DOI 10.1007/s11094-016-1368-3
Pharmaceutical Chemistry Journal, Vol. 49, No. 11, February, 2016 (Russian Original Vol. 49, No. 11, November, 2015)

SOME ASPECTS OF QUALITY RISK MANAGEMENT FOR THE FENSPIRIDE HYDROCHLORIDE (0.08 G COATED TABLETS) PRODUCTION PROCESS AT THE PHARMACEUTICAL DEVELOPMENT STAGE

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 49, No. 11, pp. 49 – 53, November, 2015.

Original article submitted July 7, 2014.

The urgency to satisfy pharmaceutical regulatory requirements, including drug quality risk management, prompted the application of risk assessment methodology during the pharmaceutical development (PD) stage of an actual drug production process to be studied. Risk assessment results for the industrial process in combination with information regarding risks to the final product that were obtained during the PD allowed an objective opinion about the influence of the product properties and process parameters on critical drug quality parameters during its mass production to be formulated.

Keywords: risk, quality risk management, pharmaceutical development, process, risk assessment, risk analysis, risk assessment methods, FMEA.

Risks must be effectively managed and a program to reduce the negative impacts of possible external and internal factors must be developed in order for a modern pharmaceutical company to survive under fiercely competitive conditions. Such programs can be developed exclusively on a scientific basis. Then, the risks typical of the company operations not only have to be studied but also should be identified, classified, analyzed, and assessed correctly.

Obviously, all stages of the drug life cycle are associated with risk. A modern drug quality assurance system is designed primarily to guarantee that drugs are developed and studied considering good manufacturing practice (GMP) requirements. The optimum pharmaceutical development (PD), being an indispensable component of the initial phase of the drug life cycle, is an important factor in drug quality assurance during their subsequent industrial mass production. Therefore, effective drug quality risk management allows their quality at the PD stage to be assured.

Current PD requirements for Ukrainian companies are given in several documents, the main one of which is Guideline ST-N MOZU 42-3.0:2011 [1]. According to it, the quality of drugs cannot be fully checked. The quality must be instilled during development and guaranteed during production. Therefore, the goal of PD is to create a drug of the appropriate quality and to validate its production process to manufacture a product with given functional characteristics [1].

Information and knowledge obtained during PD provide a basis for establishing draft parameters, specifications, and production control in addition to quality risk management [2]. Quality risk management plays a special role in combining PD with subsequent phases of the drug life cycle and directly with production according to GMP standards [3].

Our last research was focused on a general quality risk assessment and optimization of the composition of "fenspiride hydrochloride, coated tablets, 0.08 g" (**I**) during the PD stage. This drug was used as an example during the research to elaborate a procedure for a general product risk assessment using the appropriate methods to identify, analyze, and assess qualitatively and quantitatively the identified risks [4]. Furthermore, our research was extended to the identification of quality risks of the production process for this drug [5, 6].

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The goal of the present research was to perform a general risk assessment using a procedure for analyzing and assessing quality risks of the production process for **I** at Interchem Company (Odessa, Ukraine).

EXPERIMENTAL PART

The production process of **I** was based on the developed scheme. All processing operations carried out in the scheme

