ISSUES OF TRANSITION FROM THE PHARMACEUTICAL DEVELOPMENT PROCESS TO THE TECHNOLOGY TRANSFER PROCESS WITHIN THE PHARMACEUTICAL QUALITY SYSTEM

Valeriy Nikityuk¹, Eugene Shakin³, Natalia Asmolova³, Tatiana Yarnikh²

¹Scientific Consulting Centre "VADEMECUM", Kiev, Ukraine

²National Pharmaceutical University, Kharkiv, Ukraine

³Pharma Start LLC, a company of Acino Pharma AG, Switzerland

ABSTRACT

The principles of the pharmaceutical quality system (PQS), which is mandatory for all modern pharmaceutical companies, provide for the expansion of the good manufacturing practice (GMP) requirements for the initial stages of the life cycle of medicines: the pharmaceutical development stage and the technology transfer. The proper functioning of the pharmaceutical quality system largely depends both on full coverage of all processes by the quality system procedures, and on the correctness of these procedures, especially those that are transitional from one process to another (they "link" individual processes of the quality system). This publication is devoted to the question of "linking" the processes of the pharmaceutical development and technology transfer by determining the effectiveness of pharmaceutical development for the possibility of properly following the transfer of technology. At the same time, one of the options for technology transfer is considered - the scaling of the technological process between the pharmaceutical development (laboratories and pilot sites of R&D) and the operating industrial production site.

Keywords: medicinal products, pharmaceutical development, technology transfer, pharmaceutical quality system, quality system procedures

INTRODUCTION

Modern requirements of the pharmaceutical quality system (PQS) include the stages of Pharmaceutical Development and Technology Transfer as mandatory components of the good manufacturing practice (GMP) rules (1,2,3,4).

However, the GMP and PQS regulations establish only the need to expand the quality system and the need to implement the basic principles of the quality assurance system during the initial stages of the drug life cycle, but do not contain relevant detailed guidelines and how existing GMP rules and PQS principles should be implemented. The general principles and provisions for pharmaceutical development are defined in the ICH Q8 guideline [5] and some recommendations regarding the technology transfer process can be found in the ICH guidelines, in the WHO technical reports (5,6,7), as well as in the technical recommendations of some professional associations (in particular, ISPE - International Society for Pharmaceutical Engineering) (8).

Address for correspondence:

Valeriy Nikityuk
21A L. Rudenko St
02140 Kiev
Ukraine
e-mail: nvalery@ukr.net

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MATERIALS AND METHODS

In order to implement the requirements of GMP rules and PQS principles, the provisions of the guidelines and recommendations of international organizations and associations, each pharmaceutical company must:

1. define its own strategy of pharmaceutical development control and technology transfer,
2. develop and implement appropriate procedures for the practical implementation of these processes (regulate the process tactics), which must be in the form of appropriate written methodologies (SOPs).

According to the definition given in one of the WHO technical reports, technology transfer is “a logical procedure that controls the transfer of any process along with its documentation and professional experience between development and production sites” (7). Variations of the technology transfer while scaling the technological process, taking into account the specifics of the company and possible variations of the transfer itself, as an example, are formulated by the authors and presented in the scheme in Fig. 1.

We will consider only one of the options for the transfer of technology – transfer (scaling) between pharmaceutical development (laboratories and/or pilot sites of R&D) and the existing industrial production site.

RESULTS AND DISCUSSION

As practical experience shows, one of the problem points of any quality system, including PQS, is the “link” between different processes and/or procedures, especially those that are performed by different structural divisions. Given that the pharmaceutical development process and the technology transfer process are relatively new components within the mandatory processes under the GMP rules, the “link” between them can potentially be a new problem point of the pharmaceutical quality system. In this regard, it is important to identify and regulate the issues by which it is possible to evaluate the effectiveness of pharmaceutical development, the ones significant for the next stage in the life cycle of the product - the technology transfer (scaling) - and the ones, which should be prescribed in appropriate procedures (methods, SOPs). The scheme of the basic

Fig. 1. Example scheme of variations in the transfer of technology when scaling the technological process, taking into account the specifics of the company and possible variations of the transfer itself

stages of product creation at the stage of pharmaceutical development and transition to the stage of technology transfer, formulated by the authors, is presented in Fig. 2.

This scheme of the main stages of product creation during the stage of pharmaceutical development and transition to the stage of technology transfer allows the definition and regulation of the corresponding written procedures, those key aspects that allow the evaluation of the effectiveness of pharmaceutical development for the stage of transfer (scaling) of pharmaceutical product technology.

2. the integration of quality into the product (both for subsequent stages of the life cycle, and for components of the pharmaceutical quality system);
3. drawing up production documentation for the scaling of the process.

