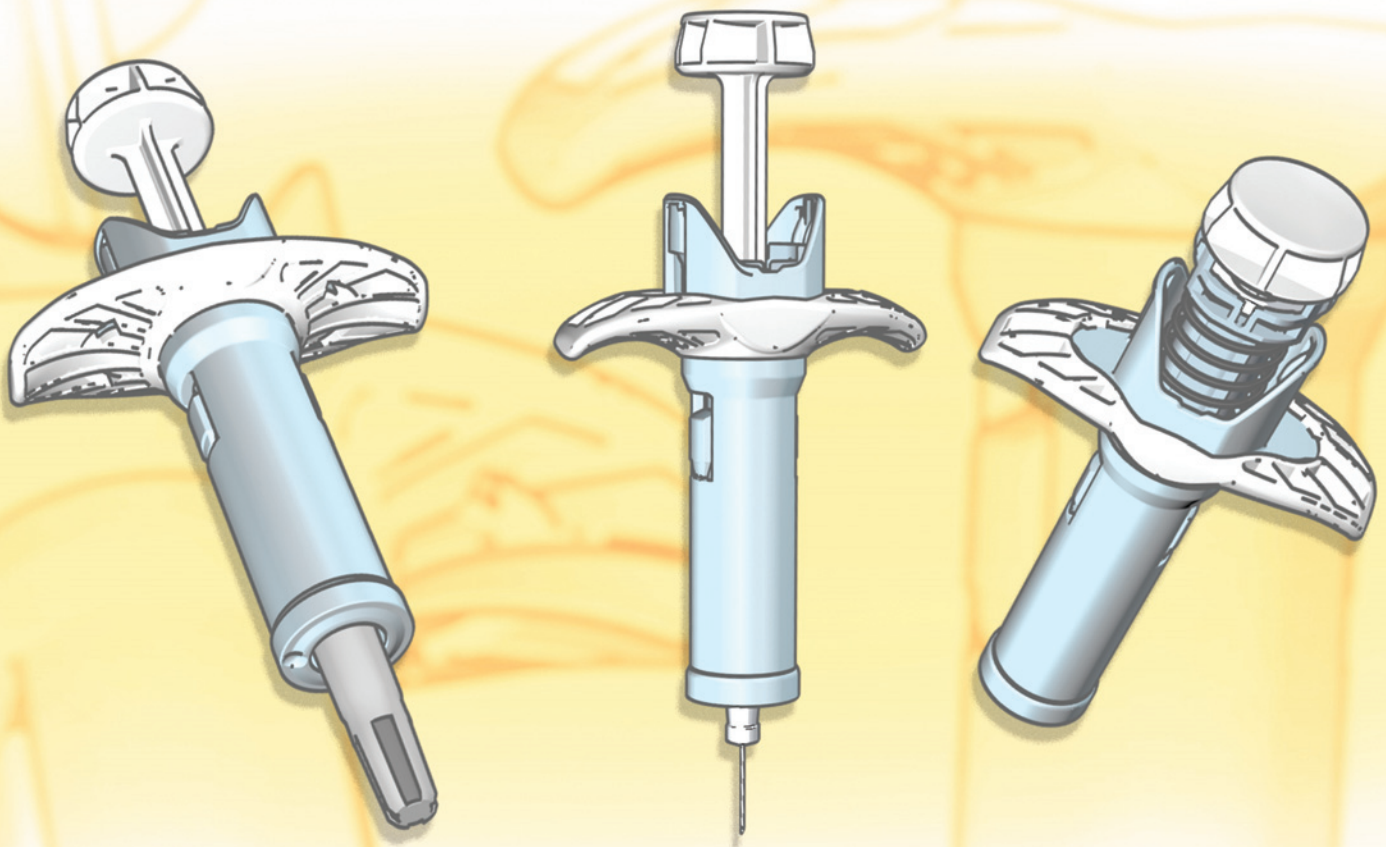


# PREFILLED SYRINGES



ONdrugDelivery Issue N° 52, September 25<sup>th</sup>, 2014

## Prefilled Syringes

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

### EDITORIAL CALENDAR 2015

Jan Ophthalmic Drug Delivery  
 Feb Prefilled Syringes  
 Mar Transdermal Patches, Microneedles  
 & Needle-Free Injection  
 Apr Pulmonary & Nasal Drug Delivery  
 May Injectable Drug Delivery: Devices Focus  
 Jun Novel Oral Delivery Systems  
 Jul Wearable Bolus Injectors  
 Oct Prefilled Syringes  
 Nov Pulmonary & Nasal Drug Delivery  
 Dec Delivering Biotherapeutics

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ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd. Registered Office:  
 The Candlemakers, West Street, Lewes,  
 East Sussex, BN7 2NZ, United Kingdom.

Registered in England: No 8348388.  
 VAT Registration No: GB 153 0432 49.  
 ISSN 2049-145X print  
 ISSN 2049-1468 pdf

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Front cover image: "Design concepts for the Safe'n'Sound® safety device", provided by Nemera (see this issue, page 32). Reproduced with kind permission.

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## ONdrugDelivery 2015 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January 2015	Ophthalmic Drug Delivery	December 8th
February 2015	Prefilled Syringes	January 12th
March 2015	Transdermal Patches, Microneedles & Needle-Free Injection	February 3rd
April 2015	Pulmonary & Nasal Drug Delivery	March 2nd
May 2015	Injectable Drug Delivery: Devices Focus	April 13th
June 2015	Novel Oral Delivery Systems	May 4th
July 2015	Wearable Bolus Injectors	June 1st
October 2015	Prefilled Syringes	September 7th
November 2015	Pulmonary & Nasal Drug Delivery	October 5th
December 2015	Delivering Biotherapeutics	November 9th



# EDITORIAL COMMENT



Prefilled Syringes is just one of a range of drug delivery subjects across the board that we cover in the various issues of this magazine (see 2015 Editorial Calendar, p4), but our issues on this particular topic have a special place for us. Prefilled Syringes is the topic on which ONdrugDelivery Magazine was founded, almost a decade ago now, with our first ever issue back in January 2005, and every year throughout these past ten years, Prefilled Syringes has remained an essential issue topic on our annual schedule. Without exception, every issue on this subject has been strongly supported by excellent contributions from the industry, imparting fresh and engaging new ideas and concepts, including this edition, Issue 52.

Two broad themes that appear to be emerging as talking points in the parenteral drug delivery industry at present, reflected in the articles that follow, are: 1) the use of training devices; and 2) device companies developing their role as expert consultants to biopharmaceutical companies, rather than simply specialist product/technology suppliers.

Training devices are coming to the fore as part of the tide of parenteral products designed for self-administration at home rather than in the clinic. It's desirable that the design of any product for the public should ensure that using the product is intuitive, so that following the correct steps is self-evident and, ideally, impossible to get wrong. However, self-injection of a medicine for the first time is an unfamiliar, intimate and potentially worrying process, yet for many disease indications, the medication is significantly life enhancing and sometimes life saving.

So self-injection training devices ("trainers") that contain no drug and have no needle can therefore overcome an important hurdle, allowing patients to get familiar with the look, feel and operation steps of the device before going on to use the real thing. Trainers, their applications and benefits – including advantages for patients, pharma companies and in terms of health outcomes and cost – are described in two articles in this issue. In his article on Page 24, Steven Kaufman of SHL Group highlights the trainer that is being launched with SHL's Molly auto-injector, and states that the majority of new auto-injectors will be launched with a trainer. Focusing on the area of user learning, training and training device approaches in-depth, Ian Scrimgeour of Shore Design Consultancy highlights the

consequences of inadequate training, examines two styles of training device (precise replication of parent device and multi-sensory enhanced educational devices) and sets out in detail the manifold benefits of the right trainer device (Page 42).

The second theme emerging in this issue is that of device companies emphasising to their existing and potential new pharma partners the value of their specialist and often extensive experience in the area of drug delivery device design and development. Ypsomed's Andreas Schneider points out in his piece (Page 18) that "biotech and pharma companies working toward their first market introduction ... may have little experience in evaluating drug delivery devices". In contrast, long-established device companies like Ypsomed have done this many times and as such are well placed to guide customers through all stages from design to end-assembly, and including in particular the compilation of data required for regulatory approval. Likewise, Steven Kaufman points to SHL's long experience as being a valuable resource available to its clients. He also touches on the key role of consultancy companies in device development too – especially in areas such as Human Factors studies, but raises a slight note of caution: "It is important to keep in mind that device companies may have some issues providing [consultants with] full access ... If a device company offers both industrial and mechanical design services, and the consultant offers the same, then the device company would be cautious providing a third party the same level of access to their staff, facilities and technologies as they give a customer."

We always try to maintain a balance of delivering content for you in ONdrugDelivery Magazine that comes both from regular, long-standing contributors, and also from companies featuring here for the first time. In this edition, I'm happy to be able to introduce no less than five companies that have never before appeared in ONdrugDelivery. First, Credence MedSystems, Inc, of Menlo Park, CA, US, presents the Credence Companion Safety Syringe System (Page 10), a passive needle-safety technology with modular design that, uniquely in the market, snaps onto syringes of any needle size. The device avoids the need for any change to the primary drug container.

As mentioned, we have a detailed article on at-home training devices from Shore – this

is the first of what I hope will be many contributions to ONdrugDelivery Magazine by Shore Design, based in Edinburgh, UK.

Then we have two equipment manufacturers to introduce. Zahoransky AG (Freiburg, Germany), an automation systems supplier for delivery devices, showcases its Z.BLIZZARD system for the glueless production of staked-needle polymer syringes (Page 46). "Well over 95% of all cannulas are still being glued in Europe," the company calculates. "If new developments and interrelations of all parties consider design, engineering and technical safety features, the future will certainly belong to glueless plastic syringes."

The other equipment supplier new to the pages of ONdrugDelivery is Morristown, NJ, US-based Kahle Automation. However, Kahle itself is by no means a start-up but a very well established industry veteran, since this year Kahle Automation is celebrating 95 in the business. The company states in its profile (Page 30) that it is "the only large-scale automation company in the world that focuses exclusively on automated assembly, process and packaging equipment for pharma, medical device and healthcare industries".

Finally, a fresh identity for a well-known company. Namera (Paris, France) is the new name for Rexam Healthcare Devices, following the acquisition in May by Montau Private Equity. Information about the new name, and Namera's capabilities and offering within drug delivery can be found in its profile on Page 32.

These new contributors mentioned above, together with articles from familiar contributors such as teamtechnik (Page 14), The Tech Group division of West Pharmaceutical Services (Page 6), SHL, Ypsomed and Gerresheimer (Page 35), come together in this edition to give what I hope will be a useful and engaging insight for you into what's new, and what is going on in the global prefilled syringes industry today.

You'll be able to meet the companies that feature here, and most of the other key players in the prefilled syringes industry, in Huntingdon Beach, CA, US, for PDA's Universe of Prefilled Syringes conference there on October 6th-7th. It's a must-attend event of the year, and I hope to have the opportunity see you there!

*Guy Furness, ONdrugDelivery Magazine*



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# DETECTING THE COST OF POOR QUALITY: CONTRACT MANUFACTURING BEST PRACTICES

In this article, Leigh Toole, Director, Quality Assurance, The Tech Group (West Pharmaceutical Services), provides some useful advice on how to assess and evaluate key aspects of a potential contract manufacturer partner in order to avoid pitfalls and to ensure the most fruitful relationship for both parties.

Medical device or combination product contract manufacturers are engaged by pharmaceutical companies to deliver safe and effective products. Selecting the right contract manufacturer (CM) can help to ensure a drug product's ultimate success, so several factors must be considered before entering a contractual partnership. By defining specific requirements that a contract manufacturer must have, pharmaceutical companies can narrow the options that ultimately lead to the best choice to ensure a rewarding partnership.