TABLE 1. Quality Assessment Results of Identified Process Risk Factors

Risk category	Risk factors	Quality assessment (balls) of five experts					Average assessment
		E1	E2	E3	E4	E5	
H	7. Granulation in refluxing layer. Moistener flow rate, air spray pressure and microclimate, nozzle diameter	M(2)	H(1)	H(1)	M(2)	H(1)	H(1.4)
	8. Granulation in refluxing layer. Input air flow rate and temperature	M(2)	H(1)	H(1)	H(1)	M(2)	H(1.4)
	22. Coating deposition. Suspension flow rate, air spray pressure and microclimate	M(2)	H(1)	M(2)	H(1)	H(1)	H(1.4)
	24. Coating deposition. Input air temperature	M(2)	H(1)	M(2)	H(1)	H(1)	H(1.4)
	18. Preparation of coating suspension. Suspension filtration	M(2)	H(1)	M(2)	H(1)	M(2)	H(1.6)
	23. Coating deposition. Input air flow rate	M(2)	H(1)	M(2)	M(2)	H(1)	H(1.6)
	25. Tablet packaging and storage. Blister hermeticity	L(3)	H(1)	M(2)	H(1)	M(2)	H(1.8)
M	9. Granulation in refluxing layer. Input air temperature and flow rate during drying	M(2)	M(2)	M(2)	M(2)	M(2)	M(2.0)
	4. Loading homogenization. Degree of volume filling	M(2)	H(1)	L(3)	M(2)	M(2)	M(2.0)
	12. Tableting. Nature of tablet mass flow from bunker	M(2)	M(2)	M(2)	M(2)	M(2)	M(2.0)
	15. Preparation of coating suspension. TiO_2 grinding	L(3)	H(1)	M(2)	M(2)	M(2)	M(2.0)
	16. Preparation of coating suspension. Order of mixing of components	L(3)	H(1)	M(2)	M(2)	M(2)	M(2.0)
	17. Preparation of coating suspension. Stirring time	M(2)	H(1)	L(3)	M(2)	M(2)	M(2.0)
	18. Preparation of coating suspension. Stirring rate	M(2)	M(2)	M(2)	M(2)	M(2)	M(2.0)
	26. Tablet packaging and storage. Primary packaging materials and packaged tablet storage conditions	L(3)	H(1)	L(3)	H(1)	M(2)	M(2.0)
	6. Granulation in refluxing layer. Granulator container heating temperature and time	L(3)	M(2)	M(2)	M(2)	M(2)	M(2.2)
	3. Loading homogenization. Order of adding components	M(2)	M(2)	L(3)	M(2)	M(2)	M(2.2)
	11. Batch homogenization and powdering. Degree of volume filling	L(3)	H(1)	L(3)	M(2)	M(2)	M(2.2)
	13. Tableting. Evenness of matrix filling	M(2)	M(2)	L(3)	M(2)	M(2)	M(2.2)
	21. Coating deposition. Coating suspension stirring rate	M(2)	M(2)	L(3)	M(2)	M(2)	M(2.2)
	2. Raw material sieving. Sieve pore size	L(3)	M(2)	L(3)	M(2)	M(2)	M(2.4)
	5. Moistener preparation. Temperature of HPMC* solution*	L(3)	I(4)	M(2)	M(2)	H(1)	M(2.4)
	20. Coating deposition. Nozzle diameter	M(2)	M(2)	M(2)	M(2)	I(4)	M(2.4)
	14. Coating suspension preparation. Temperature of HPMC solution	L(3)	I(4)	M(2)	M(2)	M(2)	M(2.6)
	27. Tablet packaging and storage. Blister machine hardware	M(2)	I(4)	M(2)	H(1)	I(4)	M(2.6)
	1. Raw material sieving time	M(2)	I(4)	L(3)	L(3)	M(2)	M(2.8)
L	10. Calibration. Prolongation of product contact time with air, moisture absorption	M(2)	I(4)	L(3)	I(4)	L(3)	L(3.2)

Note: H, high risk corresponding to 1 ball; M, medium risk corresponding to 2 balls; L, low risk corresponding to 3 balls; I, insignificant risk corresponding to 4 balls. *HPMC, hydroxypropylmethylcellulose.

