# Understanding the Multiple Factors Impacting Shortages of Parenteral Opioid Solutions for Healthcare Facilities

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## SUMMARY

Within the last 3 years, a persistent and worsening situation has developed with respect to the supply and the cost of parenteral opioid solutions utilized in current clinical practice for the delivery of acute and non-acute pain management in post-operative, skilled nursing and other care settings. To properly place this shortage in perspective, it is critical to understand the multitude of factors that have come into play to create the current market supply conditions at what many would classify a crisis level. One potential solution for some patients may be oral pain medications in lieu of parenteral opioids for postoperative pain management. New trends in multimodal pain management and expedited recovery after surgery protocols are focused on oral pain medications in preference to parenteral opioids. New technology as an oral Patient Controlled Analgesia (PCA) system provides patient centered pain management and robust databases for compliance with regulatory standards.

## SECTION I
## Regulatory Factors Impacting Demand for IV Solutions

Over the past 5 years, and co-incident with the changes in patient census that occur during flu season, all distributors, IDN's and individual hospitals have experienced increased patient admissions necessitating a greater demand for IV solutions. In similar fashion, growth in stand-alone outpatient surgery centers performing surgeries outside of traditional acute care hospitals has also impacted the IV solution demand. Recent hurricanes in Texas, Florida and Puerto Rico have led to increased admissions for victims of these natural disasters.

At the same time, due to an increase in the number of complaints received by the Food and Drug Administration (FDA) about the quality of IV solutions, the FDA has increased vigilance on the major IV solution providers in the USA (Baxter, Hospira and B Braun Medical), with increased frequency of inspections of the facilities, the issuance of citations indicating quality deficiencies needing remediation, and in some cases, warning letters which threaten to shut down production in multiple facilities. In the case of one provider, repetitive issues have necessitated closure of its main IV solution production plant in the USA to perform necessary maintenance and make costly upgrades to production equipment. This has led to shortages of critical Saline, Dextrose and lactated

Ringer's solutions essential in many therapeutic categories and across wide clinical usage. These production issues are expected to impact the market for more than a year.

Recently, Baxter's production facilities in Puerto Rico were brought down for a period of time due to Hurricane Irma, with those facilities experiencing significant damage and a lack of power to the island. Baxter responded expediently with repairs and installation of temporary power at the plants in an attempt to bring production totals up, but output is still not at pre-hurricane levels. Of particular note is an acute shortage of mini-bags essential to the preparation of parenteral opioid solutions for PCA.

An examination of complaints relating to manufacturing includes the presence of foreign matter in IV containers, contaminant particulates and leaking bags rendering these solutions non-sterile that have led to required changes in cleaning procedures, equipment maintenance and in some cases, outright needs to stop production completely to upgrade line equipment and capability.

One of the most significant impacts to all suppliers has been a demand by FDA to increase the holding time of finished products at the facilities. What this means is that completed products are now required to sit at the production site under controlled storage awaiting aging testing for quality issues. This leads to:
(1) Holds in shipping product to contracted customers with high demand for IV solutions. One-week holds have extended in some cases to 6 week holds.
(2) In select cases, slowdowns in current production due to too much product held in storage, further impacting supply. Storage locations are also FDA regulated.
(3) Stored product in some cases found to have quality issues over longer periods, further impacting the flow of product to customers.

It is not expected that the oversight of the FDA will abate at any time soon. Pushing production outputs in relatively older solution production facilities can lead to more non-conforming lots of product that are rejected and cannot be shipped. As facilities reach capacity, they also require more frequent maintenance and cleaning shutdowns.

Therefore, many Group Purchasing Organizations, Integrated Delivery Systems, and individual hospitals have needed to source IV solutions from multiple suppliers in the hope of meeting demand. In the case that one or two suppliers are short of certain volumes of solutions, this creates severe clinical impacts such as delaying elective surgeries and rationing IV solutions over long periods of time.

## Resulting Parenteral Opioid Shortages

Why would this impact Parenteral Opioid Solutions? Due to pharmacy regulations, The Joint Commission requirements and state pharmacy requirements, most IV opioid solutions are formulated in 50 ml and 100 ml mini-bags only to limit the total amount of opioid in the container: for instance, the standard mini-bag preparation of IV morphine for PCA is a concentration of 1 mg/milliliter of morphine delivery; 50 ml bags contain 50 mg of morphine and 100 ml bags contain 100 mg of morphine in solution. In addition, the lock boxes that secure IV PCA bags for administration can only accommodate these sizes under lock for safety. In some practice environments, 250 ml bags may be formulated for chronic care or palliative care patients but subject to practice decisions in facilities by Pharmacy and Therapeutics committees.

A shortage of 50 ml and 100 ml mini-bags needed to formulate IV PCA solutions has had a profound impact on pharmacy departments, who have struggled to manage patients on equivalent dosing conversions to oral formulations. Stock opioid solutions available to formulate bags have risen in cost markedly in the past year.

