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# Parenteral Manufacturing MARKET TRENDS

*Switching from concentrated formulas to premixed solutions that are ready to use for injection*

Photo courtesy of Grifols Partnership.

In the pharmaceutical world where cut prices and generic products create a lot of pressure, enhancing your product packaging can have a direct impact on clinician and user preference and consequently help you to increase sales and extend the final phase of the product life cycle. It's as simple as it's real.

The parenteral containers, among all pharmaceutical packaging products have evolved due to the availability of new biotechnology products, patient comfort requirements and also due to new therapies that require specific features such as prefilled syringes, single-use vials and IV premixed bags.

One of the most popular and probably the oldest containers available on the market is the small volume vial, containing a drug—concentrated, dried, lyophilized—that has to be diluted prior to injection. The main concern and the most frequent source of contamination is through the nursing staff and hospital workers.

Millions of vials are currently manufactured worldwide and millions of dilutions are performed in hospitals. Consequently there is a high potential for contamination and medical errors that could occur daily in hospitals around the world. Faced with this scenario the current trend to move from vials to premixed bags in order to reduce risks and medical errors is growing and pressuring the parenteral market to make the process safer. The use of premixed solutions obviates the need for admixtures and manipulation prior to clinical use, improving efficiency and patient safety and minimizing waste and costs.

Antibiotics, pain management drugs and cardiovascular agents will continue to lead the demand for premixed IV solutions.

## POTENTIAL RISKS RELATED WITH VIAL DILUTION PROCESS

As mentioned, the main risk related to the dilution process is microbial contamination that may arise from different sources such as the lack of maintenance of a protected environment, gowning errors, contamination of product through contact during manipulation by the operator, among others. Specific training in aseptic techniques and careful design of clean areas can help to reduce these risks. An important progress in this area is the use of robotics and automation technology to reduce the impact of human factors and consequently provide safer procedures.

Other risks related with vial dilution are medical errors due to wrong dose calculation, which can result in an overdose or a lower dose than that prescribed. Administration of the wrong dose to a patient could have serious consequences producing severe side effects and even death.

Another possible risk is the use of an incorrect diluent, such as saline instead of water for injection, to reconstitute lyophilized powder for injection since the vials are similar in appearance.

The labeling on the container, whether it's a bag, flask or bottle, where the drug has already been reconstituted is also a potential source of error due to incorrect identification or illegible text.

Although the pharmacist is the most qualified health professional to prepare the drug combination, he or she may be unaware of how these drugs interact. Drug incompatibilities can occur and produce undesired reactions, such as drug inactivation or the formation of a precipitate, which may or may not be visible to the naked eye. Several health complications

for patients can occur as a consequence of injecting particles directly into the vein, including mortality.

One clear and quite common example of potential risk is the potassium used in clinical care units. Small vials of concentrated potassium chloride are used to prepare electrolyte solutions. The compounding errors can give rise to a higher dose and a higher concentration than prescribed. The Joint Commission prohibits storage of any concentrated potassium chloride in patient care units and recommends its use and reconstitution only in Pharmacy units. The Institute for Safe Medication Practices (ISMP) has strongly recommended the use of prediluted potassium solutions in place of concentrated vials. This is just one example, but there are hundreds.

As a result of the guidelines published by these health institutions, the availability of premixed IV products and the importance they have in hospitals has grown and physicians acknowledge the safety issue as the main benefit of this type of product.

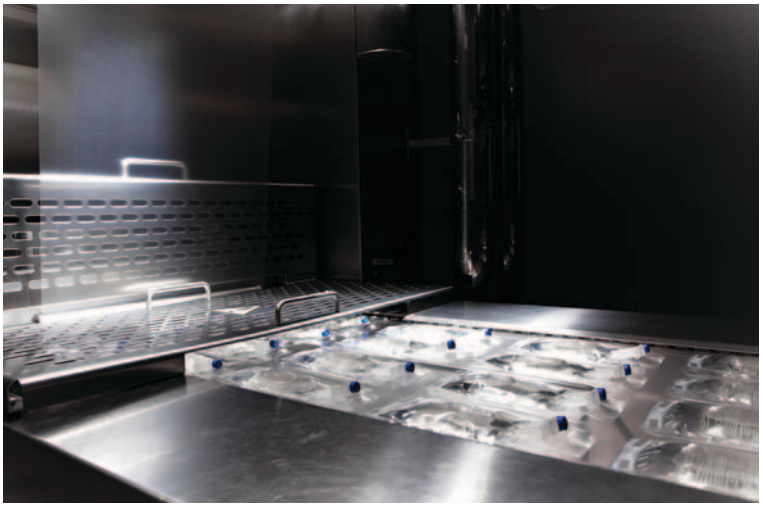

Photo courtesy of Grifols Partnership.

By minimizing the compounding workload, the use of premixed IV solutions can increase quality assurance in the hospital, reducing the total cost related with compounding and allow the pharmacist to focus on more valuable tasks.

The ideal option is to use premixed solutions that have been manufactured in facilities that comply with cGMP standards. This type of manufacturing facility has been designed and constructed specifically for the purpose of producing sterile products, and follows operating procedures that guarantee the level of quality required for safety and effectiveness.

## IMPROVING CONTAINERS TO AVOID RISKS

By eliminating the multiple preparatory stages required for reconstitution of a vial, a premixed formulation offers a more efficient and economical delivery system, for the hospital pharmacy and nursing department.

