

# Syringe Solutions for Generic Drugs

Danielle Labreche of Laboratoire AGUETTANT explains how inefficient drug delivery technology can cause serious safety issues in hospitals, and gives examples of innovations that can help

In the early 90s, the generic industry's mission was to provide at patent expiry the same drug, in the same pharmaceutical form and dosage, and the same presentation as a branded medicine, yet at a more affordable price. But ferocious competition fuelled by the size of the market opportunity and low barriers to entry into a non-differentiated market, rapidly forced companies to seek strategies to capture, grow and retain their market positions and profits.

Initially, companies tried to sustain the price war by introducing concepts such as ultra-generic, branded generic and added value generic. They have also differentiated their services. More recently, we have witnessed patent battles challenging their validity. We will see more brand and generic companies negotiating early entry into the market together to reduce endless court action and the associated waste of time and money. In every case, however, after patent dissolution or negotiated entry, the market becomes open to all. Aside from a few months gained by the first to launch, eventually each player gets a fair chance to compete.

## THE GENERIC EFFECT

Let us look again at the strategy consisting of launching added value generic drugs. For the community and in the industry it seems a win-win strategy as it answers unmet customer needs while providing the vendor with a valuable differentiation. The race for improved quality encouraged by free competition raises the level of a nation's patient healthcare system. However, for an organisation this might not be enough to guarantee long term favourable returns, especially if the benefits are easily copied. So how is it possible to sustain valued differentiation?

One answer is through innovation and patent protection. The large pharmaceutical companies took this direction more than half a century ago with patent filing, extensions and data protection to auto-finance appropriate level of R&D funding for the future while limiting competition. The generic industry can do the same, in a similar quest. We have to agree that innovation will be successful if it resolves true problems or meets unsatisfied customer needs.

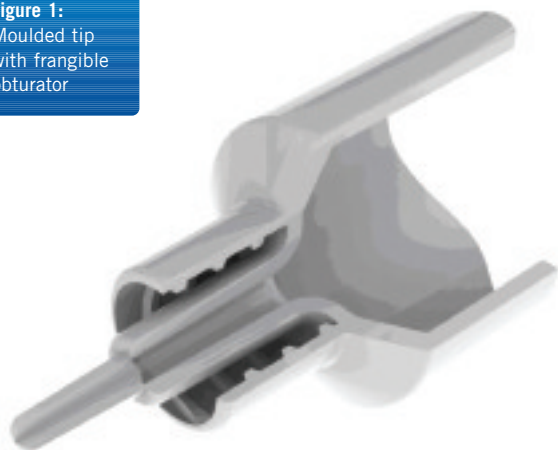
Innovation requires time – time to listen to groups of patients, as well as to healthcare professionals, from general practitioners to specialists, key opinion leaders, pharmacists, health authorities and other key stakeholders. Innovation requires appropriate organisation, processes and mindset; in other words, the basis to develop capacity to generate, evaluate and transform ideas into projects, and ultimately the launch of products. So how can a product be innovative and generic simultaneously?

As an example, if we admit that the innovative pharmaceutical companies have raced to launch new chemical entities to cure and improve therapies, it is not entirely true that molecules are all commercialised in a ready-to-use form, creating a potential for further development. This is the case in the hospital sector, as managers of public and private clinics are facing critical issues often associated with injectible drug delivery, such as nosocomial infections, injuries to medical staff, blood exposure, medication errors, waste management and cost-cutting exercises. To demonstrate the level of concern, and what would be of alarm to the public, here are some key results of recent publications.

## Nosocomial Risks and Costs

In February 2010 a study revealed the impact of infection contamination during operations in hospitals (1). This study analysed 69 million patients' dossiers from 40 states, who were hospitalised between 1998 and 2006. The study confirmed that the most commonly contracted infections during hospitalisation – pneumonia and sepsis – are the cause of 48,000 deaths per year in the US. The researchers commented that "These infections are most of the time avoidable and originate from sterilisation problems during surgery". Additional costs related to prolonged hospitalisation due to nosocomial infections have reached €6 billion (£5 billion) in 2006 alone. This is a real social challenge.

**Figure 1:**  
Moulded tip  
with frangible  
obturator



**Figure 2:**  
Protective cap  
(blue part)



#### Medication Errors

The French health authorities reported in 2005 that there could be as many as 190,000 avoidable severe adverse effect events each year (2). These events have the potential to cause death, induce a handicap or prolong the hospitalisation. Data from other countries confirms the size of the issue.

