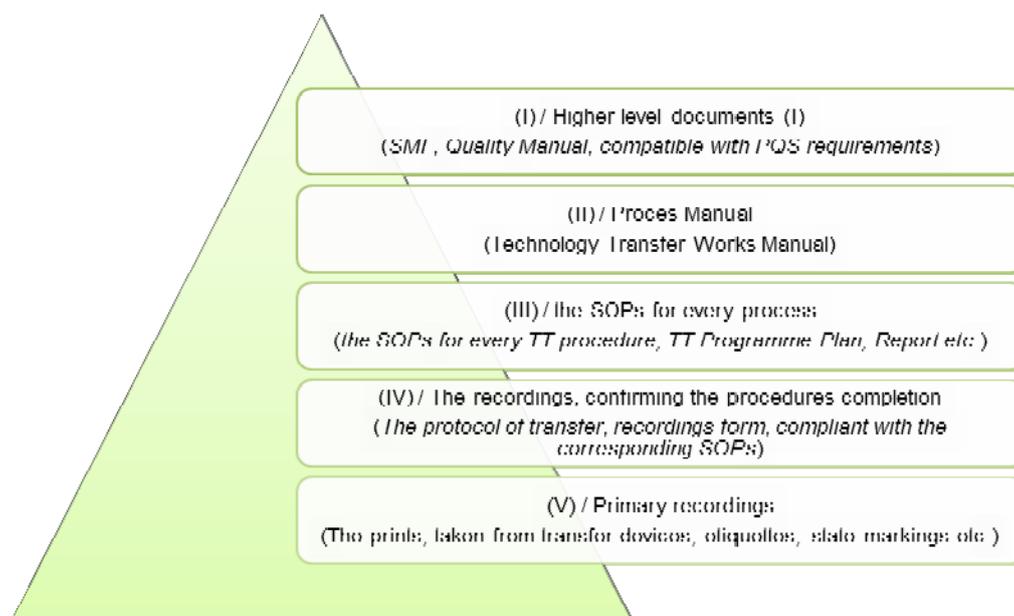


Fig. 6 A pattern of documentation system structure with the definition of possible document levels and documents levelling principle, based on the Technology Transfer Process.

also require their own SOPs, Master Validation Plan, Validation Protocols and Reports and so on.

4. Conclusions

So we built and drew the TTP model (represented on Fig. 4), including the following main stages: process start → process preparation → direct transfer execution → transfer process finishing → process analysis and evaluation, based on the process validation results (PV itself is the separate (sub-) process of quality system) → process finishing. We also defined the TTP stages to be based on the *Knowledge and Quality Risk Management Systems* (which are also the separate processes). The involving of other separate process procedures into the TTP demonstrates it as the “built-in” process in the PQS, which is vital for the practical functioning of separate processes and the whole quality system.

The model scheme helps to understand the main possible procedures, needed to be developed and be able to help the realization of TTP principle and strategy. The scheme also helps to understand the interaction points between the structural units and company personal and its industrial plots or the interaction between different companies (e.g. during the works of outsourced technology transfer).

Here we offer the formed TTP model, as the separate PQS process:

- it forms the principles and strategy of the TTP works control, considering the possible variation of this process;
- it helps to unify the process, which itself provides the procedures connection between the “transferring”

and “receiving” units, independently from their interrelations and legal affiliation;

- it demonstrates the complexity of PQS, due to the providing of matching with other PQS processes;
- it helps to understand the main possible procedures, needed to be developed and helping to realize the process principle and strategy.

The offered TTP model seems to be used by the pharmaceutical companies to form their own approaches and procedures for the TTP, considering the specifics of the companies, industrial plots, products and the technology of their production.

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