The first step when selecting a contract manufacturer is to perform a comparative analysis of the various CM options. Such an analysis can be completed quickly with minimal expense, and will narrow the list considerably. Additionally, prior to entering into a contractual partnership, site audits must

In order to avoid pitfalls and make a data-driven decision when comparing CMs, pharmaceutical companies should evaluate the following key aspects that, when used in conjunction with a comparative analysis and site visit, will identify the potential risks associated with outsourced manufacturing:

- Quality Management System
- Risk management
- Manufacturing capability
- Design control system
- Root cause analysis
- Quality agreement.

## QUALITY MANAGEMENT SYSTEM

Performing an audit of a potential CM's Quality Management System (QMS) can establish the firm as an approved, certified or qualified supplier. To start, request a copy of the organisation's quality manual in preparation for a potential audit. Use comparative analysis as a filtering tool to compare the quality manuals of three to six potential CMs. Differences will surface during this exercise, and some firms may deny the request, which may be indicative of the transparency (or lack thereof) to be expected if the relationship moves forward. Comparing quality manuals from multiple firms can identify differences and determine how the CM will meet the predetermined requirements.

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"Comparative analysis can determine if the requirement has been missed or if the firm has invested the time required to define key processes, sequence and interaction, and the control strategy associated with these processes"

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be conducted to further compare the CM's ability to meet specific needs. Site audits can prevent a selection that might result in the high costs associated with poor quality.



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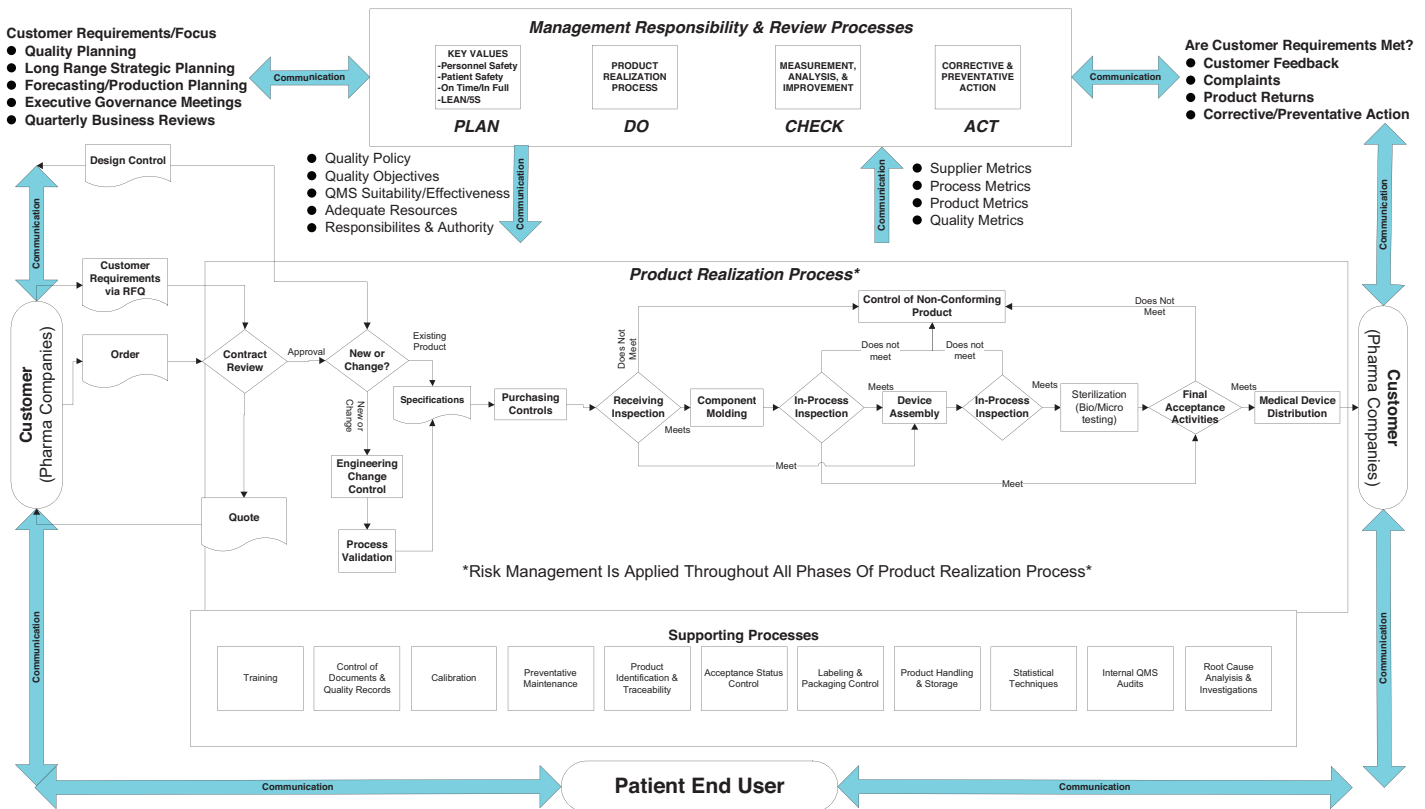


Figure 1: Quality Management System flowchart.

During a QMS evaluation and comparison, focus on how the CM has elected to meet the ISO 13485 requirement established in section 4.1 (a) to “identify the processes needed for the quality management system and their application throughout the organisation”, and section 4.1 (b) which requires the CM to “determine the sequence and interaction of these processes”. Many firms have failed to define key processes, let alone the sequence, interaction and associated control strategy for these processes. When a firm attempts to meet this QMS requirement, it is typically expressed as a diagram referred to as the “model of a process-based quality management system” with graphic representation of Plan-Do-Check-Act methodology. Although not the intent of the guidance, the example from the standard is often copied into a quality manual. Comparative analysis can determine if the requirement has been missed or if the firm has invested the time required to define key processes, sequence and interaction, and the control strategy associated with these processes (see Figure 1). This requirement has implications on the quality culture of the organisation and the strength of its management team.

Review the quality policy and quality objectives with the management team. Ensure there is documented, objective evidence that all employees have been trained

to the quality policy and objectives. Evidence of training does not necessarily translate to training effectiveness. Ask the management team to demonstrate that the quality policy and objectives are understood and have been implemented throughout the organisation. An all-employee survey that includes a written response where employees describe what the quality policy and objectives means is an effective tool to ensure that the principles have been internalised. Reviewing the strength of the QMS can be an early indicator of things to come. Pharmaceutical companies should look for a CM whose approach aligns with its own QMS.

### RISK MANAGEMENT

Evaluate the strength of the CM’s risk management program. In ISO 13485 section 7.1 (d) the requirement states that “the organisation shall establish documented

requirements for risk management throughout product realisation”. This section also indicates “ISO 14971 [for] guidance related to risk management”. It is not uncommon for an organisation to struggle with compliance to these requirements, and it can be a challenge to establish rules regarding when to use a particular risk management tool. Questions to ask include: When should a preliminary hazard analysis be performed? When should a design Failure Mode and Effects Analysis be generated? What are the rules of engagement for risk priority numbers (RPN) in terms of when risk mitigation activity is appropriate?

Since one entity may be more risk tolerant than another, it can be difficult to align the risk management approaches of two companies. If the potential CM’s comfort level of residual risk varies greatly, they may be more accepting and comfortable with higher RPN outcomes than the pharmaceu-

“Evidence of training does not necessarily translate to training effectiveness. Ask the management team to demonstrate that the quality policy and objectives are understood and have been implemented throughout the organisation”

tical company's system allows without the need for mitigation, reduction or the elimination of the source(s) of the risk.

When reviewing the strength of a risk management programme, evaluate how the firm has applied risk management into some of the key QMS elements: internal audits, nonconforming product, complaints, corrective and preventive action (CAPA) and change management. Evaluate whether the firm applies a risk assessment that provides a documented evaluation based on frequency

- Does the CM have a history of successfully producing the projected volumes?
  - Does the CM have a robust equipment calibration, qualification, process validation, preventive maintenance and statistical process control system in place?
  - Does the CM have the ability to perform manual, semi-automated and/or fully automated assembly; final acceptance activities; final packaging, drug handling and labelling?
- Most often, past performance is a predictor of future performance and dealing with

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“Any organisation can appear to be in a state of control for a period of time, but the true measure of control associated with sustaining manufacturing is long-term supply ‘on time, in full’ and ‘right the first time’ without disruption”

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and severity that establishes a documented, defensible rationale regarding when issues will be investigated and when issues will be escalated to the CAPA system. When seeking a medical device contract manufacturer, look for evidence of the best practices described above as another early indicator of future success. Upon reviewing these policies, determine if the CM has the freedom to operate with little to no intervention. Recognise that shortcomings in this area will translate to greater oversight along with a secondary review and approval of the issues if a partnership were entered into with this entity.

### MANUFACTURING CAPABILITY

Quite often, medical device or combination product CMs are sought based on technical fit/manufacturing capability core competency. When using comparative analysis to evaluate manufacturing capability, evaluate the answers to the following questions to help reduce risk:

- Is this particular product need a core competency or is the technology associated with product realisation a stretch for this potential CM?
- Has the CM produced product with similar features and characteristics?
- Does the CM's technical staff possess the education, background, training and experience to be successful with this endeavour?
- Does the facility and infrastructure align with the overall contamination control strategy for the product?

a company that has a history of high costs associated with poor quality is not a decision that should be taken lightly.

### DESIGN CONTROL SYSTEM

A potential CM must be evaluated on the strength of its design control system. Has the firm established and does it maintain a compliant design control system that could be leveraged in an effort to design and develop components, sub-assemblies, medical devices, pharmaceutical primary packaging components, combination product constituents and combination products? If a design control system has been established, does the system end with product launch or does it include post-market surveillance activities designed to provide input to management review to drive continuous improvement as the product and process is “monitored and measured” in accordance with section 8.2.3 and 8.2.4 of ISO 13485?

### ROOT CAUSE ANALYSIS

Any organisation can appear to be in a state of control for a period of time, but the true measure of control associated with sustaining manufacturing is long-term supply “on time, in full” and “right the first time” without disruption. When problems arise, how will the organisation respond? How has it responded previously? Problems offer an opportunity to demonstrate the organisation's ability to deploy root-cause analysis tools established for such an occasion.

An effective CM will deploy resources based on risk derived from a risk assessment that defines the frequency and severity associated with a given issue. Although an investigation can be performed at any time per The Tech Group's QMS, Level 1 (low occurrence, low risk) issues per procedure do not require investigation. Level 2 issues require a documented justification if an investigation is not performed. Level 3 (high occurrence, high risk) issues require investigation and a documented justification if the issue is not escalated into the corrective and preventative action (CAPA) system. These principles and methodologies, along with a robust investigation process that combines proven quality tools, enable a CM to be compliant while at the same time drive efficiency while applying risk management throughout all-product realisation.

When evaluating a potential CM, spend adequate time in the critical quality systems to determine the strengths or weaknesses associated with the firm's ability to: recognise a problem; quickly and methodically determine the root cause; effectively contain the problem; apply corrections; and issue corrective and preventive actions that drive significant sustainable continuous improvement.

### QUALITY AGREEMENT

A robust quality agreement must include guidance and rules of engagement associated with the critical quality systems. The quality agreement must define specific roles and responsibilities of each organisation and identify shared responsibilities.

Finally, the quality agreement must define formal governance expectations for the working team, the management team and management with executive responsibility. These keys will drive continuous improvements and accountability to a predetermined and agreed-upon scorecard that measures the success of the partnership.

Using the keys described above along with comparative analysis will greatly affect the CM selection process by uncovering issues prior to entering a contractual partnership. It is important to know specifically what constitutes a great fit in a strategic contract manufacturing partnership. CM's are not “one size fits all” and pharmaceutical manufacturers must invest adequate time in the selection process. By doing so, the reward is an exponential return on the initial investment that will lead to the long-term successes associated with a highly effective collaborative team.



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# CREDENCE MEDSYSTEMS, INC & THE CREDENCE COMPANION SAFETY SYRINGE SYSTEM

Featuring for the first time in *ONdrugDelivery Magazine*, John A. Merhige, Chief Commercial Officer, Credence MedSystems, introduces the Credence Companion Safety Syringes System. This innovative, modular technology provides fully customisable needle safety without coming into contact with the drug prior to use and without any change to the existing primary drug container.

