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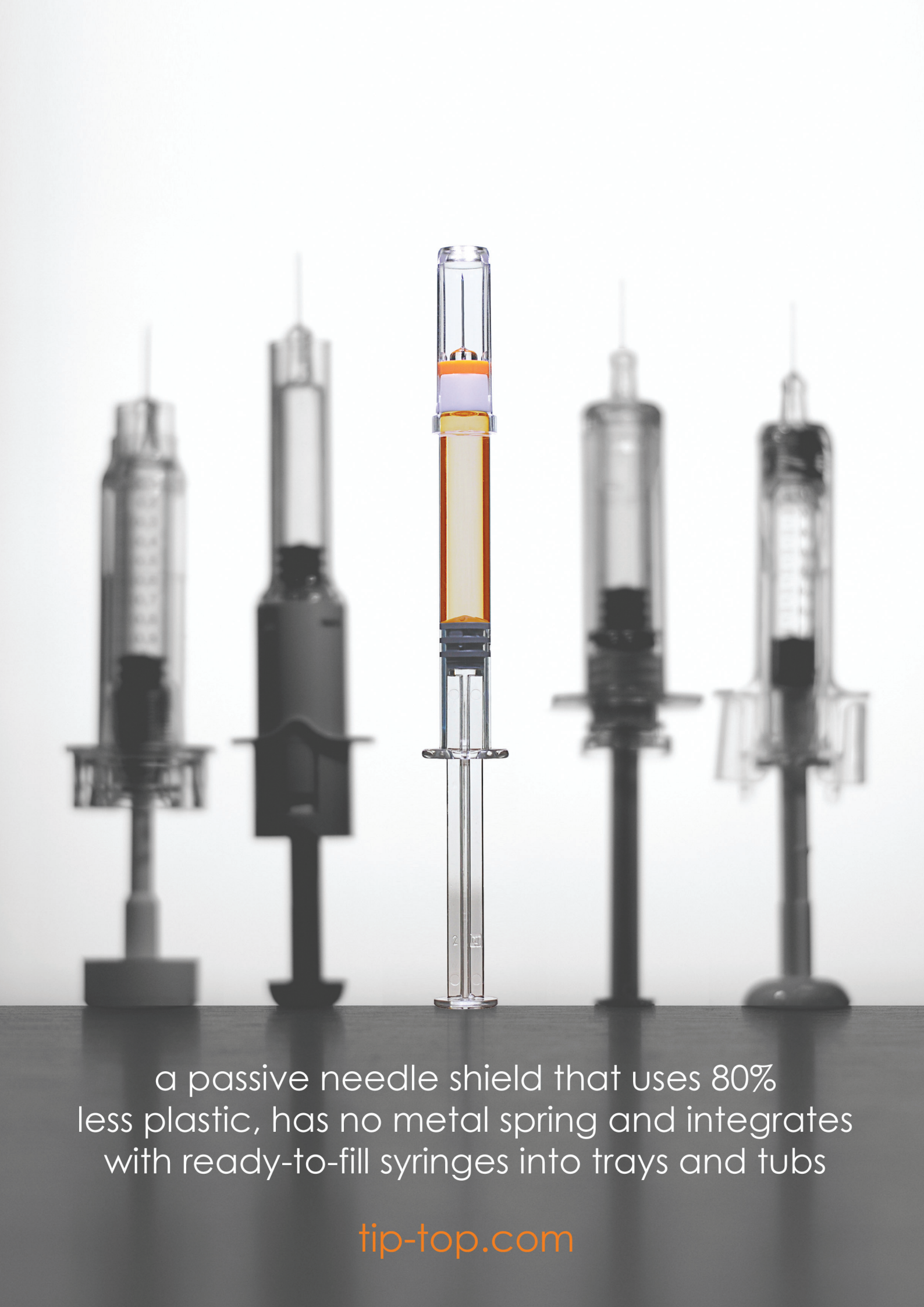
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USABILITY IN INJECTABLE DRUG DELIVERY

In this paper, Iain Simpson, PhD, Principal Consultant in Drug Delivery, and Kay Sinclair, Human Factors and Usability Expert, both of Sagentia, provide an overview of some of the applications of Human Factors Engineering for injection devices, issues that can affect their usage, and an overview of a process that Sagentia uses to ensure good practice and demonstrate compliance with IEC 62366.

Advanced injection devices such as auto-injectors and injector pens offer many benefits over conventional syringes, including ease of use, convenience and patient feedback, all of which can drive up compliance and improve clinical outcomes.

However, a number of injection devices recently entering the market have suffered from product recalls, some of which can be attributed to use errors. This has prompted regulators to demand evidence that usability issues have been identified and addressed throughout the development process and a number of standards have been published recently to help device developers meet regulatory requirements and provide practical guidance.

"A PROCESS THAT INTEGRATES HUMAN FACTORS ENGINEERING THROUGHOUT THE DEVELOPMENT CYCLE CAN ADDRESS BASIC SAFETY ISSUES AS WELL AS RESULTING IN A MORE DESIRABLE PRODUCT THAT CAN DRIVE COMPLIANCE."

One of the primary standards is IEC 62366, which sets out a process to explore and validate usability throughout development. The US FDA now expects companies developing drug delivery devices to follow these standards or at least demonstrate an equivalent approach.

The emphasis of these standards is primarily related to addressing safety through elimination of use errors that affect device safety, rather than focusing on other aspects of device design that might, for example, improve product appeal. However, in addressing safety, desirability should also be considered as a key aspect of usability. Addressing the softer issues of design may also drive improvements in patient motivation to use and subsequent compliance, hence supporting one of the commercial drivers for adopting advanced injection devices.

By using the right combination of techniques and skill sets, it is possible to develop a process that integrates human factors engineering (HFE) throughout the development cycle so that basic safety issues are addressed and you end up with a more desirable product that drives compliance.

APPLICATIONS FOR ADVANCED INJECTION TECHNOLOGY

Pen injectors have been available for the treatment of diabetes for around 30 years and have now achieved 90% market penetration in some European countries. For the latest generation of disposable devices, published data shows very low use error rates – in one study all 60 participants achieved 100% of the delivered dose specification for a total of 360 injections.[1] A recent study showed good usability (conformance with the correct operating procedure) for two of the leading pens, SoloSTAR (sanofi-aventis, Paris, France) and FlexPen (Novo Nordisk, Copenhagen, Denmark), with more than 90% of experienced users and 80% of pen-naïve users able to operate the pens correctly.[2]

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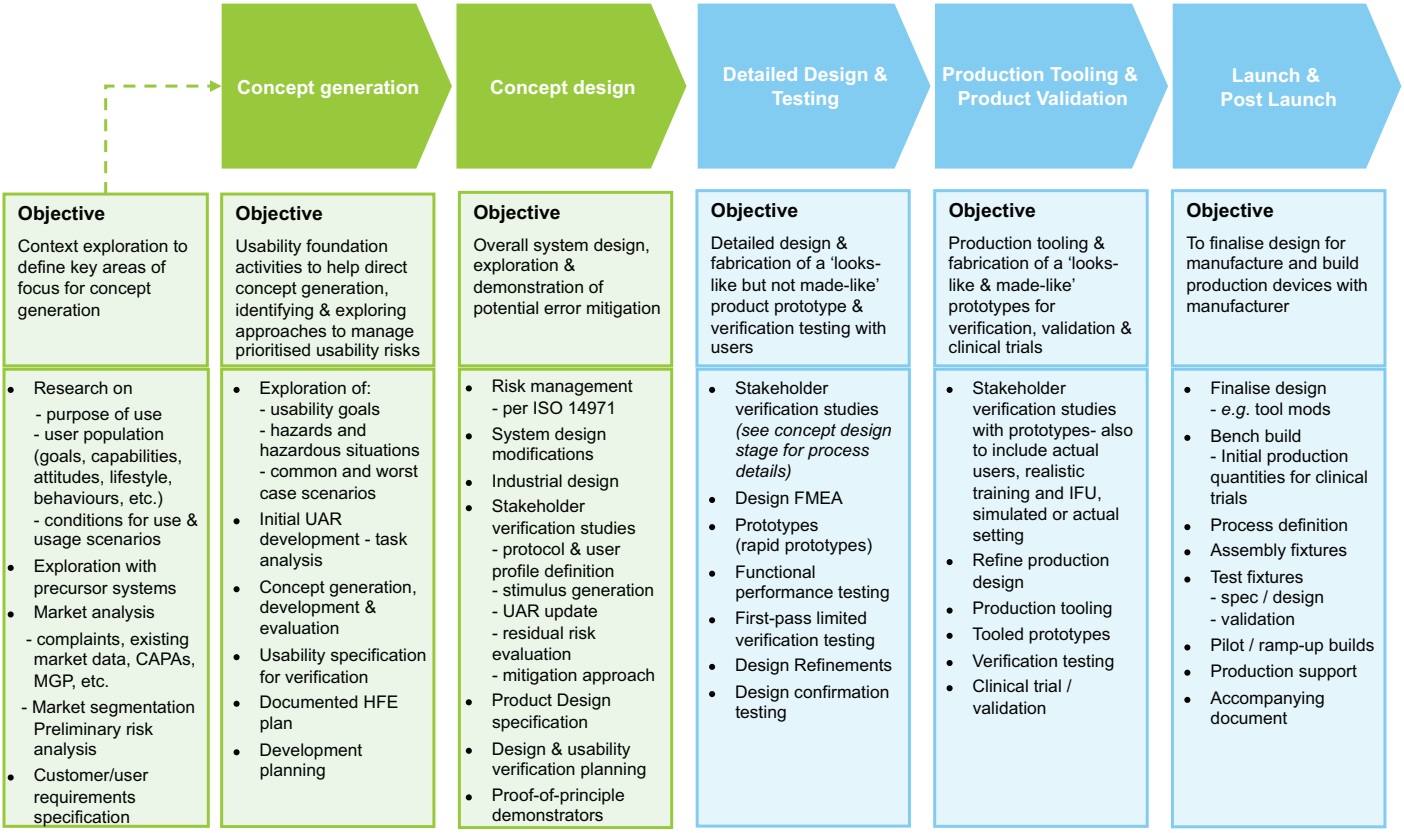

Figure 1: Integrating user research into the development process.

Treatment of acute anaphylaxis is generally administered using a single-use auto-injector but has the added complication that the user will only occasionally use the device and hence might be more prone to errors due to their inexperience of device use and also the urgency and stress of the usage scenario. A recent study of two of the leading epinephrine auto-injectors found that 0% and 12% of untrained users were able to use them correctly.[3]

Mathez *et al* reported that up to 16% of doctors tested in a user study in which they read the instructions for the Epipen® before attempting to self-inject with an Epipen® trainer device actually injected their thumbs because they held the device the wrong way round. [4]

Single-use auto-injectors are now also increasingly being used for the treatment of chronic diseases, such as rheumatoid arthritis. These devices no doubt offer usability benefits over conventional syringes and are generally easy to use with failure rates of less than 0.5% being reported. However, usability issues have been encountered with some of these devices which should be addressed in future design iterations.

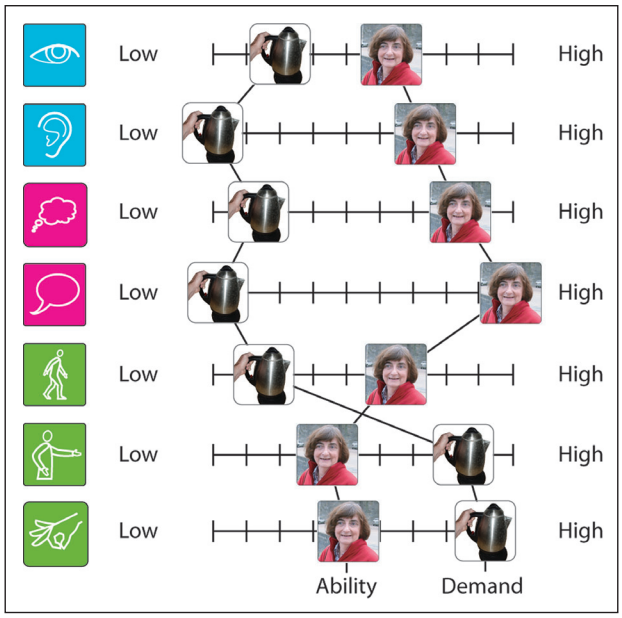

Figure 2: Seven capability categories are helpful to measure a person's capability, or assess the ability level that a device demands in order to use it. (Source: www.inclusivedesigntoolkit.com).

APPLYING HUMAN FACTORS ENGINEERING IN THE DEVELOPMENT OF INJECTION SYSTEMS

HFE should be a key but flexible part of the product development process. Figure 1 shows how HFE might fit into the overall development process for a device. The main principle for integrating usability into a product development programme is that the specific nature and objectives of each device are understood and addressed. Once the importance of usability is understood, the immediate question is around what methods and tools should be used to gain the appropriate insights.

USER PROFILING & CONTEXT EXPLORATION

Context exploration tools help define and understand the target user(s) and their use environments. This will involve task analysis and the exploration of use scenarios, potential user errors and hazards, based on the output of appropriate user research with precursor systems. Exploring capability, including the physical, cognitive and sensory boundaries of each user profile, should also be a key part of human factors testing.

USER PERSPECTIVE EXPLORATION

User study tools come in a number of different forms but the aim is to explore potential use errors and hazards, user preference and instinct, physical and cognitive demand, user performance and capability boundaries, for example. This should include a cross-section of all potential user types including patients, care givers and health professionals and should ideally be conducted in the real scenario of use or under appropriate simulated conditions.

Tools exist to allow human factors engineers to explore and understand how user capability will impact on usability. Capability can be

ID	User Task (TA)	ID	User Sub-task 1	Capability Type	Capability Demand	ID	Usability Targets
2.2	**Screw injector body and base together**	2.2.1	Orientate the body and the base for screwing together	Cognitive	Low	2.2.1. UTA	The user must be able to understand how to assemble the device by looking at it
		2.2.2	Assemble (screw together) the body and the base until reaches end stop	Cognitive Sensory Physical	Med High Med	2.2.2. UTA	User must be able to assemble the device correctly and easily

ID	Potential Use Error	Observed Use Error (document ID)	Actions Required	Action Owner	Action Status
2.2.1.1	The user cannot identify how to orientate the two parts for screwing together	4 users hesitated and reoriented the device before assembly	Visual indicators are required to assist users to orientate and understand the assembly process colour coding mating components, knurling to indicate rotation, etc.	JB /AS	In Progress
2.2.2.1	The user has sensory difficulty aligning the two parts	4 users hesitated and reoriented the device before assembly	Visual indicators are required to assist users to orientate the two parts - colour coding mating	JB /AS	In Progress
2.2.2.2	The user has physical difficulty aligning the two parts	6 users out of 15 needed to repeat the process to assemble the device correctly	The components must be of an appropriate size and form to hold and enable orientation for the target user profile	JB /AS	In Progress
2.2.2.3	The user has difficulty gripping one or both parts		The components must be of an appropriate size, form, material and texture to assist with gripping the parts (at the appropriate point on the components)	JB /AS	In Progress
2.2.2.4	The user has difficulty screwing the two parts together completely		The screw thread should not require more than one full turn	JB /AS	In Progress
2.2.2.5	The user doesn't screw the two parts together sufficiently	6 users out of 15 needed to repeat the process to assemble the device correctly	The device must provide sensory feedback to indicate when the rotation is complete	JB /AS	In Progress
2.2.2.6	The user screws injector body and base too tightly		The design should not require force to be applied to assemble Once the end stop is reached applying additional force should not make any difference to the users ability to disassemble the device	JB /AS	In Progress
2.2.2.7	The user assembles the device with crossed thread	4 users out of 15 initially cross threaded the two parts on first attempt	The thread design should prevent cross threading The thread design should provide feedback to the user if it is incorrectly threaded	JB /AS	In Progress
2.2.2.8	The user is not aware that	3 users out of 15 failed to	The device should provide	JB /AS	In Progress

Figure 3: Screenshot showing part of a Usability Action Record.

measured on seven different levels: vision, hearing, cognitive, communication, locomotion, reach & stretch and dexterity (see Figure 2). The importance of each level of capability will depend on the device that person is expected to use and their experience and confidence with like devices. Their ability to achieve the required level of capability determines the level of inclusion that can be attained.

Most drug delivery devices have to cater for a significant range of capability due to one device servicing all stages of disease progression. This leads to a significant challenge for the design, one solution for more mature device markets being a market segmentation and product platform approach.

JUSTIFICATION AND DOCUMENTATION

All US FDA documentation now needs to include a number of obligatory HFE documents and documentation of HFE activities. However, an explanation of the company's plan for managing and demonstrating possible and observed risk mitigation is one of the primary requirements.

One of the tools available to achieve this is the single document approach such as the Usability Tracker that we have developed, an example of which is shown in Figure 3.

This approach is driven by goals and tasks, documenting potential errors, implementation approaches and evidence of error mitigation and provides easy access to the relevant usability information both during the project and also at the approvals stage. Regardless of format, companies will need to justify their device decisions from the perspective of the user. Whereas the FDA may have once accepted a design goal that "80% of users must be able to open the device first time", they now want to know more about the 20% that couldn't – what they did, why they did it, and what is the resulting safety risk. A plan to mitigate or control expected or actual usage error will also be required.

"WHEREAS THE FDA MAY HAVE ONCE ACCEPTED A DESIGN GOAL THAT "80% OF USERS MUST BE ABLE TO OPEN THE DEVICE FIRST TIME", THEY NOW WANT TO KNOW MORE ABOUT THE 20% THAT COULDN'T – WHAT THEY DID, WHY THEY DID IT, AND WHAT IS THE RESULTING SAFETY RISK."

