Identification of key factors for improving the process of pharmaceutical development of generic drugs

Feofilova Anna Evgenyevna

Quality Director

"Medisorb" JSC

Foteeva Alexandra Valeryevna

Candidate of Medical Sciences, General Director

"Pharma Clinical" LLC

Rostova Natalya Borisovna

Doctor of Pharmaceutical Sciences, Full Professor

Perm State Pharmaceutical Academy

Abstract. Harmonization of regulation of the process of pharmaceutical development (PD) of reproduced drugs within the EAEU contributes to the development of drugs with specified quality indicators that are safe and effective for the patient. In order to develop such drugs in the development companies of medication, the pharmaceutical quality system (PQS) must function correctly, including a risk management system in its structure, and a clear algorithm of the PD process must be defined in the companies.

The aim of this study was to identify the key factors for improving the process of PD of drugs in the form of liquid for inhalation, as well as the application of modern approaches to PD of generic drugs.

The study identified the need for such key improvement factors for the qualitative PD process as the use of tools and methods for identifying, analyzing and assessing risks to the quality of drugs at each stage of PD, the inclusion of additional preparatory stages for the theoretical assessment of PD.

Keywords: harmonization, pharmaceutical development, quality by development, target quality profile.

Harmonization of requirements in the field of development and circulation of medicines at the stage of transition from national regulation to a single one within the framework of the Eurasian Economic Union has led modern domestic developers to the need to develop drugs with specified and controlled quality indicators.

The regulation of the pharmaceutical development (PD) process of other international integration associations is based on documents describing the need to apply a modern concept based on a risk-based approach to pharmaceutical development of reproduced medication - Quality By Design. Based on the guidelines ICH Q9 and ICH Q10 However, the application of this approach is impossible without an efficiently functioning PQS company developing reproduced medication, supported by a key improvement factor - a risk management system for the quality of the product being developed [1].

The aim of the study is to identify the key factors for improving the PD process of reproduced drugs, the application of modern approaches to PD.

Available sources of literature, the State Pharmacopoeia, regulatory documents and guidelines for pharmaceutical development of medicinal products, documents of the registration dossier, developer reports on pharmaceutical development were used as research materials in this work.

Achievement of the set goals in the work was carried out on the basis of general scientific research methods within the framework of logical analysis, as well as through the analysis and interpretation of the data obtained on the pharmaceutical development of drugs.

In the course of the research, audit management of PQS documents, documents of registration dossiers for drugs, PD reports of the manufacturer of reproduced drugs was carried out - it was revealed that the lack of a risk management system at the PD stage led the drug developer to negative consequences associated with refusals in the state registration of drugs with a regulatory authority at the stage of drug quality examination, the need for additional stages of PD due to this significant time and financial costs and, as a result, possible negative consequences for the company's reputation, reduced competitiveness in the pharmaceutical market [2]. In the course of the study, insufficient elaboration of certain issues prior to the stages of PD was determined, which predetermined the need to identify key factors for improving the PD process, develop an algorithm for conducting PD of reproduced drugs, include a preparatory PD stage aimed at determining the exact concept of PD of a new reproduced drugs and subsequent use of the obtained data for creating a targeted quality profile of developed drugs within the framework of the concept of improved medication development, applying a risk-based approach at almost all stages of PD.

Based on the above facts, the research team decided to create an algorithm for conducting PD with identifying key factors for improving the process of creating a medication molecule by testing a modern approach to the development of Quality By Design applicable to the activities of this drug developer organization using the example of PD reproduced drugs in a liquid dosage form for inhalation.

At the first stage of the study, the concept of choosing drugs was worked out - as a preparatory and necessary stage of PD. The main criteria of which were: determination of the approximate composition of drugs, determination of the pharmacological group of drugs, nosological classification, pharmacological action, information on studies in the territory of the Russian Federation conducted with original drugs and necessary for carrying out with the developed drugs, planned target sales markets, forecasts for sales volume, pharmacological prospects, analysis of the registration strategy, data on controlled impurities, estimated quality indicators controlled in the finished product, the need to separate into a separate production / site, requirements for the class, type of separate production, dosage form parameters, packaging parameters (taking into account climatic zones), methods of cleaning equipment (standard, specific), storage conditions (taking into account the planned sales markets), peculiarities of working with drugs, the possibility of quality control, financial indicators of the drug development project. This preparatory stage was previously absent in the development company during the development and was subsequently identified as a necessary and key improvement factor for the process of high-quality PD drugs with specified quality indicators.