## CREDENCE MEDSYSTEMS, INC

Credence MedSystems is focused on delivering medications safely for the benefit of our patients, caregivers and biopharmaceutical partners. The Credence team brings curiosity, a fresh perspective and an intense desire to understand the needs of both the end-user and pharmaceutical manufacturer to the overriding goal of improving patient care.

## THE CREDENCE COMPANION SAFETY SYRINGE SYSTEM – INNOVATION WITHOUT CHANGE

The Credence Companion Safety Syringe System offers best-in-class drug delivery and a vastly simplified path to

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“Credence understands that the journey (the path to commercialisation) is as important as the destination (the end product)”

---

market for our biopharmaceutical partners. This philosophy of *Innovation Without Change* resonates throughout Credence and is applied to the design of the Companion as well as to the company’s partnering business model. By offering the innovation

of the final device without the traditional primary packaging changes that require substantial development and regulatory work, Credence MedSystems has shifted the paradigm for commercialising a drug in a differentiated delivery system. Credence understands that the journey (the path to commercialisation) is as important as the destination (the end product).

## THE JOURNEY: A SIMPLIFIED COMMERCIALISATION PATH FOR OUR BIOPHARM PARTNERS

Drug manufacturers face significant obstacles in the effort to make improvements to existing products or launch new drugs in advanced delivery systems. This is due to the development and regulatory effort traditionally required to modify a drug/device combination product. While the resulting resistance to change is understandable and often warranted, it has had the undesirable effect of keeping technological advances in delivery systems out of the market.

The Credence Companion addresses this challenge with its modular approach, thereby significantly simplifying the commercialisation path. Biopharm manufacturers have complete freedom to choose and source the critical syringe, plunger/stopper and tip-cap primary package components from any vendor(s) they choose. The Companion plunger rod, Flex



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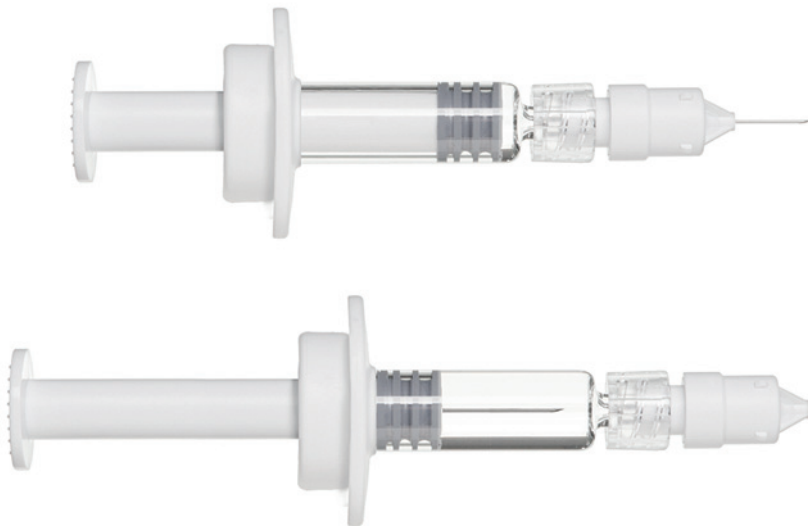


Figure 1: At the completion of the injection, the needle automatically retracts into the barrel of the syringe and the device is permanently disabled.

Finger Flange and Guide-On Needle components accompany and ‘snap on’ to the pre-filled syringe. The primary drug container is undisturbed and there is no contact between Companion components and the drug product prior to use. This approach dramatically impacts the development requirements and reduces the sourcing risk for the biopharm partner. The Companion offers drug companies a new option to differentiate their products while delivering the best technology available to their patients and providers.

### THE DESTINATION: A BEST-IN-CLASS DRUG DELIVERY DEVICE

#### Safety and Compliance:

For the end-user, the Companion Syringe is a best-in-class safety device with passive needlestick prevention features. The user can perform standard air bubble removal and aspiration techniques without fear of prematurely engaging the safety mechanism. At the completion of the injection, the device provides visual, audible and tactile cues and the needle automatically retracts into the barrel of the syringe (see Figure 1). The syringe is then automatically and permanently dis-

abled from future use. The Companion allows the choice of any size needle (Figure 2), offering passive safety even with long needles – 2” (5.1 cm) and beyond if needed. This is unique in the market.

### DIFFERENTIATION THAT GOES BEYOND NEEDLESTICK PREVENTION

#### Reconstitution:

Conventional safety devices often fail in lyophilisation applications due to premature activation of the safety features during reconstitution of the drug product. When the Companion is pre-filled with a diluent, the user can deliver the solution into the vial for reconstitution and then draw the reconstituted drug product back



Figure 2: The Companion allows passive safety with any size needle. This is unique in the market.

into the syringe, all while maintaining the passive safety intact for the subsequent injection into the patient (Figure 3).

#### Connection Integrity:

Credence has developed the Guide-On Needle Cover to address the prevalence of poor luer connection issues between conventional needles and syringes. These failures, whether from inadequate design and instructions or user error, have serious consequences including inaccurate dosing, wasted drug product, and needles being left in patients. The Guide-On Needle Cover will not allow the needle to be exposed until it has been attached properly and then provides the user audible, tactile and visual feedback that the connection is secure (Figure 4).

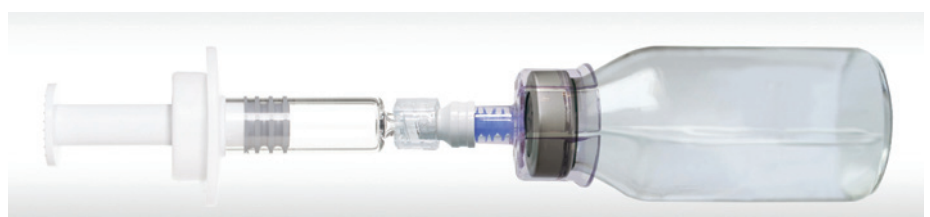


Figure 3: The safe solution for reconstitution applications – conventional reconstitution with passive safety.



“By offering the innovation of the final device without the traditional primary packaging changes that require substantial development and regulatory work, Credence has shifted the paradigm for commercialising a drug in a differentiated delivery system”



Figure 4: The Guide-On Needle Cover provides “Click” confirmation that the needle is secure.

**CUSTOMISATION & FLEXIBILITY:  
IN THE PRODUCT & THE  
BUSINESS MODEL**

In addition to the Companion’s safety and usability end-user benefits, vast opportunities exist to customise the design for

“The Companion plunger rod, Flex Finger Flange and Guide-On Needle components accompany and ‘snap on’ to the prefilled syringe.

The primary drug container is undisturbed and there is no contact between Companion components and the drug product prior to use”

the specific requirements of the application (Figure 5). Credence can incorporate various needle sizes, Flex Finger Flange and thumb pad designs, materials, colours and packaging configurations, all without deviating from the core modular approach of the Companion design.

This passion for offering our partners *Innovation Without Change* extends to our business model and the supply chain flexibility it provides. Just as our biopharm partners have the freedom and flexibility to choose and source the critical primary package components of the syringe, they also have complete freedom to choose their preferred moulding and assembly partners. Credence provides its expertise in technology transfer and automation to deliver a seamless integration into the filling line.

Credence approaches every challenge with the philosophy of offering *Innovation Without Change* in order to improve patient care by truly addressing the needs of both the end-user and our pharmaceutical manufacturer partners.



Figure 5: Customisable designs: Credence can incorporate various needle sizes, Flex Finger Flange and thumb pad designs, materials, colours and packaging configurations.

THE CREDENCE  
COMPANION  
SAFETY SYRINGE SYSTEM

Please reach out to John A Merhige to discuss how Credence and the Companion can help bring *Innovation Without Change* to your drug product.

*This product has not been evaluated by the US FDA.*



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This product has not been evaluated by FDA.



# PROFITABLE AUTOMATION FOR DEVICE ASSEMBLY & FUNCTIONAL TESTING VIA STANDARDISED PLATFORMS

In this article, Reiner Zeidler, Sales Manager, Medical Systems, teamtechnik Group, outlines how the company's modular TEAMED production system meets industry's need for new solutions in this area – from early development applications right through to commercial-scale manufacture.

There is increasing demand for new solutions to automate the manufacturing of medical products from early-stage clinical trials through to a successful, high-volume production programme. Teamtechnik Group is a leading supplier in the development and implementation of turnkey production systems for medical devices.

## THE TEAMED PLATFORM

With its TEAMED platform, teamtechnik offers a scalable linear production system for both automated assembly and

functional testing of devices (Figure 1). TEAMED is a multi-purpose automation platform, specifically developed to address the particular challenges associated with the assembly of medical devices and designed to meet the needs of pharmaceutical production systems.

The TEAMED platform enables the integration of sophisticated assembly processes (Figure 2) with up to 100% end-of-line testing. It also facilitates production that is compliant with international standards such as cGMP, US FDA and CE – and is certified to Class 6 Clean Room specifications.

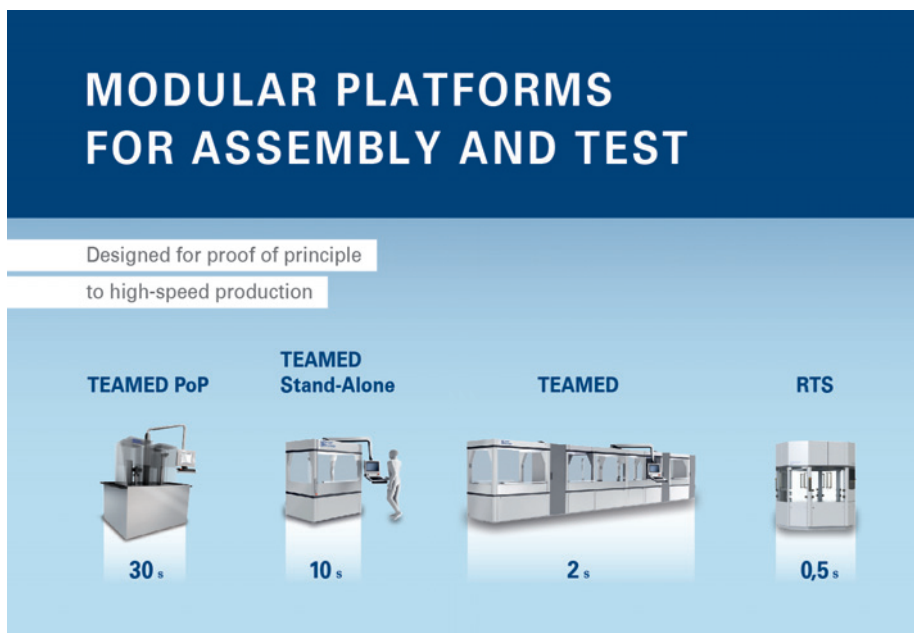


Figure 1: Modular platforms for assembly and function test.



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“To ensure that customers have access to relevant expertise during post-installation and ramp-up phases of their projects, teamtechnik provides resident engineers – based locally and available on-site – during this critical phase of a programme”

The TEAMED platform has been developed to cater for proof-of-principle applications as well as for high-speed industrialisation and enables the incorporation of processes which have been utilised for prototype production, directly into series manufacturing. This means that critical process steps are verified at the earliest possible stage, providing reassurance for future commercial-scale production from the outset of a programme. For example, Figures 3-5 show steps in the assembly of an injection device.

Drawing upon teamtechnik’s comprehensive library of processes and its engi-



Figure 2: Assembly system at TEAMED platform.



Figure 3: Testing and positioning the shell of an injector device.



Figure 4: Laser engraving the injector’s dial.



Figure 5: Testing and inserting the injector’s dial.



“The TEAMED platform has been developed to cater for proof-of-principle applications as well as for high-speed industrialisation and enables the incorporation of processes which have been utilised for prototype production, directly into series manufacturing.”

neering expertise, the TEAMED solution optimises assembly processes and reduces time to commercialisation for new products.

