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PHARMACY PRACTICE

Using risk analysis to guide changes to compounding formulae

Luis A. del Rio, PhD, Carmen Trives, PhD

School of Industrial Pharmacy and Pharmaceutics. Faculty of Pharmacy, CEU San Pablo University, Madrid, Spain

Abstract

"Frame formulations" are a framework for extemporaneously preparing pharmaceutical products. Alterations to the frameworks are allowed, e.g. by changing the quantity of active ingredients or by changing the percentage of excipients, as long as the variations do not affect the level of risk associated with the final product or their efficacy. Here we detail a method of analysing the risk of changes to frame formulations by assigning a risk priority number to the changes using Failure Modes Effects Analysis. The risk priority number estimates the severity and probability that changes to the formulation would have.

Keywords: Compounding, risk analysis, framework.

INTRODUCTION

The pharmacist and treating physician have a great responsibility to provide consumers with quality medications to treat their medical conditions. Pharmacy practice involves ensuring that medications are used to improve the health of the community. This practice is guided by quality assurance procedures. However, quality assurances procedures can fail. Most medications available in a community or hospital pharmacy dispensary have been commercially manufactured and are not often compounded by the dispensing pharmacist. The main difficulties associated with in-pharmacy compounding include: understanding the pharmacokinetic and pharmacodynamic properties of included ingredients; and the high costs associated with compounding.

In addition to these challenges, a rigid focus on adherence to existing compounding formulae may not allow for innovation and flexibility when such approaches are required. If recognised guidelines, such as 'Good Compounding Practices',[1] are reviewed, they provide a sound level of quality assurance but they do not assist all day-to-day instances of in-pharmacy compounding or compounding undertaken using experimental procedures and formulae. The US Food and Drug Administration (FDA) has highlighted the importance of regulated compounding and inspections to ensure compounding follows established guidelines.[2,3] Despite this, there is a lack of European guidelines to direct compounding practices, even though some countries have regulated it with confidence and commitment to the regular review of standards.[4] In Australia, the Pharmaceutical Society of Australia has edited a handbook that provides formulations along with scientific, professional and clinical support to pharmacists.[5] However, there is a need for a comprehensive, scientifically-sound compounding guideline for use internationally – a guideline based on risk minimisation in compounding practices, and therefore allowing for qualified variations to established compounding formulae when necessary. At the very least, such a system requires a matrix to categorise preparations[6] and direction regarding the assessment of the physical and chemical properties of compounded ingredients.

Here, we propose a framework for determining qualified compounding variations; this framework incorporates risk management to guide the compounding practices undertaken by a community pharmacy, helping to ensure the quality, safety and efficacy of the medicinal products that they manufacture. This framework allows for constructions of different 'frame formulations' for a widely recognised product. These 'frame formulations' can be defined as formulations which build a composition in *ranges* (i.e. with respect to the dose, the dosage form, and the physicochemical state of the drug and the groups of excipients used), managing the variations within these ranges to ensure that the efficacy of a drug – and the level of contingency/risk

Address for correspondence: Luis Alberto del Rio, School of Industrial Pharmacy and Pharmaceutics, Faculty of Pharmacy, CEU San Pablo University, 28760 Boadilla, Madrid, Spain.
E-mail: delrio@ceu.es

associated with it – is not affected despite changes to an established formulation for that medication.

DESIGN

Current compounding guidelines support a comprehensive understanding of the manufacturing process associated with the practice of compounding and its associated risks. Guidelines for the pharmaceutical industry were originally established by the FDA,[7] and they were later consolidated with quality risk management policies.[8] These policies can define three levels of impact to a 'frame formula' that can be brought about by formula variations: unlikely to have a detectable impact upon the frame formula; possibly creating a significant impact upon the frame formula; and, likely to create a significant impact upon the frame formula. At each of these levels, values can be assigned corresponding to the impact of a variation to the formula will have on formulation quality, size, site of application, process, use of equipment and performance of the final pharmaceutical product. In this study, we build upon the current expectations regarding the understanding of compounding formulations and processes by applying a Fault Mode Effects Analysis[9] to a hypothetical *variation* to a current, established compounding formulation. This analysis illustrates the proposed new approach to in-pharmacy compounding practice.

ASSESSMENT

The principles of Good Pharmacy Practice[10] include providing standards to guide pharmacists in their provision of healthcare services. However, current standards only consider the workforce and economic factors associated with practicing as a pharmacist. In the Cosmetics Products Notification Portal (CPNP), we have found several such frameworks referenced.[11] In contrast, the approach used in the present study aims to support a guideline focused on the category or function of each ingredient, their concentration in each product, and other relevant quantitative or qualitative information arising with each new formulation.

