ORAL DRUG RECONSTITUTION: MAKING IT EASY AND ACCURATE VIA PACKAGING INNOVATION

In this article, Anna Malori, PhD, Business Development Manager, Bormioli Pharma, discusses the oft overlooked challenges and difficulties of standard packaging systems for oral medications requiring reconstitution before use. Following on from this she highlights dual-chamber systems as a potential solution to this problem, with reference to a case study from Bormioli Pharma's own experience.

THE POTENTIAL RISKS UNDERLYING RECONSTITUTION

Every year, more than 900 million units of drugs are sold worldwide in a "to be reconstituted" state, with a corresponding value of about US$3.0 billion (£2.25 billion).[1] Among these, orally administered drugs are the most common. But what does reconstitution really imply and how is it carried out normally? With standard reconstitution, a powdered drug is packaged in a glass or plastic bottle and the patient has to add the solvent themselves. The solvent – often water, but occasionally another liquid – can be provided by the pharmaceutical company in a separate container or may not be provided at all. If solvent is not provided, the solvent choice and dosing are left in the hands of patient.

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Let's try to imagine how a standard reconstitution process takes place when solvent is not provided. After receiving the medicine, the patient goes home and opens the drug package. At this stage, it is possible to run into one of two different kinds of packaging configurations:

- The first one is a bottle with a level mark, accompanied by an instruction leaflet. This is the case of a glass or plastic bottle containing the powder: the patient has to add water up to the level mark by following the instructions, mix and consume.
- The second one is quite similar but does not include the level mark on the bottle. In this case, the patient has to check the correct quantity of solvent in the instruction leaflet, autonomously dose it and add it to the bottle. The rest of the procedure does not change.

In both cases, human error is a significant concern. An untrained patient

Dr Anna Malori
Business Development Manager
T: +39 3346 182 183
E: anna.malori@bormiolipharma.com

