BJNS
Brazilian Journal of Natural Sciences

Brazilian Journal of Natural Sciences
www.bjns.com.br

ISSN 2595-0584 -V.3- N.3
Novembro 2020
Revista Eletrônica

Review Article: Open Access

APPLICATION OF FMEA TOOL TO ANALYZE NOTIFICATIONS OF TECHNICAL COMPLAINTS OF SOLID DOSAGE FORMS IN THE CONTEXT OF QUALITY BY DESIGN

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Abstract

The quality control in pharmaceutical industries has been gradually improved with the implementation of new strategies and technologies, in order to make it possible to obtain increasingly effective and safe products. With the advent of the Quality by Design (QbD) concept, the production of medicines started to be optimized by delimiting the quality parameters of the products from the initial stages of development and formulation planning based on the characteristics of the active pharmaceutical ingredient, aiming defect prevention and continuous improvement of the production chain. Therefore, the present study constitutes a quantitative analysis of notifications of irregularities in solid medicines published on the National Health Surveillance Agency (ANVISA) official website during the period from 2017 to 2019, using the Failure Mode Analysis and Effects (FMEA) methodology in QbD context. Of the 421 notifications of irregular pharmaceutical products analyzed, 28.5% corresponded to technical complaints and, of this total, 60.0% were related to solid medicines. After evaluating the data, it was found that approximately 80.0% of the non-conformities found were related to aspect, dissolution, packaging, dosing and purity. Thus, it can be inferred that the QbD is an efficient strategy for the management of risks related to production, aiming at cost reduction and implementation of strategies that allow the gradual reduction in the number of technical complaints of these products.

Keywords: Quality by Design; quality control; solid dosage forms

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DOI: https://doi.org/10.31415/bjns.v3i2.105 - Article received on: July 17, 2020; accepted October 21, 2020; published in November 2020 in Brazilian Journal of Natural Sciences, Vol. 3, N.3, Online, ISSN: 2595-0584 – www.bjns.com.br. All authors contributed equally to the article. The authors declare no conflict of interest This is an open access article under the CC - BY license: http://creativecommons.org/licenses/by/4.0

Introduction

According to a report by the World Surveillance and Monitoring System of the World Health Organization (WHO), it is estimated that, in underdeveloped countries, about one in ten drugs marketed does not present acceptable quality standards, either due to irregularities related to falsification of products or caused by manufacturing errors (1).

With the expansion of the pharmaceutical industry and the production of medicines, new products are constantly made available on the market. Solid dosage forms stand out in relation to the others because they have significant advantages, such as ease of administration and transport, longer shelf life and good physical-chemical stability (2).

At the same time, there was a need to increase the monitoring of the quality of these products, causing the pharmaceutical industries to start investing in the implementation of new strategies and technologies aimed at obtaining products that are increasingly effective and safe. One of the main forms of monitoring in the post-marketing phase is through the notification of technical complaints, which can be defined as any irregularity related to technical or legal aspects, capable or not of causing damage to individual and collective health (3).

Quality control is a key element of any industrial process to give credibility to products and stability for companies in the respective sector. With the emergence of the era of total quality management since 1980 (**Figure 1**), the focus of industries has shifted to controlling variables that can affect the desired quality of products from the planning stage, through guided strategies mainly in the concept of QbD (4,5).

Figure 1: Main elements of Total Quality Management

Source: The author

According to Nadpara *et al.* (6), QbD is a modern approach to pharmaceutical products that provides guidance for industries to improve their manufacturing processes, by optimizing operating systems and managing production-related risks.

However, the main challenge is the identification of all potential points of failure capable of compromising the quality of the products, since most processes do not have a carefully defined standard. In this context, the use of quality tools becomes an important alternative to assist in decision making involving the directing of resources to continuous improvement practices in stages considered most critical (7,8).

In view of the breadth of the bibliography regarding risk management in industrial processes, the FMEA methodology was the most appropriate tool for this study, since it allows the identification of irregularities that represent greater risks, enabling the planning of actions corrective and preventive measures capable of reducing the occurrence of non-conformities (9,10).

In this sense, the objective of the work was to quantitatively assess notifications of irregular solid medicines published by ANVISA during the period from January 2017 to December 2019, using the FMEA tool within the context of QbD.