In 2009, The French Health Authority (AFSSAPS) published a report on medication errors, based on four years of operation of the Guichet des Erreurs Médicamenteuses, an adverse effect events reporting entity (3). According to this study, the most common errors involve drugs (42 per cent), dilution (28 per cent), dosage (seven per cent) and route of delivery (six per cent). The sources for such errors are attributable to 'look-alike' packaging (39 per cent), medical procedure errors (27 per cent), use error (12 per cent) and missing information (10 per cent). It is clear from these figures that medication errors have a dramatic social and economic impact.

#### Medical Staff Accidents and Risks of Blood Contamination

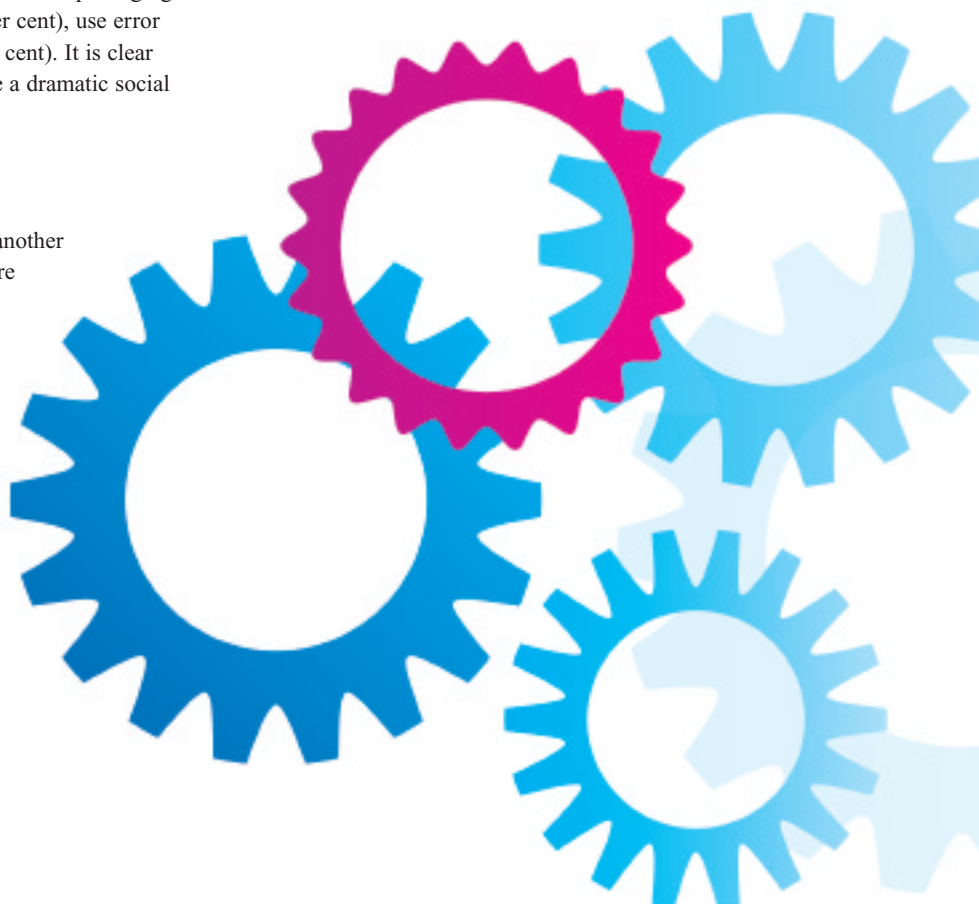
Another study demonstrated that injuries are another concern for nursing staff. The conclusions were that the most common accidents originate from needles (74 per cent), projectiles (14 per cent) and cuts (10 per cent) (4). The materials causing concern were needles, syringes and injector pens. The report also demonstrated that these events occur during injection (19 per cent), infusion (10 per cent), surgery (nine per cent) and waste transportation (five per cent). Although no evaluation of the associated costs was performed, we can assume that they were the cause of a great deal of stress for the concerned staff, plus inevitably create a cost for prevention, and a cure when required.

#### Environment, Waste Management and Costs

Environmental concerns, and waste reduction in a cost-contained environment are also areas of concern for the hospital, and where improvements from the industry are still expected.

#### PLASTIC PRE-FILLED SYRINGE (PFS)

Why develop a new PFS? Up until now, pre-filled syringes have been designed and commercialised globally in various shapes, sizes and materials. Plastic syringes give a true benefit over glass as they provide improved robustness against breakage and better ergonomics, while delivering an adequate stability performance level of water/gas permeability as well as extractable/leachable.