TABLE 2. FMEA of Risks for **I** Production Process

Step No.	Risk factor	Degree of criticality					
		S		O	D	RPN	RPN_m
		S_i	S_m				
1	Raw material sieving time	7, 5, 5, 7, 6	6.0	5, 5, 3, 5, 5	4, 5, 3, 2, 6	140, 125, 45, 70, 180	112.0
2	Raw material sieving. Sieve pore size	7, 10, 5, 8, 8	7.6	4, 2, 5, 10, 5	3, 5, 3, 3, 5	84, 100, 75, 240, 200	139.8
3	Loading homogenization. Order of adding components	7, 10, 3, 9, 5	6.8	5, 5, 3, 10, 5	4, 5, 5, 2, 7	140, 250, 45, 180, 175	158
4	Loading homogenization. Degree of volume filling	7, 10, 5, 8, 5	7.0	5, 5, 3, 7, 4	3, 8, 3, 4, 7	105, 400, 45, 224, 140	182.8
5	Moistener preparation. Temperature of HPMC solution	8, 10, 5, 7, 10	8.0	4, 2, 3, 3, 5	2, 2, 3, 4, 5	64, 40, 45, 84, 250	96.6
6	Granulation in refluxing layer. Granulator container heating temperature and time	8, 10, 5, 7, 5	7.0	5, 5, 5, 2, 3	3, 5, 3, 1, 5	120, 250, 75, 14, 75	106.8
7	Granulation in refluxing layer. Moistener flow rate, air spray pressure and microclimate, nozzle diameter	8, 10, 7, 10, 10	9.0	4, 8, 5, 3, 8	4, 8, 3, 3, 9	128, 640, 105, 90, 720	336.6
8	Granulation in refluxing layer. Input air flow rate and temperature	8, 10, 10, 10, 7	9.0	4, 8, 5, 3, 5	4, 8, 5, 3, 5	128, 640, 250, 90, 175	256.6
9	Granulation in refluxing layer. Input air temperature and flow rate during drying	8, 10, 5, 9, 5	7.4	4, 5, 5, 2, 5	4, 5, 3, 4, 5	128, 250, 75, 72, 125	130
10	Calibration. Prolongation of product contact time with air, moisture absorption	7, 5, 3, 5, 4	4.8	4, 2, 3, 3, 3	4, 5, 5, 2, 5	112, 50, 45, 30, 60	59.4
11	Batch homogenization and powdering. Degree of volume filling	7, 10, 5, 8, 5	7.0	4, 5, 3, 7, 5	2, 5, 3, 4, 7	56, 250, 45, 224, 175	150
12	Tableting. Nature of tablet mass flow from bunker	8, 10, 7, 9, 8	8.4	5, 5, 7, 1, 4	4, 2, 3, 1, 6	160, 100, 147, 9, 192	121.6
13	Tableting. Evenness of matrix filling	9, 10, 5, 9, 8	8.2	5, 5, 7, 1, 4	3, 2, 5, 2, 6	135, 100, 175, 18, 192	124
14	Coating suspension preparation. Temperature of HPMC solution	7, 10, 7, 7, 8	7.8	4, 2, 3, 3, 4	3, 2, 5, 4, 8	84, 40, 105, 84, 256	113.8
15	Coating suspension preparation. TiO_2 grinding	8, 10, 7, 7, 8	8.0	4, 5, 3, 4, 4	3, 5, 7, 4, 8	96, 250, 147, 112, 256	172.2
16	Coating suspension preparation. Order of mixing components	7, 10, 7, 9, 7	8.0	5, 5, 5, 5, 4	3, 5, 7, 5, 7	105, 250, 245, 225, 196	204.2
17	Coating suspension preparation. Stirring time	8, 10, 5, 9, 8	8.0	5, 5, 3, 5, 4	4, 5, 3, 2, 6	160, 250, 45, 90, 192	147.4
18	Coating suspension preparation. Suspension filtration	8, 10, 7, 9, 8	8.4	4, 5, 5, 2, 4	7, 5, 5, 2, 7	128, 250, 175, 36, 224	162.6
19	Coating suspension preparation. Stirring rate	8, 8, 5, 9, 8	7.6	4, 5, 5, 3, 6	4, 2, 3, 3, 3	128, 80, 75, 81, 144	101.6
20	Coating deposition. Nozzle diameter	8, 10, 7, 9, 5	7.8	5, 1, 3, 5, 3	4, 5, 3, 3, 2	160, 50, 63, 135, 30	87.6
21	Coating deposition. Coating suspension stirring rate	8, 8, 7, 9, 6	7.6	4, 5, 5, 3, 4	4, 2, 3, 3, 5	128, 80, 105, 81, 120	102.8
22	Coating deposition. Suspension flow rate, air spray pressure and microclimate	8, 10, 5, 10, 10	8.6	4, 5, 3, 3, 5	3, 5, 3, 3, 8	96, 250, 45, 90, 400	176.2
23	Coating deposition. Input air flow rate	8, 10, 7, 9, 10	8.8	4, 5, 3, 3, 5	3, 5, 3, 2, 4	96, 250, 63, 54, 200	132.6
24	Coating deposition. Input air temperature	8, 10, 7, 10, 8	8.6	4, 8, 5, 3, 4	3, 7, 3, 2, 8	96, 560, 105, 60, 256	215.4
25	Tablet packaging and storage. Blister hermeticity	8, 10, 7, 10, 5	8.0	3, 5, 3, 3, 3	2, 5, 5, 3, 6	48, 250, 105, 90, 90	116.6
26	Tablet packaging and storage. Primary packaging materials and packaged tablet storage conditions	9, 10, 5, 10, 5	7.8	3, 5, 3, 10, 3	2, 5, 3, 3, 6	54, 250, 45, 300, 90	147.8
27	Tablet packaging and storage. Blister machine hardware	9, 7, 7, 10, 8	8.2	5, 1, 5, 5, 2	2, 2, 3, 1, 1	90, 14, 105, 50, 16	55