USABILITY TO ADDRESS COMPLIANCE AND EFFICACY

Product safety is a minimum requirement for any medical device, but even a safe product will be rendered ineffective if the intended users cannot operate it properly or choose not to use it. If the effective delivery of the drug depends on proper (not just safe) injection, then device developers must adopt inclusive design principles in order to gain a thorough understanding of the usage drivers and barriers. It is therefore important not to make assumptions about large patient groups.

A person's ability to operate an injection device will depend on his or her cognitive, sensory and motor skills: if a device intended for use by a patient population known to have poor grip requires a sharp twist to release an interlock, it is unlikely to be effective. Some auto-injectors require a user to press the device firmly against the skin before the actuation button can be pressed to deliver the drug. Although this is a sensible step to avoid the device being triggered when not in contact with a patient, the interaction between the needleshield and the button may result in user confusion. Also if the needleshield is too short it might be difficult to achieve enough force to move it when in contact with the patient.

Even if physiological factors don't prevent a patient from being capable of using a device, they may affect the performance of that device or the patient's motivation to use it.

A person's ability to remember to administer his or her drug is also an important factor to consider when designing a drug delivery device. It is crucial to find the right balance between reducing the burden on a patient's day-to-day life and making the treatment so unobtrusive that the patient could forget it altogether.

USABILITY TO BUILD BRAND LOYALTY AND PROMOTE USAGE

The powerful combination of good usability and design of a device can have an important

impact on consumer motivation and can be a key market differentiator for drugs in mature markets where the drug and formulation patents have expired. Not only can it impart brand loyalty amongst patients and subscribers, it can also have a major impact on user compliance and, therefore, clinical outcomes.

Rather than focusing on their own brand identity as a means of maintaining consumer loyalty, device manufacturers would do well to remove barriers to use by focusing on the lifestyles and preferences of their target users. By designing devices that blend in with a person's lifestyle and daily routine, the patient is less likely to be embarrassed, irritated or frustrated and hence reluctant to use it. For example, Figure 4 shows disposable insulin pens with a non-medical look to be more discreet, more desirable and easy to use.

Figure 4: Disposable insulin pens - a non medical look to be more discreet, more desirable and easy to use.

Market segmentation is therefore crucial: the leading diabetes pens have gone a long way to achieving this objective, whereas the size of many of the current single-use auto-injectors can be an issue if a patient needs to use it discreetly in a public setting.

Medical device manufacturers can learn from the consumer industry in this regard but must also pay due consideration to the impact that style and discretion could have on practicality and safety. As mentioned earlier in this article, for some auto-injectors it can be hard for a user to distinguish the needleshield at one end of the device from the actuation button resulting in them injecting their thumb by mistake, therefore sensible cues remain crucial within the realms of designing for improved aesthetics and social considerations.

SEIZING THE OPPORTUNITY

The importance of human factors is clear to see; not only is consideration at every stage of the product lifecycle now a regulatory requirement, but it is also good design practice. Ensuring a product's usability can be challenging because so many human factors interact and conflict with one another, but the challenge should also be viewed as an opportunity for pharmaceutical companies striving to prove comparative effectiveness.

Compliance is recognised as a big issue, impacting in real settings on the effectiveness of many drugs that showed good performance in controlled clinical studies. Although new drugs may help improve compliance by providing a more convenient usage regimen, they also incur high development costs and commercial risks as well as presenting possible patient risks from unexpected side effects.

Innovating around the improved use of existing drugs carries much lower R&D costs than developing new molecules and hence has gained increased interest within the industry in recent years. Considering that in many instances the immediate effects of a drug are less obvious to a user than their interaction with the device, it can be argued that one of the best ways to address compliance is through the improved design of devices. Developing injection devices that offer users improved safety and convenience but which also make users feel more in control of their diseases may well be an important direction forward for the industry.

"CONSIDERING THAT IN MANY INSTANCES THE IMMEDIATE EFFECTS OF A DRUG ARE LESS OBVIOUS TO A USER THAN THEIR INTERACTION WITH THE DEVICE, IT CAN BE ARGUED THAT ONE OF THE BEST WAYS TO ADDRESS COMPLIANCE IS THROUGH THE IMPROVED DESIGN OF DEVICES."

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ABOUT THE AUTHORS

Iain Simpson is a Principal Consultant in Drug Delivery at Sagentia, and has more than ten years' experience in drug delivery including technical due diligence and project management on inhaled and injectable delivery technology development programmes. He has a degree and PhD in Physics and an MBA in Technology Management. Outside drug delivery, Dr Simpson maintains a broad interest in R&D and the uptake of new technologies, and is a past chairman of the R&D Society.

Kay Sinclair is a human factors and usability expert at Sagentia and has more than 15 years' experience focusing on early-stage product and service development. Her expertise ranges from the diversity of customer understanding approaches and inclusive design to large scale advisory project management. She has a degree in Product Design Engineering from the University of Glasgow & Glasgow School of Art, and a Masters in Design, Manufacture and Management from Cambridge University.

A RIGID NEEDLE SHIELD FOR AUTO-INJECTORS

The growing use of prefilled syringes in injection devices has required the development of closures that both comply with existing devices and that facilitate the conception of upcoming platforms. Here, Stelmi describes how, capitalising on years of experience in the production of rigid needle shields for prefilled syringes, it has designed a specific rigid needle shield for injection devices.

Stelmi's Rigid Needle Shields (RNS) are the mechanical assembly of a soft needle shield in a polypropylene cover, combining the sealing properties of elastomer with the rigidity of polypropylene.

Developed at the end of the 1990's, Stelmi's RNS for prefilled syringes has had considerable success. In 2010, Stelmi launched an RNS specifically for auto-injectors, which incorporates the beneficial characterstics from the previous RNS for prefilled syringes.

Figure 1: The Rigid Needle Shield for Auto-Injectors.

CAPITALISING ON THE EXPERIENCE

The aim of developing an RNS for auto-injectors was to have an efficient component for auto-injection devices that could benefit from the performance of the existing RNS for prefilled syringes in terms of:

- Functional properties
- Mechanical properties
- Physical properties
- Chemical properties

Thus, the RNS for auto-injectors (shown in Figure 1) was made with the same materials as the RNS for prefilled syringes and benefits from the same main characteristics: the anti pop-off patented design as well as the harmonised elastomer formulation. The prefilled syringe RNS was described in the article: *"Stelmi Rigid Needle Shield: The Successful Concept with the Anti Pop-Off Patented Design"* (ONdrugDelivery, Prefilled Syringes: the Container of Choice for Today's Injectables, 2008, pp 14-16).

An anti pop-off patented design

One of the main features of Stelmi's RNS for prefilled syringes is the anti pop-off design. This patented design provides excellent stability of the RNS on the syringe during steam sterilisation.

Positioning of Stelmi's RNS is much more stable during and after the sterilisation cycle compared with that of a standard rigid or soft needle shield.

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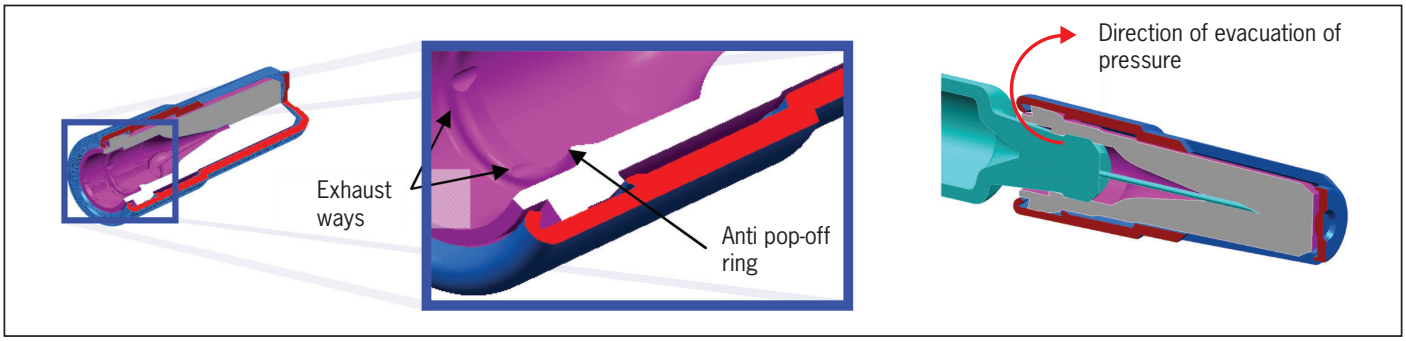


Figure 2: Diagram Showing the Patented Design with Exhaust Ways and an Anti Pop-Off Ring.

Figure 2 shows how the design functions, specifically:

- The anti pop-off ring prevents slipping and makes possible a better hold of the needle shield on the syringe.
- The four exhaust ways allow the overpressure to escape and thus play the role of a valve.

Optimised formulations

The rigid needle shield was originally developed with synthetic thermoset rubber as the soft part or the rigid needle shield. The major formulation used for needle shields on the market is Stelmi's latex-free formulation "4800GS" (characteristics summarised in Figure 3). Based on synthetic polyisoprene, this formulation has proven its substantial gas permeability and its optimal properties for needle guard functionality. It notably provides:

- High gas permeability for short sterilisation cycles which, associated with the windows of the rigid shell, allows efficient sterilisation either by steam or ethylene oxide.
- Optimised mechanical properties for resistance to coring by the sharp edge of the needle.

Another option is available in a more recently developed formulation made of ThermoPlastic Elastomer (TPE): formulation 8550NR.

NEW FUNCTIONALITIES: A QUALITY-BY-DESIGN APPROACH

The RNS for auto-injectors has been developed in collaboration with injection device manufacturers in order to provide a relevant solution compatible with most existing auto-injectors using RNS, and future projects.

The implementation of this solution is the result of a Global Design Verification, taking into account the whole design and its components (injection device, prefilled syringe and RNS) in order to be of benefit to injection device manufacturers, glass manufacturers, pharmaceutical companies and patients.

Formulation 4800GS	
Free from	Latex (Natural Rubber), Thiazoles (2McBT), Nitrosamines, Phthalates, Bisphenol A
BSE risk	Complies with "Note for Guidance on Minimising the Risk of transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products", EMEA/410/01 Rev.2 – October 2003
Non cytotoxic	Complies with USP <87>, USP <88>
Specifications	Complies with E.P. 3.2.9, USP <381>, ISO 8871

Figure 3: Table Summarising the Characteristics of Formulation 4800GS.

Based on a Quality-by-Design approach taking into account safety, ergonomics and the constraints of the production processes of pharmaceutical laboratories, the part has been optimised regarding primary functionalities, notably its removal.

As it is for the RNS for prefilled syringes, the RNS for auto-injectors is assembled in a way which makes it possible to obtain substantial solidarity between the two elements to avoid deshielding during the RNS removal. To ensure maximum quality and like Stelmi RNS for prefilled syringes, the ones for auto-injectors are 100% visually inspected.

However, new functionalities have been considered to adapt the RNS to the use in an auto-injection device. Indeed, the uncapping of the RNS in the auto-injector is done using a cap remover and has to be safe and easy for the patient. The two following forces have been taken into account (see Figure 4):

- The "pull-off force"/"removal force" between the RNS and the syringe.
- The "gripping force" between the cap remover and the RNS.

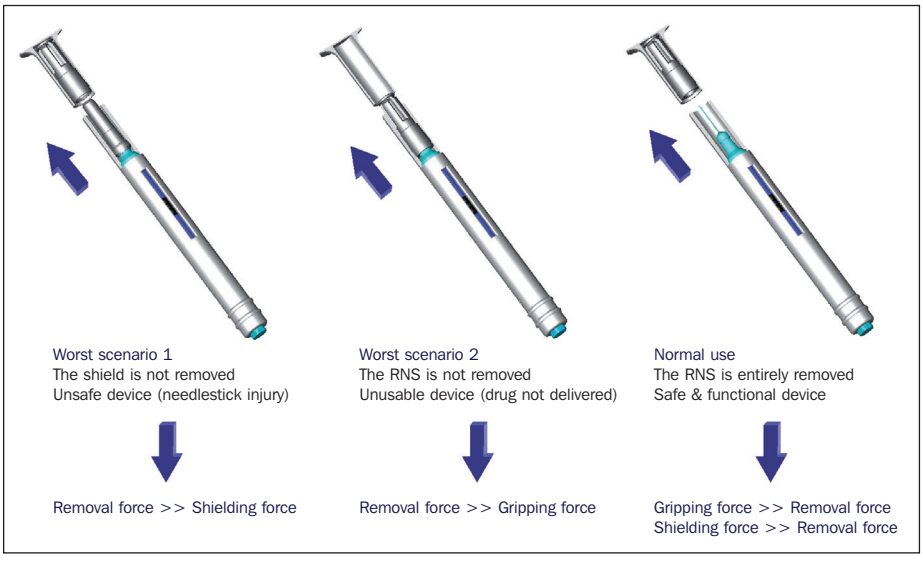


Figure 4: The Importance of Designing the RNS to have Correctly Balanced Forces to Ensure it is Properly Removed.

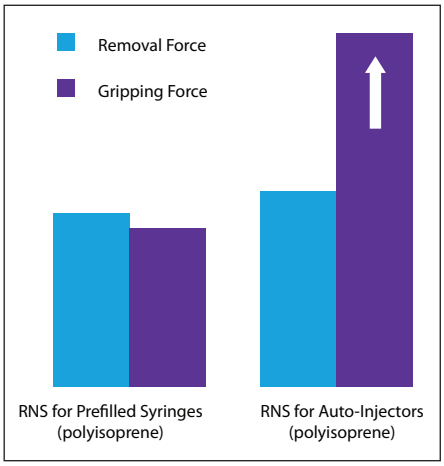


Figure 5: Disposable Auto-Injector Removal Force and Gripping Force Comparison After Steam Sterilisation Cycle.

"NEW FUNCTIONALITIES HAVE BEEN CONSIDERED TO ADAPT THE RNS FOR USE IN AN AUTO-INJECTOR DEVICE."

Figure 6: The RNS has been Designed to be Easily Gripped by the Cap Remover at the Bottom or at the Top (Circled Areas).

The Removal force

Compared with the RNS for prefilled syringes, the safety interval between the gripping and removal forces has been significantly increased as shown in the graphs in Figure 5.

Gripping the RNS

One of the major innovations in the RNS for auto-injectors lies in the fact that it offers new possibilities of gripping. The RNS has been designed for easier gripping by the cap remover at the bottom or at the top (see Figure 6).

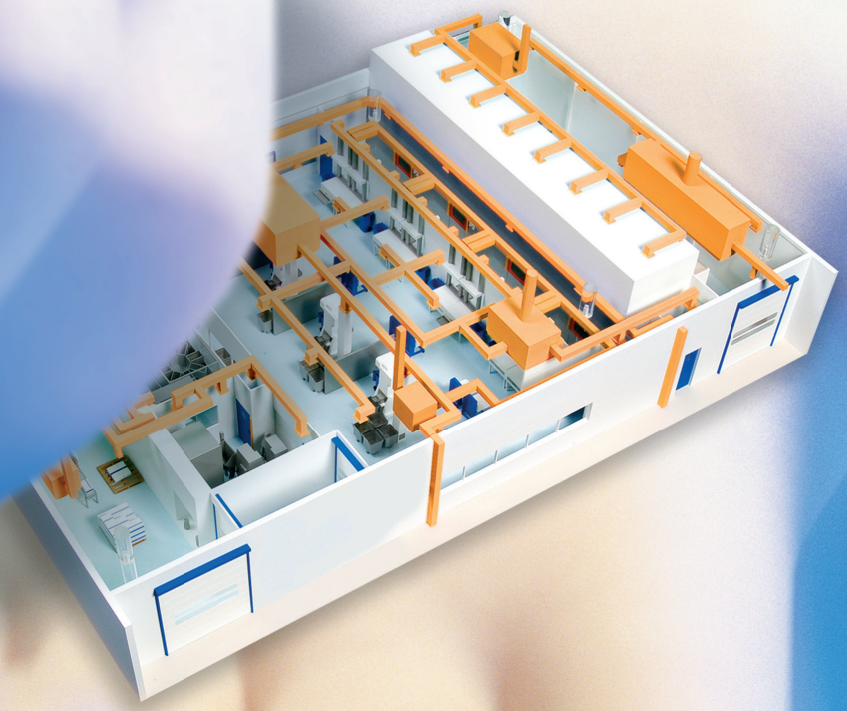
This solution has in fact led to a simplified cap remover design and reduction of its size.

CONCLUSION

As well as the functionality of its products and the considerations and requirements of the final users, Stelmi is always considering the production processes of its industry customers in order to provide them with as many advantages as possible. In this respect, the RNS for auto-injectors offers new and exciting perspectives for the development of devices that could be smaller, safer and more accurate. Moreover, the RNS for auto-injectors is suitable on the same filling and assembly lines as the RNS for prefilled syringes.

INNOVATION IS PROMISING

when it is cleaner,
safer and more efficient...



PREMIUMFILL
CONCEPT

STELMI new production concept to manufacture sterile stoppers
and sterile prefilled syringe components

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FUTURE INJECTION TECHNOLOGIES

THE REQUIREMENTS OF AN INJECTION DEVICE: A CLINICAL PERSPECTIVE

Here, Bob Sharp, BMBCh, FRCS, Medical Director, and Paul White, PhD, MBA, Chief Executive Officer, both of Future Injection Technologies, provide an analysis of drivers in the pharma and biotech sector affecting injectable delivery device development. Formulation characteristics such as increased viscosity and the impact on device design are also discussed together with likely future requirements of injection devices with a focus on prefilled-syringe-compatible auto-injectors.