Bormioli Pharma
V.le Martiri della Libertà 1
43036 - Fidenza (PR)
Italy

www.bormiolipharma.com

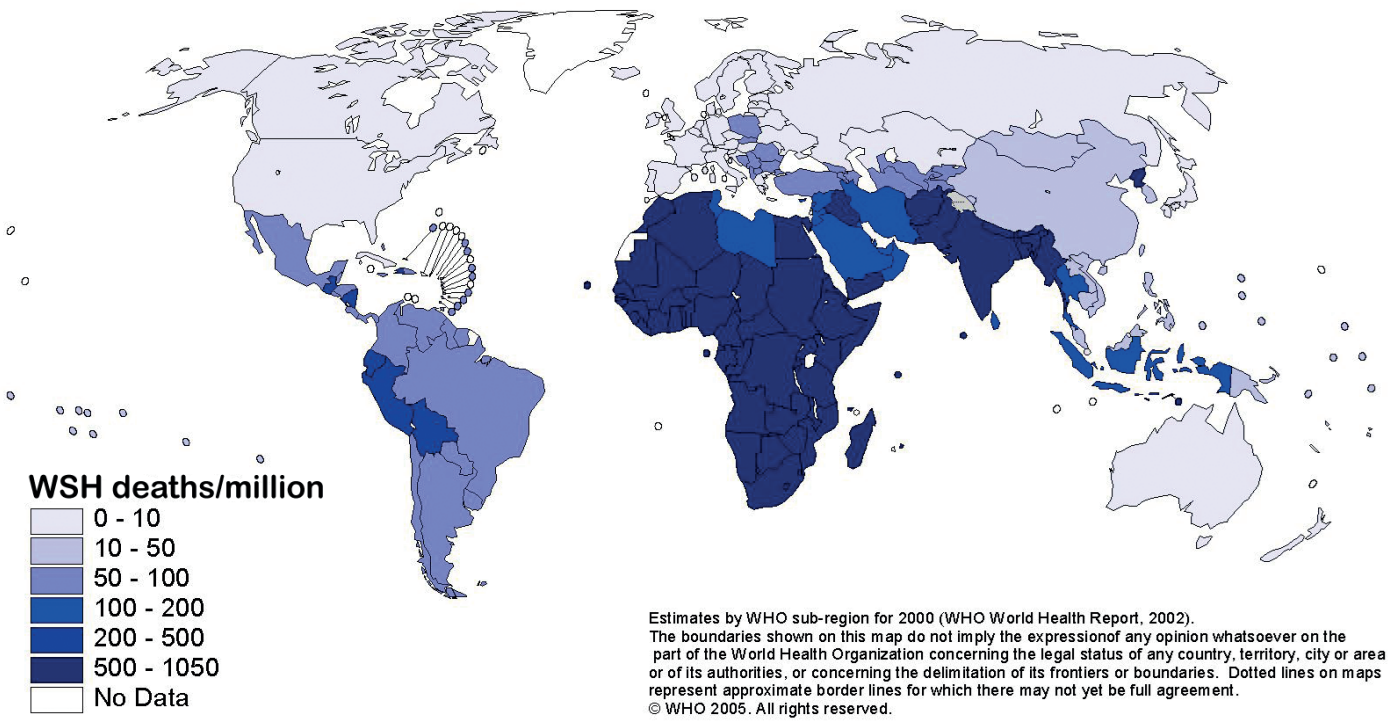

Figure 1: Map of deaths from unsafe water, sanitation and hygiene elaborated from World Health Organization (2005).

often undervalues the importance of some critical elements for drug reconstitution, such as the quality and the correct dosage of the water used during the procedure.

When discussing reconstitution, water quality is not a simple issue. An article from the American University of Sharjah (UAE) underlines all the possible concerns about the use of the wrong type of water while reconstituting.[2] First of all, it is uncommon for patients to be aware that, depending on the particular pharmaceutical process at play, a different type of water is required (e.g. purified or highly purified, mineral, spring, drinking, distilled) and that the wrong type of water can negatively impact on the drug's effectiveness. Secondly, patients often use tap water which may contain contaminants that exceed specific limits and as a result may lead to health problems.

This consideration is all the more true for those countries dealing with water pollution. A study conducted by the WHO (Figure 1) shows that deaths due to unsafe water are a daily issue in many countries.[3] For example, across almost the entire African continent there are anywhere from 550 to 1050 deaths per million inhabitants each year. It is clear that, in such countries, using tap water for reconstitution is not inappropriate, but actively dangerous.

Another potential error that can occur when reconstituting oral drugs is making a mistake in dosage. This could be either accidental or voluntary. Accidental mistakes happen when the patient does not use the prescribed dosage of water or powder, due to distraction or the poor level of accuracy of the measuring device (e.g. poorly designed or manufactured graduation

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Figure 2: An example of a dual-chamber system with main features highlighted.

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marks on cups and spoons). Voluntary mistakes are primarily caused by incorrect assumptions or fundamental misunderstandings of the product. For example, some people add more water than the stated quantity because they erroneously believe that this will allow them to have a greater quantity of the drug, thereby saving money.

It is important to note that both using either an excess or insufficient amount of water negatively impacts on the efficacy of the reconstituted drug. On the one hand, the direct consequence of adding too much water is a disproportionate dilution of the active ingredients, resulting in a loss of effectiveness. On the other hand, using not enough water can lead to serious problems of toxicity, as the active ingredients remain too concentrated.

INNOVATIVE PACKAGING SYSTEMS CAN BE AN ANSWER

As a pharma packaging manufacturer, Bormioli Pharma is well positioned to understand and tackle the challenges presented by reconstitution – namely complexity, dosage errors and poor safety features – by the design of novel packaging solutions. Specifically, this refers to the design of dual chamber systems (Figure 2) that allow for the reconstitution of oral drug product directly in the packaging itself, simply by following a guided procedure. A dual-chamber system is normally composed of a plastic bottle pre-storing the solvent and a cap pre-storing the powder. When the packaging is closed both the solvent and the powder are unavailable to the patient, who has no possibility of tampering with the pre-stored doses. The integrity of the packaging is ensured by a tamper-evident ring, which must be removed to make the reconstitution possible. After removing the tamper-evident ring, the patient