**Figure 3:**  
Opening of  
the syringe



In the industry, standard empty glass and plastic syringes are proposed in a ready-to-fill format, arranged in nest, pre-siliconised and pre-sterilised. It is true that the main advantage of the 'nest' manufacturing process over 'bulk' lies in its flexibility for development, and multiple format production independent of the volume produced. However, these nested pre-fillable syringes

(in glass or plastic) and the associated manufacturing equipment still remain cost prohibitive for most inexpensive generic emergency drugs, whereas pre-filled syringes are highly anticipated by health professionals.

With this in mind, a new generation of polypropylene pre-filled syringes is clearly necessary, with the intention of improving safety and quality of care at an acceptable cost for the market. The ideal syringe can be produced in bulk very easily, and can be sterilised terminally with steam in a peelable blister pack. In addition, we should also consider as examples two newly-patented design innovations that have recently come into use, which can provide real enhancement of function and efficiency.

#### A Simple and Secured Opening System

The design of the opening system is critical to the overall efficacy of any PFS system. In the following example, the syringe is sealed at its end by a frangible obturator which is injection moulded in one embodiment with the barrel of the syringe (see Figure 1). The frangible obturator itself is covered by a protective cap (see Figure 2).

A simple rotation of the protective cap breaks the frangible obturator and opens the tip of the syringe. After opening and



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## A PFS is admittedly more expensive than an ampoule, but the savings per patient provided by design innovations have been estimated at more than €0.5 per patient. And that is not counting the benefits from the reduced preparation time, reduced medication errors with pre-dilution and reduced nosocomial risks with a sterile closed system and ready-to-use design.

removal of the protective cap, a Luer Lock male connector at the end of the syringe allows a secured connection with any transfer set, catheter or any other compatible female port for a needle-free delivery or reconstitution device (see Figure 3, page 33).

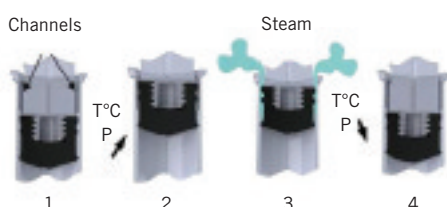
This concept offers several advantages:

- Closure integrity: the integrity of the syringe at the tip end is guaranteed by design
- Reduction of leachables: the plunger stopper and the barrel of the syringe are the only two components in contact with the product; the protective cap is not. The risk of interactions between the container and the solution is reduced
- Sterility of the connector: the sterility of the solution and the external surface of the syringe is guaranteed through a terminal sterilisation process. The Luer connector is not in contact with the cap and consequently the sterilisation efficiency is enhanced
- Convenience and security of use: the opening system is simple and fast without any risk of manual contact with the Luer Lock connector and thus no risks of user-generated contamination of this critical area. These features have a special importance in emergency situations. Tamper-evidence is also provided by this opening system and pre-perforated labelling

### IMPROVEMENT OF THE STOPPER STERILISATION EFFICIENCY

We should also consider an innovative concept to improve the sterilisation efficiency by vapour of the annular chambers created between the barrel and the stopper sealing lips. The plastic barrel of the syringe which is injection moulded is provided with two channels leading to the open end of the syringe. When the stopper is inserted into the syringe after filling, it is placed below these two channels (see Figure 4.1). As the temperature and pressure increase during the sterilisation process, the plunger is pushed back up to a backstop annular bead that prevents the plunger from being ejected from the syringe (Figure 4.2). At this step the channels in the syringe barrel create a passage for the vapour between the lips of the stopper (Figure 4.3). During cooling, the temperature and pressure decrease in the syringe, and the stopper reinitiates its position below the channels, ensuring a perfect

Figure 4: Stopper terminal sterilisation by moist heat



sterile barrier (Figure 4.4). This concept improves sterilisation efficiency in a critical area which may be important for heat-sensitive drugs, as the stability would detrimentally be affected by an excessive sterilisation time.

A PFS is admittedly more expensive than an ampoule, but the savings per patient provided by design innovations have been estimated at more than €0.5 per patient (5). And that is not counting the benefits from the reduced preparation time, reduced medication errors with pre-dilution and reduced nosocomial risks with a sterile closed system and ready-to-use design.

### CONCLUSION

These examples are a good demonstration of successful innovations arising from the generic industry. It is clear that innovation is highly anticipated in areas where the generic is predominant. By creating new technologies such as these, the generic industry can contribute to resolving critical issues of the healthcare system, while creating for itself product differentiation and economic value and growth.

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Danielle Labreche graduated from Hautes Etudes Commerciales (HEC) Montréal, Canada, and has worked for the last decade in the pharmaceutical industry in Paris. As the Business Development & Innovation Director at Laboratoire AGUETTANT, she is responsible for the innovation process for new product development and is in charge of the licensing activities of proprietary dossiers and patented delivery devices.  
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