Given that the term GMP is sometimes half-jokingly treated as "Give Me Paper", which emphasizes the importance of documenting all procedures and actions performed in any pharmaceutical company and having direct or indirect relation to the production of pharmaceutical products and ensur-

Fig. 2. Scheme of the main stages of product creation at the stage of pharmaceutical development and transition to the stage of technology transfer

These aspects can be conditionally divided into the following components:

1. formation of knowledge about the product and process (in particular, within the knowledge management process - Knowledge Management System);

ing its quality, we will focus our attention, first of all, on the last mentioned component.

Properly and fully-formed documentation based on the results of pharmaceutical development allows:

- ◆ systematization of information and formalizing the effectiveness of pharmaceutical development for the next stage of the product life cycle (technology transfer);
- ◆ to properly link the process of pharmaceutical development and the process of technology transfer;
- ◆ regulation of the procedures for scaling the technological process (actually, the transfer itself) on the basis of the results of pharmaceutical development (the documented effectiveness of the pharmaceutical development for the transfer stage);
- ◆ ensuring proper communication with respect to knowledge of the product, the technological process of its production and qualitative characteristics;
- ◆ identifying and justifying the quality elements that should and can be embedded in the product at the initial stages of its life cycle - the definition, justification and formalization of the quality target product profile (QTPP - quality target product profile) and critical quality attribute (CQAs - critical quality attribute);
- ◆ conducting a comprehensive, forward-looking risk assessment (within the framework of the Quality Risk Management process, including identification and justification with the help of appropriate critical control points (CCP));
- ◆ justifying the approaches and procedures for the subsequent process validation.

Variations of the manufacturing documentation are associated with possible variations of technology transfer, which are schematically presented in Fig. 1. These can be:

- ◆ documentation, which regulates the technology of obtaining and operating the laboratory samples in the laboratory R & D,
- ◆ documentation, which regulates the testing of technology in the “pilot” stage and the development of prototypes for their further testing (for example, for the preliminary study of stability, for tests for the dissolution test, for preclinical studies, etc.)
- ◆ documentation, which regulates the development of the manufacture production process and the development of pilot industrial samples

on the scale of industrial series (including, for example, a stage preceding the validation of the process);

- ◆ other necessary additional documentation for related processes.

A set of documentation for all process regulation variations must include the same mandatory documents as those for batch production, namely: a production formula, a technological instruction(s), a corresponding production protocol(s), a packing instruction(s), the relevant protocol(s) of packaging, as well as other necessary written procedures (methods, SOPs) relevant to the technological process with appropriate forms for logging and specification, purification methods, other types of documentation of the quality system.

What is the most important and in relation to which should the regulatory standards in the specified documentation be? Without limiting ourselves to the following, the most significant are the following:

- a. the hardware scheme and the rationale for its selection;
- b. technological environments for the implementation of the technological process and their characteristics;
- c. the process itself, including a brief visualized schematization of the entire process (block diagram) and a detailed description in the logical sequence of each step, including all CCPs and their parameters;
- d. the monitoring strategy of the technological process, which confirms not only its control and correctness, but also the invariability and identity of each series;
- e. control (monitoring) strategy of intermediate products, including sampling, as confirmation of the quality of this product and the finished product;
- f. clean-up strategy (as a defining element for preventing and eliminating cross-contamination of pharmaceutical products).

(a) In compiling the hardware circuits (or, where appropriate, a few schemes, for example, for different sizes of the series) it is important not only to define the list and the main characteristics of the equipment for each respective stage of scaling, but also to dem-

onstrate the identity or similarity of the principles of conducting each operation process at each stage of pharmaceutical development and technology transfer to the same principles that are used for industrial production of commercial batches at the manufacturing site.

(b) An important element that requires attention and regulation at each stage of process scaling is “clean” technological environments that must also be “tied” to the conditions of an industrial production site. First of all, qualitative characteristics must be defined for them (to be available or to be drawn up based on the corresponding specifications, analytical methods are developed and validated), sampling techniques for monitoring their quality, monitoring strategy for these media (for example, on-line or periodic monitoring), sources (for example, cleanroom class, supply of clean compressed air from the compressor through the piping system, etc.), evaluation of the sufficiency of the quantity (especially at “peak” consumption, if appropriate), technological preparation (for example, the degree of inert gas filtration) and other aspects.

(c) The process includes the steps for the preparation of the finished dosage form and the primary packaging (together with the preparation of the primary packaging and capping materials) and, if necessary, packaging in the consumer packaging should be described and regulated for each stage when received at the “pilot” site and the production site. It is important not only to describe the process in detail, adhering to a step-by-step logical presentation of the sequence of actions composing it, but also to not forget the detailed description of the actions in preparation for each stage of the process (for example, equipment adjustment, preliminary controls) and at the end of each stage. The regulation should include all necessary calculations (downloads, recalculations of components introduced into the product, not at the beginning of the process, etc.) to determine (at least roughly) the expected outputs, as well as contain a general and detailed scheme of the process. Given that the technological process at the stages of pharmaceutical development and the subsequent transfer of technology is not yet finalized, it is critically important to take into account: what parameters or components of the technological process are subject to changes in the management process (like the

PQS process) and which are not. For example: part of the process parameters can be clearly and definitively established at the appropriate stages, some are not established accurately (not conclusively), some are not installed at all (there is no definition at subsequent stages of technology transfer after pharmaceutical development). From this point of view, it is critically important to define and prescribe: what, how, in what range, who can adjust, adjust and change in terms of technology and monitoring at these stages of the product life cycle.