In the proposed model, if pharmacists wish to introduce changes according to different prescriptions, they must minimise uncertainty/risk by adhering to the predefined 'frame formulation'. In this context, a variation allows for a change in the proportion of the active or inactive ingredients as long as the risk is similar or reduced and the efficacy is maintained. To adhere to the 'frame formulation', first, the physical and chemical properties of the medications and their excipients must be described. Second, the critical and noncritical components of the prescription must be determined by the scientist, using The United States Pharmacopoeia as a reference.[12] It is important to note that, in this proposed model, maintaining the integrity of the frame formulation does not alone ensure the safety and efficacy of compounded medicines – the pharmacist must also maintain caution regarding the physicochemical properties of individual ingredients and the technological aspects of the compounding process.

Some formulations include 'additional ingredients' which are excipients that comprise no more than 10% of the formulation and do not contribute significantly to the quality and safety of the formulation. Compatibility between medications and excipients in the formulation must be established. The excipients chosen, their doses and the characteristics that can influence the drug product performance or manufacturability, should be considered relative to the respective function of each excipient. The excipient function should be considered in light of its dose and other characteristics. The ability of excipients to perform as expected throughout the life of the compounded product should also be demonstrated. Excipients can assist in the manufacturing process by providing product stability, bioavailability and patient acceptability. Excipients may also enhance the overall safety and efficacy of the compounded medication. It is acceptable to adjust the proportion of noncritical excipients in compounded products with limited justification. However, all ingredients listed in the compounded product should be included. Information about the active pharmaceutical ingredient is used to justify the quality of the compounded product. However, information regarding the safety of excipients should be referenced. In such cases, the FDA's inactive ingredients database lists the safety limits of excipients based on prior use in FDA-approved drug products.[13] Through reference to the predefined frame formulation, risk analysis evaluates whether a new formula (changed or not) is critical or not critical.

Likewise, a list of *technological* variables must be established to correspond with the frame formula. This must include information about the compounding process (time, steps, order of adding formulation components, temperature, humidity etc.), technical restrictions (infrastructure, mass, equipment), quality of raw materials and their physicochemical aspects. Additionally, one must consider controls, an evaluation of stability, and the possibility of reproducing similar formulae. And further, when fitting a prescription formula to a frame formulation, adhering to the main principles of good compounding practice (personnel, machines and

premises, materials and methods) is necessary. When encountering different formulae, consider these as opportunities to establish new framework formulae. If a prescription does not comply with a frame formulation or if there is no frame formulation for a given prescription, then the pharmacist must use their past experience to consider the quantitative and qualitative formulation details.

Once the new formula scenario is defined, it should be assessed by means of risk analysis according to the differences to the frame formulation. Risk analysis consists of identifying changes and evaluating outcomes resulting from these changes. Specifically, compounders should ask the following questions:

1 What effects on the compounded medicine are possible due to changes to the formula?
2 What is the likelihood of these effects occurring?
3 What are the consequences if these effects occur?
4 Can changes to the final product (arising due to the effects) be detected?

A risk priority number, R, can be calculated using the following equation:

$$R = S \times \mathrm{p} \times D$$

where S is the severity of impact to the compounded medicine due to adherence changes, p = probability of adherence changes resulting in changes to the compounded medicine, and D = detectability of changes in compounded medicine arising due to adherence changes.

Each parameter ranges from 1, reflecting a negligible risk due to changes in adherence, to 5, reflecting increased risk.

The judgement and experience of individual compounders will define their approach, however, they must be prepared to defend all decisions made. An example of R scores and risk meanings is shown in Table 1. There is no single, optimal approach. Different groups of frameworks need to be developed using criteria established according to the prescription category. To create a 'design space' to relate the calculated R value to the effect of changes to a frame formula, three different value ranges for R are proposed, providing for each compounding formulation an indication of the relationship to the frame formula (Table 2). The medication concerned should not be taken into consideration, as this should be done on an individual basis, as in Table 2.

Table 3 shows an example of an oral adult compounded solution with an active pharmaceutical ingredient (e.g. API #1) and a predefined frame formulation. We have developed a list of the main critical compounding attributes to be considered, shown in Table 4; risk analysis is then applied to the oral adult compounded solution (e.g. API #1) based on the frame formulation.