The aim of all pharmaceutical treatments is to offer the patient optimum control of their condition with minimal side effects. Delivery devices need to facilitate optimum compliance and ease of administration and dosing via a route that is without pain or inconvenience for the patient. Ideally they should offer minimal administration at widely spaced time periods, and safety and reliability are essential. Devices also need to evolve to meet emerging market driven and regulatory requirements – many first-generation devices are not suitable for these emerging requirements.

MARKET DRIVERS OF DEVICE DEVELOPMENT

Biologics

Around two thirds of drugs in development are biologics and the optimum delivery route for many is subcutaneous or intramuscular injection with a target delivery volume of 1 ml or less. Delivery of high volumes by infusion is less than ideal as it is costly and clinical attendance by the patients inconvenient. Many formulations are highly viscous due to a high protein concentration in a small volume, and/or lyophilised. Biologics are driving a need for auto-injectors that can deliver high-viscosity and lyophilised formulations.

Improvement of existing drugs

Drug levels in the body of many first-generation injectable drugs rapidly decline due to rapid absorption or excretion. For chronic conditions, injections may be required several times a day, possibly for the lifetime of the patient leading to poor compliance, which itself leads to increased complications of the disease.

An emerging trend for exisiting therapeutics is the development of improvements that alter their physical and chemical characteristics to enhance efficacy, reduce frequency of administration and therefore increase patient compliance. This trend to make existing drugs better is being driven on the one hand by the success of some biologics and the opportunity to improve these therapies (known as "biobetters), and on the other hand by a general lack of productivity in the development of new therapies. The perception of a failure to develop new drugs is reinforced by big pharma's recent actions such as: cost cutting; the closure or often low-profile relocation of research facilities to lower-cost countries or those with more favourable tax domiciles; a focus on outsourcing drug development and in-licensing; and the creation of pharma's own venture funds.

Sustained release & increased drug half-life

The trend to improve existing drugs is being enabled by new technologies that increase drug half-life and reduce dosing frequency. Strategies include the use of microspheres, suspensions, liposomes, gels, lipophilic solutions, nano-particles and other biodegradable polymeric drug delivery systems. PEG and related technologies for increasing the circulating half-life of proteins are also available. Modified-release parenteral drug products that in general terms alter therapeutic release, absorption or metabolic breakdown are now available. As for biologics, these

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technologies create highly viscous and/or lyophilised formulations that, as mentioned, are ideally delivered sc or im in 1 ml volumes or less.

Whilst the effects on the pharmaceutical products of such delivery systems are beyond the scope of this article (*the next issue of ONdrugDelivery will focus on formulation aspects of injectable drug delivery*), in general terms drug designers need to make sure that such carriers allow a linear release profile, although in cases where intermittently raised concentrations are required, a pulsed profile might be preferred. Similarly the pharmaceuticals need to avoid the burst-release phenomenon whereby immediately after injection an excess amount of drug is made available and causes a peak in plasma concentrations. Similarly, drug carriers need to be stable, biodegradable, biocompatible and meet all safety requirements required by the patients and regulators.

EROSION OF ESTABLISHED INJECTABLE MARKETS

While the above factors are creating new opportunities for injectable drug delivery, certain market opportunities are diminishing with the development of new non-injectable routes of administration.

Oral formulations to replace injectable delivery

Oral administrations are now available with coatings and nanotechnologies that offer enhanced gastric and intestinal protection, whilst allowing enhanced release via an enteral route.

Inhaled delivery as an alternative to injection

Metered-dose inhalers similarly can provide administration of many pharmaceuticals via the respiratory epithelium, although there have been problems in recent history with the failure to administer proteins and small peptides successfully via this large membranous area due to the immune and physical rejection of the applied proteins.

Mucosal and transdermal technologies as an injection alternative

In mucosal and transdermal drug delivery, where systemic bioavailability of a drug is limited by its own permeability across the barrier, we have seen the evolution of simple drug patches that elute their drug across the membrane and microneedle arrays which offer micropenetration and may overcome the barrier problems seen with penetration of the stratum corneum by drugs formulated in simple patches.

Microneedle arrays are further developing with the use of pressure pumps (for example generated by the pressure of boiling liquids activated by body temperature), iontophoresis and phonophoresis pumps, and other similar devices that use the electrochemical characteristics of the pharmaceuticals or carriers to help penetrate the epidermis.

Implantation as an injection alternative

New implants are similarly in design and development and offer the possibility of micro-reservoirs or micro-electromechanical pump. In the case of diabetes, for example the ability to offer a synthetic pancreas would be the gold standard treatment for the patients, especially if one could combine an automated glucose monitoring system within the pump to offer a failsafe control of insulin release. Maintaining glucose levels within the normal range would have a dramatic effect on the complications of diabetes seen by most patients.

REDUCING DEVICE DEVELOPMENT COST AND RISK

Injection remains a low-cost and low-risk development route

Parenteral drug delivery by intravenous, sc or im injection offers a route of easy access to the systemic circulation without the first-pass metabolism that affects oral therapeutics. In addition, use of conventional syringes and needles for drug administration is low risk compared with the development of new delivery technologies such as needle-free injectors, micro-infusion pumps or reformulation for solid implantable dosage forms.

Whilst continuous intravenous infusion is used in many clinical situations, it ties the patient to a healthcare environment, is expensive and absorbs huge healthcare resources. An emerging trend is parenteral drug reformulation for injection via the sc or im routes to minimise the frequency, cost and inconvenience of injections.

Prefilled syringes

For the vast majority of parenteral injections, the market is rapidly changing towards prefilled syringes (PFS) as the benefits of increased safety, security, accurate dosing and anti-tampering and counterfeit protection provided by such devices have become widely recognised. An exponential rise in the use of PFS has been witnessed with a doubling of units sold every three to four years. Inevitably as PFSs become the accepted route, auto-injectors that can incorporate PFS are a natural market evolution.

Reducing device development risk and cost

A low-cost and faster route to market for a new device is to work with the existing drug packaging – that is, the PFS. Needle-free jet injectors and other non-needle dependent technologies may be a viable alternative for some drug categories but they require formulation of the pharmaceutical product at early stage to meet the delivery requirements. Why take this technology development risk when an auto-injector that incorporates existing needles and syringes and can deliver high viscosity and lyophilised formulations will meet your needs?

REGULATORY DRIVERS OF INJECTABLE DEVICE DEVELOPMENT

Needle safety

All devices now need to be needle safe, and emerging requirements are likely to stipulate that the needles need to be inside the main device at the start and end of the injection cycle. This regulation, which will make non-needle-safe devices obsolete, is driven by the approximately one million needle-stick injuries per year in the US and Europe.

COST DRIVERS OF INJECTABLE DEVICE DEVELOPMENT

Growth of auto-injectors incorporating PFS

Auto-injectors have been shown to reduce primary healthcare costs by as much as 95% as being able to send patients home to self-medicate offers huge clinical cost savings to healthcare providers. Patients, the regulators and healthcare providers are now demanding needle-safe auto-injectors. These proprietary auto-injectors also offer pharma companies a way of extending their product lifecycle where ease of delivery is a key market differentiator.

Given that the PFS has become an accepted format and because of the high cost of developing new non-standard needles and syringes it is inevitable that auto-injectors that can work with the exisiting PFS formats will dominate the market.

EMERGING TECHNICAL CHALLENGES

High viscosity injectable delivery

Many emerging new drugs products are viscous liquids and many show non-Newtonian characteristics during delivery – that is, under pressure, their viscosity increases further and they may even form gels, making them even more difficult to deliver. Patients want painless injections that administer drug as efficiently and painlessly as possible. As discussed, this means that formulations need to be concentrated to minimise the volume required, and delivered by high-quality, fine-gauge needles of a minimum of 25G and preferably 27G or 29G.

However, such physical requirements present challenges for delivery device manufacturers. Concentrating these drugs makes them viscous, and the application of sustained-release technlogy or PEGylation to these molecules increases the viscosity of the product still further.

Many existing devices will fail to deliver such highly viscous products safely and may result in failure of the primary container. Devices, such as Future Injection Technologies' SafeClick™ Visco, are therefore evolving to offer increased force of delivery while utilising existing PFS, allowing higher drug concentrations, lower volumes and a smaller diameter of needle.

DEVELOPMENT STAGE OF PRIMARY PACK SELECTION

Earlier selection of PFS/auto-injector combination

For new biologics drugs, it is becoming clear that the interactions between pharmaceutical products, components of the prefilled syringe and the needle are far more complex than those seen with simple aqueous drugs. The US FDA now holds databases of any interactions and there have been a few notable disasters, where change of, for example, the glue holding the needle to the syringe, or forming techniques in the manufacturing of the needle, have led to failures of batches of pharmaceuticals and regulatory involvement. This is leading to an earlier selection of the drug primary-pack in the development process. Identification at an early stage of a PFS/auto-injector pairing that is compatible with painless high viscosity delivery is important as having to change the PFS at a late stage in the development process can cause high-cost clinical delays and slow development to market.

LYOPHILISED FORMULATIONS

Other parenteral formulations are available, such as lyophilised preparations which require reconstitution with a solvent before injection. Dual-chamber cartridge systems are increasingly being used. Other methods of drug reconstitution involve multi-chamber transference techniques or simple injection of the solvent into the solute, but these is increasingly frowned upon in healthcare due to the risks of needle-stick injury, misdosing, contamination and incomplete or unsuccessful process. Devices are now evolving to allow reconstitution and injection from dual-chamber cartridges to avoid these problems.

CONSOLIDATION – THE DEVICE/FILL FINISH/PHARMA TRIUMVIRATE

Currently the trend is for fill-finish companies gradually to bring all processes under one roof to minimise the risks of a fault in production, such that the drugs will be entirely packaged within one line in a continual process rather than moving from plant to plant. Such logic has led some fill-finish companies to buy in their own drug delivery devices with the added advantage of offering pharma clients an entire solution to their development and fill-finish requirements from early stage drug development to production.

We now see a triangle forming between the pharmaceutical companies in one corner, the fill-finish and packaging companies in another and the drug delivery device organisations in the third. These parties and those associated with them need to work together from an early stage of drug delivery to minimise the risk of disaster at a later stage, which could result in the expense and loss of time of patent protection resulting from alterations required a late stage in any of the processes required to get the product to market. Early-stage co-operation between all parties will allow the drug delivery device companies to optimise the physical requirements of their devices to meet the requirements of the pharmaceutical product and optimise selection of the needle and syringe solution.

THE FUTURE – A REQUIREMENT FOR INCREASED VERSATILITY OF AUTO-INJECTOR PLATFORMS

As the pressures to reduce cost in the industry build, the days of a new auto-injector for every indication are over. Device design has moved to "platform design" and the platform for delivering injections needs to be scalable to incorporate any primary pack as well as requiring many features to meet the emerging demands of the market, regulators and patients.

These platforms that will incorporate existing needles and prefilled syringes will require the following technical features:

- Scalable to accept any "primary pack" (i.e. any needle and any syringe)
- Abilty for im and sc administration
- Ability to deliver high-viscosity drugs using existing syringes and via fine-gauge needles
- Option to work with non-siliconised syringes
- Excellent protection of the glass syringes from high "breakout" forces
- Full and automatic needle protection inside the device – no needle shields
- Fully automatic needle insertion and retraction
- Drug delivery only at the correct needle depth
- Lyophilised delivery using dual chamber cartridges
- Needle hidden from sight of user at all times
- Secondary safeties inherent in design – option but not necessity for a button
- Plunge activation option for musculoskeltally impaired e.g. rheumatoid patients
- A viewing window or visual indicator of administration
- Audible "clicks" on initiation and completion
- Low cost – i.e. only 6/7 plastic components, single split moulding
- Amenable for automated assembly

ABOUT THE AUTHORS

Both authors are employed by Future Injection Technologies Limited and are responsible for the development of FIT's SafeClick auto-injector platform developed for delivery of high viscosity, lyophilised and standard injectable formulations using existing pre-filled syringes.

Bob Sharp is the Medical Director of Future Injection Technologies. A Consultant Orthopaedic Surgeon at the Nuffield Hospital, Oxford, UK, he leads their departmental research team and has a special interest in rheumatological diseases. He has been widely published and his current roles include advising the UK National Institute for Health & Clinical Excellence (NICE) on modern technologies in his field, as well as being Medical Director of the UK Professional Jockeys' Association. Mr Sharp undertook his medical training at Cambridge University followed by Oxford University. He then completed his orthopaedic training on the Oxford Rotation before completing a Fellowship in Australia. He was awarded the Gold Medal by The Royal College of Surgeons of England for The Most Outstanding Achievement in the FRCS Trauma and Orthopaedics exam in 2000, and was awarded The President's Travelling Scholarship in 2001.

Paul Whyte is Chief Executive Officer of Future Injection Technologies. He has experience in commercial leadership roles spanning the pharmaceutical, academic and emerging technology environments, from partnering late-stage pharmaceutical products to exploiting innovative emerging products and technologies. Paul was responsible for leading the commercial development and partnering of therapeutic medicines at Evolutec PLC as Director of Business Development and prior to this for partnering the cancer and inflammatory therapies and therapeutic discovery platform at Avidex Ltd (now Medigene). He also spent several years at Cancer Research Technology (CRT) in a commercial role, and was instrumental in forming a joint venture company - Cancer Therapeutics Limited - with Antisoma PLC to develop a late-stage cancer therapy. He has an honours degree from Warwick University, a PhD in Immunology and an MBA.

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COMPANY PROFILE - BESPAK INJECTABLES

bespak Injectables

Bespak Injectables specialises in the design, development and manufacture of innovative devices for the delivery of injectable drugs. Designed to accommodate prefilled syringes, Bespak's disposable auto-injectors enable patients and other non-clinicians to easily undertake comfortable and safe injections in a convenient manner.

OTS™ AUTOINJECTOR - MEETING MARKET NEEDS

When Bespak Injectables set about developing an off-the-shelf delivery device to incorporate the most common syringe and needle configuration, its market research consistently identified three key needs.

The first was a high degree of flexibility, from both the product and its provider. Secondly, the new product would need to provide exceptional performance to succeed in an already competitive environment. Third, it was clear that pharmaceutical companies were looking to partner with an organisation that could demonstrate a solid track record of innovation and manufacturing success with drug delivery devices.

With the launch of OTS™ Autoinjector, Bespak has met these needs. By bringing together an established technology platform, a novel and flexible product embodiment and world-class manufacturing facilities, Bespak has created a market-ready device that is equally suited to meeting the low-volume needs of clinical trial work and the high volumes associated with commercially-successful drug products.

An OTS™ Autoinjector is shown in Figure 1.

OTS™ AUTOINJECTOR - FLEXIBILITY

- **Established technology.** OTS™ Autoinjector is based on Bespak's patented platform. With a fully automated injection process, the simple yet effective platform has already been customised across a number of design variants (see Figure 2).
- **Simplicity.** The simplicity of the platform allows the external geometry of OTS™ Autoinjector to be adapted and optimised swiftly, without the risks, costs and timescales commonly associated with device customisation programmes.
- **Responsiveness.** Bespak's willingness to incorporate and undertake product optimisation is integral to its service offering and is backed by fully resourced in-house design and engineering expertise.
- **Market-ready.** OTS™ Autoinjector can be supplied either "off-the-shelf" or quickly and easily tailored to address specific needs in relation to actuation mechanism, injection volume and external device geometry.
- **Supply volumes.** Bespak's manufacturing flexibility enables the company to supply OTS™ Autoinjector in volumes ranging from sample quantities to facilitate early-stage decision making, through to commercial supply.

OTS™ AUTOINJECTOR - PERFORMANCE

- **Industry standard.** OTS™ Autoinjector incorporates industry standard 1ml "long" prefilled syringes with ½-inch staked needles.
- **Simple, effective design.** OTS™ Autoinjector has one of the smallest component counts of any comparable product on the market. Clinicians and patients alike benefit from a device that is both robust and easy to use.
- **Choice of actuation.** Two-step "push" and three-step "button" actuation options make OTS™ Autoinjector ideal for a range of patient populations, for example where physical dexterity may be an issue.
- **Viscous liquids.** Bespak leads the field in the delivery of viscous formulations. Liquids up to 40 Cps can be routinely handled by OTS™ Autoinjector with a capability to deliver beyond this figure where necessary.

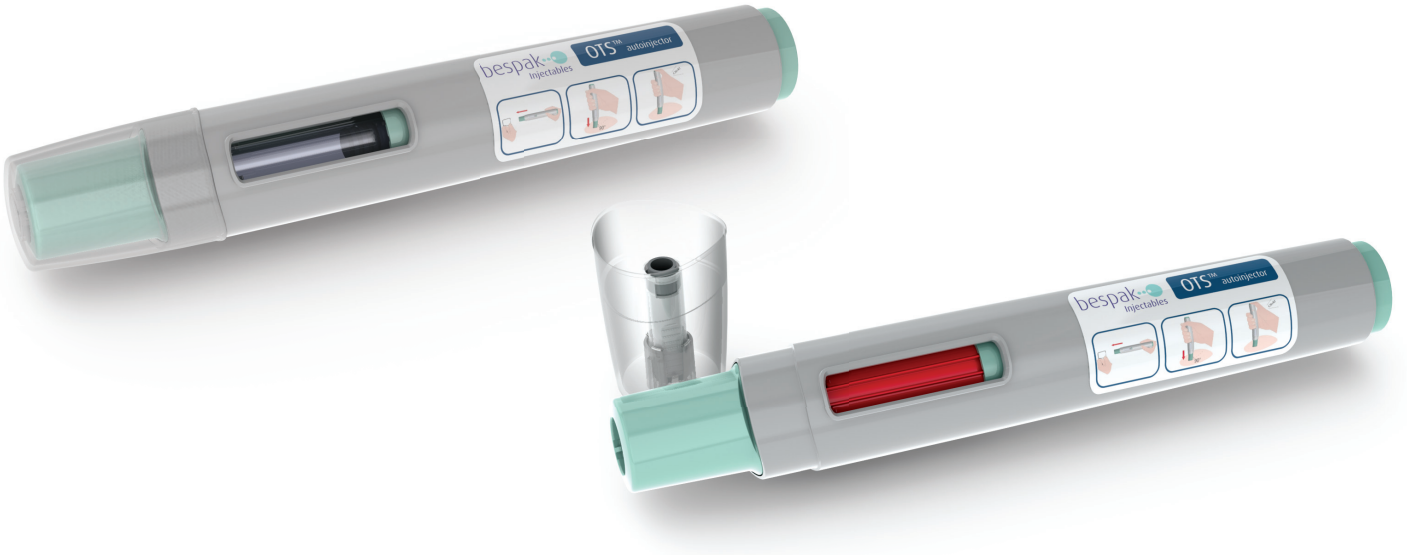

Figure 1: OTS™ Autoinjector - shown (left) before and (right) after use.