A typical cycle of a development project and commercialisation for a new injectable device, utilising the TEAMED platform, is described below.

### “TEAMED POP” FOR PROTOTYPE PRODUCTION

#### Phase I Clinical Trials

Injectable device assembly involves many complicated processes, which must either be monitored in-process, or results verified after the process. Ideally, in order to minimise time to market, a device design and assembly process would be completely defined from the outset of Phase I. For reasons of cost, risk and design evolution, this ideal is often not achievable and teamtechnik’s TEAMED PoP (proof-of-principle) platform provides a solution for such a challenge.

Incorporating both automated and manual elements, TEAMED PoP offers the ability to perform and monitor critical assembly processes with automatic solutions at a very early stage in a project, whether or not a device design has been fully defined at that point. Able to accommodate up to five process operators working at the machine, it is often the case that a customer will engage with teamtechnik and utilise TEAMED PoP, whilst a device is still in development.

### “TEAMED STAND-ALONE” FOR SMALL-VOLUME PRODUCTION

#### Phase III Clinical Trials

Providing continuity from the Phase I experience utilising TEAMED PoP, the same process units can then be integrated into a TEAMED Stand-Alone machine for small-volume production to support Phase III clinical trials.

TEAMED Stand-Alone is a semi-automated assembly line with process materials

fed by operators, and with process stations being linked by a carrier transport system. The carrier features have the same design as in the corresponding TEAMED PoP machine, although typically incorporating additional nests for manually pre-loaded parts. Although most of the assembly operations will be performed automatically, the refined process stations are based on similar technologies to those on the precursor TEAMED PoP system.

### “TEAMED” FOR INDUSTRIALISATION

#### Commercial Scale

For high-volume, commercial-scale production, teamtechnik provides a fully-automated TEAMED line with all device components being delivered by bowl feeders or palletising systems. The carrier design is ideally based on the same concept as used for the earlier TEAMED PoP and TEAMED Stand-Alone machines.

A number of critical processes – such as dosing, gluing or welding (ultrasonic or laser) – will typically have been refined and validated with the TEAMED PoP and TEAMED Stand-Alone systems, and are continued through in the design of the high-volume manufacturing line. The simple replication of validated processes can significantly reduce time to market for a new device, thereby improving return on investment. This benefit can be realised due the modular design of the TEAMED system, using individually customised processes and a machine concept which combines the flexibility and operational efficiency of pre-validated servo-actuated motions and cam-driven units.

### “RTS” CAM-DRIVEN PLATFORM FOR HIGH-SPEED PRODUCTION

Drawing on the considerable experience and expertise of teamtechnik’s Pfuderer division, RTS is the company’s high-speed

automation platform. Typically operating at up to 120 cycles per minute, RTS offers a cam-driven ring transfer system, providing between eight and 32 individual stations, and is designed for processes which require the highest outputs.

### MARKET LEADERS TRUST IN TEAMTECHNIK

Customers rightly expect robust, reliable and cost-effective production systems for their medical device products. Providing the foundation for long-lasting customer relationships, teamtechnik’s engineers are well-versed in the design and building of process technologies which offer sophisticated assembly and functional testing for a wide range of production applications.

### ABOUT TEAMTECHNIK GROUP

Based in Freiberg, Germany, teamtechnik Group is an international leader in highly flexible automation technology and has been providing intelligent and reliable automation solutions for medical, pharmaceutical, diagnostic and other industries for several decades.

With 850 employees throughout the world, and annual revenues of more than €150 million (£120 million), teamtechnik supports customers from its bases in Germany, Poland, France, China, Korea and the US.

To ensure that customers have access to relevant expertise during post-installation and ramp-up phases of their projects, teamtechnik provides resident engineers – based locally and available on-site – during this critical phase of a programme. Through its global service network, teamtechnik also ensures that production equipment is available around the clock, providing customers with dedicated service team contacts, each with comprehensive knowledge of a particular customer’s manufacturing system.



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- Excellent product and process expertise
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- Solutions for proof of principle and prototype production

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# FROM CUSTOMER NEEDS TO COMMERCIAL PRODUCTS: FAST & LOW-RISK CUSTOMISATION OF INNOVATIVE INJECTION SYSTEMS

In this article, Andreas Schneider, Business Development Manager, Ypsomed, highlights new emerging requirements of biopharma companies and describes how Ypsomed has established a range of innovative platform products, based on proven expertise and capabilities, and well-honed development and manufacturing processes, in order to meet its biopharma partners' and customers' needs fully and completely.

With the global increase in diabetes, the large number of new biologics, and the surge in biosimilar product launches, the importance of subcutaneous self-injection of biopharmaceuticals continues to grow. Modern therapy concepts that fulfil patients' and payers' needs for convenient, discreet, safe, compliant and cost-efficient drug administration further accelerate the trend towards self-injection.

Biopharmaceutical companies increasingly focus on self-injection devices as a mechanism for differentiating the drug product. As a result, manufacturers of innovative drug delivery systems have become

of injection systems to equip biopharmaceutical companies, in a flexible manner, with novel injection pens and auto-injectors customised to their individual needs.

Responding to these emerging requirements, Ypsomed has built up comprehensive platform products that each meet key customer needs yet are specifically designed to be modified into customer-specific products. The platform products enable flexible customisation while minimising project risks and shortening time to market. Ypsomed decouples the development of new platform products from the customer project and thereby moves risk in-house

to cover platform development and installation of manufacturing infrastructure (see Figure 1). Each customer project stems from an existing platform based on an established patent position and proven technology.

Driven by patient needs, market intelligence and new technology, the development of novel platform products also requires significant investments in manufacturing capacity.

key partners for the successful development and commercialisation of the final combination product. Increased pressure on healthcare product prices, increased complexity in drug formulation, and more stringent regulatory scrutiny require manufacturers

Ypsomed supports its partners not only by customising the injection systems to market demands, dosing needs, and to the primary container but also by incrementally expanding its installed manufacturing infrastructure to match customer capacity

“Manufacturers of innovative drug delivery systems have become key partners for the successful development and commercialisation of the final combination product”



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# Ypsomed Custom Products

## Low risk and short time-to-market

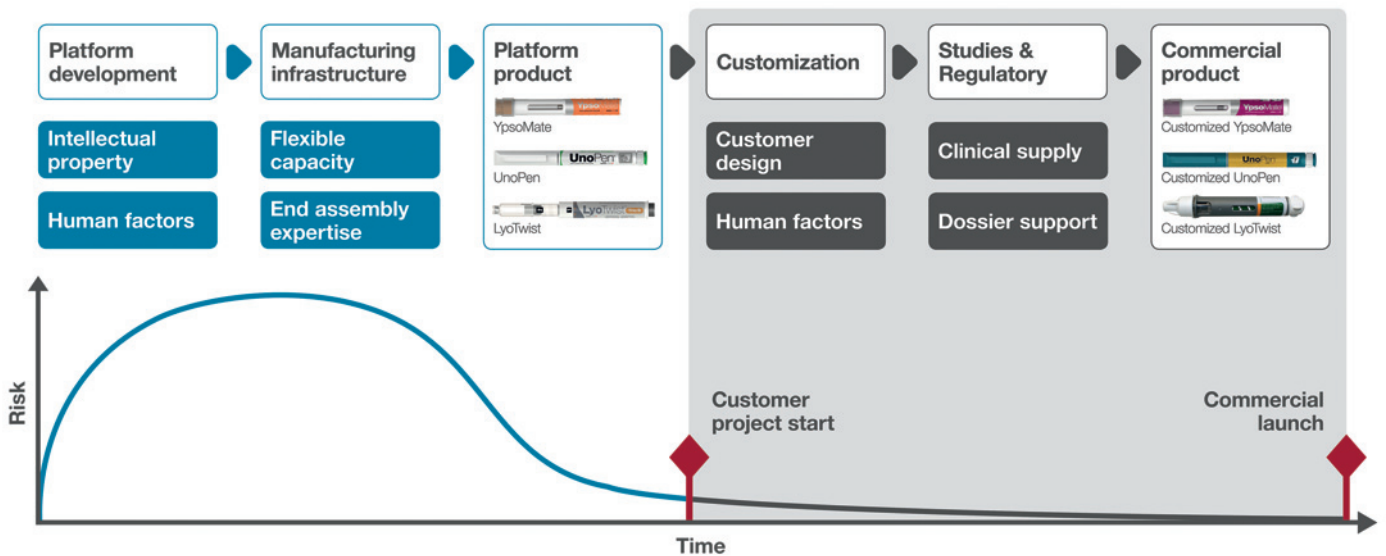


Figure 1: Ypsomed’s platform-based product strategy lowers risk and shortens timelines during customer projects.

requirements. Ypsomed today offers one of the broadest ranges of pen and auto-injector platforms (Figure 2) and supports its customers in selecting the ideal device for their specific application.

Consider the UnoPen (shown in Figure 2), Ypsomed’s variable and multi-dose disposable pen platform that offers key features such as intuitive dial and dose handling, audible feedback during dosing and delivery, or the last-dose stop functionality to ensure that the dialled dose cannot exceed the remaining volume in the cartridge. Customisation

to individual design, dosing, and cartridge requirements makes the UnoPen platform ideal for use across a range of hormone-based therapies including – but not limited to – insulin, glucagon-like peptide-1 (GLP-1), human growth hormones (hGH), follicle stimulating hormone (FSH), or parathyroid hormone (PTH).

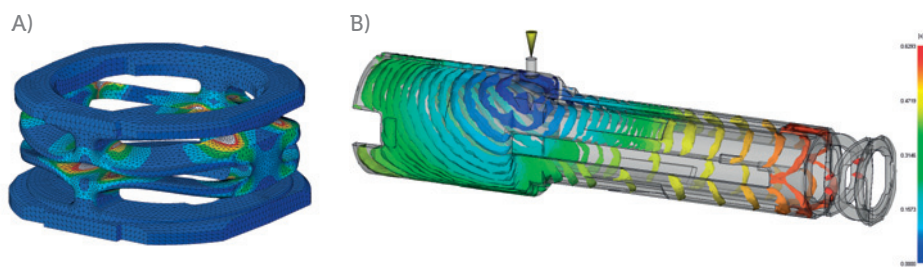
Ypsomed’s platform products also include the growing auto-injector segment for pre-filled syringes. The YpsoMate (Figure 2) disposable auto-injector provides patients with an easy and convenient two-step auto-

matic injection. The patient first triggers the injection by pushing the auto-injector on to the skin. The device then signals completion of the injection through a clearly audible end-of-injection click and visual feedback in the large viewing window. The needle remains hidden during injection and is shielded after use.

The platform-based strategy for injection systems accelerates time to market and lowers project risk only if accompanied by appropriate capabilities. It is precisely the unique combination of the platform-based strategy and capabilities that

	Pens								Autoinjectors			
	ServoPen®	YpsoPen®	UnoPen™	UnoPen™ Fix	LyoTwist™ Trio	LyoTwist™ Trio S	LyoTwist™ Vario	LyoTwist™ Vario S	YpsoMate®	YpsoMate® Control	YpsoJect®	VarioJect™
Reusable	●	●										
Disposable			●	●	●	●	●	●		●	●	●
Automatic injection	●						●	●	●	●	●	
Multiple-dose	●	●	●	●								
Single-dose					●	●	●	●	●	●	●	●
Adjustable dose	●	●	●	●			●	●				●
Fixed dose				●	●	●			●	●	●	

Figure 2: Ypsomed’s range of pen and auto-injector platforms.



**Figure 3: Computational modelling techniques used for development, evaluation, and testing of self-injection devices. The two examples are based on the mechanic holder, a key component of YpsoMate, the two-step auto-injector: (a) Finite Element Analysis of the mechanic holder front part, (b) Simulation of the flow characteristics after injection of the molten thermoplastic into the mould cavity.**

enables Ypsomed to manage all processes during the development of innovative injection systems effectively – from early-stage innovation, clinical supply, and commercial launch, to customer support throughout the product lifecycle. Specifically, Ypsomed's ability to develop novel platform products and to supply tailored injection systems flexibly and efficiently for almost any customer need rests on four key capabilities:

- (1) Key expert functions centralised in one location in Switzerland
- (2) The consistent use of state-of-the-art development methods for device design and testing
- (3) Installed automated manufacturing capacities
- (4) Expertise as consultants in drug delivery and injection systems.