Identifying critical sources of variability provides the necessary understanding to adapt the prescribed formula without incurring increased uncertainty and to accurately and reliably predict product quality. The degree of flexibility is based on the level of scientific knowledge provided. Nevertheless, for each formula, appropriate data demonstrating that this knowledge is based on sound scientific principles should be

Table 1 Risk analysis for compounding adherence to a determined frame formulation

Severity (scores)		Probability (scores)		Detection (scores)	
Negligible effect on final product performance.	1	Never happened and is unlikely to occur.	1	Can always detect changes before it reaches customer.	1
The formula has a technical impact.	2	Event occurred 2-3% of the time.	2	High confidence a random change will be detected.	2
Slight deviations can arise that require moderate measures. Patient will require product to be changed.	3	Event occurred 4-10% of the time.	3	Confident systemic changes will be detected. Changes are easy to recognise.	3
Reasonable expectation that the event will cause product recall.	4	Event occurred 10–20% of the time.	4	No confidence that a random or remote change will be detected.	4
Reasonable expectation that the event will cause hazard to the patient.	5	Event occurred >20% of time. Failures usually occur.	5	Virtually impossible to detect changes.	5

Table 2 Design space criteria

Design space	Risks of adherence
Level I (Inside design space)	Framework identity not transformed. Negligible risk ($R < 12$).
Level II (Near design space)	Framework identity possibly transformed. Tolerable risk ($R = 13$–39).
Level III (Off design space)	Framework identity transformed. Unacceptable risk ($R > 40$).

Table 3 Example for formulation (API #1) and its oral adult frame formulation

Frame formulation API #1		Formulation API #1	
API #1	<2.0%	API #1	4.0%
Cosolvents (e.g. ethanol)	<5.0%	Ethanol	4.0%
Humectants (e.g. glycerin, propylene glycol)	<15.0%	Macrogol 600	5.0%
Edulcorants (e.g. sugar, sorbitol)	<85.0%	-	-
Viscosity agents (e.g. cellulose ethers, povidone)	<5.0%	Povidone K-90	3.0%
Sweetening agents (e.g. sodium saccharin)	<0.5%	Aspartame	0.3%
Preservatives	<0.3%	Methyl paraben	0.2%
Flavour (mostly essential oils, e.g. cherry)	<1.0%	Banana flavour	0.4%
Colorants	<0.1%	Sunset yellow E-110	0.1%
Buffers	<2.0%	-	-
Additional ingredients	<3.0%	-	-
Water	To 100	Purified water	To 100

Table 4 Critical attributes for compounding adherence. Example for formulation API #1

Main critical attributes	Levels of impact	S	P	D	R
Drug dosage	20% change	3	3	2	18
Reactivity and compatibility	If applied, to be established	2	2	2	8
Particle size	If applied, to be established	1	2	1	2
Solubility	20% change	2	3	2	12
Bioavailability	20% change (Log P)	2	3	2	12
pH	pH unit	2	2	2	8
New excipients	Safety assessment	2	3	2	12
Bioburden	If applied, to be established	2	1	2	4
Stability	If applied, to be established	3	2	2	12
Analysis method	Useful availability	2	2	2	8
Manufacturability	Size, process and equipment equivalence	2	2	2	8
Good compounding practice	Personnel, raw materials, sites etc.	2	2	2	8
Packaging material	If applied, to be established	2	1	1	2
User-friendly dosage form	Bitterness, pourability, etc.	3	2	2	8

presented. Thus, a frame formula for androgenetic alopecia could be used to compound minoxidil using medications such as tretinoine, biotin, vitamin B_6, melatonin, latanoprost, finasteride, 17-α estradiol, progesterone and clobetasol 17-propionate. If the main formula has a low-level risk score and each changeover does not alter the risk, this would allow us to exchange medications and excipients in different dosage forms (e.g. lotions, foams, etc.).

CONCLUSION

Compounders can handle risk–change balance and create their own compounding rules if they have sufficient additional product information, by defining the design space of the proposed formula. In addition, pharmacists may conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a range of material attributes and processing parameters. If it wishes to remain worthwhile and relevant to today, pharmacy practice cannot use the methods and tools of the past. However, this process is not feasible if each compounded product requires laboratory testing to confirm that the medication produced in the compounding process is of sufficient quality and its quality will be maintained.[14] This article has described new methods of formulation, and has suggested using a standardised methodology for setting up 'frame formulations', ensuring that they are adapted regularly to stay in step with technical and scientific progress. The framework proposed in this article can be used to complement the lists of Standard Terms drawn up by the European Directorate for the Quality of Medicines[15] as this database contains terms and definitions to describe pharmaceutical dose forms, routes and

methods of administration, containers, closures, administration devices and units of presentation.

Conflict of interests statement

The authors declare that they have no conflicts of interest.

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