Figure 2: Examples of the OTS™ Autoinjector as an optimisable device.

ABOUT BESPAK INJECTABLES

Bespak, a Consort Medical company, is a leading global supplier of drug delivery devices for injectable and inhaled products. Headquartered in the UK and with representation in a number of key territories, the company was established in 1959 and today employs nearly 650 staff in the UK and overseas.

More than 500 million medical devices are manufactured by the company each year, supporting device programmes from pilot-scale to commercial supply. The company's solid manufacturing credentials are demonstrated by many long-established partnerships with leading pharmaceutical and biotechnology company clients, with a number of products successfully launched and marketed worldwide.

Bespak has experience with a wide range of technologies including inhalers, nasal, ophthalmic and diagnostic systems in addition to its injectors portfolio.

Bespak Injectables (formerly The Medical House) was acquired by Consort Medical PLC (Hemel Hempstead, Hertfordshire, UK) in 2009, and specialises in the design, development and supply of innovative devices for the delivery of injectable drug products. Bespak Injectables offers customised injection devices for specific applications, as well as off-the-shelf products. Its patented technology portfolio includes both auto-injectors and needle-free jet injectors.

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PATIENT COMPLIANCE SHAPING THE FUTURE OF DRUG DELIVERY

In this feature article, Fran DeGrazio, Vice-President, Marketing & Strategic Business Development, West Pharmaceutical Services, highlights how the pharmaceutical and biotech industry is paying ever closer attention to the issue of adherence to prescribed medicines, the increasing recognition that adherence impacts directly on drug safety and efficacy and that improved adherence leads to significant commercial as well as health benefits. Ms DeGrazio describes how drug delivery devices (and the natural continuum into primary and also secondary packaging), which are designed by considering carefully how the patient interacts with the product, can play a central role in increasing adherence.

The author would like to thank Amy Asselta and Diane Paskiet for their contributions to this article.

Adherence to taking the prescribed amount of medication at the appropriate times is mutually beneficial to the health of both patients and pharmaceutical companies. The World Health Organization (WHO) cites adherence to long-term therapy for chronic disease in developed countries averages 50%.[1] Typically, a combination of factors contribute to non-compliance, including poor communication, complex dosing regimens, inadequate instructions for use, disabilities, forgetfulness, and lack of confidence in and comprehension of treatment benefits. Factors such as the occurrence or fear of side effects, high costs, the need for chronic dosing and the resulting treatment fatigue, and emotional reactions can all cause stress, which also leads to non-adherence.

Patient adherence can be improved through simplifying medication packaging, providing effective medication reminders and improving patient education. However, it is the connectivity between drug product administration and patient compliance that will be significant for the future of drug development. A paradigm shift for drug product manufacturers from a product-centric focus to a patient-centric focus can positively influence clinical outcome, leading to a higher return on investment.

PricewaterhouseCoopers (London, UK) predicts specialist therapies will be the medicines of the future and will require totally different manufacturing and distribution techniques from those used to produce small molecules. It expects a more diverse range of products by 2020, which includes fixed-dose combinations, imaging for diagnostics, new antibody treatments, biomarkers, tissue engineering, nanocarriers, and gene-based and stem cell therapies. Over the next decade, it expects that the pharmaceutical industry supply chain will undergo three key changes: it will fragment, with different models for different product types and patient segments; it will become a means of market differentiation and source of economic value; and it will become a two-way street with information flowing upstream to drive the downstream flow of products and services.[2]

> "PERSONALISATION OF DRUG DELIVERY CAN BE TAILORED FOR CHRONIC TREATMENTS AS WELL AS OFFERING CONTROL FEATURES FOR DRUGS USED IN AREAS SUCH AS ONCOLOGY."

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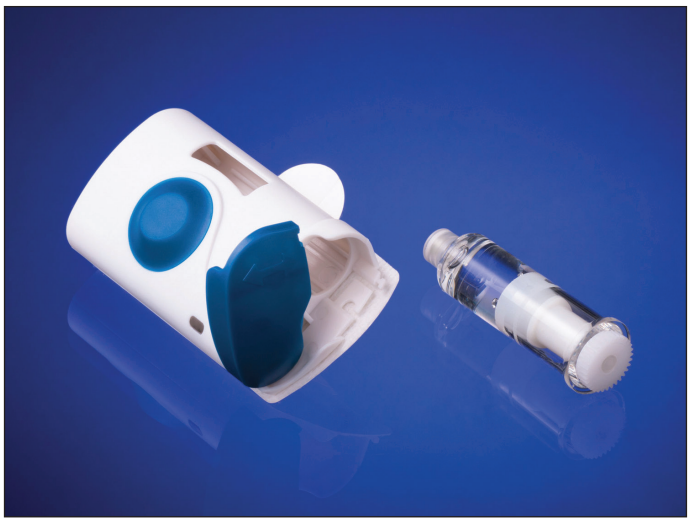

Figure 1: Drug delivery devices and systems, including electronic patch injectors such as the one pictured above, can be tailored for chronic treatments that may require a dose to be given over a period of time.

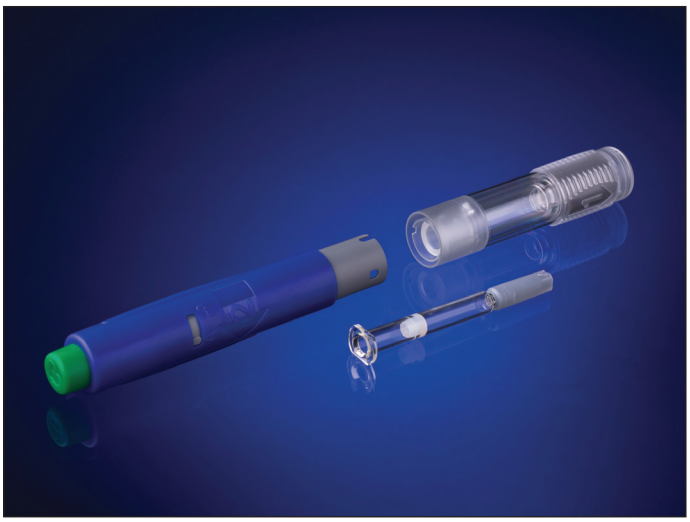

Figure 2: Pen or auto-injector systems, such as West's ConfiDose auto-injector system which is designed to be used with prefillable syringes, provide patient's with convenient, easy-to-use systems for self-administration.

The trend towards personalised therapies will drive pharmaceutical manufacturers to focus on drug efficacy and safety, as well as administration systems to meet end-user needs. Innovative delivery systems that can effectively deliver new dosage forms and differentiate products throughout the drug product lifecycle will be needed to meet future demands.

DRIVE FOR PERSONALISED THERAPIES

The patient experience can enhance the therapeutic effect by increasing adherence to self-care regimens needed to manage chronic conditions.[1] Patient/caregiver preferences and treatment requirements should influence the delivery options. Availability of generics, biosimilars and new therapies will drive the need for unique administration modes and increased patient loyalty. Personalisation of drug delivery can be tailored for chronic treatments (example shown in Figure 1) as well as offering control features for drugs used in areas such as oncology. Accessibility of a variety of delivery platforms with varied dosage forms throughout the drug product lifecycle can support efforts to differentiate product, and increase patient preference and compliance.

The increasing availability of medications dispensed by pen or auto-injectors such as West's Confidose (see Figure 2) improves a patient's ability to continue daily routines with the guidance of a healthcare provider. Medications available for self-administration in prefilled syringe or cartridge format include treatment of infertility, growth hormone deficiency, diabetes, osteoporosis, acute allergic reactions and more. Single- or multi-dose pen designs vary and may include visual and acoustic clues to remind patients of dosage schedule. Magnifying dosage clips may be part of the medication delivery system design to aid the user when setting appropriate dosage. With a variety of designs available, clear labelling for use in both acute care and home-based settings is key.

Medications for chronic diseases such as rheumatoid arthritis dispensed by "manipulation-friendly" auto-injectors provide an option for administration which obviates the need for clinic or healthcare provider visits for intravenous infusion. The convenience of self-administration may improve the chances of disease remission and avoid the costly consequences of uncontrolled disease.

For pharmaceutical manufacturers, the variety of delivery options offers a way to differentiate their product, but also requires considerable development and testing to ensure safety. By partnering with a packaging manufacturer early in the development process, pharmaceutical companies can work quality into their product from early phase through commercialisation.

USER REQUIREMENT INSIGHT AND DEVELOPMENT CONSIDERATIONS

The foremost considerations in the development of a new drug or biopharmaceutical product are its ability to be efficacious and safe. Packaging and delivery systems are critical in assuring that there are no issues that could negatively impact these characteristics over the drug's shelf-life and its administration.

Historically, the package and delivery system has, at times, been relegated to an afterthought. In the recent past, however, the importance of these critical systems has taken a more substantial role in the industry's view, especially in the case of industry-leading pharmaceutical and biotech organisations.

If we view the area of injectable drug packaging (containment) and injectable drug delivery systems (administration) as two segments of a continuum, there are six primary tactics that should be evaluated to deliver effective therapies throughout the product lifecycle:

- Drug Product Efficacy
- Patient Safety
- Functionality of Container/Delivery System Design
- Patient Administration
- Manufacturing Convenience
- Regulatory Compliance.

EFFICACY AND SAFETY

The characteristic of the drug is at the core of this issue. However, if the drug achieves its therapeutic objective, the packaging and delivery system should enhance the experience without causing any negative impact from a compatibility or stability standpoint. When identifying and assessing risk to the efficacy and safety of product, the following factors should be considered:

- Storage and shipping environments
- Integrity of primary and secondary containment
- Delivery of accurate doses
- Change in drug product potency and physical characteristics
- Impact of sterilisation on container closure systems
- Sensitivities to moisture
- Extractability of organic and inorganic substances from containers
- Toxicity of substances that may to leach into drug product.

Figure 3: Specialised materials, such as cyclic olefins including Daikyo Crystal Zenith®, can be used in place of glass to help alleviate safety issues associated with glass, including breakage and delamination.

Contamination by harmful substances migrating into the drug product from contact materials, as well as counterfeit defense, trouble-free administration and protection of the caregiver are all strategic considerations for safety. Both the primary package and the delivery system can have an impact on the patient's well-being and should be factored into the drug product lifecycle plan.

In the case of delivery systems, safety is extremely important as there are immediate implications to the patient. One of the most significant aspects is the relationship of needle safety to both the caregiver and the patient. The mandate by the US Occupational Safety & Health Administration (OSHA) to ensure caregiver safety from exposure to blood-borne pathogens and other potentially infectious diseases has led to many device innovations surrounding prefilled syringes for safer administration of subcutaneous, intravenous and intramuscular medications.

The use of passive safety needle systems is a way to address this issue while reinforcing product differentiation. Planning during product development to identify attributes to support drug product safety and efficacy in relation to container closure and delivery systems can provide means to mitigate risks to encompass drug product lifecycle.

FUNCTIONALITY AND ADMINISTRATION

Certainly there are many critical considerations that relate to the functionality of delivery systems to ensure accurate dosing. When working with a device supplier it is essential to understand if they have applied techniques such as a Human Factors Analysis (HFA) to anticipate the ways a device or delivery system can be misused in the field – especially with systems intended for self administration or home healthcare.

Delivery systems can be designed around specific and personalised therapeutic categories. For example, those suffering from rheumatoid arthritis may have dexterity issues that can be mitigated by producing an easy-to-use system that has a single, large, push-button activation. Those suffering from diabetes, where feeling may be lost in hands, may require audible or visual cues that the injection is complete. As the market moves more toward self-injection, the ability to differentiate a product based on a delivery system's features will accelerate consumer acceptance. Specialised materials such as cyclic olefins, as used in Daikyo Crystal Zenith® (see Figure 3) in place of glass, which can easily break, or the use of color-coded aluminum seals and plastic Flip-Off® buttons can bring benefits to the market place and with the drug product end-users

The function of a delivery system, whether used by a healthcare professional in a clinical setting or by an individual in a home setting, is extremely important and is a critical complement to the safety and compliance of a drug product. Options such as kitting, combining the drug and delivery system together, can aid in end-user convenience while also delivering on the aspect of differentiation.

There are cases where the addition of a reconstitution, transfer or delivery system has allowed for growth of a drug in a relatively stagnant or super competitive marketplace by facilitating administration. An example of this is Watson Pharmaceuticals' (Parsippany, NJ, US) freeze-dried drug Trelstar® (triptorelin pamoate for injectable suspension). To market Trelstar in the US, Watson formed a partnership with West Pharmaceutical Services, in an effort to provide a safe and convenient delivery device. West's MixJect® drug transfer device provides reconstitution with a diluent prior to injection by syringe (see Figure 4).[3] The entire process makes administration and disposal significantly easier and safer for patients and caregivers. Watson has found the response from patients and physicians to be very positive. Patient compliance is the lifeline to preserving product loyalty and is the most valuable asset in maintaining a competitive advantage.

MANUFACTURING CONVENIENCE AND REGULATORY COMPLIANCE

Pharmaceutical and biotech organisations must evaluate options that can allow them to be as efficient and lean as possible. Many industry business models are changing to build a greater focus on understanding a company's core expertise and then work with supplier-partners to utilise products and services that fall outside of the company's core areas. Often, there may not be significant expertise relating to packaging and delivery systems within an organisation. In addition, with the limitations of resources in general, it may be much more effective from a strategic standpoint to work closely with partners to adopt packaging and delivery systems that will minimise the expertise and manpower needed in R&D studies and in actual commercialisation.

Packaging manufacturers have met this need for high quality and efficiency with ready-to-

Figure 4: The MixJet® delivery system used in Trelstar® is an example of the addition of a reconstitution / transfer / delivery system to a drug product. This strategy can allow for product growth relatively stagnant or super-competitive marketplaces by facilitating administration.

sterilise or ready-to-use options. Components that are already formatted for barrier isolators are convenient ways to minimise labour and capital expenditure in component preparation.

nents, medical device components and medical device production requirements.

With respect to components, Drug Master Files (DMFs) are typically used and are the

realised as patient compliance is improved. Manufacturers of compliant, innovative packaging components and delivery system will be an integral part in helping pharmaceutical companies meet those objectives.

"PATIENT COMPLIANCE IS THE LIFELINE TO PRESERVING PRODUCT LOYALTY AND IS THE MOST VALUABLE ASSET IN MAINTAINING A COMPETITIVE ADVANTAGE."

In regard to delivery systems, the use of sterile, ready-to-use devices is quite common. Not only does this facilitate filling and packaging, but puts the responsibility for issues such as validation squarely on the shoulders of the system supplier. In addition, such devices are convenient for the end user.

Regulatory compliance is another route to maintaining a competitive advantage. By building a relationship with a supplier to push the compliance of a container closure/device system upstream, a pharmaceutical company can minimise its exposure and expense to package a drug product. It is critical that the supplier has a full understanding of the cGMP and quality systems requirements associated with packaging components, medical device components and medical device production requirements.

With respect to components, Drug Master Files (DMFs) are typically used and are the responsibility of the supplier to submit and coordinate with the US FDA. If these are not adequately built or updated, this can impact the pharmaceutical company's drug application – thereby losing valuable time in the approval process. In the case of medical devices or similar delivery systems, a 510(k) notification is submitted by the device manufacturer, who is clearly responsible for the cGMP and quality aspects of the delivery device. In both cases there is a critical partnership to be developed between the pharmaceutical/biotechnology industry and its suppliers for the purpose of achieving both technical and strategic objectives.

The goal of the pharmaceutical industry to provide effective therapies can be more fully realised as patient compliance is improved. Manufacturers of compliant, innovative packaging components and delivery system will be an integral part in helping pharmaceutical companies meet those objectives.

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REXAM

IMPACT OF PASSIVE SAFETY DEVICES ON PREFILLED SYRINGES DOSE DELIVERY

In this article, Pascal Dugand, Product Development Leader, Christelle Robelin, Category Manager, and Sandrine Mayer, Category Manager, all of Rexam, report a study comparing the impact on non-injected volume, dose consistency and dose accuracy of the company's Safe'n'Sound™ passive needle-safety device for prefilled syringes with that of other marketed passive safety devices.

INTRODUCTION

For several years now, the pharmaceutical industry has been moving from vials to prefilled syringes for injectable drugs. Indeed prefilled syringes are becoming the preferred way of administration with a market growth of nearly 10% per year.[1] Preferences of pharmaceutical companies and healthcare workers for prefilled syringes can be explained by several advantages over traditional packaging in vials such as ease of use and better dose accuracy. Prefilled syringes also respond to the growth in drug self-administration allowing patients to self-inject prescribed medications at home thus reducing the healthcare costs. In addition, prefilled syringes do not require drug overfilling, compared with up to 25% overfill for vials.