## Regulatory Factors Impacting Suppliers of Stock Opioid Solutions

In similar fashion to the oversight of IV solution suppliers by FDA, a cumulative effect on supply has also resulted from FDA regulatory actions on IV opioid solution providers. Many generic opioid solutions, nominally sourced from U.S. companies are, in fact, manufactured abroad notably in India. Indian-based generic drug providers have recently been under intense scrutiny due to citations of violations and consent decrees causing production shutdowns for extended periods of times. Resulting cutbacks in drug suppliers for periods over a year has placed increasing demands on remaining suppliers to increase production to their limits. Pfizer does not expect to return to full production of its supplies of opioid solutions until 2019. Of note is the fact that the startup cost to bring up a new plant to manufacture controlled substances is extremely difficult due to the very stringent regulations governing such facilities.

Another critical factor impacting market supply is the long-standing issue of tight control of raw material imposed by the DEA on manufacturers. This requirement has been in place for many years in an attempt to reduce or limit the amount of highly addictive drugs, notably opioids, that make their way to addicts. Recently, a consortium of care organizations, including the American Society of Anesthesiologists, The Institute for Safe Medical Practices, The American Society of Clinical Oncologists and the American Society of Healthcare Pharmacists wrote to the Commissioner of the DEA requesting a relaxation of the imposed limits due to the potential need to cancel essential surgeries and to deny pain management to chronic cancer patients.

## Limitations on the Manufacturing Yields of Mini-Bags and Changing Customer Demands Environmentally friendly IV solution containers.

For a very long time, the standard material used in the manufacturing of the majority of IV bags has been Polyvinyl Chloride (PVC). PVC material is amenable to sealing processes for the bags that are low cost and highly effective. A growing concern about both the cost of disposal of PVC bags and the fact that with the administration of certain drugs, a common plasticizer linked to newborn toxicity and other negative impacts on patients, DEHP (diethylhexyl-phthalate), has caused a mass shift in the marketplace demanding more environmentally friendly and safer polymers to produce IV bags.

Combustion of PVC releases toxic chlorinated hydrocarbons prohibited under the Clean Air Act and therefore requires incineration of the bags under sophisticated facilities. This cost is significant for hospitals that must dispose of medical waste on a weekly or monthly basis in the level of thousands of pounds of waste. Alternative forms of polymers for bags which are DEHP-free and "landfill" friendly have lower production yields, are more expensive to produce and in some cases, are much less durable during storage and usage, which may require overwraps to the bag and increased costs. Baxter, Hospira and B Braun have all released new polymeric bags in response to this market shift. These bags are more expensive, and supply is still scaling up.

More notably, many 50 and 100 ml mini-bags are opaque and are made from a class of polyolefins that have relatively low production yields as raw materials. This has compounded the limitations on mini-bags and the increased cost of those bags designed to formulate the final IV PCA solutions needed by patients.

In summary, a plentitude of factors occurring simultaneously in the market based on regulatory actions, needs to strongly ramp up production due to demands during seasonal periods, quality issues and/or embargoes on foreign production of generic opioid solutions and low yields of polymers used to produce mini-bags have all served to compound the duration and severity of shortage of parenteral opioid solutions.

To illustrate the end customer impact to pharmacies, one chief pharmacist has detailed a cost increase of 300% on bulk opioid drug solutions over a one-year period. It is expected that this will continue for at least several years.

## SECTION II
## A Solution to the U.S. Parenteral Opioid Drug Shortages

The discussion above portends a long duration of parenteral opioid drug shortages in the future. Recent pain management trends for surgical patients are timely since they provide other approaches for pain management without the need for parenteral opioids for many surgical patients (see Conley, 2018).

Multimodal pain management for surgical patients is now preferred as the optimum approach for postoperative pain management (Apfelbaum, et al., 2012; Parvizi & Bloomfield, 2013). This approach first emphasizes anesthesia methods to block pain signals to the brain e.g. peripheral nerve blocks, local wound infiltration with slow release anesthetics and epidural nerve blocks. With these anesthesia techniques, parenteral opioids are often unnecessary as they are being replaced with combinations of oral pain medications using different drugs with different pain blocking abilities. A typical multimodal pathway may deploy oral scheduled acetaminophen, a non-steroidal antiinflammatory drug (NSAID) and a nonconvulsant oral medication shown to reduce post-operative pain. In addition, an as needed oral opioid is provided to complete the pain management regimen. Recent recommendations for surgical patients from multiple national pain control groups recommends oral over parenteral pain medications for patients who can take oral medications (Chou, et al., 2016).

The oral PCA system called the MOD® for Medication On Demand is gaining adoption for use in multimodal pain pathways. The benefit of this PCA is the ability to provide smaller doses of opioids or NSAIDs more frequently to achieve better pain control and enable patients to control their own PRN oral medication administration while concurrently saving nursing time for the PRN delivery process. The MOD oral PCA is becoming the evidenced based approach for the delivery of PRN oral pain medication (Rosati et al, 2007; Lambert & Cata, 2014; Pizzi, Bates, Vulakovich & Chelly, 2017).

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