Materials and methods

The present study was carried out through a data survey of notifications of technical complaints of solid dosage forms published in the form of Specific Resolutions (SR) in the "Irregular Products" area of the official website of ANVISA (11), during the period from January 2017 to December 2019.

After a systematic search, notifications were collected according to the dosage form and the type of irregularity presented by the products. Were considered data related to pharmacotechnical problems, contamination, non-compliance with general manufacturing standards and non-conformities in packaging, for further subdivision into 12 categories (**Table 1**).

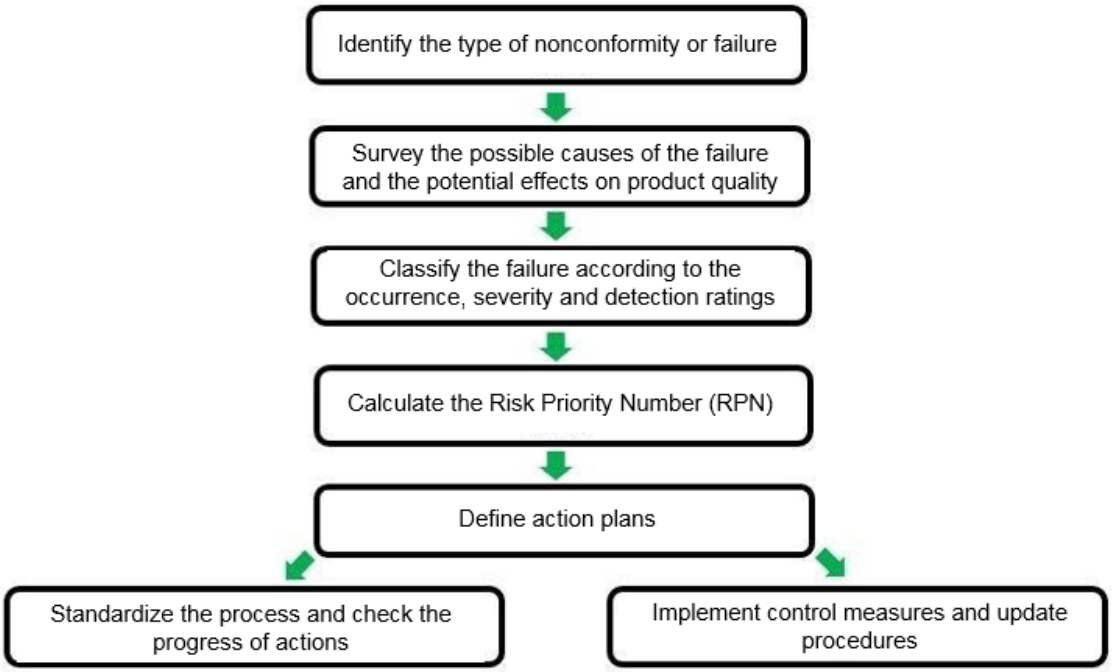
Table 1: Categorization of notifications of technical complaints related to medicines

CATEGORY	IRREGULARITIES INCLUDED
Aspect	- Alteration of organoleptic characteristics (color, flavor, odor and texture).
Microbiological contamination	- Microbial count above the specification or presence of pyrogen.
Contamination by active substance	- Presence of substances not described in the formulation.
Description	- Differences between the description and the appearance of the product.
Disintegration	- Disintegration test failure.
Dissolution	- Dissolution test failure.
Dosing	- Active ingredient content out of specification.
Packaging	- Product characteristics different from those in the original packaging; - Absence of information on labels or failures in recording product data on packaging; - Product packaging with different material than registered; - Lack of content in the product bottle or problems with filling.
Stability	- Stability test failure.
Formulation	- Presence of lumps or irregularities on the surface of the drugs.
Average weight	- Weight out of specification or variation range.
Purity	- Presence of impurities or less active polymorphic forms; - Out of specification results for related substances test; - Use of irregular or prohibited raw materials.

Source: The author

Right after, the numbers of notifications were counted separately according to the respective categories and proceeded to the subsequent steps of application of the tool (**Figure 2**).

Figure 2: Application steps of FMEA tool for analysis of nonconformities in solid formulations between January 2017 and December 2019



Source: Adapted from Saxer (10).