However, needlestick injuries, which expose healthcare workers to bloodbourne pathogens (the Hepatitis B and C, and HIV viruses, for example) remain a main concern. Legislation in several countries nowadays mandates the use of sharps safety devices to reduce needle exposure during medical procedures (The US was the first country, in 2001, to enact the legislation, followed by Europe and Canada).

Safety devices that can be attached to standard prefilled syringes have been developed to reduce needle exposure. They are classified into two categories: passive, if they automatically shield the needle without user intervention; and active, if they need to be activated manually when the injection is complete.

Rexam has developed Safe'n'Sound™, a platform of passive safety devices that can be attached by simple clip-on to standard prefilled syringes sold on the market. The platform was also designed to deliver a consistent and accurate dose thanks to a patented mechanism. Design optimisation for these output parameters is key for pharmaceutical companies as they have an impact on the treatment efficiency and drug overfilling.

Figure 1: Rexam Safe'n'Sound™ devices staked and luer lock versions before and after activation.

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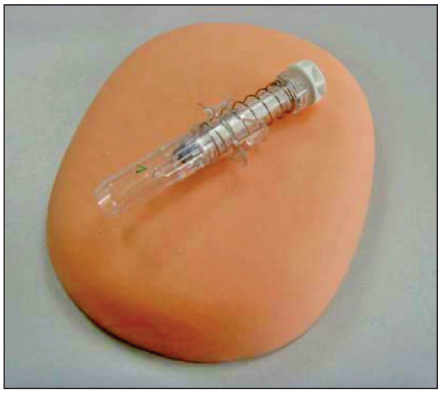

Figure 2: Safe'n'Sound™ with safety feature activated on a silicone pad.

BACKGROUND

The safety feature of marketed passive safety devices is based on the same concept: when the head of the plunger rod reaches the position corresponding to the theoretical end of the injection, a spring is released and the needle is instantaneously covered by a sheath.

In reality, activation is designed to be triggered just before the theoretical end of the injection to ensure activation will happen despite high tolerances on the height of the syringe glass barrel. The user has limited control on the activation. That is the main advantage of these products. However if the activation trigger is not well calibrated, a limited volume of drug may not be injected.

EVALUATION OBJECTIVE

Here we present results from a study the objective of which was to compare the non-injected volume from 1ml prefilled syringes equipped with three passive safety devices after the simulated injection by healthcare professionals and non-healthcare professionals.

MATERIALS AND METHOD

Three registered nurses and seven non-healthcare professionals were involved in the study. They performed six injections simulated in a silicon pad (see Figure 2) for three devices each equipped with a 1 ml prefilled syringe from the same batch filled with 0.5 ml of distilled water and a stopper from the same batch. To reach these conditions, marketed devices were disassembled from the syringe containing the marketed drug and mounted with a new syringe and with a new stopper screwed on their specific plunger rod. So, the only difference between the three systems was the safety device. Injection force was the same for the three systems due to the use of identical syringes, stoppers and liquid. The Safe'n'Sound™ device was used in the system referenced as Safe'n'Sound™ System. The other marketed devices are referenced as Device A and Device B, which were used with System A and System B respectively.

The tests were performed according to Rexam internal protocol P084-02.[2] The main steps were:

1) Assembly of the empty syringe with the device
2) Stopper screwing on the device specific plunger rod
3) Plunger rod insertion (syringe temporarily uncapped)
4) System weighting without syringe needle shield (mass1)
5) Syringe filling with 0.5 ml of distilled water by suction
6) System weighting (mass2)

The non-injected volume is defined as the difference between the weight after injection and the weight of the empty system (mass2 - mass1).

RESULTS

180 injections were performed. Bias was minimised by selecting a sufficient number of evaluators each using a large enough sample of systems (18).

As shown in Figure 3, average non-injected volumes and variability of the non-injected volume were very different between systems and significantly lower for the Safe'n'Sound™ System than for the two comparators. For system A, three values out of 180 of the residual volumes were larger than 50µl, representing 10% of the filled volume.

DISCUSSION

The safety device design clearly impacts the amount of residual fluid in the syringe after use.

The better performance of Safe'n'Sound™ can be explained by the following three reasons:

Firstly, just before the end of injection, a low additional force applied by the user on the plunger activates the safety feature. This additional force is not felt by the user who continues to push on the plunger to complete the injection. A spring is then released which pulls the syringe back, while the user finger is still pushing on the plunger. These two opposite forces help emptying the syringe (Figure 4).

This patented mechanism compensates the advanced release of the safety feature that happens on the three passive devices. If the additional force is too high so that the user can feel it, it can give him the false perception that the injection is completed and make him stop pushing on the plunger. In some cases, the spring can be located at the syringe tip and prevent the user from checking the completeness of the injection. The adjustment of this additional force is critical for safety devices. That is why it has been validated by a user test on the Safe'n'Sound™.[3]

The second reason for the better performance of Safe'n'Sound™ is that, in addition to its patented mechanism, the device features improved ergonomics compared with other devices so that users can push smoothly and continuously on the plunger until the end of the injection. It increases the precision of the injection. Users can activate the device in a very convenient and repeatable way. Safe'n'Sound™

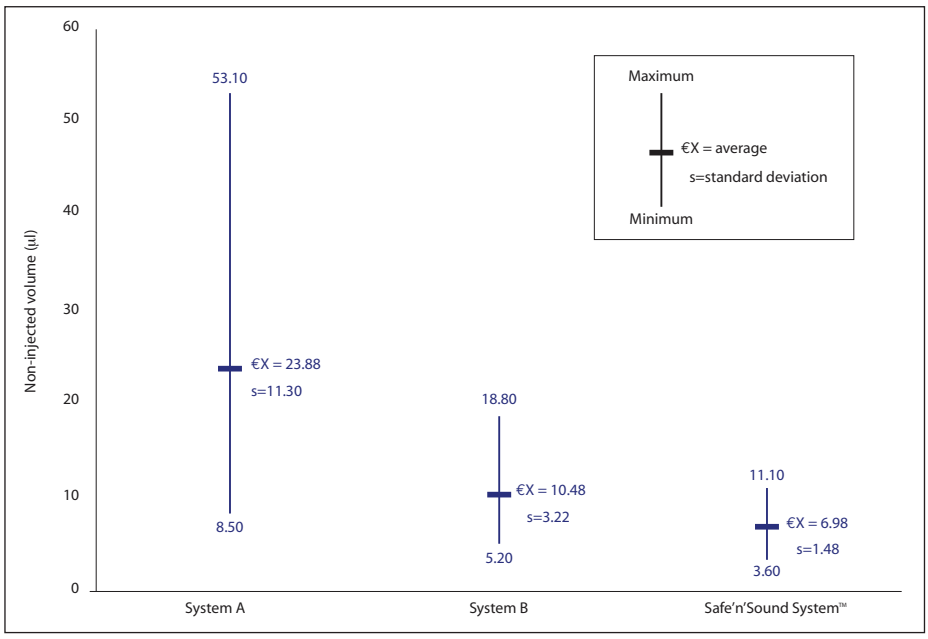

Figure 3: Statistical data of the measured non-injected volume versus systems.

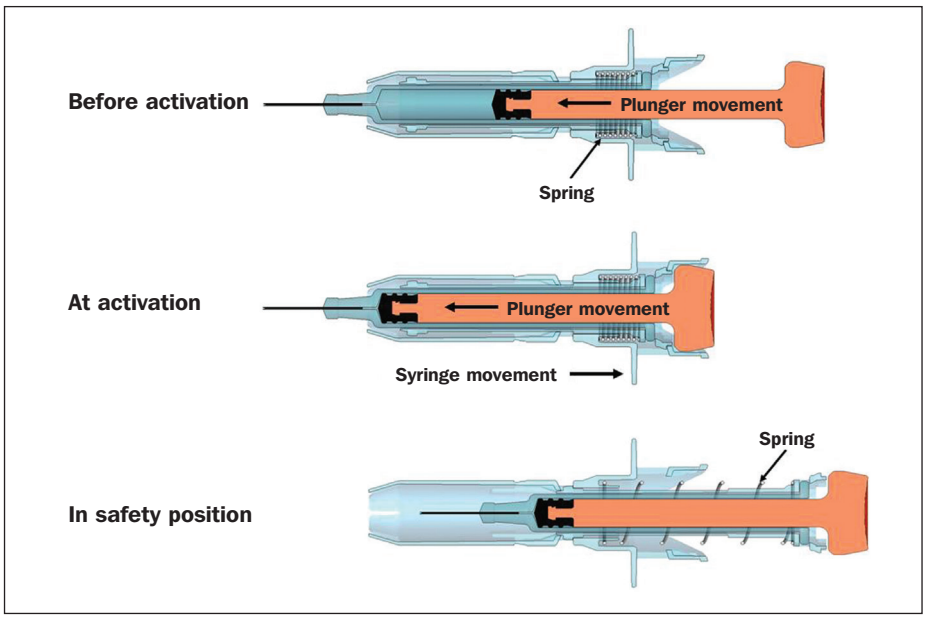

Figure 4: Movements during safety feature activation.

is less user dependant than the two other safety devices. This advantage is becoming critical for non professional people.

And the final reason, on which nurses agree, is that Safe'n'Sound™ does not modify the standard injection process.[3]

CONCLUSIONS

This study shows that using Safe'n'Sound™ allows the delivery of a more complete and consistent drug dose compared with other commercially available passive safety devices. It reduces the costs attributed to drug overfill volume and increases treatment compliance.

The performance of Safe'n'Sound™ over competitive devices is the result of a design fine tuning process based on a system approach. Safe'n'Sound™ tolerances have been specified according to the dimension variability of marketed syringes and stoppers.

Tests were also performed that highlighted much better results in terms of injected volume for a syringe equipped with the Safe'n'Sound™ device than for a naked syringe.[4] Thanks to the Safe'n'Sound™ specific safety feature activation mechanism the variability attributed to human error is reduced.

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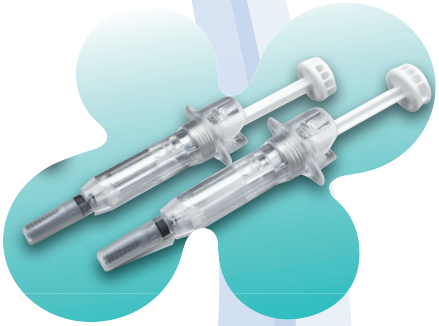

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DOES THE USE OF INFUSION BAGS PLAY A ROLE IN COMPLIANCE AND OVERALL SAFETY?

Here, Danielle Labreche, Head of Business Development & Innovation at Laboratoire Aguettant, asks some searching questions about the performance, safety and efficacy of conventional infusion bags as major injectable delivery systems, and proposes an innovation to improve compliance and security for patients and medical staff.

The delivery of injectable drugs by gravity in plastic infusion bag has been widely used in hospitals for decades and increasingly for the home care market. While hospitals must now contend with several issues that involve quality of patient care, medical staff safety, organisational efficiency, evolving treatment protocols, costs curtailment driving allocation of resources, and environmental issues with managing dangerous waste, we can ask a simple question: **"Is there a link between these concerns and the mode of delivery procured by infusion by gravity?"**

Does it have an impact on any of those critical concerns the first one being treatment compliance? Does it contribute to the risk of exposure to potentially dangerous drugs? What about the risk of nosocomial infections for the patient and creating waste that is damaging to our environment?

The pharmaceutical industry has used this mode of delivery as an inevitable constraint to infuse drugs to patients. Over the past decade, we have seen improvement initiatives in the connectivity area, and manufacturing processes to drive cost down such as blow-fill-seal (B/F/S) technology; but very little to improve efficiency.

This article aims to raise awareness about existing critical issues and the availability of alternatives that provide improved compliance and safety when treating patients with medicines delivered by infusion. First let us look at some facts.

ABOUT INFUSION PERFORMANCE

There are only a few publications on the matter, but it seems to be a well known fact that dead volume is introduced by the use of infusion bags and this prevents the complete dose being delivered to the patient.

A 2008 study conducted at the University Edouard-Herriot (Lyon, France) revealed that for infusion bags of 50-100ml, about **20% of the active product is not infused to the patient**, being trapped either in the infusion bag, the drip chamber or the tubing, when a manual flushing is not performed.[1]

Similar results have been found more recently in a Swiss study in 50-100 ml glass vials, Miniflac bottles and Ecobag infusion bags. In fact, it was found that the dead volume varied between **24-47%** when the drip chamber was filled to the mark and **15-32%** when the drip chamber was empty.[2]

A third study, performed in Brussels in 2010 investigating betalactam (antibiotic) serum concentration indicated that delivering the right dose into the blood is critical for reaching the efficacy level when treating patients.[3]

These results raise other important questions.

ABOUT UNDER-DOSING AND EFFICACY OF TREATMENT

What exactly is the proportion of adverse effects events that can be attributable to underdosing from the infusion bag? Can this "non-

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compliance to treatment" induce inefficiencies in cancer or antibiotic treatment, for example?

ABOUT WASTE: FINANCIAL IMPACT

What is the cost impact on the industry and national health systems when as much as 20% of expensive drugs such as cytostatics, monoclonal antibodies, stem cells and blood derivatives are potentially wasted?

To overcome the drug loss, the advice of the authors of the French 2008 study [1] is as follows:

1) Inform medical staff and patients of the inherent risk of under-dosing.
2) Use a syringe pump.
3) Flush the syringe or bag using sodium chloride.

ABOUT NOSOCOMIAL RISK & PREPARATION TIME

Let us assume for a moment that the most cost effective and pragmatic way to overcome under-dosing is to flush manually with a saline diluent directly into the tubing or bag.

Here are two new questions on manual flushing. Firstly, does manual rinsing increase risk of contamination for the patient as it adds steps to the connection/disconnection protocol? Secondly, does manual flushing increase staff preparation time and create additional waste of supplies? We could probably all agree that the answer is yes to both.

Nevertheless, a systematic flushing between drugs must be performed to maintain the catheter functions and whenever there is a risk of drug incompatibilities or precipitation, creation of biofilm and risk of infections. In the case of molecules with a narrow therapeutic window, the criticalness of compliance with the prescription means that flushing is imposed in the routine treatment protocol.

So, saline flushing is currently performed in hospitals, but at what cost and to what extent, it is not precisely known.

ABOUT DRUG EXPOSURE RISK

Finally, one issue not yet discussed here but of the highest importance for infused drugs relates to toxic molecules, such as in cytostatics, and the risk of exposure and contamination for the medical staff. On this topic, in 2007, the French Health Agency (AFSSAPS) published guidelines for Good Preparation Practices for dangerous molecules.

It stipulated: **"If possible, preparations containing dangerous substances are presented ready to use, i.e. including the delivery device connected and purged with diluent, in order for the medical staff to provide care that is free of risks to their health."**

Hospitals' centralised reconstitution units have in place high security measures and expensive means to control the risks of drug presence in their environment (on the floor, on the working surfaces such as tables and counters, and on the infusion bag surface) before they are dispensed. Yet despite the good practice recommendations, implementation is not always simple and often risks are present when the final preparations are performed on the wards.

The problem of toxic drug exposure is even more pertinent in the home-care arena where oncology treatment will be increasingly present. Consequently, as a social responsibility, it is important that a fully secured system be designed and becomes soon available to contribute to reducing risks of exposure, providing safe working conditions for carers and medical practitioners.

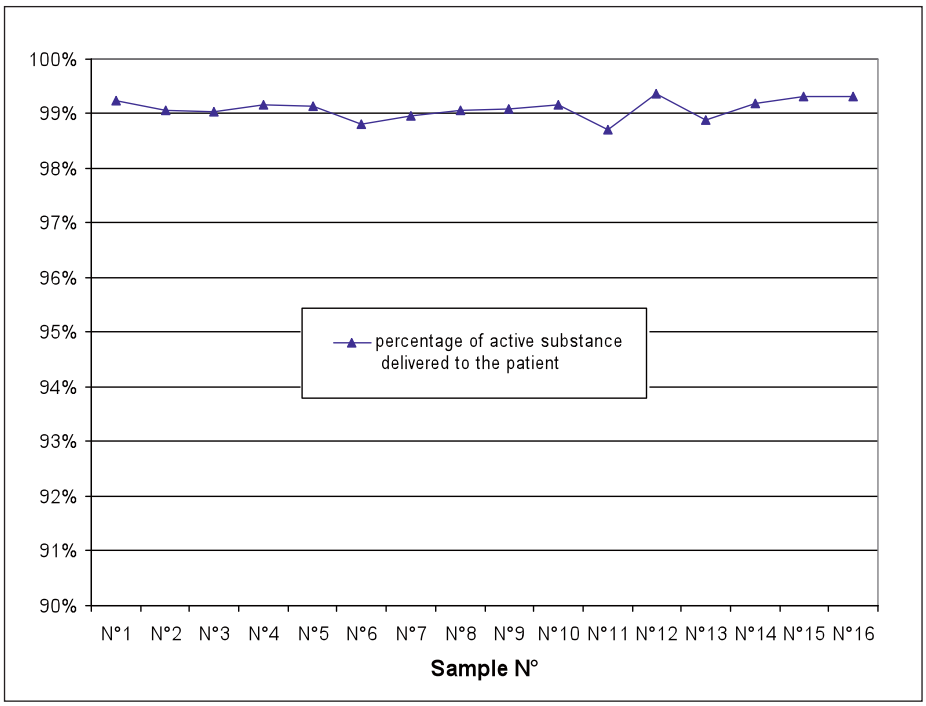

Figure 1: Aguettant's Self Flushing Infusion Bag showing that more than 98.5% of the active ingredient is delivered.