#### Centralised expert functions:

Ypsomed views the integration of specialised in-house expertise as an essential instrument for effectively adapting platform products to its customers' needs. Accounting for the uniqueness of each customer project, Ypsomed equips project

injection devices directly shapes Ypsomed's organisational set-up.

Throughout all customer project phases, such as customisation to individual design requirements, human factor studies, clinical supply, or regulatory filing, all competencies are centered at Ypsomed headquarters in Burgdorf, Switzerland. Co-location enables a richer and more efficient dialogue among experts, supports rapid learning processes across specialisations, and helps to establish as well as sustain effective risk management programmes. Tight cross-functional integration is essential for early-stage, in-house new product platform development as well as for the installation of manufacturing infrastructure. Ypsomed seamlessly integrates knowledge from market research (e.g. patient feedback, emerging user needs, or novel therapy concepts) with insights from design ideas, intellectual property and technical calculations.

#### State-of-the-art development methods:

To accelerate the development of new platforms and customisation of platform products while mitigating any technical risks, Ypsomed leverages a comprehensive toolbox for device design and testing.

finite element analysis is routinely applied to develop and evaluate functional designs of new device parts (see Figure 3a).

Generating a mathematical model that accurately reproduces material properties; finite element analysis helps generate the optimal design solution through repeatedly twisting and deforming the virtual prototype with the help of dedicated software. Other computational methods used for the investigation of manufacturing processes (see Figure 3b) further contribute to shortening turnaround times and lowering risk.

Similarly, in-house rapid prototyping, or prototype tooling, enable Ypsomed to prepare prototype parts and functional devices quickly, independent of the project stage. Rapid prototyping provides models in less than 24 hours for demonstrational purposes or initial functional evaluations. Despite the apparent technology-driven approach to the development of new devices, experts at Ypsomed integrate the abilities, preferences, and limitations of the device user in their design considerations following appropriate human factor studies.

Reflecting an essential information package required to work towards market authorisation, human factor (HF) studies minimise any use-related risks. Early formative HF studies, for instance, are accomplished to iteratively adapt the initial design of the device and refine the instructions for use. Constant involvement of end-users throughout new product development ensures that the final injection system avoids potential user-related errors.

#### Installed automated manufacturing capabilities:

New platform development requires timely investment in manual, semi-automated, and automated manufacturing capacities specifically designed for platform products. Strengthening its manufacturing sites in Switzerland, Ypsomed leverages already available technical expertise and continuously improves the manufacturing process. Ypsomed manufacturing facilities can be easily scaled to meet changing customer demand and account for future expansion. In addition, the facilities are able to manufacture different customer variants with unique industrial and technical designs with the appropriate level of automation.

For the UnoPen platform, Ypsomed has invested significant amounts in building up generic manufacturing capacity to meet initial customer demand. In so doing, Ypsomed pools investments in manufacturing infrastruc-

"Ypsomed decouples the development of new platform products from the customer project and thereby moves risk in-house to cover platform development and installation of manufacturing infrastructure"

teams with specialists from project management, product and process development, customer management, regulatory, risk management, quality assurance and control, purchasing, and complementary expertise beyond its organisational boundaries, such as industrial design and human factors research. The need for tight cross-functional integration in developing innovative

The technical experts employ a range of cutting-edge tools and technologies, such as finite element analysis, rapid prototyping, design for manufacture, mould flow analysis, and human factors engineering. During all stages of development these methods help shorten timelines, improve device performance, meet regulatory requirements and minimise any residual risk. For instance,



ture across customer projects and lowers the overall costs for customers to access a platform and develop their own commercial product.

#### Expertise as consultants in drug delivery and injection systems:

Ypsomed's depth of expertise as a consultant in drug delivery is highly valued by its customers. In particular, biotech and pharmaceutical companies working toward their first market introduction of an originator biologic or biosimilar may have little experience in evaluating drug delivery devices. Based on their unparalleled expertise as consultants, Ypsomed specialists have guided numerous customers through the design and development of innovative self-injection devices or the compilation and review of data required for product registration.

For instance, the US FDA and international regulatory bodies have increased requirements for combination product human factor studies. Ypsomed supports its customers with necessary know-how and device samples to conduct formative and comparative patient studies early on in the customisation process. Ypsomed serves as a single partner from customisation, to regulatory submis-

sions, to the launch of the final product and customer support during later stages of the product life cycle. As such, Ypsomed similarly guides its customers through drug and device end-assembly. For each device Ypsomed has detailed machine specifications for end-assembly available and reaches out to its network of dedicated machine partners with their ready-to-use automation concepts for low-, mid-, and high-volume capacity.

Ypsomed has moved beyond its traditional role as developer and manufacturer of injection devices, by facilitating collaboration outside its organisational boundaries from the full customer project up to final drug and device assembly.

The unique combination of a platform-based product strategy with the distinct set of organisational capabilities enables Ypsomed to support its customers throughout all stages of injection system development and supply as a single point of contact (see Figure 1).

#### ABOUT YDS - YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innova-

tive pen and auto-injector systems for self-administration. Products and services at Ypsomed Delivery Systems centre on the customisation of injection systems, contract development and/or manufacturing, as well as drug and device end assembly. The product platform covers disposable pens for cartridges, re-usable pens that include spring-assisted injection mechanisms, single-dose auto-injectors for prefilled syringes, and reconstitution devices for lyophilised drugs in dual-chamber cartridges. Patented click-on pen needles complement the broad self-injection systems product portfolio.

The injection systems are developed and manufactured in Switzerland with strong in-house competencies covering product development, tool-making, injection moulding and assembly. All processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's FDA-registered manufacturing facilities are frequently inspected by both customers and regulatory agencies. Spanning more than 30 years, Ypsomed has well-established working relationships with leading biopharmaceutical companies.

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# OVERCOMING THE CHALLENGES COMBINING INJECTABLE DRUG WITH SELF-INJECTION DEVICE

Continued growth in the demand for self-injection devices such as auto-injectors is putting increased pressure on biopharmaceutical companies to establish in-house device teams and external consultants with expertise in related areas. In addition, top executives are requiring their teams to be on the lookout for suitable partners in the device field and to keep abreast of trends and “what’s new”. Here, Steven Kaufman, Vice-President, Marketing, SHL Group, talks openly about a broad range of challenges that biopharmaceutical companies and their partners will likely face on the road to taking their biologics, biosimilars, generic injectables and even biobetters to market in combination products. After introducing these challenges and some potential solutions, he also touches on the importance of participating in innovation programmes with partners and related learnings.

When attending conferences such as the upcoming PDA, Pharmapack and DDP events (Figure 1), device companies such as SHL will staff their booths with experienced business development staff as well as industrial and mechanical engineers. In many

cases the topics discussed will focus on the existing pipeline of launched auto-injectors and pen injectors with one of the key questions being asked being: “What’s new?” These events are good opportunities to connect with current and potential customers,



Figure 1: SHL will be at the upcoming PDA, Pharmapack and DDP conferences.



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as well as to network with a vast array of sub-suppliers. Discussions are polite but people will often choose their words carefully and hesitate to go into detail about potential bottlenecks. Thus, as it would seem that we don't often get the chance to talk candidly about the many challenges that are faced in any typical device project, I thought it could be very useful to highlight a few challenges here, and to share some comments from others involved in supporting the industry.

### PRIMARY CONTAINERS: PREFILLED SYRINGES, CARTRIDGES & STOPPERS

Before looking at establishing a device project, biopharma companies have often selected a prefilled syringe (PFS) or cartridge for their drug. In recent years, we have seen increased demand for better control of PFS and in particular making them more compatible with auto-injectors. Needle gauges such as 27G/29G thin-wall are becoming more common and it is well established that the gauge itself and the quality of the needle will impact injection time, as does the viscosity of the drug. A range of Rigid Needle Shields (RNS) are also being proposed by an increasing number of suppliers. Stoppers with coatings that improve glide force and offer other benefits are being used more frequently as well. With all of this to consider, biopharma companies must address the challenge of choice and cost. New biotech glass PFS and plastic PFS can offer increased security and would appear to be a good fit with some of the next generation devices coming to market.

Standard PFS (Figure 2) have been getting a makeover and many are now introducing biotech versions of their PFS. Manufacturers are developing products with tighter tolerances, specifically designed for auto-injector applications.

While recently visiting the production facility of OMPI in Italy, I asked Alessandro Morandotti, Front End Technical Manager, to comment on this trend and what chal-

**Figure 2: Standard PFS have been getting a makeover and many manufacturers are now introducing biotech versions of their PFS.**

lenges they are looking to overcome. He replied: "Containers like cartridges and syringes have become a critical part of the device optimisation for self-injection devices like auto-injectors as part of an effort to minimise assembly and functional issues. To address this, we worked closely with various biotech pharmaceutical companies and drug delivery device manufacturers to develop the Nexa PFS [EZ-fill™] platform, which tackles many of the critical issues encountered during the combination of drug primary packaging and delivery system. It minimises the potential interaction coming from contact with the glass, needle, needle glue, needle shield, plunger, and silicone oil used as lubricant inside of the syringe barrel. The flange and shoulder have a high degree of resistance and we

the primary container becomes less of a challenge as more companies look to launch their drug in a self-injection device.

### TESTING, TESTING & MORE TESTING

One of the more interesting challenges related to the testing of your PFS or auto-injector is knowing what to test and how much to test. And even then, you need to have enough of the product, API in primary container and later devices, to test at the right time. Having these capabilities in-house as a device company is vital.

Before getting too far into a device project, many device companies must look at conducting primary container characterisation. Basically, they will request samples of API, several batches ideally at different timespans, from the biopharma company. The biopharma company should get the primary container and stopper from the supplier that will be working with them when they go commercial.

The filling company will use a filling line that is representative of the filling line that will be used for final production. The device company will be looking at break-loose and glide force to help establish the profile of the PFS or cartridge and to then use this

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"Innovative electronic & communications tech such as smart phones & other devices will enhance the patient experience. One example is the use of near field communication"

---

also have tight flange dimensional control. Another vital advantage is gliding performances, since it was developed based on a specific profile where superior force performances were studied while considering the application of a polymeric-coated plunger stopper."

Other key players in the industry are offering a range of solutions to ensure that

data to optimise the powerpack or spring of the device. Most device companies utilise a broad range of equipment such as Instron and customised equipment like COIS (Completeness of Injection Stroke) that is made for SHL Medical by SHL Automation. Regardless of the equipment used, it's essential that qualified staff are available to inter-

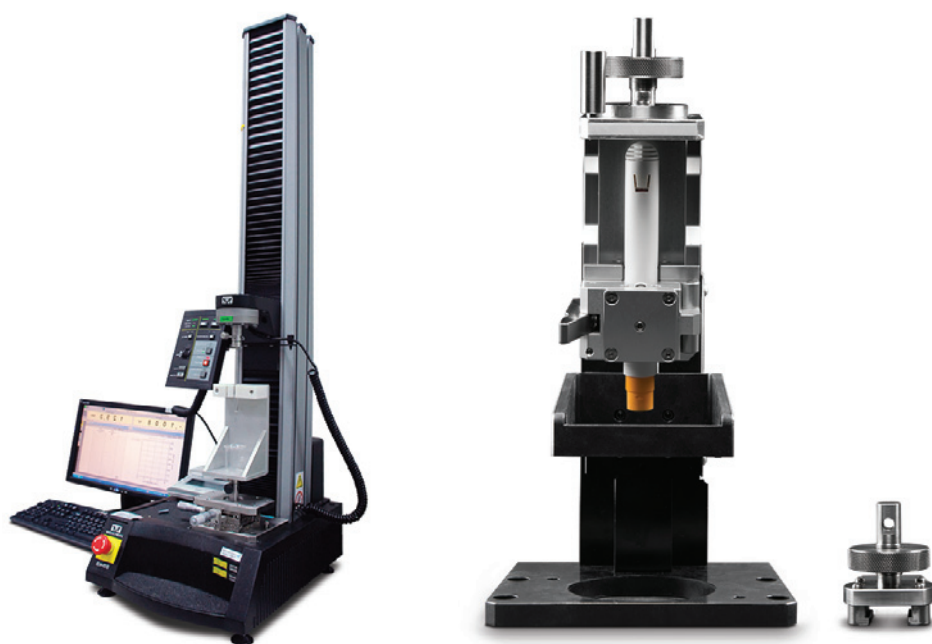


Figure 3: Testing of auto-injectors will require the use of a standalone machine or the use of a standard Instron with customised fixtures and a vision system.

pret the results and make recommendations to the device development teams.