In the occurrence classification (**Table 2**), the main criterion adopted was the frequency at which a given failure was repeated during the period studied. On the other hand, the severity index was defined according to the possible consequences that the failure can bring, so, the main criterion adopted was the dangerousness of the effects, considering aspects such as risks to the health of patients, effectiveness commitment and loss of credibility of the product. Finally, the detection scale was established based on the probability of avoiding failure, thus, the smaller the amount of pre-existing controls, the higher the value assigned, considering that there will be an increased risk of a non-compliance reaching the customer (9,10).

Table 2: Occurrence, severity and detection rating scale

RATING	OCCURRENCE		SEVERITY		DETECTION	
	Definition	Criteria	Definition	Criteria	Definition	Criteria
1	Remote frequency	Once every 3 years	No effect	- No impact on the effectiveness or safety of the product; - Failures that are not notified by the customer but represent a non-compliance with Good Manufacturing Practices.	Failure certainly detected	Failure immediately detected by automatic control or simple tools (e.g.: monitoring the average weight of medicines automatically)
2	Very low frequency	Twice every 3 years	Very minor	- Failures that do not cause health risks, but are detectable (e.g.: missing capsule) - Process problems that affect products sporadically (e.g.: empty packaging).	Very high probability of detection	Failure avoided or detected by sampling control (e.g.: quality control analysis)
3	Low frequency	3 times every 3 years	Minor	- Failures that do not have meaningful impact on the effectiveness of the product but may cause questions about integrity or stability.	High probability of detection	Failure avoided or detected by continuous visual/manual control
4	Infrequent	4 times every 3 years	Low	- Failure can represent regulatory non-compliance.	Moderate probability of detection	Failure prevented or detected by periodic visual/manual control (random checks)

5	Occasional frequency	5 times every 3 years	Noticeable	- Organoleptic characteristics different from the usual (e.g.: unpleasant smell, atypical taste); - Perceptible quality deviations that can compromise the effectiveness of the medication (e.g.: open capsules).	Failure eventually detected	Failure avoided or detected during the execution of Standard Operating Procedures
6	Moderate frequency	6 times every 3 years	Moderate	- Failures that are easily noticed by the customer, affecting the amount of sales of the product; - Noticeable loss of performance (e.g.: medication has no effect).	Failure regularly detected	Failure can be detected or prevented, but in certain situations, such as internal inspections and audits
7	Frequent	7 times every 3 years	High	- Missing or incorrect information in leaflets, package inserts or labels; - Label errors (e.g.: incorrect expiration date); - Failure to close primary and/or secondary packaging.	Low probability of detection	Failure prevented or detected by sporadic verification (not officially foreseen)
8	High frequency	8 times every 3 years	Very high	- Production irregularities; - Failure can cause withdrawal or suspension of drug sales.	Very low probability of detection	Failure can be avoided, but there is no defined mechanism for detection
9	Very high frequency	9 times every 3 years	Hazardous	- Incorrect product (inconsistency between label and content); - Medicines have constituents in concentrations different from the specifications of the standard formula, which can cause serious clinical consequences.	Failure usually not detected or prevented	Failure without any technical, manual or visual control that allows detection

10	Highest frequency	10 times every 3 years	Critical	- The failure represents a potential risk to patient safety, life or health; - Microbiological, chemical or physical contamination, with possible clinical consequences.	Almost undetectable failure	Neglected or imperceptible failure

Source: Adapted from Stersi e Rito (9).

From the attribution of the occurrence, severity and detection indices, the RPN was calculated according to the following formula: **Risk Priority Number (RPN) = Occurrence x Severity x Detection**

The calculation of the RPN allows the assessment of the criticality levels of the failures and the definition of which stages of the process should be prioritized. For the determination of the most critical faults, it should be considered that, if the scales range from 1 to 10, the maximum RPN value for a fault that simultaneously presents maximum indexes of O, S and D is equal to 1000. Therefore, to obtain 90% statistical confidence for the process, 90% of the highest RPN values must be prioritized. Thus, all RPN values equal to or above 100 must be classified as critical or unacceptable (4,9).