At the second preparatory stage for the developed drugs, a target quality profile was created based on indicators that are critical for the quality of drugs, the interests of the company, the planned ways to promote the product, in accordance with the requirements of the regulatory documents EMA, ICH Q8 "Pharmaceutical Development", which includes such sections how: purpose of drugs, principle of its action, modes of administration, indicating the dosage form and composition of the original drugs, dosage, method of drug delivery, quality attributes (shelf life, stability, sterility, suspected impurities and contaminants, drug release route, data on primary packaging medication, indicating the main properties and requirements for materials), information on the transfer of the developed technology with an indication of the volume of the proposed experimental-industrial batch, the requirements of the current regulatory documents regarding this medication, etc. [3,4,5].

After that, the PD stage was carried out - the stage of theoretical assessment, which includes the definition and justification of the list of critical attributes of the quality of the finished product, raw materials and materials, excipients, primary packaging materials, production processes using risk assessment and analysis tools. The identification and assessment of risks for reproduced drugs in DF liquid for inhalation was carried out, critical indicators of the finished DF, active ingredient, primary packaging material, production process parameters were identified. In the process of theoretical assessment, a register of risks was obtained for the process of PD drugs in DF - liquid for inhalation (see table 1).

Table 1 Risk register of the PD process by the degree of impact on the quality of the developed drugs

Risk name	**Classification (By applicability to a specific DF)**	**The need for control in PD (+/-)**
Risks associated with the preparatory phase of PD		
Wrong name for drugs	Universal	+
Incorrectly selected original drugs	Universal	+
Incorrectly selected information on research on the territory of the Russian Federation, the EAEU and other international integration associations	Universal	+
Pharmacological viability is incorrectly determined drugs	Universal	+
The analysis of the registration strategy was performed incorrectly	Universal	+
No data on controlled impurities	Universal	+
Assumed quality indicators controlled in the finished product are missing or incorrectly defined	Universal	+
The need to separate into a separate production / site was not found, the requirements for the purity class, the type of separate production were not determined	Universal	+
The parameters of the dosage form are not formulated	Universal	+
Packaging parameters are not determined (taking into account climatic zones)	Universal	+
No suggested cleaning methods for equipment	Universal	+
Peculiarities of working with drugs have not been identified	Universal	+
The possibility of quality control has not been determined	Universal	+
Risks associated with the properties of the finished DF and deviations from the standard indicators (theoretical PD stage)		
Deviation in terms of authenticity	Universal for any DF being developed	+
Quantitation	Universal for any DF being developed	+
Related impurities	Universal for any DF being developed	+
Water content	Specific for DF - liquid for inhalation	+ (for certain DF)
Deviation from the volume of the contents of the package	A critical indicator for any DF. Most critical for liquid DF, in particular for liquid for inhalation - it is related to	+

	the volume of liquid to be poured into the evaporator.	
Microbiological purity	A critical indicator for any DF.	+
Risks associated with the properties of the substance and deviations from standard indicators		
Deviation in terms of authenticity	Universal for any DF under development.	+
Quantification of the active substance	Universal for any DF under development.	+
Related impurities	Universal for any DF under development.	+
Water content	Specific for DF - an inhalation liquid.	+ (for certain DFs)
Microbiological purity	Critical indicator for any DF.	+
Risks associated with the use of excipients and deviations from standard values		
Authenticity	Critical indicator for any DF.	+
Microbiological purity	Critical indicator for any DF.	+
Risks associated with the parameters of the manufacturing process of generic drugs in DF liquid for inhalation		
Pressure drop across filters during filtration	Specific for DF - liquid for inhalation, for drugs for oral administration (solutions, drops, etc.)	+ (applicable if it is planned to use equipment similar in parameters in the technological process)
Deviations in the CIP parameters of the mixer during the mixing stage	Specific for DF - liquid for inhalation, for drugs for oral administration (solutions, drops, etc.)	+ (applicable if it is planned to use equipment similar in parameters in the technological process)
The presence of sterilizing filters at the filling stage	Specific for DF - liquid for inhalation, for drugs for oral administration (solutions, drops, etc.)	+ (applicable if it is planned to use equipment similar in parameters in the technological process)
The presence of aspiration from the working environment of the machine	Specific for DF - liquid for inhalation, for drugs for oral administration (solutions, drops, etc.)	+ (applicable if it is planned to use equipment similar in parameters in the technological process)
Primary packaging screw position	A universal critical parameter. Most critical for liquid DF.	+
Tightening force of the cover	Specific for DF - liquid for inhalation, for drugs for oral administration (solutions, drops, etc.)	+ (applicable if it is planned to use equipment similar in parameters in the technological process)
Risks associated with the primary packaging material of the generic drugs being developed		
Primary packaging material composition	A universal critical parameter for any DF.	+
Cover material, adapter	Specific for DF - liquid for inhalation	+ (for DF - liquid for inhalation. For other DF - assessed individually)
Shape and size of cover, adapter	Specific for DF - liquid for inhalation	+ (for DF - liquid for inhalation)
Valve travel in adapter	Specific for DF - liquid for inhalation	+ (for DF - liquid for inhalation)
Primary packaging material	Universal critical parameter for any DF	+