Testing of auto-injectors will require the use of a standalone machine or the use of a standard Instron with customised fixtures and a vision system as shown in Figure 3. Force testing equipment performs functional testing on devices such as cap removal force, injection depth, injection time and needle cover override forces.

More recently, one new test has been added to the mix. ZebraSci (Temecula, CA, US) developed a non-destructive method of evaluating the uniformity and amount of silicone oil in primary containers. This

data has been correlated to device performance and break-loose and extrusion test data. Now, primary container suppliers, fillers, device companies and biopharma companies themselves are purchasing the equipment to help mitigate a known risk of inadequately siliconised syringes.

ZebraSci has developed a lab system that can both lubricate and analyse the lubricant layer in seconds. Now customers can test a range of siliconisation amounts and distributions with their drug product and device combination (Figure 4). These tests will give the customer useful data to provide a specification to the device and syringe

supplier. Once this specification is derived, ZebraSci's high-speed analysis system (600 parts per minute) can inspect 100% of syringes produced or filled to ensure gliding force and device performance as it relates to the quality of dispersion and control of amount of lubricant.

ZebraSci President Rob Schultheis commented: "Over the years we have developed a standard which is correlated to glide force and device performance. This standard can help to resolve any glide force or device issues related to poorly lubricated syringes as it is a scalable technology from lab to production floor."

ZebraSci has been making in-roads in the market and is now found in the testing labs of CMO fillers, primary container suppliers, device manufacturers and also biopharma companies. New solutions are available for non-destructive testing of syringe siliconisation.

## HUMAN FACTORS

Gone are the days of human factors (HF) testing being a "nice to have". It is now clearly a "must have". But one of the key challenges related to HF testing is identifying which organisation is qualified to conduct the HF testing. This organisation will also need to have a clear understanding of regulatory practices and the ability to write a systematic and comprehensive report. Biopharmaceutical companies and their device partners will need to balance the feedback they receive from this testing, with speed to market pressures to ensure that the device development programme stays on track. Be prepared that changes may need to be made to the device based on patient feedback. And to overcome this challenge some device companies are starting to get more involved in this field to get a better understanding of patient preferences and best practices.

With the spotlight now clearly on the importance of HF engineering, the ergonomics of device designs to enhance user experience and to ultimately improve patient compliance has become crucial. Regulatory guidelines, such as those provided from the US FDA and related authorities, state how biopharma companies need to conduct HF testing with a third party, and cannot rely on studies done by the device supplier. Testing done by device companies with regards to HF is generally just going to be used for reference only or perhaps marketing, if at all. The authorities require that the proposed device utilises the same PFS/cartridge that will be used commercially and, most impor-



Figure 4: ZebraSci has been making in-roads in the market and its equipment is now found in the testing labs of CMO fillers, primary container suppliers, device manufacturers and also biopharma companies.

tantly, with the appropriate patient group. Formative and summative studies will need to be conducted. Of course, special attention will be paid to labelling, packaging and instructions for use (IFU).

Dr Anthony Andre, Founder and President of Interface Analysis Associates (Saratoga, CA, US), an HF consulting firm specialising in validation of drug delivery devices, commented on the challenges of running a good HF programme, stating: “There are many more facets and skill sets applicable to a comprehensive human factors programme than most companies initially expect. Successful human factors programmes toward achieving validation with the FDA require design evaluation inputs, risk analysis techniques, solid formative testing, interpretation of test results into actionable design changes, labelling design and, of course, the sophisticated process of both planning, executing and reporting the all-important validation study. The best results are achieved when a human factors group can interact well with the device manufacturer so that together they achieve the objectives of the device for the intended user audiences. The challenges stem from two sources: a) biopharma companies that don’t understand the complexity of human factors activities required to successfully validate a new combination drug product or drug delivery device platform, and b) the failure of these companies to allow their human factors consultants to be involved early in the design process and to work hand-in-hand with the device developers.”

An increase emphasis on HF means that new devices are becoming more ergonomic and even easier to use. SHL recently implemented the feedback from several HF studies into the industrial design of some of their latest devices such as the Amber auto-injector, utilising ‘Pushclick’ technology with advanced labelling / packaging (Figure 5).

### CONSULTANTS CAN HELP FILL SOME KEY GAPS

In recent years, the need to enlist the support of consultants has become increasingly important for some companies. Several new biopharma companies have no prior experience bringing a biologic to market and the same can be said of their experience with devices. Several players are now getting involved in generic injectables, biobetters and biosimilars. Therefore, as these companies expand their internal teams and start to get involved with pen injector and auto-injector projects, consultants with experi-



Figure 5: Amber auto-injector, utilising ‘Pushclick’ technology with advanced labelling / packaging.

ence in areas such as regulatory, HF, project management and more will be needed.

Although these consultants can help both new and more experienced biopharma companies with their efforts, it is important to keep in mind that device companies may have some issues providing full access to project details and the inner workings of their organisations. The primary reason for this is technical expertise and market intelligence. If a device company offers both industrial and mechanical design services, and the consultant offers the same, then the device company would be cautious providing a third party the same level of access to their staff, facilities and technologies as they give a customer. Regardless, balanced solutions are needed and clearly the right consultants can make significant contributions to help get combination products to market.

One of the firms actively involved with supporting companies getting into this area, Combination Product Partners (CPP), was asked to comment on the role that they see

for consultants working with biopharma and device companies. Company CEO Rosemary Gonzales explained, “The successful development and launch is not the end of the effort for an auto-injector programme. It is also critical to manage the lifecycle of the product according to the broader technology strategy, the evolving expectations from health authorities, and revisions to relevant international standards. The ability of a consulting company to provide effective support for both new development programmes and legacy products is a key differentiator in the sector.”

With more device companies now offering final assembly options, the next step naturally is to integrate labelling and packaging services too (Figure 6). In addition companies are looking to support in areas such as peripherals like injection pads.



Figure 6: Packaging, labelling and more.





Figure 7: The majority of new auto-injectors will be launched with needleless training devices.

### SUPPORT SERVICES

Some biopharma companies are now looking to device companies to provide additional services to assist them in their efforts. With increasing numbers of companies getting in the biopharma space, certain companies will need to rely more heavily on suppliers such as device companies, filling CMOs and consultants. If successful, they will likely follow the model of building up a device team that is made up of cross-functional experts, but that will take time. In the near-term, more will be asked of the above groups.

For example, test equipment and final assembly equipment may be commissioned from device partners to set programmes up. This equipment can be located at the filling CMO, device company or the biopharma company itself.

In addition, companies like SHL have developed in-house capabilities in the areas of final assembly operations in the US, with labelling and packaging and of course training device development expertise. This will give biopharma companies more choice. They can handle some activities themselves, use external vendors or consultants or consider working with device companies that can handle more of the value chain operations. Regardless of who is performing which activity, cooperation and increased communication between all parties is cru-

cial. Multi-party confidential disclosure agreements (CDAs) are becoming the norm, and with increased pressure on timelines, a greater openness will be the only way to overcome challenges. Device companies will be required to expand their partnerships with primary container suppliers, develop closer relationships with consultants and third-party suppliers, and to retain staff that have an understanding of the key areas such as: drug, primary containers (standard, biotech & plastic), stopper/plungers, filling, mechanical and industrial design of devices, project management, HF, regulatory, testing and assembly equipment, final assembly, labels and packaging, trainers and more.

Training devices without needles are an essential tool for helping end-users become familiar with the correct handling-sequence of a device (Figure 7). These tools are now seen as increasingly important.

### FUTURE CONSIDERATIONS & INNOVATION PROGRAMMES

Challenges will continue to be part of any programme, but one way to mitigate this will be to work with experienced partners. As a result, staff and their knowledge will become increasingly sought after. New staff should be given the opportunity to get involved with a range of programmes, attend various international and regional conferences and also receive advanced training courses. Mentor programmes that allow experienced staff to pass on knowledge will become increasingly important. In addition to some of the challenges mentioned, there will also be several technical challenges in the area of device development that will need to be addressed to support injectables that have higher viscosities, greater injection volumes and more.

Companies co-operate more in coming years to ensure that innovative electronic and communications tech such as smart phones and other devices (Figure 8) will enhance the patient experience. One example is the use of near field communication (NFC).

Innovation programmes can be set up in any organisation. SHL has established the "innovation initiative" in three locations: North America, Europe and Asia. With this structure, teams of experts will jointly and independently work on cutting-edge solutions to address current and future device needs. While many solutions will be developed in house, SHL will work with various partners to assist with better project integration and more. Of course this will involve the increased investment of resources, time



Figure 8: Communications tech such as smart phones and other devices will enhance the patient experience.

and money, but it will be well worth it. The initial feedback from biopharma companies about this initiative and similar efforts has been very positive. With numerous device launches planned for 2016-2020, these clearly are exciting times for the industry as a whole. Billions of dollars in injectables are coming to market in one form or another, and with increased co-operation between key stakeholders solutions will be developed and challenges overcome.

### ABOUT SHL

SHL is the world's largest privately-owned designer, developer and manufacturer of advanced drug delivery devices. We have more than 2,600 staff globally, with primary design centres in Sweden and the US, and manufacturing centres in Asia. Final assembly, labelling and packaging services for drug delivery devices are offered at our newest facility in the US.

SHL supplies auto-injectors, pen-injectors and inhaler systems to global biopharmaceutical companies. Significant investment in R&D has enhanced our broad pipeline of next-generation drug delivery systems. These innovative devices include a range of disposable and reusable injectors with fixed or variable dosing, enhanced precision and the ability to accommodate high viscosities.

### ACKNOWLEDGEMENTS

Special thanks to Frank Isaksson, David Markham and Patty Sa for article review and image support.




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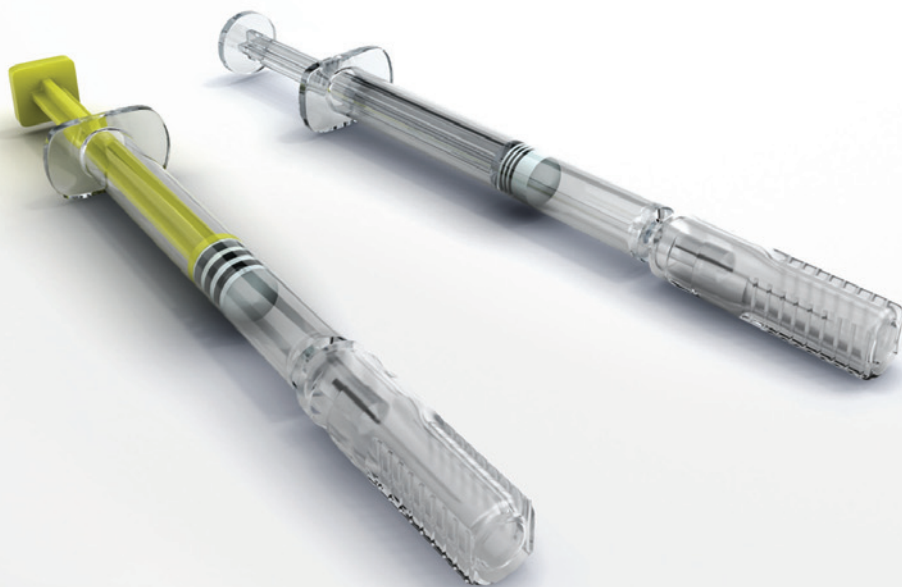
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## COMPANY PROFILE: KAHLE AUTOMATION



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REQUIRES AN AUTOMATION  
PARTNER THAT GUARANTEES  
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## COMPANY PROFILE: NEMERA

# Nemera

The healthcare business formerly known as Rexam Healthcare Devices has become Nemera. This name change follows the May 2, 2014 acquisition by Montagu Private Equity. Nemera will continue to operate with the same management team and its choice of name signifies a renewed commitment to its mission of providing patients with safe and accurate delivery devices.