Results and discussion

During the years 2017 to 2019, ANVISA has published a total of 421 notifications of irregular pharmaceutical products, of which 136 were for the year 2017, 108 for 2018 and 177 for 2019. Of this total, 120 (28,5%) were related pharmacotechnical problems, contamination, non-compliance with general manufacturing standards and non-conformities in packaging. Of these notifications, 72 (60,0%) were about solid medicines, such as tablets, capsules, lyophilized powders, suspension powders and sugar-coated tablets (**Table 3**).

Table 3: FMEA table of notifications of technical complaints for solid dosage forms

Dosage form	Failure type reported	Number of notifications	Potential causes	Potential effects	O	S	D	RPN
Tablet	Packaging	10	- Packaging materials out of specifications; - Absence of a labeling control mechanism; - Failure in the packaging closing mechanisms.	Absence or error of information that can compromise the treatment	10	7	9	**630**
	Dissolution	10	- Failures in formulation development; - Polymorphism in raw materials; - Failures in qualification of raw material suppliers; - Low robustness in process.	Recall or suspension of drug sales	10	8	2	**160**
	Aspect	7	- Incompatibility between drug and excipients; - Problems related to product stability; - Product contamination.	Effectiveness commitment or risk of non-adherence to drug treatment	7	5	3	**105**
	Dosing	5	- Equipment failures (e.g.: calibration or maintenance); - Absence of effective control mechanisms; - Failure to define specifications for the product's active ingredient content.	Risk of clinical consequences from underdose or overdose	5	9	2	90
	Purity	4	- Poor quality of raw materials; - Use of irregular or prohibited raw materials; - Absence of effective control mechanisms.	Clinical consequences resulting from product ineffectiveness	4	9	2	72
	Average weight	2	- Low robustness in process. - Absence of effective control mechanisms; - Equipment failures (e.g.: calibration or maintenance).	Recall or suspension of drug sales	2	8	2	32
	Description	4	- Non-compliance with regulatory standards; - Use of the incorrect standard formula or exchange of raw materials during the manufacture of the product; - Absence of effective detection mechanisms.	No health risks, but can be detected by the customer and generate consumer complaints	4	2	3	24

Capsule	Packaging	2	- Packaging materials out of specifications; - Absence of a labeling control mechanism; - Failure in the packaging closing mechanisms.	Absence or error of information that can compromise the treatment	2	7	9	**126**
	Purity	2	- Poor quality of raw materials; - Use of irregular or prohibited raw materials; - Absence of effective control mechanisms.	Clinical consequences resulting from product ineffectiveness	2	9	2	36
	Contamination by active substance	1	- Insufficient sanitization of production lines; - Presence of contaminants in raw materials; - Use of the incorrect standard formula or exchange of raw materials during the manufacture of the product.	Potential risk to patient safety, with possible clinical consequences	1	10	2	20
	Dosing	1	- Equipment failures (e.g.: calibration or maintenance); - Absence of effective control mechanisms; - Failure to define specifications for the product's active ingredient content.	Risk of clinical consequences from underdose or overdose	1	9	2	18
	Average weight	1	- Low robustness in process. - Absence of effective control mechanisms; - Equipment failures (e.g.: calibration or maintenance).	Recall or suspension of drug sales	1	8	2	16
	Disintegration	1	- Failures in formulation development; - Poor quality of raw materials; -Failures in qualification of raw material suppliers; - Absence of effective control mechanisms.	Drop in performance (reduced pharmacological effect)	1	6	2	12