The questions and potential problems raised here are significant. With these issues in mind, Aguettant has developed and patented worldwide a concept of infusion bag that is bringing, increased quality of patient care and solutions to important hospital and globally social concerns.

The innovation resides in the automatic rinsing of the infusion bag and line. This novel functionality substantially increases compliance with the treatment regimen for both doctors and patients as the **full prescribed active drug dose** is infused. Equally importantly, the system provides protection against the risk of exposure before, during and after delivery. Furthermore, the flushing is performed in a closed environment and thus contributes to the waste reduction with simple, safe handling procedures.

Aguettant's Self Flushing Infusion Bag outperforms the current gravity infusion systems. As shown in Figure 1, research conducted by Aguettant on its prototypes (100ml / 30ml) demonstrated more than 98.5% of the active ingredient being delivered to patients (unpublished results).

Two concepts are proposed:

- The Aguettant® Self-Flushing Infusion Bag provides a POST Flushing to address mainly compliance improvement (see Figure 2a).
- The Aguettant® Self-Flushing Infusion Bag PLUS - providing a PRE and POST flushing, so that the medical staff is never in contact with the drug during connection/ disconnection and automatically executes a POST flushing (see Figure 2b).

In summary, a systematic self flushing guarantees to:

- Improve compliance for the patient
- Reduce risks of exposure to toxic drugs for healthcare professionals and carers
- Minimise risks of nosocomial infections for patients (it is a closed system)
- Prevent drug incompatibilities and maintain catheter functions
- Free up healthcare workers' time for attending to patients
- Reduce the need for supplies and drug wastage

Aguettant announced in August 2010 that it has entered into an exclusive licence agreement for the Self-Flushing Infusion Bag patent with Pfizer in Europe for its antifungal portfolio.

AGUETTANT SYSTEM®

The new delivery device described here is part of the AGUETTANT System® range, which includes only patented devices such as its Plastic Prefilled Syringe and its Multi-Dose, Multi-Usage Self-Injector Pen.

It is Aguettant's plan to deploy such novel concepts and products to the pharmaceutical industry so that the hospital and homecare markets can provide improved quality of patient care in a safer environment for all.

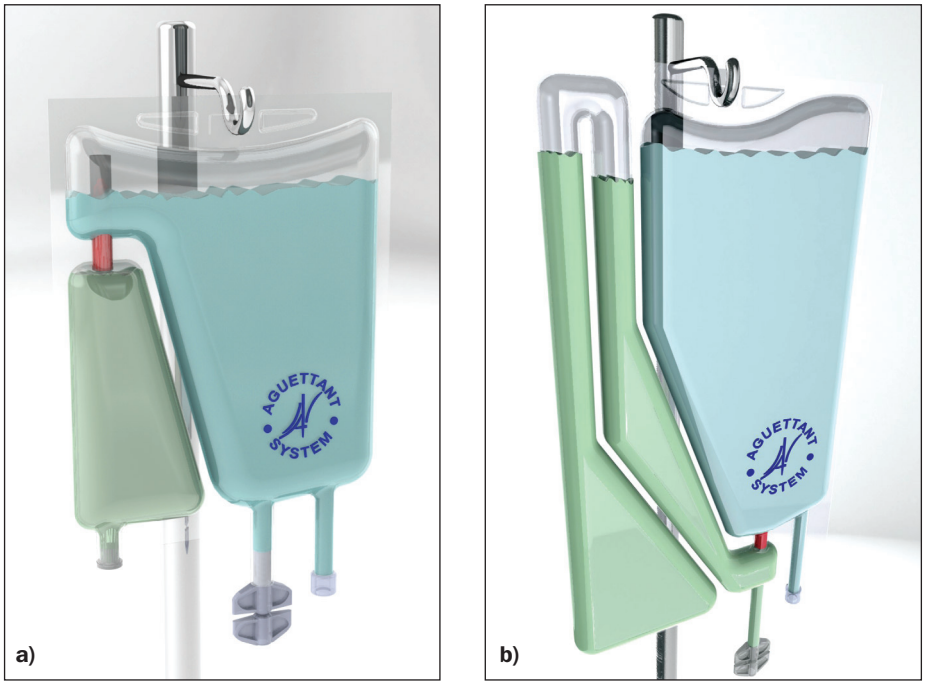

Figure 2: a) the Self Flushing Infusion Bag and b) the Self Flushing Infusion Bag PLUS.

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ADVANCED INJECTION DEVICES:
DEVELOPMENTS, DRIVERS AND DIRECTIONS FOR THE FUTURE

Here, Andy Fry, Founder and Director of Team Consulting, provides an analysis of the advanced injection devices landscape including historical perspectives, observations on current and recently developed devices, and likely future trends.

OVERVIEW

At one time injection meant a hypodermic needle, a syringe, an ampoule and a clinical setting. As we enter the second decade of the 21st Century, self-injection of prescription medication is an increasingly common part of life, helping to make normal life possible for an increasing number of people.

Treating diabetes with insulin has a long history and in more recent years diabetes treatment has shared a number of similarities with the treatment of a wide range of conditions with other biologically derived drugs. In both cases, the medication itself is a protein which cannot be delivered orally and is thus delivered by injection. Hence in the simplest terms, a needle and syringe are the most obvious means of administration.

"DESPITE A NUMBER OF SIMILARITIES BETWEEN INSULIN AND BIOLOGICS, THE SIGNIFICANT DIFFERENCES BETWEEN THE THERAPIES AND BETWEEN THE PATIENTS CONCERNED REQUIRE SIGNIFICANTLY DIFFERENT DELIVERY DEVICES."

The science and technology which has made biological drugs available has transformed lives, won a Nobel Prize and founded major corporations. But what of the technology used to deliver these molecules? This, after all, provides the essential 'drug-to-patient' interface. What will the market expect or even demand of these technologies in the future, and how might the device industry respond?

A LITTLE BIT OF HISTORY

Insulin was discovered in 1921 and until the marketing of animal-derived insulin in 1923, a diagnosis of diabetes was, in effect, a death sentence. Synthetic insulin, produced by recombinant biology, was developed in 1978 and first marketed in the early 1980's. Novo Nordisk launched the first insulin pen type injector in 1985 offering greater patient convenience and today, 90 years since the discovery of insulin, there are numerous companies marketing insulin pens.

Pens are extensively used in Europe (by 88% of diabetics), but are less common in the US, where 17% use pens as many patients still use a needle and syringe. Conversely the continuous subcutaneous insulin infusion (CSII) pump is well established in the US with a growing number of users, but its use remains relatively uncommon in Europe.

The number of diabetics, both type 1 and type 2, is projected to increase by around 50% from current levels, exceeding 430 million glob-

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Figure 1: Lilly's Memoir pen incorporates sophisticated electronics. ***Image of Memoir Pen courtesy of Eli Lilly & Co. Reproduced with kind permission.***

ally within 20 years (IDF Atlas, 4th Edition, International Diabetes Federation, 2009) representing a growing market opportunity.

Similarly, biologically derived drugs emerged from the same roots as recombinant insulin in the late 1970's. Whilst insulin is specifically for the treatment of diabetes, biologic compounds, particularly monoclonal antibodies, have been developed to treat chronic conditions (for instance rheumatoid arthritis (RA) and multiple sclerosis) with lifelong, regular, dosing regimens; or subacute conditions (in particular, types of cancer) with regular dosing regimens but often for shorter periods than for chronic conditions.

Means of administration have evolved. Remicade, a TNFα blocker used in the treatment of Crohn's disease, RA and other auto-immune conditions, was launched by Johnson & Johnson (New Brunswick, NJ, US) in 1998 as an intravenous infusion. In 2004, Amgen (Thousand Oaks, CA, US) repositioned Enbrel, its own TNFα blocker for similar indications, in a prefilled syringe for subcutaneous injection, followed by a single-use auto-injector in 2006 for subcutaneous self-administration. Dosing frequency for biologics is generally weekly, fortnightly or even less frequently. In a post-blockbuster age, biologically derived drugs, which command premium reimbursement potential are now major features in most pharmaco portfolios.

Insulin and biologics have a shared heritage in the use of recombinant engineering. They are both used to produce positive, life-transforming results in the treatment of serious or even life-threatening diseases. Both types of drug have to be injected to remain effective so both are dependent on a delivery device or system, even if this is simply a syringe. Despite a number of similarities between insulin and other biologics, the significant differences between the therapies and between the patients concerned require significantly different delivery devices.

INSULIN DELIVERY DEVICE TECHNOLOGY

From the outset in the early 1920s, diabetics have had to be able to inject frequently to maintain correct blood-sugar levels. Furthermore, insulin dose titration demands delivery device adjustability. So a compact, portable adjustable device – the injector pen – responds directly to patient need. A "dial-up, dial-down, press to deliver" sequence of pen use has emerged as a *de facto* standard operation procedure. Needle insertion into the skin is done by the patient in virtually all pens. The dental vial ("cartridge") is the universally adopted container closure system.

Pens are essentially mechanical devices in all aspects of adjustment and delivery. Display of dose is mechanical in most cases, though electronic dose display has been used and the Humapen Memoir from Eli Lilly (see Figure 1) incorporates a sophisticated electronic memory.

Overall, pens are now either re-usable items with replaceable insulin cartridges or are supplied as prefilled devices to be disposed of when empty. Functionally, adjustment, display and overall usability is broadly the same in either case, with sales of disposable pens growing compared with more modest forecasted growth of re-usable pen sales. Patients interviewed by Team Consulting describe keeping "one in the office, one in the kitchen and one in my pocket" in the same manner that many asthmatics treat inhalers, and this may be a factor in sales growth.

Reduced cost and improved safety are the key market pull factors coming from payers, prescribers and regulators and ultimately reflect the demands of patients themselves. As an example, in the UK, 3,881 patient safety incidents involving insulin delivery were reported between 2004 and 2009. Although this statistic includes clinical based delivery by health care professionals, it stressed the importance of correct interpretation of dosing, such that in 2010, the UK National Patient Safety Agency (NPSA) issued guidance to help reduce the incidence of insulin-related errors.

BIOLOGIC DELIVERY DEVICE TECHNOLOGY

By comparison, dosing for a biologic is regular but infrequent (monthly dosing is not uncommon). Hence device portability is not a major issue, indeed keeping the delivery device – the auto-injector in most cases – in a bedside table or bathroom cabinet is a common habit (if storage conditions allow). In addition, the dose size is determined by the prescribing physician so dose adjustment is generally not a requirement.

DRIVER 1 – IMPROVING COMPLIANCE THROUGH USABILITY AND FUNCTIONALITY

Less frequent treatment would appear to be an advantage to patients. However, unlike the diabetic who generally becomes familiar with his or her therapy and adept in its administration, the patient on a monthly regimen tends not to develop such familiarity. An infrequent injection can also be overlooked, taken late or even taken early. All this emphasises the need for compliance with therapy. Auto-injectors should minimise much of the physical and cognitive burden of delivering a dose by:

- ensuring device reliability / consistency of performance in hands of users
- reducing significant use-related risks
- accommodating a full range of user input (e.g. grip styles, dexterity limitations, operation styles) and maximise ease of use
- minimising delivery pain / anxiety.

Addressing these needs is not just good practice; it is now a regulatory necessity (ANSI/AAMI

Figure 2: EasyPod® uses an electronic-based interface to enhance ease of use, reliability and convenience. ***Image reproduced with kind permission from Merck Serono.***

Figure 3: Molly is a more cost-effective, disposable auto-injector. ***Image reproduced with kind permission from SHL Group.***

Figure 4: Zogenix' 1ml Needle-Free Injector DosePro™

HE75:2009) to follow usability engineering / human factors process so as to improve compliance.

Auto-injectors which meet all the above guidance and standards (including the forthcoming ISO standard – 11608-5) are being used to deliver a wide range of therapies successfully. But what can be done to further reduce the cognitive and emotional burden on patients of managing their treatment to improve compliance, given that forgetting to use even a "perfect" device is still a failure to comply? This is where on-board electronic features could offer:

- powered injection (needle insertion and drug delivery)
- reminders
- dose logging / memory
- links to other devices and resources :
  - smartphone self-management apps
  - integration – physical and communications – of these devices
  - links to social networks (e.g. "www.patientslikeme.com").

DRIVER 2 – HEALTH AND ECONOMICS

If the above sounds futuristic, it shouldn't, as the technologies involved are all well proven. For example, the EasyPod® from Merck Serono (Geneva, Switzerland), launched in 2007, uses an electronic-based interface to enhance ease of use, reliability and convenience (see Figure 2).

If the idea of on-board electronics sounds unrealistically expensive, that may be because we are using the wrong cost model. For prolonged/chronic treatment, the cost per shot with an electronically enabled delivery device (EEDD) can be very competitive compared with a single use mechanical device. For the 'traditional' mechanical single-use device, the cost of goods, excluding drug and container closure system, is the cost per shot.

For an electro-mechanical, multi-use device which is loaded with a container closure system (typically a prefilled syringe) when a dose is required, the cost per shot is the lifetime device and disposables cost, divided by the number of shots delivered over the lifetime of the device (for example, three years).

It is well documented how poor compliance can be a major hurdle to effective treatment especially in chronic conditions. A WHO report in 2003 indicated that 30-50% of medicines prescribed for long-term conditions are not taken as instructed, and that "poor medication adherence is the primary reason for sub-optimal clinical benefit of therapy".

Admittedly, drug delivery devices have some part to play in this much broader and complex range of topics, but in that role as 'drug-to-patient interface' they are key to supporting treatments and therefore ultimately contribute to the economic argument for improved compliance. After all (in very simple terms) improved clinical outcome can and does mean a reduced overall cost burden.

Addressing this broader cost model hints at the opportunity and provides some justification in certain situations, for the highly functional retained delivery device. That is, where the functions aim to support improved adherence and provide an opportunity for reduced cost per dose case.

At the other end of the spectrum, however, and suiting a different market situation, there continues to be a fit for the disposable device with a more cost-effective and speedy route to market, such as the Molly device from SHL (Taoyuan City, Taiwan), aiming to provide a compact, simple-to-use, convenient solution in the same way that insulin pens have evolved (see Figure 3).

OTHER INFLUENCES FOR THE FUTURE

Rather than speculate on a wide range of 'what might be', two areas which have seen a lot of development activity in recent years are:

Advances in Materials

Advances in materials technology, for example the emergence of COC/COP primary containers, improvements in elastomers and lubricants, and the development of sharper, thin-walled needles, are already enabling more compact, more efficient injection devices to be designed and produced. There are challenges to be managed in these in all areas, but also opportunities to improve device convenience, usability and safety.

Alternative delivery technologies

Two radically different delivery device technologies provide interesting alternatives for the delivery of biologics and may form a part of the landscape moving forward.

Bolus injection of volumes in excess of 1ml is generally avoided in self-administration devices, mainly for reasons of patient discomfort. For this reason, formulations are developed which concentrate the drug to reduce dose volume, but these may increase viscosity substantially.

Needle-free delivery, though, has an interesting characteristic in that injection duration is largely unaffected by viscosity, hence delivery of 1ml of a 100cP formulation will take a similar time to the delivery of 1ml of water. Zogenix (San Diego, CA, US) has developed the DosePro technology platform (Figure 4). The 0.5ml version is currently the only prefilled needle-free injector on the market and offers a potentially interesting solution for the injection of biologics. The DosePro is powered by a charge of high-pressure nitrogen and uses a type 1 borosilicate primary container.

Large volume "patch pump" technologies tackle the issue from the other direction and a number of companies are developing these disposable subcutaneous auto-infusion devices. They utilise short (2-3mm), narrow-gauge needle or microneedle technology to deliver a rela-

tively large (typically 5-10ml) volume of drug formulation within a limited timeframe (typically less than 1hr). The patch pump is worn by the patient and can be gas pressurised or spring or elastomer energised. The MicroInfusor from BD (Franklin Lakes, NJ, US) is an example.

TRAJECTORIES FOR THE FUTURE

Over the next few years, more therapies will emerge, more patients will require treatment and the pressure to control cost of treatment can only be expected to increase. This will apply in all areas of medicine, but looking at the two areas examined in this short article, it appears likely that in each case, two trajectories may well be fulfilled.

In diabetes management, we expect to see a continued growth in demand for prefilled, disposable devices which offer excellent usability and technical performance, with a 'design consensus' on the patient interaction ('dial-up, dial-down, press to deliver') for disposable and the anticipated smaller population of re-usable devices.

Whilst electronics probably has a more minor role to play in pen-based delivery, CSII pumps are already well established, albeit with a minority of patients, and have already raised awareness of the possibilities of electronics enhancing disease management.

For auto-injection of high-value biologics, a design consensus around single-use devices seems likely to settle on two standard interactions; 'push to activate' and 'push interlocked button to activate' and many products are expected to be offered in single use devices which have excellent usability and technical performance. The high cost of entry for sophisticated re-usable EEDDs is expected to discourage some from early adoption. However, the lifetime cost and cost per-shot proposition is expected to be taken seriously by payers, prescribers and regulators so we fully anticipate that electronic devices of this type will be taken up in parallel with the traditional disposable devices.

"NEEDLE-FREE DELIVERY, THOUGH, HAS AN INTERESTING CHARACTERISTIC IN THAT INJECTION DURATION IS LARGELY UNAFFECTED BY VISCOSITY, HENCE DELIVERY OF 1ML OF A 100CP FORMULATION WILL TAKE A SIMILAR TIME TO THE DELIVERY OF 1ML OF WATER."