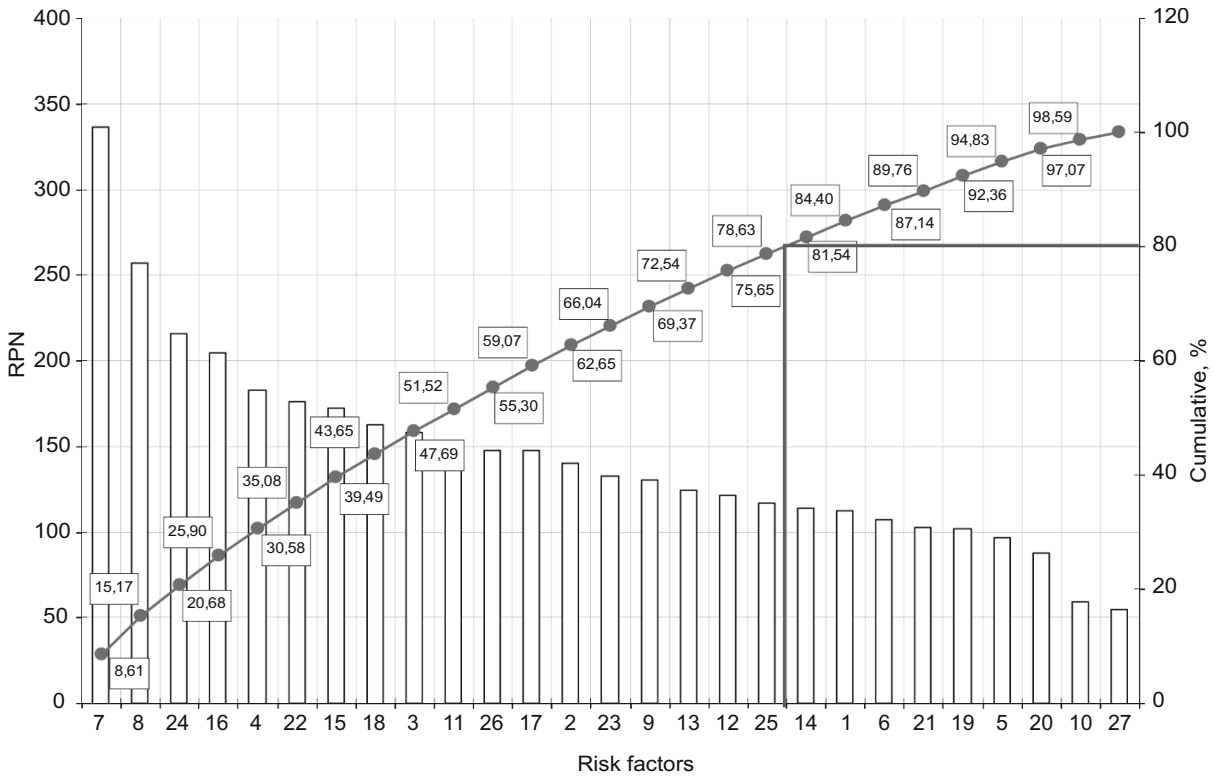

Fig. 1. Pareto chart constructed from RPN for **I** production process risks.

were first examined in order to satisfy requirements for the completeness of the hazard analysis and risk identification [5]. Then, these operations were broken down into elemental actions. This enabled possible risks of the drug (**I**) production process to be identified [6].