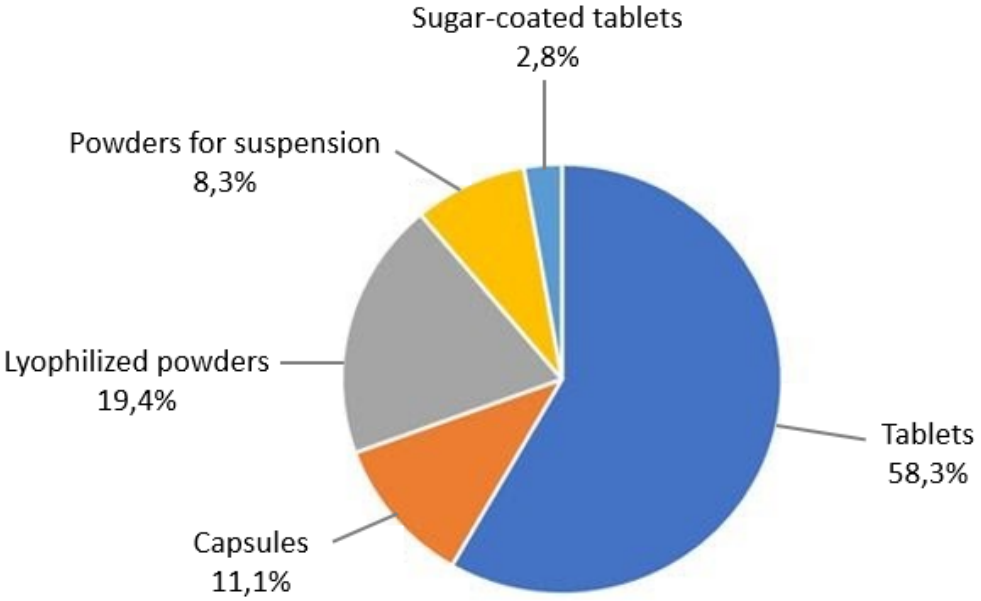
Lyophilized powder	Packaging	4	- Packaging materials out of specifications; - Absence of a labeling control mechanism; - Failure in the packaging closing mechanisms.	Absence or error of information that can compromise the treatment	4	7	9	**252**
	Microbiological contamination	4	- High water activity in the formulation due to failure in the lyophilization process; - Poor quality of raw materials; - Uncontrolled environmental conditions during production; - Failure in the packaging closing mechanisms; - Insufficient sanitization of production lines; - Inadequate employee attire.	Potential risk to patient safety, with possible clinical consequences	4	10	2	80
	Aspect	5	- Incompatibility between drug and excipients; - Problems related to product stability; - Product contamination.	Effectiveness commitment or risk of non-adherence to drug treatment	5	5	3	75
	Dosing	1	- Equipment failures (e.g.: calibration or maintenance); - Absence of effective control mechanisms; - Failure to define specifications for the product's active ingredient content.	Risk of clinical consequences from underdose or overdose	1	9	2	18
Powder for suspension	Packaging	2	- Packaging materials out of specifications; - Absence of a labeling control mechanism; - Failure in the packaging closing mechanisms.	Absence or error of information that can compromise the treatment	2	7	9	**126**
	Formulation	2	- Stability problems; - Poor quality of raw materials. - Absence of studies regarding the physical-chemical characteristics of the drug.	Recall or suspension of drug sales	2	8	3	48
	Aspect	2	- Incompatibility between drug and excipients; - Problems related to product stability; - Product contamination.	Effectiveness commitment or risk of non-adherence to drug treatment	2	5	3	30

Sugar-coated tablets	Packaging	1	- Packaging materials out of specifications; - Absence of a labeling control mechanism; - Failure in the packaging closing mechanisms.	Absence or error of information that can compromise the treatment	1	7	9	63
	Stability	1	- Absence of studies regarding the physical-chemical characteristics of the drug; - Inadequate conditions during the manufacture, storage and transportation of the product.	Drop in performance (reduced pharmacological effect), which may impact product sales	1	6	2	12

Source: The author

According to the survey, the solid dosage forms that presented the highest number of notifications were tablets (58,3%) and lyophilized powders (19,4%), as shown in **Figure 3**.