Flexible bags are the container of choice for packaging premixed parenteral drugs; they are simple and easy to use. One of the main advantages of this type of packaging is that no air-exchange is required and the bag collapses allowing the solution to flow down easily.

Additional advantages offered by premixed bags are that they are delivered directly from the manufacturer and correctly labeled. Different options are also available in terms of colors, size, graphics and overwrapping to clearly differentiate strengths or types of solution. Premixed formulations provide an efficient approach to administering IV therapy; however it is important to assess the products and their labeling to ensure the correct dose required for each patient.

Once a vial has been reconstituted the solution has to be used in the next 24-48 hours, whereas a premixed bag has a shelf life of up to two years, allowing hospitals to manage stocks efficiently.

Premixed products do however also involve certain safety concerns for physicians. These are not related to the pharmaceutical preparation but to the correct labeling and packaging. Premixed bags look very much alike and can potentially be easily confused at the point of administration. This has forced the pharmaceutical industry to work to improve labels in order to avoid confusions and medical errors.

When is the right moment to switch from using vials to premixed bags? Here is a true case example.

As a CDMO we are currently in discussion with a number of customers to advise them on switching from vials to premixed bags. In a nutshell, the answer to this question is that it depends.

It depends on the product, it depends on the country, and it depends on existing competitors. But in the end, it depends on your business strategy.

Product lifecycle management should start as early as possible and be part of the product strategy portfolio in order to remain competitive. For this reason the right approach when choosing a CDMO should be to consider those that are able to offer development and manufacturing from a vial to a premixed container. This will enable a long-term relationship between both companies as strategic partners. Working with the same CDMO for both containers means saving time, money and being able to rely on someone you already trust.

If we aim to extend product life, we should first launch the concentrated vial onto the market and later, if improvements are requested by the customer, or a high number of competitors appear in the market, or if prices start to drop, then it would be the right moment to launch an improved container.

There are however other scenarios that require a more strategic standpoint. Let's take a look at an example. Company A launches a drug of a given therapeutic class in a concentrated vial form that requires dilution on the U.S. market where there is no other competitor for that product. When the drug starts to form part of the regular protocol used in hospitals and sales stabilize, Company A decides to launch the product in Europe in the same format. The same drug does not exist in Europe, but there are other drugs with similar indications in RTU format, and physicians show considerable interest for the prediluted form as opposed to the vial;

the hospitals are also faced with strict budgetary constraints. Company A contacts a CDMO to develop and manufacture a prediluted version of the drug with the intention of launching it in the U.S. and extending the product lifecycle, but maintains its initial intention of launching the vial format in Europe. The CDMO has considerable experience in manufacturing sterile products, but above all it has important knowledge of the hospital sector giving it a clear perspective as to the needs of nursing staff and allowing it to foresee the market reaction.

Given the above scenario, is it better to launch the vial in Europe and later launch the prediluted drug, or is it a better idea to launch the product in the European market directly in the RTU format?

Launching the drug in a concentrated vial format in Europe carries the risk of competitors detecting a clear opportunity to launch the same product in a prediluted form and leaving Company A at a clear competitive disadvantage.

In this case the negotiations between Company A and the CDMO concluded in launching the drug in a prediluted format on the European market and offering all the advantages of the RTU container from the beginning. In the U.S., the product would continue to be available in the concentrated vial format, but with a view in the medium-term to migrate to a premixed bag.

Reaching the final decision is never easy, because the strategy for both companies has to be agreed upon, but in this case the market experience in the hospital sector, contributed by the CDMO, was a determining factor in the decision making process.

A CDMO with experience and extensive knowledge of the hospital market can deliver added value, because it can help to define the best market approach and strategy. Experience in the hospital market will enable you to identify customer perceptions, thoughts and feelings and assist in implementing new ideas in packaging design. Dealing with final customers and users provides insight and helps to identify concerns, so you can act quickly and save time and money.

## MANUFACTURING PARENTERAL READY-TO-USE PRODUCTS

The current environment creates new opportunities in drug development for the pharmaceutical industry.

Parenteral manufacturing products are always a challenging process due to the high cost, pressure from competitors and the requirements of the regulatory authorities. These types of products are different from all other pharmaceutical dosage forms mainly because they must be sterile, free from pyrogenic contamination and free from visible particles, even after being reconstituted. Many pharmaceutical companies do not have the resources, experience and expertise to manufacture this type of product, and only specialized manufacturers can be flexible enough to switch a drug from one container to another with the speed required.

The process required for preparing sterile products starts with the procurement of approved raw materials including drugs and excipients, and primary packaging components such as containers, seals and labels, and ends when the sterile product is properly sealed in the container. Each step in the process is controlled and validated carefully to guarantee the quality required. Process validation is an integral part of cGMP requirements, and is intended to ensure the safety of the product.

The flow of materials from raw materials, in-process and final products and equipment, and the movement of staff through the facility have to be carefully designed by expert engineers following cGMP standards in order to minimize contamination.

Everyone involved in the manufacturing process must adopt the right attitude in order to accomplish all the safety requirements. The product is not just another item; behind each product there is a patient, and we should never forget this. Our work ethics and responsibility form part of the commitment made by the pharmaceutical industry towards the patient.

As markets and customers are becoming more demanding, all medication should be provided and available in the most ready-to-use format, and the pharmaceutical industry will continue to make a significant impact in the future. **CP**

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