According to the procedure used by us to assess risks to the product **I** during the PD stage, an expert quality analysis using a matrix of consequences and probabilities over categories H, M, L, and I preceded the quantitative analysis of the consequences [4, 8]. The experts were five specialists with the appropriate experience in risk management and competency on PD issues.

Table 1 presents the qualitative analysis data using the matrix of risk consequences and probabilities. The data made the quantitative analysis and subsequent risk assessment meaningful because risk factors ranked high and medium (Table 1, categories H and M) required urgent preventive measures.

We used the failure modes (non-conformities, defects) and effects analysis (FMEA) method to develop a system of preventive measures [7, 8]. FMEA suggests assessing possible non-conformity risks using the three parameters S (severity), O (occurrence), and D (detection), which are determined based on statistical data and the opinions of experts, i.e., members of FMEA teams using the corresponding type scales. A 10-ball scale was also used in our research for all three assessment numbers (S, O, and D). Ultimately, a risk priority number (RPN) that was the product of these parameters ($S \cdot O \cdot D$) was determined. A system of preventive measures relative to the identified risks could be developed by analyzing the RPN [7].

Considering the dimension of the scales used by us, each RPN ranged from 1 to 1000. Risk factors (potential non-conformities) with the greatest RPN values (RPN > 100) were given priority treatment.

Table 2 presents data for the quantitative risk analysis for **I** production process quality that was performed by the expert panel.

The results of our qualitative and quantitative risk analyses indicated that they converged so that further work on the process quality risk assessment could be optimized.

It was understood that not all identified and analyzed risks would require equivalent approaches to their treatment. We formed a group of risk factors that presented the greatest threat by utilizing a data-ranking method, i.e., a Pareto chart [8], in order to distribute efforts adequately. The Pareto chart (Fig. 1) constructed based on RPN data and the calculated relative fraction and cumulative percent allowed those 18 risk factors of 27 that were most critical for the **I** production process and included 80% of all possible problems associated with the quality of this process.

The research identified 27 risk factors characteristic of the **I** production process during its PD stage. Identified risks were assessed qualitatively using a matrix of risk consequences and probabilities. The FMEA procedure with RPN

determination was used for the quantitative risk assessment. The results of both approaches were in excellent agreement. The Pareto chart was used to analyze and rank risks and to identify the following 18 most critical process risk factors.

1. Granulation in the refluxing layer. Moistener flow rate, air spray pressure and microclimate, nozzle diameter (factor 7);
2. Granulation in the refluxing layer. Input air flow rate and temperature (factor 8);
3. Coating deposition. Input air temperature (factor 24);
4. Coating suspension preparation. Order of mixing components (factor 16);
5. Loading homogenization. Degree of volume filling (factor 4);
6. Coating deposition. Suspension flow rate, air spray pressure and microclimate (factor 22);
7. Coating suspension preparation. TiO_2 grinding (factor 15);
8. Coating suspension preparation. Stirring rate (factor 18);
9. Loading homogenization. Order of adding components (factor 3);
10. Batch homogenization and powdering. Degree of volume filling (factor 11);
11. Tablet packaging and storage. Primary packaging materials and packaged tablet storage conditions (factor 26);
12. Coating suspension preparation. Stirring time (factor 17);
13. Raw material sieving. Sieve pore size (factor 2);
14. Coating deposition. Input air flow rate (factor 23);
15. Granulation in refluxing layer. Input air temperature and flow rate during drying (factor 9);
16. Tableting. Evenness of matrix filling (factor 13);
17. Tableting. Nature of tablet mass flow from bunker (factor 12);
18. Tablet packaging and storage. Blister hermeticity (factor 25).

The drafted field of critical process parameters should be optimized considering the results of the present research during pilot-scale validation of the stages Granulation in refluxing layer, Calibration, Mixing and powdering, Tableting and dust removal, Coating suspension preparation, and Coating deposition.

The results of the risk assessment must be considered for standardization of the production process and development of the technical documentation, namely:

by considering the specifics of the used raw material (HPMC solubility) and necessarily developing an equipment cleaning procedure and validating it;

by using allowed limits on the selected risk factors determined in the PD stage when determining the standards (deviations and tolerances);

by having the quality control section examine the probability of introducing additional quality control parameters characterizing the starting component tableting technology during development of specifications for intermediates.

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