Figure 3: Notifications of solid dosage forms from January 2017 to December 2019



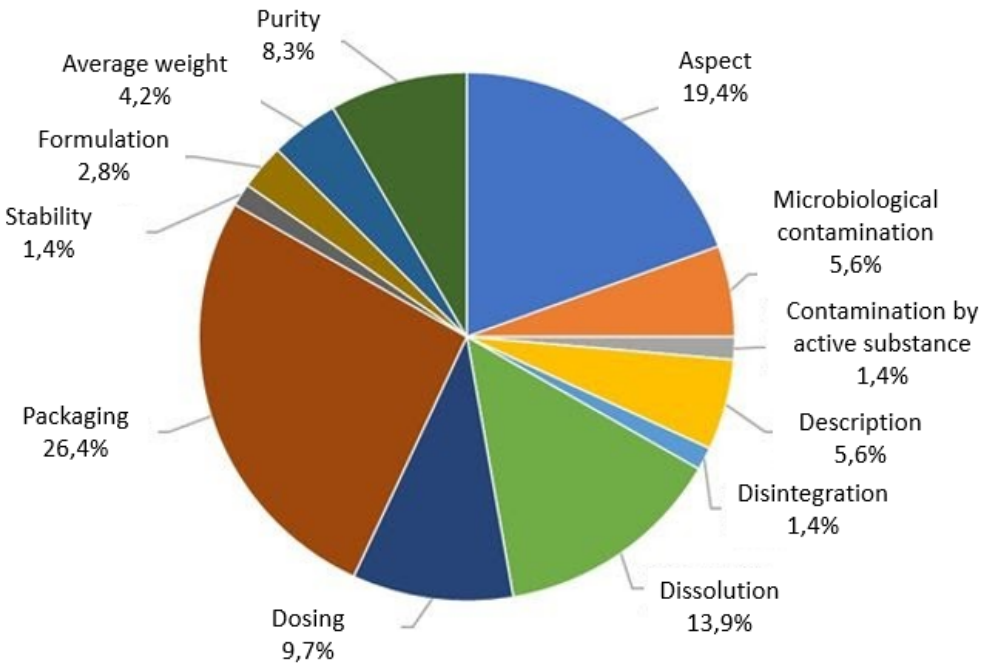
Source: The author

Juliani (12) explains that although have some advantages over other dosage forms, the tables have significant disadvantages, such as limiting the amount of drug in the preparation and difficulty in adjusting the dose of the final medication, which can be determining factors for a higher number of notifications of irregularities if not carefully formulated.

On the other hand, the dosage form that presented the lowest number of notifications was the sugar-coated tablet, with 2,8% of the total. However, due to the dredging process takes time and technique, increases the size of the tablet by 50% weight/volume and has a higher cost, the sugar-coated tablets are being increasingly replaced on the market by film-coated tablets, which may justify the low number of notifications (12).

Of the 72 notifications, approximately 80% were related to aspect, dissolution, packaging, dosing and purity (**Figure 4**). In addition, based on the analysis of the RPN obtained, irregularities related to the first three parameters were classified as critical, due to the high number of notifications and significant impact on the quality of the products.

Figure 4: Categories of irregularities related to solid dosage forms notified between January 2017 to December 2019



Source: The author

Regarding packaging, the Design Space strategy, in the context of QbD, can significantly contribute to reducing the number of notifications related to the packaging of medicines. In this study, the Design of Experiments (DoE) lead to a set of experiments, whose statistical analysis may point to the main factors capable of impairing the stability of the product or the packaging function, such as dimension, color, flexibility, diagramming, format and graphic aspects (5,13).

Another relevant non-conformity observed for tablets and powders was the aspect. This parameter is important for the credibility of the product, because through the organoleptic characteristics (such as color, odor, flavor and

texture) is possible to identify the occurrence of physical-chemical changes, contamination or degradation processes capable of compromising the stability or effectiveness of the medicine, which may represent risks to patient safety (14,15).

Chemical and biological properties such as purity, pKa, photolytic and oxidative stability, partition coefficient and permeability to biological membranes should also be considered, since they directly influence the choice of pharmaceutical adjuvants and the most suitable materials for product packaging (5).

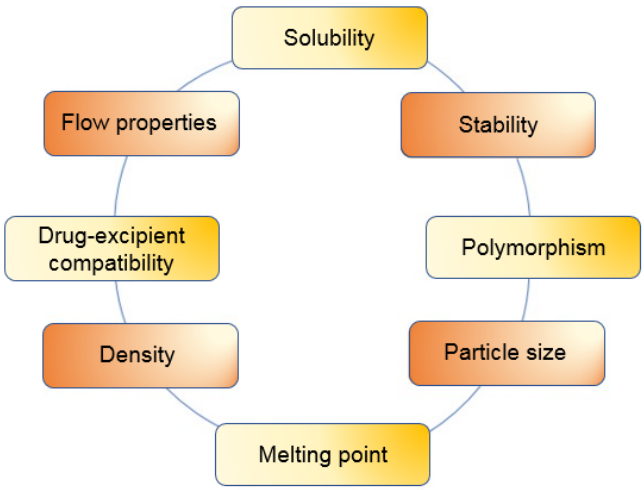
According to Andrade Jr. (16), another study of paramount importance for the development of drugs is that of drug-excipient compatibility, carried out mainly through analytical techniques that employ thermal methods, such as differential exploratory calorimetry (DSC), differential thermal analysis (DTA) and thermogravimetry (TGA), whose main objective is to minimize problems related to possible reactions between the active pharmaceutical ingredient and the other components of the formulation, such as loss of stability and variability of aspect. In addition, they can be useful for maximizing the shelf life of the product, improving the understanding of interactions between medicines and avoiding waste of raw materials.