ABOUT THE AUTHOR

Andy Fry is a mechanical engineer with 25 years' experience in medical product development, with particular emphasis on drug delivery devices. A founder of Team Consulting, a leading medical product development organisation based in Cambridge, UK, he takes an active role in product development and client relationship management. Andy is a member the Parenteral Drug Association (PDA) and the Aerosol Society, and is a UK representative on the ISO committee developing the forthcoming 11608-5 auto-injector standard.

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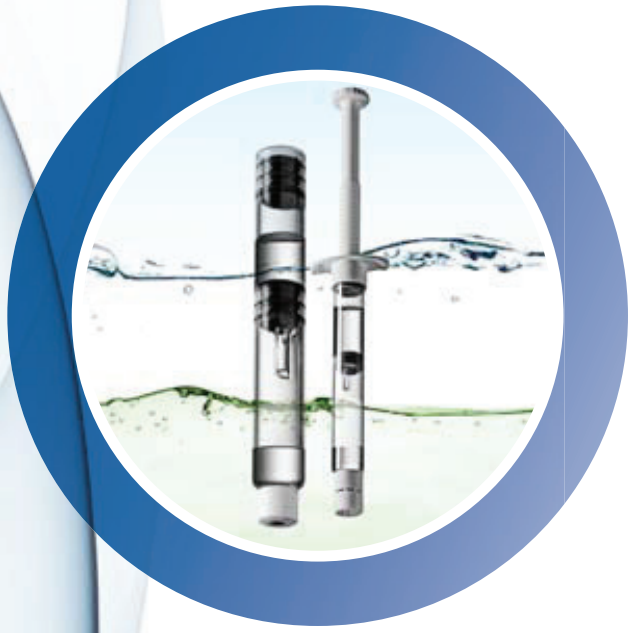

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All products are developed and manufactured in Switzerland, where internal capabilities include R&D, tool-making, injection moulding, clean-room manufacturing and assembly facilities. Ypsomed provides not only marketing and technological expertise but also production expertise according to the latest regulatory requirements, for both low and high-volume production. Ypsomed manufactures in FDA-registered facilities, is inspected regularly by its customers and regulatory authorities, and supplies devices approved for all leading markets including the US, Europe and Japan.

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Today, Haselmeier is one of the leading designers and manufacturers of pen and auto-injector systems. Many of these systems feature Haselmeier's patented hidden needle system, which is designed to help patients overcome the fear of self-injection, provide a more comfortable injection and help increase compliance of the patient's medication.

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Our capabilities include design and development from concept to finished device using Haselmeier's strong IP portfolio or tailoring of existing Haselmeier designs to meet customer and therapeutic needs.

All designs undergo comprehensive testing, in addition to risk management, risk analysis and FMEA design review. Three-dimensional CAD designs are utilised for creation of customer-specific concepts or customisation of existing designs.

Our development approach is summarised in Figure 1.

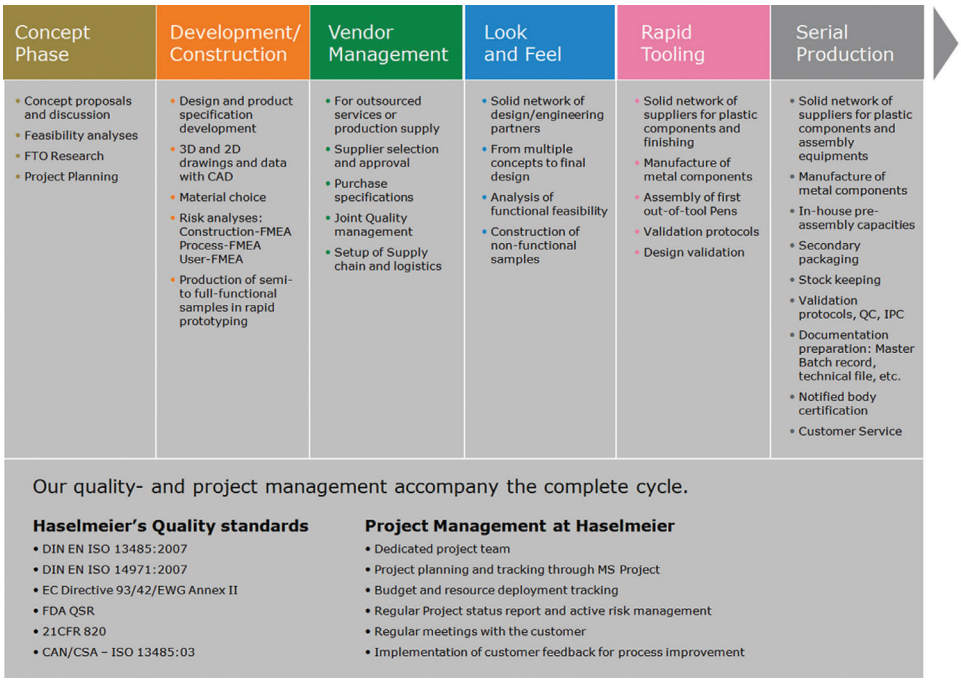

Figure 1: Summary table showing Haselmeier development approach from product concept to serial production.

MANUFACTURING AND QUALITY

As a specialist in the manufacture of complex system assembly, product integrity is assured by Haselmeier's manufacturing processes. All new device concepts are created with an "Integrated Design Approach" which focuses on both the device and the efficiency of manufacture and assembly.

All manufacturing is within compliance with applied standards EN ISO 13485:2003 and annex ll section 3 of the directive 93/42/EEC on medical devices. CE certification is certified by TÜV product services.

Last year, a new manufacturing facility was opened in Dnesice, Czech Republic. The 3,000 square meter facility provides additional capacity, including a 400 square meter class D cleanroom for sub-assembly of the disposable Penlet and Axis-D pen platforms (see below) and increased capacity for the processing of metal outer bodies for re-usable pens.

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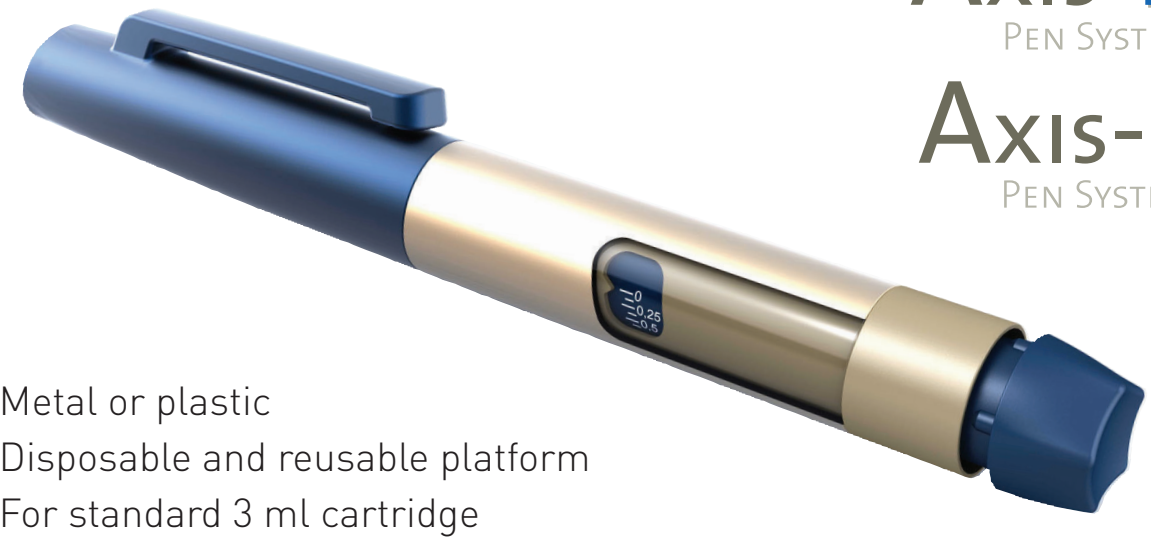

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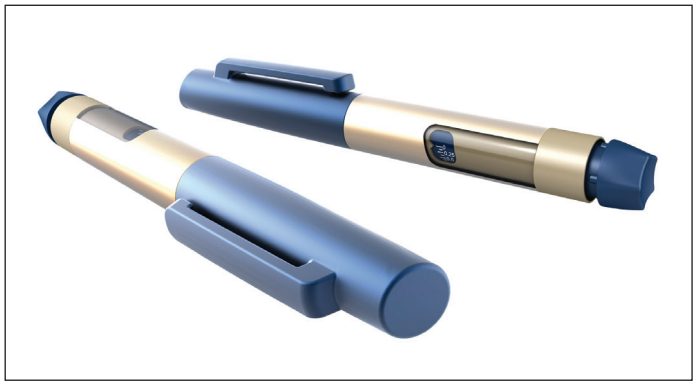

Figure 2: Axis Pen System – variable dose injection device.

Figure 3: i-pen – re-usable, variable dose injection device designed with an intentionally 'non-medical' appearance.

PLATFORM & PRODUCTS

Axis Pen System – variable dose injection device

The Axis Pen System (shown in Figure 2) is a variable dose injection device for manual injection. It is available in a disposable or re-usable presentation. The Axis-D and Axis-R Pen Systems provide a new, unique technical function.

The Axis-D and Axis-R Pens Systems feature:

- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale

I-PEN – RE-USABLE, VARIABLE DOSE INJECTION DEVICE

The Haselmeier i-pen is a re-usable, variable dose injection device for use with a standard 3 ml cartridge. The i-pen is designed with an elegant and intentionally 'non-medical' appearance (see Figure 3) which is the result of extensive research and patient testing.

The i-pen is available as a standard Haselmeier design or can be customised to specific requirements.

The i-pen features:

- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enablings easy handling and portability
- Large, easy-to-read dose indicator

SOFTPEN – RE-USABLE INJECTION DEVICE

The Softpen (Figure 4) is a fully automatic, re-usable injection device featuring Haselmeier's patented hidden needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution.

The Softpen features:

- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3ml cartridge

PENLET – DISPOSABLE, FIXED-DOSE INJECTION DEVICE

The Haselmeier disposable Penlet is a fully automatic, fixed-dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue which is followed by delivery of the solution.

The Penlet features: (figure 4)

- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection

CONCLUSION

Haselmeier's devices feature unique function, design and technology and are marketed by pharmaceutical and biotechnology companies around the world.

The company offers experience, competence and expertise in:

- The development/production of pen- and auto-injectors for self-administration of medicines through subcutaneous injection.
- Custom design and production of medical devices.
- Product design in simultaneous engineering to optimise the development and production processes.
- Quality Management System to guarantee a cost effective, consistent and high quality product.

Figure 4 : Softpen – fully automatic, re-usable injection device featuring Haselmeier's patented hidden needle design.

Figure 5: Penlet – fully automatic, fixed-dose injection device

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DRUG PATCH PUMP OR CLASSICAL DRUG INFUSION PUMP

WHAT IS THE RIGHT DEVICE FOR YOUR APPLICATION?

In this article, Derek Brandt, Chief Executive Officer, and Marika Buratti, Junior Product Manager, both of Sensile Medical, outline the advantages and disadvantages of patch pumps compared with classical infusion pumps.

Modern drug delivery infusion pump systems offer localised medication administration to target tissues with great accuracy. Such pumps for drug administration manage pain and treat neurodegenerative disorders. Examples of some neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Additionally several companies are working on solutions to administer oncology products into the subcutaneous tissue instead of via the intravenous route.

Patch pump technology has been on the verge of breaking through for several years and all the indications are that now it may actually happen. Patch pumps are becoming popular because they avoid the tethered approach of "classic" pumps. Instead of having your pump connected to your body via an infusion set and tubing, the patch pump is worn directly on the body, discreetly attached at the infusion site and wirelessly controlled by a separate device.

For a lot of different applications the question is: "Which pump solution is the right one for the specific treatment schemes?"

ADVANTAGES OF A PATCH PUMP USED FOR DRUG DELIVERY

Discreet:

Wearing a patch pump is very discreet. As the pump is placed directly on the body and is flat enough, it can be covered with clothes.

Few handling steps:

Due to the direct placement without infusion catheter and with an automated inserter mechanism, the patch pump has few handling steps to be performed.

Little dead volume:

The infusion needle is placed directly below the patch and therefore the dead volume of the drug is minimised. Especially with very expensive drugs, this can be a significant advantage compared with conventional pumps. The dead volume can be reduced by as much as 60-80 µL.

DISADVANTAGES OF A PATCH PUMP USED FOR DRUG DELIVERY

Pain:

There is a risk of hitting a nerve while inserting the infusion catheter. In this situation it is necessary to change the infusion site. If you consider a fully disposable infusion pump, there is a certain risk (about one out of 50 times) that the patch including the expensive drug needs to be thrown away due to the fact that it cannot be used a second time at a different location.

Size and Weight:

Especially with bigger drug containers exceeding 3 ml, the size and weight of the patch might become an issue. The adhesive, which needs to hold the patch, must have a considerable footprint and a strong adhesive force.

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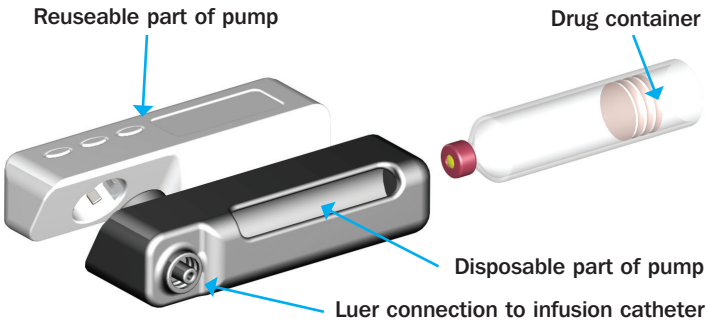
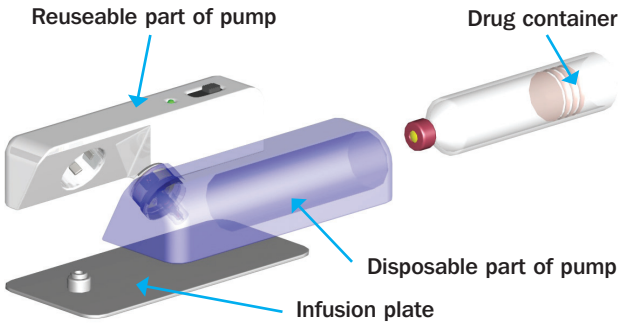


A) "Classical" drug infusion Pump



B) Semi-disposable patch pump

Figure 1: Comparison of A) the Concept of a "Classical" Drug Infusion Pump and B) the Concept of a Semi-Disposable Patch Pump.

Complexity:

The integration of a drive mechanism, electronics, battery and other system relevant components including the miniaturisation of such components is a complex task. The assembly of the components to a final product might especially be a cost-intensive task which results in a costly product concept.

ADVANTAGES OF A "CLASSICAL" PUMP USED FOR DRUG INFUSION

Standard Infusion set:

Standard off-the-shelf infusion sets with luer connections can be applied, and therefore a well known component is used and does not need to be developed.

Minimal skin irritation:

Thanks to the use of a standard infusion set, the footprint and therefore the adhesive force is minimal and the skin irritation of the adhesive can be reduced to an absolute minimum.

Infusion set exchangeable:

If a nerve is hit (described above) the infusion site needs to be changed. Using the classical pump approach, the infusion set only will be replaced, without the need to throw away the pump device including the drug reservoir.

DISADVANTAGES OF "CLASSICAL" INFUSION PUMPS

Too many handling steps:

If a classical pump is used for the drug infusion, more handling steps as compared with a fully disposable patch device need to be considered. This is mainly due to the separate infusion set which needs to be applied to the skin, merged with the pump and the unavoidable priming process of the tubing.

Dead volume in system:

The longer tubing of the infusion set will result in a bigger dead volume in the system overall. Especially if the drug is very expensive, this is a cost factor which needs to be considered.

Obtrusiveness:

Compared with discreet patch pumps the classical pumps are much less discreet. This may be acceptable, if the infusion time is limited to a short period of time per week. Then the patient can perform the infusion while being at home or in a controlled environment where discreetness of the device is not too important.

CONCLUSIONS

Especially for a short application time of less than one hour per week and total volume of 3ml or more, Sensile Medical recommends using a classical pump instead of a patch pump. A conventional pump has a much smaller adhesive and therefore generates less pain while removing the infusion set.

However, for more chronic use and for a longer-term and discreet pump treatment, Sensile Medical AG suggests using either a fully disposable or semi-disposable patch pump solution. The design and concept of semi-disposable patch pumps compared with "classic" patch pumps are shown in Figure 1.

With regard to environmental aspects Sensile Medical would also recommend focusing on a semi-disposable patch pump and therefore avoid the discarding of hazardous materials like electronics, batteries and other potentially re-usable parts of the patch pump.

Another important aspect is the pain during the insertion of the infusion needle into the subcutaneous tissue. Every approximately 50th time, you will hit a nerve while inserting an infusion catheter in the subcutaneous tissue. If you use a fully disposable patch pump, you will have to replace the complete system including the sometimes very expensive drug. If you use a semi-disposable patch pump instead of a classical pump you will be able to replace the infusion catheter only and you can still use the drug at a different infusion site.

Sensile Medical has developed a unique piston pump technology, which allows patch pumps as well as "classical" pumps that are either fully or partially disposable. The main advantage of the Sensile approach is the price, the delivery accuracy even with more highly viscous substances as well as the mass production capability of its technology.

IMPROVING PROCESS QUALITY OF PHARMACEUTICAL LIQUIDS:

ASEPTIC BLOW/FILL/SEAL TECHNOLOGY VERSUS TRADITIONAL ASEPTIC PROCESSING

Here, Chuck Reed, Director of Sales & Marketing at Weiler Engineering, explains how blow/fill/seal technology, acknowledged by the US FDA as an advanced aseptic process for the packaging of sterile pharmaceutical liquids, is gaining increasing acceptance by providing a high assurance of product sterility, eliminating the need for human intervention, improving flexibility in container design and increasing process uptime.