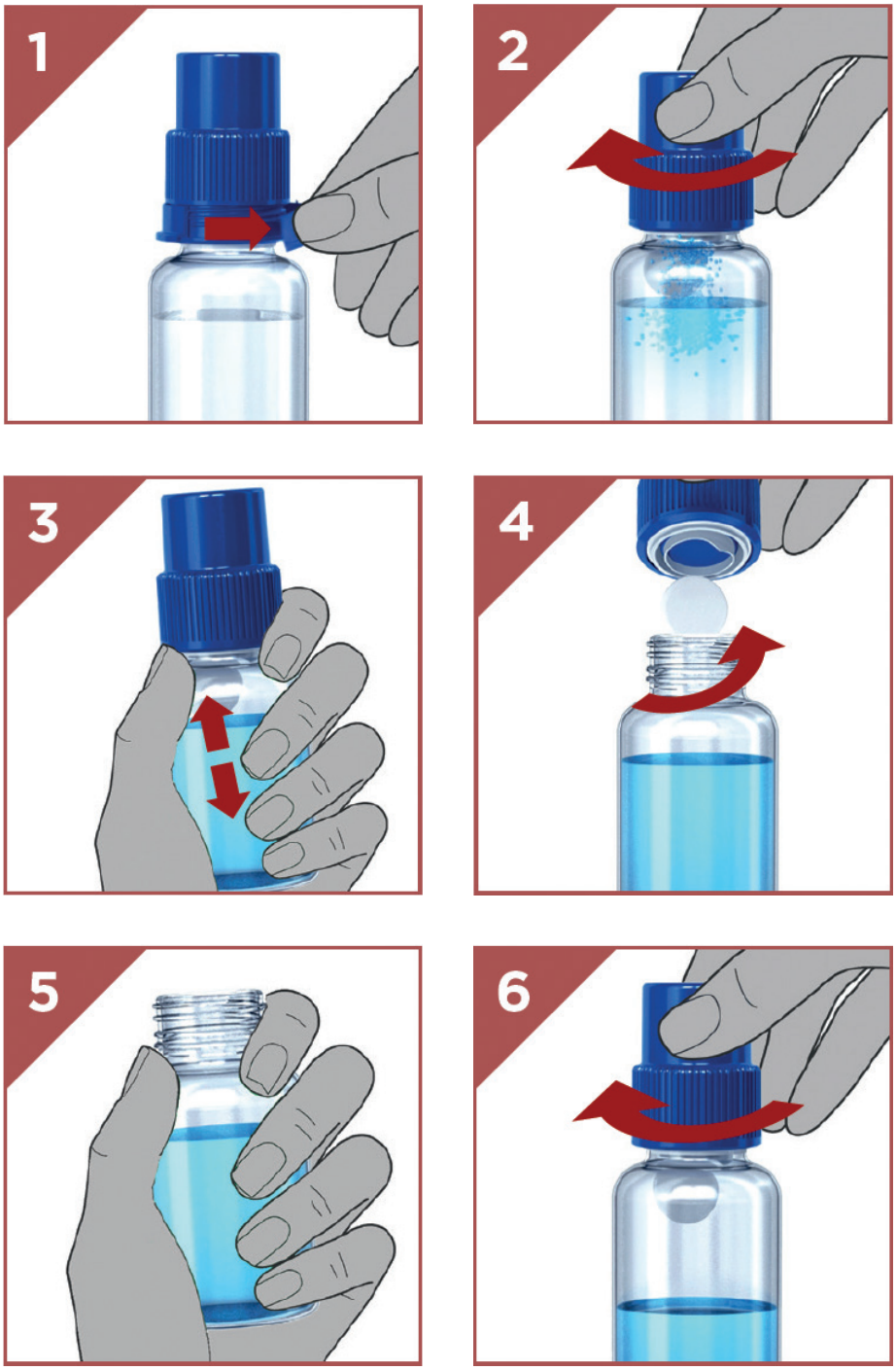

Figure 3: Functioning of a dual-chamber system in six steps.

only has to screw down the cap. This way, the powder falls down into the solvent and then the drug reconstitution procedure can be safely and accurately completed by shaking the bottle (Figure 3).