## NEMERA'S INNOVATION CENTRE

Innovating for patients is at the core of Nemera's mission. More than 50 engineers and experts work to achieve this at the Innovation Centre at La Verpillière, near Lyon, France.

The scope of the Innovation Centre includes the collection of patients' insights, market watch, concept generation, IP monitoring, regulatory expertise, detailed risk-based design, design for manufacturing and support to plants for product life-cycle management and problem solving when appropriate.

### Patient Insights & Human Factors Studies

Technical expertise and patient usability always work hand-in-hand. Along with the many fields of technological expertise (like material, mechanical and manufacturing engineering, mathematical models and other), creative design and usability assessment including Human Factors (HF) studies, are central to product development. The Innovation Centre carries real-world evaluations, through impartial volunteers and collects user feedback. Sophisticated technologies, like fast-camera tracking, give

## NEMERA IN FIGURES

- 4 plants in Europe and the US
- 50 engineers and experts working at the Nemera innovation center
- >1,300 employees
- >30,000 square meters of manufacturing clean-rooms

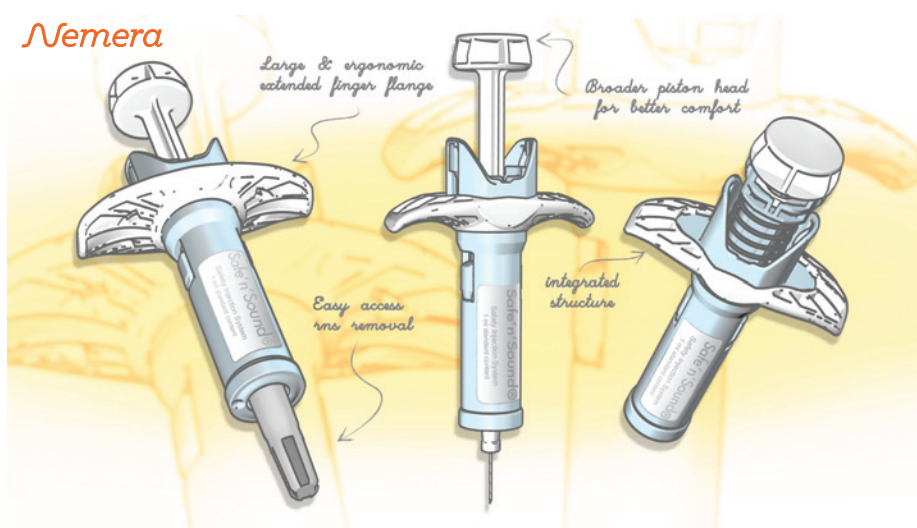


Figure 1: Concept drawings for an ergonomic Safe 'n' Sound® needle-safety device.

"More than five million diabetics and ten million asthmatics rely everyday on devices manufactured by Nemera"

engineers an inside view of the way the device is used, making it safe and accurate for the patient.

### Proprietary Devices & Contract Development

We apply the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories. The development quality team guarantees full compliance not only of the final device but of all the development chain. Strong programme management ensures that the project is delivered on time and within budget.

## A WORLD LEADER IN DRUG DELIVERY SOLUTIONS

Nemera is one of the world leaders in the design, development and manufacturing of drug delivery solutions. Nemera's expertise encompasses five modes of delivery: ophthalmic (preservative-free droppers), nasal, buccal, auricular (sprays pumps, etc); pulmo-

nary (DPIs and standard valves for pMDIs); dermal and transdermal (dispensers); and parenteral (injectors, pens, safety devices).

More than five million diabetics and ten million asthmatics rely everyday on devices manufactured by Nemera.

### Parenteral

Nemera's Safe 'n' Sound® device provides safety from needle-stick injuries. Adding

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“Adding a passive automated safety feature to prefilled syringes, Safe ‘n’ Sound® protects patients and caregivers from contamination by blood-borne diseases.”

a passive automated safety feature to prefilled syringes, Safe ‘n’ Sound® protects patients and caregivers from contamination by blood-borne diseases. Robust and versatile, it comes in different formats and can be combined with ergonomic accessories (see Figure 1).

#### **Pulmonary**

Consistency and reliability are critical for respiratory patients. Inhalia® is a new generation of valve for pressurised metered dose inhalers (pMDI).

#### **Nasal, Buccal, Auricular**

Following the SP270, a standard spray pump for ear, nose and throat, Advancia® is a new breed of pharmaceutical pump combining user-independence and preservative-free features in one single system. Advancia® offers a new alternative to improve treatment compliance in an increasingly demanding nasal spray market.

#### **Ophthalmic**

Preservatives are harmful to patients’ eyes and may jeopardise adherence to treatments, therefore Novelia® is the user friendly, preservative-free eye dropper with a precision blue tip.

#### **Dermal/Transdermal**

Sof’Bag™ is a high-performance airless dispensing device designed especially for pharmaceutical gels and creams. It brings precise dosing and protection for topical and transdermal formulations.

### **A NEW NAME THAT STANDS FOR LIFE & EFFICIENCY**

The name Nemera comes from two sources: “Emera” from Greek meaning “day” and suggesting renewal, fresh hope and life; and “Nemer” from Hebrew and Arabic, meaning “leopard” and suggesting swiftness, efficiency and agility.

Nemera CEO Marc Haemel commented: “Today, an exciting new adventure begins. I am very pleased to introduce you to Nemera, our new company name. We work hand-in-hand with pharmaceutical companies to design, develop and manufacture the drug delivery devices that help patients every day.

“There is no limit to Nemera’s ambition to serve patients. We already market devices in over 40 countries for millions of users. We’ll keep investing in new products and in state of the art manufacturing equipment, to help even more patients with high quality devices all over the world.”

Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing. Montagu has also bought Rexam Prescription Products, the industry leader in prescription packaging for over 100 years, which is now known as Centor.

Find Nemera on the web at: [www.nemera.net](http://www.nemera.net)

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# GERRESHEIMER

## INSPECTION TECHNOLOGIES FOR GLASS SYRINGES

The quality demands for pharmaceutical glass syringes are high; quality levels for critical defects approach or even come below ppm rates. In practice, these standards are achieved with a combination of visual and camera-based inspection technologies. In this piece, Bernhard Hinsch, PhD, of Hinsch-Consulting (Hamburg, Germany), consultant to Gerresheimer, argues that both technologies deliver reliable results if all relevant input variables are known and a model of their interaction has been created, but even though the influence of individual visual inspection capacity can be minimised, camera-based inspections are the preferred solution. Today, suitable camera technology is available for the detection of practically all dimensional and the majority of cosmetic defects. Dr Hinsch introduces cross-functional quality management, which involves the development of process validation strategies and the elaboration of technical and organisational procedures to facilitate permanent compliance with the validated standards.

Pharmaceutical glass syringes have to satisfy increasingly high requirements of quality. In

cesses and reduce the defect rate to the minimum. A combination of visual and automated inspection technologies is used to identify defective syringes. The objective of cross-functional quality management is to install and continuously optimise these technologies. It also involves the development of process validation strategies and the definition of technical and organisational procedures

which facilitate permanent compliance with the validated standards.

“In the future, new technologies will be capable of detecting defect types that are not identifiable at this time”

practice, the benchmarks for dimensional precision and cosmetic defects are below the customary Acceptable Quality Limits (AQL). To guarantee this level of quality, a range of prerequisites have to be met. The first prerequisite is a precise definition of the defect types that can occur and their causes. Based on this definition, it is possible to optimise the production pro-

### DEFINITION AND CATEGORISATION OF DEFECTS

Glass syringes can demonstrate a variety of defects that can be categorised according to various criteria. It is most practical to use



Figure 1: Characteristic glass defects in syringes: cracks, checks and scratches.

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a system of categorisation that is oriented on the impairment of glass integrity, because this permits a direct evaluation of the potential risk for physicians, nursing personnel and, most importantly, the patients themselves. According to PDA Technical Report 43 (TR 43), “*Identification & Classification of Nonconformities in Molded & Tubular Glass Containers for Pharmaceutical Manufacturing*”, cracks pose the highest risk, followed by checks and then scratches (Figure 1).

A crack is defined as a discontinuity in the glass matrix which runs inside the glass and can influence the container’s integrity. Accordingly, cracks are categorised as critical defects which can be associated with health risks and even have life endangering consequences for the patients using the defective products. Checks are discontinuities in the glass which demonstrably do not impair the syringe’s integrity. Checks are categorised as major defects which can cause problems in the further processing or use of the product. Scratches are superficial or minor defects which do not impair the integrity of the glass. Cosmetic defects such as impurities, bubbles, air lines or (glass) particles are also categorised as minor defects.

### PRODUCTION PROCESS, DEFECT CAUSE & PREVENTION

The glass syringe production process, described here using the example of pre-fillable syringes, can be divided into three main phases. The first phase is forming. It involves tube cutting and the multi-stage process of forming the shoulder, cone and finger flange, as well as syringe printing. In the second phase, the needle is mounted. Then, in the third phase, the syringe is washed, siliconised, sterilised and packaged (see Figure 2).

Cracks – the most serious defect – generally occur in the tube cutting process, the forming process or as a result of the glass not being properly annealed. Most cracks are caused by thermal force – either due to a thermal shock as a result of too high or low quantities of water being used in the tube cutting process, excessive temperature differences between the glass and tool in the forming process or mistakes in the annealing process. These cracks can be prevented by optimising the process parameters and by reducing the temperature differences during processing. Checks and scratches are generally caused by glass-glass contact

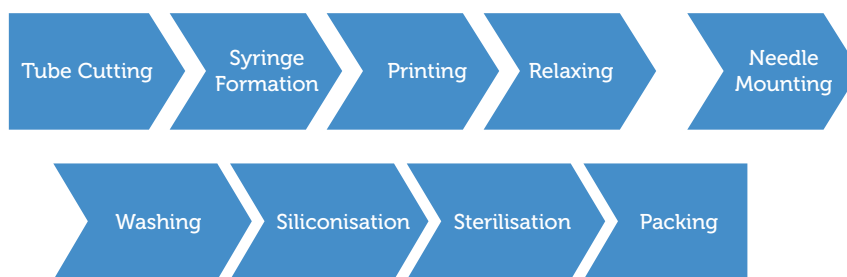


Figure 2: Simplified syringe production process.

or mechanical forces during processing. Effective measures to prevent these defects are therefore the avoidance of glass-glass or glass-metal contact and ensuring that the transport processes are as gentle as possible.

### COMBINED VISUAL & CAMERA-BASED INSPECTION

The pharmaceutical industry’s high quality requirements necessitate 100% inspections of glass syringes. In current specifications, the typical AQL is 0.01-0.065

### VISUAL INSPECTION PROCESS VALIDATION

In any reliable visual inspection process, an awareness of and control over all relevant input variables are essential, as is a viable model of their interaction. It is also important to remember that validation only applies to a defined input range. If there are too many input defects, the target output value will be exceeded. In addition to the false pass rate (FPR), the input defect rate has to be known and monitored. If

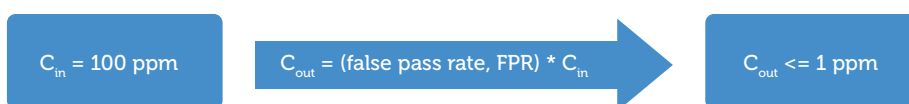


Figure 3: Validation of output quality in visual inspections.

for critical defects and 0.04-0.4 for major defects. To achieve the highest possible standard of safety, however, defect rates of  $\leq 1$  ppm for critical defects and  $\leq 100$  ppm for major defects are often demanded. From a quality management perspective, fully automated, camera-based inspection technology is preferential. At the present state of the art though, suitable inspection processes are not available for all defect types.

it becomes too high, the production line has to be stopped for both economic and quality-related reasons so that the cause can be investigated.