A preliminary analysis of the processes of modern pharmaceutical development of drugs showed that the most suitable for the purposes of assessing the selected drugs is a modified FMEA (Failure Modes and Effects Analysis) method, adapted for the purpose of ranking quality attributes in terms of their impact on the safety and efficacy of finished drugs for the consumer. The next stage of the research was the development of a list of actions to control the selected

critical attributes and reduce or eliminate possible risks associated with them and the compilation of lists of quality requirements for the components being developed by the drugs.

It was determined that the main stages that determine the result of PD are the preliminary, preparatory stage of forming the concept of reproduced drugs new for the developer company and the stage of theoretical assessment of drugs, including the assessment of critical parameters of the production process and quality attributes of both finished drugs and substances, excipients and materials of primary packaging of medication.

Thus, the risk assessment of both the main substance and the finished product in terms of determining critical indicators formed the basis for the creation of drugs with specified quality indicators, emphasizing the criticality of individual properties and determining the need for additional control in the development process and became, in this study, a tool for process optimization PD drugs and has been instrumental in identifying key factors in improving the PD process of reproduced drugs.

Application of this approach at the planning stage made it possible to create a target drug quality profile, which includes detailed data for the development of the design parameters of the study, and also made it possible to assess the risks related to the critical properties of the active substance that could affect the effectiveness and safety of drugs, contributed to the determination of quality indicators, required for inclusion in the specification for the substance and for the active substance.

The implementation of the modern concept of Quality By Design, regulated by ICH Q 8 "Quality by Development", provides for a systematic approach to processes and products at the stage of pharmaceutical development and predetermines the conduct of voluminous complex experimental research, provided by personnel with the appropriate competencies and level of training.

To date, the experimental studies carried out form the basis of a methodological approach to optimize the PD process of reproduced drugs. Pharmaceutical development based on a risk-based approach to the processes and quality indicators of the product being developed, optimized in terms of adding preparatory stages as key factors for improving the PD process, is a guarantee of the creation of effective and safe drugs, the reproducibility of the technological process in modern conditions in production, the implementation of medication with specified indicators quality.

References.

1. Agreement on Unified Principles and Rules for the Circulation of Medicines within the Eurasian Economic Union and the decision of the Supreme Eurasian Economic Council, Article 5 [Electronic resource] – Access: http://www.consultant.ru/;

2. Mollah A.Kh., Long M., Baysman G.S. Risk management in pharmaceutical production / per. ed. Alexandrov A.A. – Vialek, 2014 – 438 P;

3. ICH guideline Q8 (R2) on pharmaceutical development, 22 June 2017 EMA/CHMP/ICH/167068/2004 Committee for Human Medicinal Products, [Electronic resource] – Access: https://www.ema.europa.eu/;

4. ICH guideline Q10 on pharmaceutical quality system, September 2015 EMA/CHMP/ICH/214732/2007 Committee for Human Medicinal Products, [Electronic resource] – Access: https://www.ema.europa.eu/;

5. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities), November 2012 EMA/CHMP/ICH/425213/2011, [Electronic resource] – Access:https://www.ema.europa.eu/.