At this point, the advantages resulting from such a system should be self-evident. Firstly, a dual-chamber system leaves no dosing choice to the patient, as both the powder and the solvent are pre-dosed, ensuring a precise and accurate reconstitution and avoiding any occurrence of human error. Secondly, the solvent is chosen and provided directly by the pharmaceutical company. According to research conducted by the American University of Sharjah,[2] providing pre-packaged water with all oral formulations that require water for reconstitution is the best way to avoid any confusion and health issues. Furthermore, the pharmaceutical company is free to choose what solvent to provide inside the packaging, allowing greater flexibility in drug formulation, since it will not be tied to water as a solvent anymore.

Alongside these advantages, dual-chamber systems offer other remarkable benefits in terms of drug protection. In contrast with standard packaging formats for drugs requiring reconstitution, dual-chamber systems offer no possibility for powder loss. This is because the powder is safely stored and sealed inside the packaging and thus well protected from when it is introduced into the primary packaging through to eventual use by the patient.

Case Study of a Dual-Chamber System

To better understand the potential of dual-chamber systems with respect to improving oral drug reconstitution worldwide, a practical case can be useful. Bormioli Pharma as a primary packaging manufacturer for the pharmaceutical and biopharmaceutical industry has worked with one of the world's leading pharmaceutical companies. Bormioli Pharma was first contacted by this customer when it was dealing with a serious issue regarding one of its best-selling paediatric antibiotics, sold as powder packaged in a glass bottle with a level mark. Patients needed to add water into the bottle up to the level mark in order to reconstitute the product. But there were two problems:

1. The country where the antibiotic was sold had extremely poor water quality.
2. People were not trained to reconstitute antibiotics and they erroneously believed that the more water they added, the greater quantity of product they obtained.

Repackaging was seen as a possible solution to avoid these problems. Changing the dosage form, for example shifting from a reconstitutable powder to a solid tablet, however, was not taken into consideration because pills are difficult to swallow for children.

Together with Bormioli Pharma, the customer decided to adopt a dual-chamber system to improve the safety and the effectiveness of the medication. The first dual-chamber system prototypes were presented to the customer and a joint focus group was organised to evaluate both the ease of use and functionality of the product. From the very beginning, it was seen as an advantageous change. Indeed, Bormioli Pharma's solution would have solved their issues but wouldn't have required any drug product reformulation. Only the filling and dosing processes had to be adapted to the new packaging configuration.

The development process encompassed several phases and continuous bilateral meetings alongside the customer to ensure an optimal final packaging configuration. The result was a paediatric antibiotic, safely packed in a dual-chamber system to ensure water quality and dosing precision. In addition, simple figurative instructions were printed directly on the packaging to enhance patient compliance and to improve the correct use of the product.

SUMMARY

As has been discussed, oral drugs to be reconstituted – antibiotics, syrups or high-value treatments – represent an important segment of the global pharma industry. However, the standard reconstitution process still seems to be too complex, not completely safe, and subject to different types of human errors. Packaging manufacturers and pharmaceutical companies can work together in order to develop effective solutions to make reconstitution more precise, safer and easier. Amongst the potential solutions, dual-chamber systems appear to be a strong alternative to standard packaging methods.

ABOUT THE COMPANY

Bormioli Pharma is a primary glass and plastic packaging manufacturer serving the pharmaceutical, biopharmaceutical and nutraceutical markets. With more than 40 years' experience in the dual-chamber systems segment, Bormioli Pharma was one of the first packaging suppliers in the world to develop the bi-phase technology.

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ABOUT THE AUTHOR

Anna Malori, PhD, received a Chemistry and Packaging Technology degree from the University of Parma, Italy. As Business Development Manager at Bormioli Pharma, she works to detect unmet market needs from which to develop new business opportunities. Dr Malori is responsible for product pipeline management, leading her to collaborate closely with the R&D team.