(d) The monitoring strategy for the technological process should clearly define all monitoring objects: both the process parameters and the quality indicators of raw materials, materials, intermediate, bulk and finished products, and the environment in which the processes are carried out (for example, microclimate in production areas, clean area, etc.), technological environments for the direct implementation of the corresponding stages of the technological process (for example, water for pharmaceutical use, clean compressed air, contact, etc.), as well as other possible factors that can potentially affect the quality of products (for example, through the prevention of contamination, the correct operation of equipment, the accuracy of measuring instruments, the completeness of clothing for staff, etc.). The monitoring strategy itself should include, at a minimum, the regulation of the following: what should be monitored (or controlled) how/with the help of what supplements to monitor (accuracy and discreteness of measuring equipment, data collection, etc.), who monitors (+ who controls the monitoring process itself), what is the frequency of monitoring, where and how to document (regulating/logging/analyzing data), etc. If during the pharmaceutical development stage it is impossible to establish precise parameters for monitoring the process, it should be clearly indicated in the relevant documentation together with the rationale: by whom, how, when (at what stage, in which processes or procedures) parameters must be accurately and definitively established.

(e) Control of intermediate products, including sample selection, requires special attention and appropriate regulation. At the same time, for each stage and pharmaceutical development, and technology transfer, these components can differ significantly and, therefore, each time require a new regulation.

The very strategy and regulation of sampling procedures should include both sampling objects and, at a minimum, the following: what exactly is to be selected, who should select samples (not forgetting the questions of qualification and specialized training of such specialists), when should samples be selected, (sampling points), with the help of which to select (tools, where to take them, how to cook, how to clean), how much to take (sampling plan for each sampling point), where to select (container characteristics, where to take them, how to cook, how to seal), as well as how to handle the selected samples (including the issues of individual control of each individual sample). For all intermediate and incompletely packed products, specifications must be prepared, appropriate analytical techniques developed, and all of them should be validated. Transfer of analytical techniques should be provided in accordance with the described procedure. Transfer of analytical methods should be carried out before validation of the technological process. It should be borne in mind that analytical methods of quality control of intermediate and non-final packaged products will usually have differences (at least in detail) from the methods for the final finished product, among them there may be completely different methods (for example, the use of express methods). Also, analytical methods need to be designed to control indicators that are not controlled in the final finished product. The latter can be designed for subsequent use in the routine production of commercial series, and have a specific purpose (for example, being applied only for technology transfer or for process validation).

(f) The issue of contamination of pharmaceutical products and, above all, chemical contamination is one of the most critically important problems in terms of safety of medicines for the consumer. Accordingly, this issue should be given due attention during the pharmaceutical development. This is especially critical when there is a transferring technology to an industrial production site. Therefore, acceptance criteria for residual quantities of the product are established (taking into account already existing criteria adopted for the production site where the new product will be manufactured), cleaning procedures should be determined by this period, appropriate methods for sampling residual amounts of a new product from the contacting surfaces of equipment

are selected and prescribed, specific analytical techniques for determining product residues in samples should be properly sensitive and validated.

In addition to the above components that determine the effectiveness of the pharmaceutical development for all subsequent stages of the product life cycle, and especially for the transfer technology phase, the completeness and adequacy of the results of pharmaceutical development, taking into account the principles of the pharmaceutical quality system, also require such mandatory components, such as:

- ◆ risk assessment (Quality Risk Management System). First of all, in relation to the product, its quality, the technology of its production, including the definition and justification of CCPs, as well as the definition of cause-and-effect relationships between process parameters and quality indicators (for both intermediate and bulk products obtained at each stage of the process, and, ultimately, for the final finished product);
- ◆ preparation of a technology transfer program (taking into account the specifics of the transfer itself for a particular production site and its stages);
- ◆ preparation of a process validation program, using the results of the risk analysis and the technology transfer program.

CONCLUSION

Documenting all of these components allows the creation and organization of knowledge about the product, the quality, the technology of its production, the determination of all variables and characteristics, their variability, as well as factors affecting their variability, which is important not only to control the process, but also for the proper functioning of such processes within PQS, processes such as knowledge management (knowledge management system), deviation control (deviation control system), change management (change control system) and others, as well as for further process improvement and control of the quality of the product (Continual Improvement of Process Performance and Product Quality).

The above components are critical aspects by which to assess completeness, sufficiency and efficiency of the pharmaceutical development phase in order to fully and effectively implement the next

phase of the pharmaceutical product lifecycle – transfer technology.

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