

# PATIENT SAFETY AND PARENTERAL DELIVERY SYSTEMS

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As active pharmaceutical ingredients (APIs) become more sophisticated, drug delivery options have followed suit. Innovations in intravenous administration have contributed to an increase in patient safety.

The premixed bag, an updated parenteral option, benefits manufacturers, caregivers, and most importantly, patients. This article describes the difference between leading parenteral drug delivery options with an emphasis on safety. The advantages of premixed parenteral delivery are considered in regards to overall patient and administrator benefit. The paper also discusses the importance of selecting a highly capable contract development and manufacturing organization in order to bring a parenteral product successfully to market.

## DOSAGE FORM OPTIONS

Intravenous administration is the most common parenteral administration route, providing an immediate therapeutic effect by delivering a drug directly into circulation. Small-volume parenterals (SVP), those with a volume of less than 100 mL, and large-volume parenterals (LVP), 100 mL or greater, are both used for the intermittent or continuous infusion of fluids or drugs.



Injectable dosage forms are the preferred formulation of large molecule drug products, traditionally delivered via the intravenous (IV) admixture. A drug delivered intravenously is pumped directly into a patient's circulatory system and takes effect immediately. An admixture is dried or lyophilized drug product, packaged in a glass vial or ampoule. In order for a patient to imbibe the admixture, the dry powder concentrate must be diluted.

Premixed bags, however, can be injected into a patient without any mixing; they are packaged in plastic bags and ready-to-use. These premixed IV solutions eliminate the need for human intervention in the drug product and are therefore the safest option for administration.

## REDUCING RISK DURING DRUG DELIVERY

It is unsurprising that admixtures pose a risk to patient safety. The opportunity for error is present throughout all stages of the process, from preparation through to



dose calculation and injection. A lack of control when reconstituting the admixture powder is one opportunity for error. In this situation, the patient is solely reliant on their clinician, pharmacist or nurse to create an identical formulation repeatedly. The training and ability of this individual is an immense variable, as are the circumstances under which dilution and dosage calculation occur.

The margin of error this causes has been acknowledged as a critical issue among medical professionals. The Institute For Safe Medication Practices National Medication Error Reporting Program (ISMP-MERP) frequently receives reports regarding IV admixtures. An observational hospital study confirmed that at least 1 in 10 of these parenteral products were improperly prepared.<sup>3</sup>

The more complicated the solution, the greater the margin of error – nutritional injectables gleaned an alarmingly high error rate of 37% when prepared manually.

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Even when preparation was partially automated, formulations had a 22% error rate. The State of Pharmacy Compounding Survey, conducted in 2009, found that 30% of hospitals had experienced a patient event attributed to an admixture compounding error over a period of 5 years. The use of premixed IV solutions could have reduced such life threatening or damaging incidents.<sup>2,3</sup>

#### ADVANTAGES OF THE PREMIXED IV SOLUTION

In order to ensure patient safety, the ISMP recommends the use of commercially prepared premixed bags over manually compounded sterile products. Similarly, opting for premixed bags as opposed to admixtures ensures compliance with the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) standards and U.S. Pharmacopeia 797 guidelines. These guidelines state: **[1]** medications should be available in ready-to-administer form whenever possible; **[2]** drug concentrations should be standardized; **[3]** medications should be available to meet patient needs when the pharmacy is closed; and **[4]** preparation of admixtures by nursing staff should be minimized.<sup>1,4</sup>

By eliminating the need for admixtures, premixed bags manufactured in a cGMP compliant facility provide the highest level of safety available. In addition to reducing the risk of medical error, premixed bags greatly decrease the threat of microbial contamination. Admixtures prepared in pharmacies are particularly vulnerable to process contamination. This is due to inconsistent staffing and the variant environment of the compound area; variables that are eradicated when using premixed bags.

Premixed bags produced in facilities that are highly automated, in addition to meeting all other requirements, benefit from an assured level of quality. This is attributed to minimal human intervention, a low chance of container manipulation and accurate labeling. Received directly from the manufacturing organization, premixed bags ensure little opportunity for the mislabeling of the final product or illegibility – often a source of confusion or cause of mistakes with admixtures. Prior to shipment, the manufacturer of the premixed product further confirms its

## COMPANY HIGHLIGHTS

# GRIFOLS INTERNATIONAL, S. A.

Grifols is a global healthcare company with a 75-year legacy of improving people's health and well-being through the development of life-saving plasma medicines, hospital pharmacy products and diagnostic technology for clinical use. The company is present in more than 100 countries worldwide and its headquarters are located in Barcelona, Spain.

Grifols Partnership is a business to business contract development and manufacturing platform for sterile solutions and lipid emulsions with over 75 years' experience in producing intravenous solutions for the pharmaceutical industry.

constancy through a series of required tests. The physical, chemical, biological, microbiological and functional attributes of the product are evaluated for the ability to function in diverse environments, including those with low humidity.

### GROWTH OF THERAPEUTIC CLASSES

The demand for premixed solutions is therapeutically led. Premixed IV solutions are the preferred mode of delivery for antibiotics globally – a market segment that continues to grow. The world's usage of antibiotics has risen approximately 36% since the year 2000.<sup>5</sup> Pain management and cardiac medications, regularly delivered intravenously, also contribute to the demand for premixed bags.

Packaged in plastic to ensure flexibility, premixed solutions deliver a fixed dose in 50 mL to 1 L containers. The bags are terminally sterilized, aseptically filled or aseptically filled and frozen, again to guarantee the utmost safety. This specific dose feature not only guarantees that the patient receives an accurate amount of drug product, but also helps reduce waste.

Another positive outcome of premixed solutions over admixtures is that reasonable dosage limitations are likely to encourage providers to write more cost-effective orders. Additionally, admixtures must be used within 24 to 48 hours – premixtures can be utilized up to two years or more. This enhances the hospital's ability to manage stocks and increases patient treatment options on-hand.

### CDMO SELECTION FOR PARENTERAL DRUG PRODUCTS

Deciding between admixture and premixed IV solutions is dependent on the intended use of the drug product and most importantly, how each form will aid patients, with an emphasis on safety. Administrators must also consider the level of efficiency and convenience associated with each; the pros and cons of either is a deciding factor when developing and manufacturing parenterals.

It is both complex and costly to advance a parenteral drug product. In order to achieve success in this area, a range of specific requirements must be met. This includes expertise, resources, technology, market knowledge, a highly sterile environment and automated facility as well as aseptic manufacturing conditions. In order to reap the benefits of manufacturing parenterals without assuming the majority of the risk, sponsors are tasking specialized contract research and development organizations (CDMOs) with switching drug product from in-vial admixture to a premixed IV bag.

CDMOs have experience meeting regulatory specifics worldwide, are versed in parenterals throughout the product lifecycle and can provide strategic advice needed to go to market. Sponsors are engaging in the outsource trend, preferring to work with an organization that is equipped to take the product from start to finish. CDMOs with this capacity can take a parenteral into the commercial market from development. As innovations in delivery – exemplified by premixed bags – arise to meet the growing interest, selecting a CDMO is often the most economical and informed decision that a sponsor driven by growth can take. **P**

## → ABOUT THE AUTHOR



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**Marga** holds a Degree in Pharmacy and an MBA in Pharmaceutical Management from the University of Barcelona. With more than fifteen years of sales and marketing experience in the pharmaceutical industry and healthcare business, including Anesthesia, Interventional Cardiology and Neuroradiology, producing and implementing marketing plans for international and domestic markets, Marga has been in the field of strategic marketing for contract manufacturing parenteral solutions on an international level for the past seven years.

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