Since its introduction into the North American pharmaceutical market more than 40 years ago, blow/fill/seal (B/F/S) aseptic processing has established itself as a highly efficient and safe system for the filling and packaging of sterile pharmaceutical liquids and other healthcare products, such as creams and ointments. B/F/S product usage has been widely established in the ophthalmic and respiratory therapy markets for some time and lately B/F/S technology has been gaining increasing worldwide acceptance in the parenteral drug marketplace, replacing traditional glass vial processing in a growing number of applications.

B/F/S enables a container to be molded from plastic, aseptically filled and hermetically sealed in one continuous, integrated and automatic operation, without human manipulation. The process provides flexibility in container design and system changeovers, high volume product output, low operational costs and a high assurance of product sterility. The inherent safety of the process – packaging sterile products under aseptic conditions without human intervention – has led the US FDA, and the US Pharmacopoeia, to characterise B/F/S technology as an "advanced aseptic process".

New advances in drug delivery, the desire to improve convenience in handling pharmaceutical products, growing emphasis on combination products, the increasing focus on protein-based drugs and other biologics, and tighter regulatory criteria on product safety, have focused more attention on B/F/S technology as a better solution for the sterile, aseptic processing of pharmaceutical liquids compared with traditional aseptic methods.

PERSONNEL INTERVENTION IN TRADITIONAL ASEPTIC AREAS

Traditional aseptic sterilisation involves handling and manipulation of the material, containers, and sterilisation filling processes with human intervention. It therefore has a higher potential for contamination during processing. The US FDA's 2004 *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing* states that the design of equipment used in aseptic processing should limit the number and complexity of aseptic interventions by personnel. Both personnel and material flow should be optimised to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures or the surrounding environment.

A person, walking normally, emits roughly 10,000 skin particles per minute. Such particles can and do hold microbial contamination. A rip in a worker's uniform, a momentary exposed wrist, a mask placed too low on the nose or physical contact with an open fill port will increase microbial contamination within a critical area.

According to the FDA's guide, airborne

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contamination is directly related to the number of people working in a cleanroom and the level of congregation by personnel in areas where critical aseptic manipulations are performed. Isolation of personnel from these critical areas would eliminate the major source of contamination in traditional aseptic processing.

In traditional aseptic processing, changing or adjusting filling nozzles and heads necessitates the shutdown of the filling operation and requires re-sterilisation of the entire equipment. This increases manual intervention in this critical area. Cleaning and sterilisation which is carried out by personnel, opens the door to breaching of established procedures for microbial decontamination and potential introduction of other particulates like dirt, oil and chemicals.

Mold is common flora found on floors, walls and ceilings of buildings. Contamination occurs due to the retention of water in cracks, edges and joints that are susceptible because of inadequate sealing. Brooms, mops and anything used for cleaning can become contaminated and increase atmospheric contamination because of raised dust or splashing water. In traditional aseptic processing, significant manual intervention is required in critical areas to maintain compliance with established sterile mandates.

ADVANCED BLOW/FILL/SEAL ASEPTIC TECHNOLOGY

In advanced aseptic B/F/S processing, containers are formed from a thermoplastic granulate, filled with a liquid pharmaceutical product and then sealed within a continuous, integrated and automatic operation without human intervention.

Bulk solution prepared under low bioburden or sterile conditions is delivered to the machine through a product delivery system that has been previously sterilised using an automated steam-in-place process.

Modern B/F/S machines (see Figure 1) are fully automated, designed to require minimum human access and operate in a classified environment using the following steps:

(a) granules of a polymer resin, conforming to a predetermined set of specifications, such as polyethylene, polypropylene, co-polymers or other blow-moldable resins, are pneumatically conveyed from a non-classified area into the hopper of the B/F/S machine, from which the plastic is fed into a multi-zone rotating screw extruder which produces a sterile homogenous polymer melt (160–250°C) (see Figure 2a)

(b) then to a parison head which produces hollow tubular forms of the hot resin (called parisons). The parisons are prevented from collapsing by a stream of sterile filtered support air. Some high-speed B/F/S machines have up to 16 parisons being formed simultaneously

(c) container mold(s) close around the parisons, and the bottom of the parison is pinched closed, while the top is held open in a molten state (see Figure 2b)

(d) the container is formed in the mold by blowing sterile air or creating a vacuum (Figure 2c)

(e) filling needles deposit the stipulated volume of product into the container

(f) the filling needles are withdrawn, and the upper part of the mold closes to form and seal the upper part of the B/F/S container (Figure 2d)

(g) the mold is opened and the completed, filled containers are conveyed out of the B/F/S machine to a remote station where excess plastic is removed and the finished product is then conveyed to final packaging (Figure 2e).

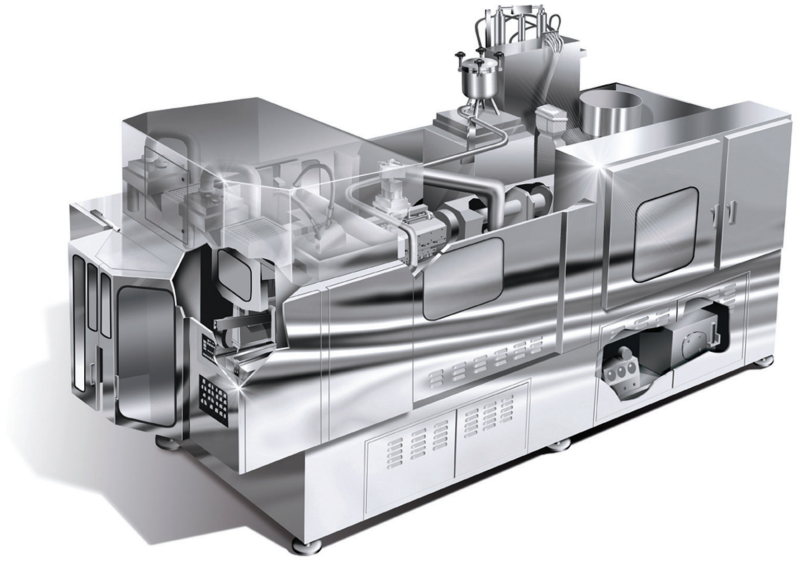

Figure 1: Advanced B/F/S Machines Can Produce Containers from 0.2-1000 ml

Various in-process control parameters, such as container weight, fill weight, wall thickness and visual defects provide information that is monitored and facilitates ongoing process control.

The forming, filling and sealing steps are achieved in one unit operation – the cycle being completed within seconds. Automation of B/F/S process steps eliminates manual intervention and reduces risk to the product. No production personnel are present in the filling room during normal operation.

ASEPTIC B/F/S SYSTEM MICROBIAL & PARTICULATE INTEGRITY

Sterility of B/F/S polymeric containers, materials and processes is validated by verifying that time and temperature conditions of the extrusion, filling and sealing processes are effective against endotoxins and spores.

Challenge studies have been conducted on the sterility levels of advanced B/F/S technology, which demonstrate a uniform capability of achieving contamination rates not exceeding 0.001% throughout the entire process. Even higher sterility assurance levels approaching 0.000001% have been achieved using high levels of airborne microbiological challenge particles.

Endotoxins are a potential pyrogenic contaminant, essentially dead bacterial cellular

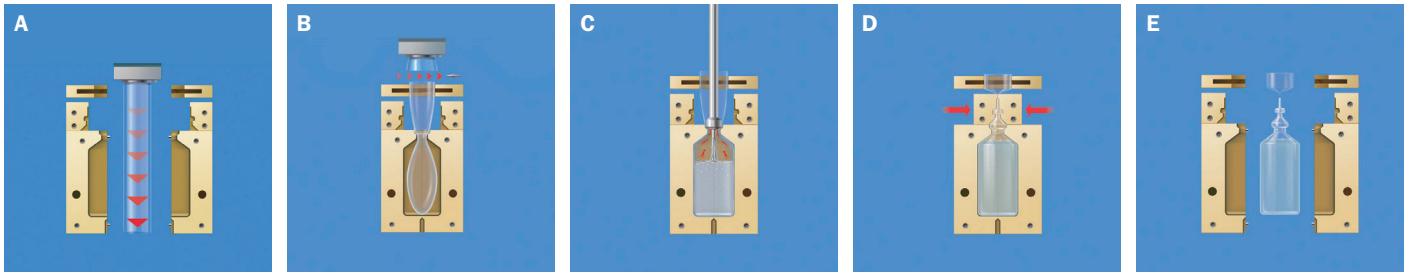

Figure 2: Selected Steps from the Aseptic B/F/S Process: a) Extrusion, b) Parison Closure, c) Container Formation, d) Seal, and e) Release.

matter. They can lead to serious reactions in patients, particularly with those receiving injections, ranging from fever to death. A critical aspect of B/F/S technology is its pyrogen-free molding of containers and ampoules. Extensive experiments confirming the efficacy of the B/F/S extrusion process have been performed using high levels of spores and endotoxin-contaminated polymer granules. The typical B/F/S extruders have demonstrated spore contamination rates of 0.000001%, and 0.00001% for endotoxins.

Control of air quality is critical for sterile drug product manufacture. B/F/S equipment design typically employs the use of specialised measures to reduce microbial contamination and particle levels that can contaminate the exposed product. The B/F/S process inherently produces a very low level of particulate matter and much of potential B/F/S microbial contamination (viable) in the air is mitigated by the absence of manual intervention in its critical areas. Non-viable particles generated during the plastic extrusion, cutting, and sealing processes are controlled. Provisions for carefully controlled airflow protect the product by forcing created particles outward while preventing any inflow from the adjacent environment. These "zones of protection" can also incorporate designs that separate them from the surrounding environment, providing additional product protection.

The B/F/S critical processing zone is continually supplied with HEPA-filtered air by an air shower device (shroud). The B/F/S critical zone is the area where the containers are exposed during filling. Air in the critical zone meets Class 100 (ISO 5) microbiological standards during operations. The critical zone is continuously monitored to ensure a positive differential pressure is maintained between the shroud and the adjacent cleanroom.

PLASTIC CONTAINERS

Domestic US drug companies have been slow to change to plastic, primarily due to the existing installed base of glass production of small-volume parenteral drugs in the US. However, the same is not the case with new drugs that are coming onto the market. These are more frequently being looked at, and submitted for FDA approval, in plastic containers produced by advanced B/F/S aseptic processing. Supporting this move is that the B/F/S processing resins, polyethylene and polypropylene, are generally considered inert by the FDA.

Many of the blow molding resins used in B/F/S processing have received international acceptance as suitable for food and drug applications, and many of the drug products produced outside of the US can be found packaged with these resins.

With the continued refinement of B/F/S technology, its acknowledgment by the FDA as a preferred technology for aseptic processing, and its growing acceptance by drug companies, the migration from glass to plastic containers used for aseptic pharmaceutical liquids is growing rapidly. It has become more cost effective to use plastic containers for aseptic liquids, which effectively costs manufacturers one-third of the cost of glass. Plastic is less expensive to ship because the containers are lighter. For small-volume parenterals, the use of plastic is inevitable, and increasingly being considered for these reasons.

Figure 3: Advanced Aseptic B/F/S Allows Easy Changeover for Varied Bottle Shapes and Formats.

Although many B/F/S systems make available only a limited number of container choices within each container category, some B/F/S machines do allow for broad versatility in container design. Advanced B/F/S machines can design virtually any container mold through the use of sophisticated CAD/CAM technology and 3D modeling. These design systems, when interfaced with the latest in CNC and EDM machinery, ensure fabrication of key components to precise tolerances.

B/F/S machines also allow mounting of separate sterile items (inserts) within the B/F/S container, and in-mold coding and engraving, which provide further opportunities for innovative design over glass products.

FLEXIBILITY WITH CHANGEOVERS GIVES SHORT RUNS, MORE UPTIME, MAXIMUM THROUGHPUT

Modern B/F/S system design is focused on simplicity and flexibility. Many B/F/S machines are configured to produce more than one bottle shape or format. This makes it easy to change over from one container size to another (see Figure 3). One B/F/S machine might produce a family of 2, 3 and 5 ml, then switch to a family of 5, 10 and 15 ml, or to one of 10, 15 and 20 ml, moving from one to the other with relative ease of machine set-up. This is ideal for manufacturers performing contract packaging of aseptic liquid pharmaceutical solutions, because of their need for changeover flexibility.

The growing usage of biologics is demanding packaging in different formats. They usually require smaller process runs and are typically heat sensitive. Many of these new biotechnological drugs do not withstand steam sterilisation or irradiation and so are best treated aseptically. More advanced B/F/S machines have been designed so they can handle these heat sensitive products.

Machine models are available that can produce containers ranging in size from 0.1 ml to 1000 ml at production rates of 15,000 units per hour, depending on container configuration.

B/F/S machine efficiency is very high. More advanced B/F/S machines can approach 99% uptime efficiency, which is significantly higher than traditional aseptic processing which is plagued with slow-downs in part because of manual interventions. To minimise potential system downtime further, some manufacturers are now segmenting their high-volume process lines into more short-run lines, in the event that if one of the lines goes down for maintenance or repair, it will not stop the entire production throughput.

When aseptic throughput is interrupted, or not running because of downtime, the entire process line is affected, which represents a significant production loss to the manufacturer.

AN ASEPTIC TECHNOLOGY DESTINED TO PREVAIL

More rapid container closure processing, elimination of aseptic critical-area personnel interventions, increased system uptime over traditional processing, pyrogen-free molding of containers and ampoules, more flexibility with container design, and an increased capability to capitalise on short runs – these are some of the benefits for manufacturers inherent in advanced B/F/S aseptic technology. And for consumers, increased safety and confidence in their drug products.

These are advances that are significant, if not fully realised yet within the aseptic liquid pharmaceutical marketplace. But it is apparent that advanced B/F/S aseptic technology is destined to become a major player in this arena.

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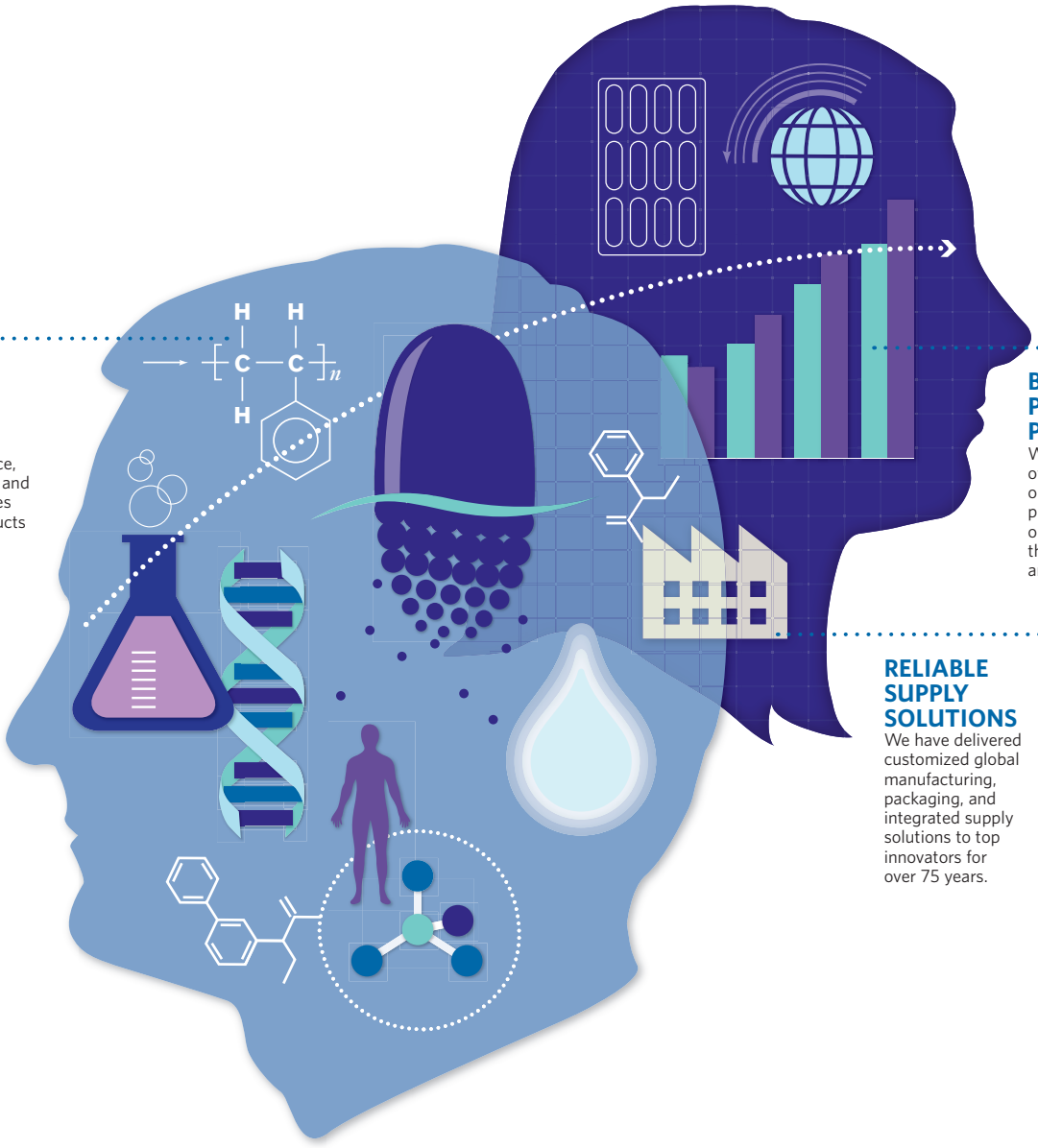

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