In addition to the aspect, other parameters directly linked to performance of the medicines that presented a significant number of notifications were disintegration, dissolution, average weight and dosing. The disintegration and dissolution tests are directly linked to the therapeutic effect of a medicine, since they are essential steps for the bioavailability of drug in body. On the other hand, the average weight and dosing tests are related to the uniformity of the medicines and therefore are important to ensure dosage aspects of the product (14).

One of the main strategies of QbD to avoid non-conformities related to these parameters is conducting preformulation studies, which consists of the development of the product based on the physical-chemical characteristics of the drug and excipients, considering aspects such as the desired clinical performance, stability, safety and effectiveness (16).

Nadpara and collaborators (6) highlighted that preformulation studies are important for the quality control of raw materials, since the variability of the properties of the inputs used in the manufacturing process increases the chance of obtaining a product outside the desired standards **(Figure 5**).

Figure 5: Main preformulation studies



Source: Adapted from Nadpara *et al.* (6)

Physical properties such as flow and density can directly impact operations such as compressing tablets or capsules filling, resulting in non-

conformities related to average weight and appearance, for example. In addition, depending on the biopharmaceutical classification of the active pharmaceutical ingredient, the solubility characteristics between different polymorphs have a direct impact on the dissolution and bioavailability of drugs. Thus, the processes of synthesis and impurities quantification and degradation products in raw materials become essential to ensure adequate purity to produce the medicine (5,13).

The analytical method used in quality control can also influence the occurrence of notifications of irregularities, especially when generating unreliable results. Although not mandatory nowadays, the QbD concept can be applied in the analytical context for the development and validation of methods (17). According to the quality guide ICH Q8 (R2) about Pharmaceutical Development proposed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (18), the technique of Analytical Quality by Design (AQbD), opposes the traditional method of Quality by Testing (QbT), because establishes the experimental variables capable of affecting the analytical method even before the start of development, enabling robust, reproducible and more reliable methods. Therefore, the application of AQbD has several advantages and constitutes an effective approach to reduce failures in quality control that can result in notifications of technical complaints.

Other types of notifications in evidence were of microbiological contamination or by active substances. According to the ICH Q7 guideline about Good Manufacturing Practices (19), some ways to mitigate contamination during the production of medicines are the implementation of adequate ventilation systems in the production environment, careful selection of formulation preservatives, cleaning validation process, pest control measures and use of appropriate equipment to control air pressure, microorganisms, dust, humidity and temperature.

Another important alternative for reducing the number of non-compliant products is the implementation of quality control mechanisms in real time, from which specific parameters are evaluated during the production of the medicine to facilitate the traceability of failures, optimize processes and reduce the number of batch release tests (6.15).

The implementation of these mechanisms can be done through Process Analytical Technology (PAT) tools, such as control measurements and analyzers on the production line or monitoring programs that perform complete product tests at defined intervals, aiming to reduce the variability of inputs and equipment during the manufacturing process, optimize the production cycle time, generate information about the products in real time during the release tests and automate the processes to reduce errors arising from human failures (8,13).

Conclusion

With the FMEA methodology, it was possible to assess notifications of technical complaints for solid drugs, according to the frequency, probability of detection and the impact generated by the failures, prioritizing them according to the level of criticality. In addition, it can be concluded that QbD strategies, use of tools based on mathematical models and real-time control mechanisms, can significantly contribute to reducing the occurrence of quality deviations, rejection of product batches, non-conformities regulatory and costs of investigating consumer complaints, by incorporating quality attributes into products since the development process.

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