In the validation process (Figure 3) it is essential to understand the visual inspection as a structured process with a known number of variables. Some of the input variables relate to the choice of personnel, who have to satisfy certain requirements

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“Agreements are increasingly being reached with the customer on the lower limits for defect relevance in order to achieve transparent quality criteria that apply for both customer and manufacturer”

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In practice, manufacturers will continue to use a combination of automated and visual inspection technologies in the foreseeable future. The regulatory authorities require the submission of comprehensive process validation data obtained in case studies according to the quality by design (QbD) concept in the drug licensing process.

of visual performance and concentration powers. The inspectors also have to be properly trained and attend regular refresher workshops to sustain the learning effect. Another group of input variables relate to the technical design of the inspection process. The main ones are light-related factors such as the colour and direction of



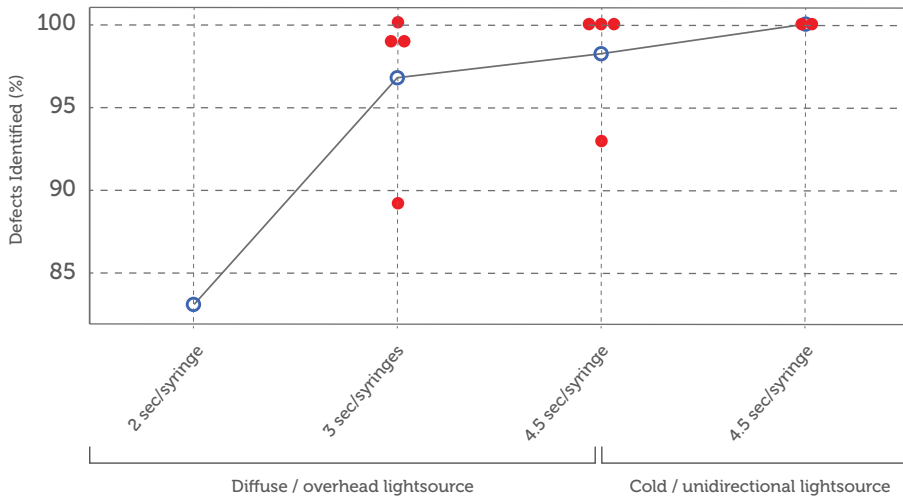


Figure 4: Results of a visual inspection efficiency study.

the inspection light source and the design of the surface on which the inspections are performed. A third group of input variables relate to the ergonomics of the inspection process. They include the design of the inspection workstation, whether the inspectors take enough breaks from their work and whether they are supported in the inspection process by visual timers such as changing light colour. This is particularly significant because the time taken to inspect each syringe has a high influence on visual inspection output quality.

An efficiency study showed the complex interactions of the individual input variables (Figure 4). The four people surveyed – two experienced and two less experienced inspectors – were given a number of syringes to inspect over a period of 40 minutes in a production environment. There were a known number of defective products in the batch of syringes, whereby the defect rate was deliberately set at the upper limit for typical defects. The defects themselves were very small in size to create challenging test conditions. The time variables in the study deviate from the actual time variables in the production environment.

The diagram shows the overall performance of the people surveyed with different inspection timeframes and conditions. One key survey finding is that the time spent on the inspection of each product is

extremely significant. With a time allowed of 2 seconds per syringe, the performance of all the inspectors was weak and they identified less than 85% of the defective products. So, even the experienced inspectors do not perform adequately in unfavourable conditions. When the time allowed for inspection was increased to 3 and 4.5 seconds respectively, the results improved considerably. However, there was some drifting, which indicates the significance of individual visual performance. The number of defects identified by three out of the four inspectors improved substantially (though not completely identically) when the time allowed for inspection was increased to 3 seconds, while one inspector's performance deteriorated considerably. This difference in performance remained unchanged when the time allowed for inspection was increased to 4.5 seconds. In fact, it did not improve until another input variable was changed.

In the first three tests a diffuse overhead light source was used. Another test sequence was then performed with a cold light source and optical conductors that bundled the light axially into the syringe barrels, making cosmetic defects highly visible. Under these conditions all inspectors – even the inspector with lower visual performance – detected 100% of the defects.

Another significant result of the study, in addition to the need to allow an appropri-

ate time for inspection of each product, is that the individual variability of test results could be effectively reversed by changing the test process structure. Another important consideration is that the results cannot be generalised. The inspection conditions for a product or product group have to be established on a case-by-case basis and depend on how easy or difficult product-specific defects are to identify.

## CAMERA-BASED INSPECTION PROCESS VALIDATION

Camera-based inspection systems to inspect the dimensions of syringes can achieve a resolution of up to 20  $\mu\text{m}$  with defects of only 2  $\mu\text{m}$ . They are therefore far superior to visual inspections, though not necessarily superior to mechanical inspection methods – e.g. use of calipers – for the inspection of complex three-dimensional geometries such as the shape of the finger flange. However, if the syringe is rotated during the camera inspection process, reliable results are achieved. The advantages of camera systems are particularly evident in the identification of bent needles which, if undetected, would cause pain to the person being injected (Figure 5).

Camera-based inspection systems perform far more complex tasks in the identification of cosmetic defects. Reliable identification is currently possible on an area of 0.1  $\text{mm}^2$  and this will be reduced to 0.03  $\text{mm}^2$  in the foreseeable future. As in visual inspections, camera-based inspections have to ensure a defect rate of  $\leq 1$  ppm for critical defects. The automated systems can tolerate a far higher input defect rate than visual inspections. However, there is a limit for process validation purposes and the production line has to be stopped if the input defect rate gets too high. A reliable inspection can only be guaranteed if the false pass rate (FPR) and the input defect rate are known and continuously monitored.

A range of relevant input variables have to be taken into consideration in the validation process. One is the minimum size of the defect and an agreement has to be reached with the customer in this respect. A second typical defect characteristic is the contrast that it produces in the camera image, which is displayed as a greyscale difference. For example, impurities generally only create low contrasts, while defects in the glass matrix such as cracks create reflections if the light is traveling in the right direction, and therefore high contrasts. Here, too,



Figure 5: Dimensional inspection of the syringe needle.

agreements are increasingly being reached with the customer on the lower limits for defect relevance in order to achieve transparent quality criteria that apply for both the customer and the manufacturer. Camera-specific identification limits and measuring inaccuracies exist with regard to defect size and contrast which have to be taken into account in the validation and in regular calibrations.

The third significant block of input variables, in addition to defect and camera characteristics, relate to inspection conditions. Firstly, all optical variables of the light sources used, such as luminosity, colour and direction, have to be optimally co-ordinated and kept constant. The direction of the camera, syringe and light source also have to be coordinated. The light should pass axially through the syringe to maximise defect visibility. Rotating the syringe permits the inspection of the entire surface area. Since some types of cracks will remain undetected if the camera is at a right angle to the light source, it makes sense to use a more acute inspection angle or work with two cameras.

In practice, camera validation involves six steps. The first step is to create a library of all defect types to be identified with both physical samples and photos of the defects. In the second step, the samples are used to create camera protocols and defect-specific algorithms for each defect. These algorithms can be very complex. Air lines in the glass create an interrupted pixel pattern whose individual elements would be below the relevance limit. This is where the algorithm comes in because it recognises the linear sequence of greyscale differences and adds them together into a relevant total length. The third step is the creation of samples which define the tolerances for each defect. Using tolerance samples, the corresponding tolerance parameters can be defined for the camera. In the fourth step the false pass rate is measured on the basis of the defined parameters. Sometimes, the parameters have to be adjusted to guarantee the required output quality. The fifth step is the definition of an upper limit for input defects which would trigger a production alarm. In the sixth and final step, the actual output quality is verified on the basis of a comprehensive performance qualification (PQ).

Figure 6 represents the dimensions of defect contrast and defect size, and it is possible to illustrate systematically the typical optical characteristics of cosmetic defects and their detectability with camera-based inspection systems. Defect that

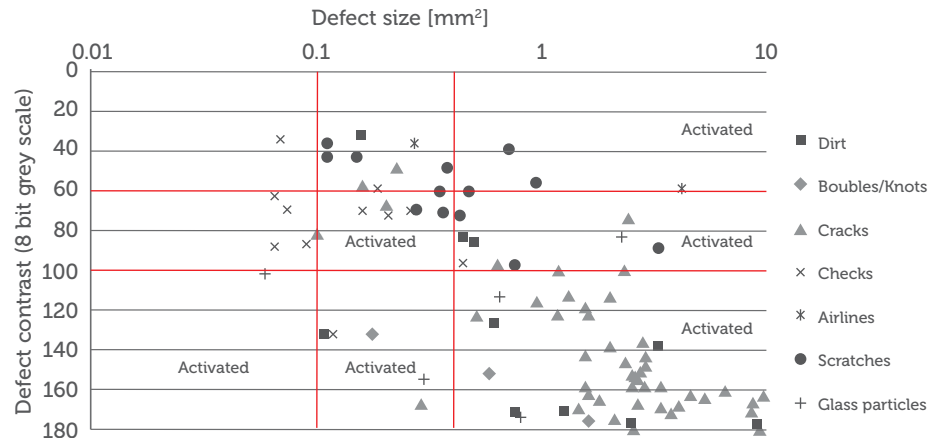


Figure 6: Typical distribution of cosmetic defects by size and contrast.

are small, low contrast and therefore difficult to detect are shown at the top left of the diagram while particularly large and high contrast defects which are easy to detect are shown at the bottom right. This makes it clear, for example, that scratches and checks are often difficult to identify in practice, while cracks (with very few exceptions) deliver large and high contrast defect patterns.

A system of inspection limits is defined in the diagram taking the camera system's power, the defect's level of criticality and the relevant quality agreement into account. Not only is a lower limit for size and contrast defined, but also a 3x3 matrix so that the defects can be recorded in a more differentiated way. To detect relevant defects, all fields with a defect size of more than 0.1 mm<sup>2</sup> and a defect contrast of over 1:60 are activated. The field with a defect size of above 0.4 mm<sup>2</sup> and a defect contrast of between 1:60 and 1:30 is also activated as the camera's measurement limit because relevant defects can still be detected in this

performs automated camera inspections as standard on the syringe barrel, neck/shoulder, cone, finger flange and needle, as well as on the positioning of the closure. It also performs automated camera inspections for cosmetic defects in needle quality as standard. Cosmetic defect inspections of the syringe barrel, neck/shoulder, finger flange and printing can also be agreed. A cosmetic inspection of the closure can be performed by the supplier. Gerresheimer AG is currently working on concepts for inspecting the cone and siliconisation for cosmetic defects.

## OUTLOOK


At the current time, both visual and camera-based technologies are used to inspect glass syringes. Despite their dependency on the individual inspectors' performance, visual inspections deliver the required output quality if the personnel are properly trained and the inspection conditions are appropriate and continuously monitored. However,

“Camera-based inspection technology is more reliable if ppm or sub-ppm level defect rates have to be achieved”

range. For safety reasons, the segment of small, high-contrast defects at the bottom left is also activated, even though there are no defects shown there in this diagram. Fields in which defect detection is technically unfeasible or not necessary on the basis of the agreed quality criteria are not activated.

Camera-based systems for dimensional inspections are available for practically all relevant syringe dimensions. Gerresheimer AG

camera-based inspection technology is more reliable if ppm or sub-ppm level defect rates have to be achieved. Here, too, knowledge and control of all relevant input processes are essential for validation. Gerresheimer AG has developed its own camera technology for the most important defect types. In the future, new technologies will be capable of detecting defect types that are not identifiable at this time.



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# MEDICAL TRAINING DEVICES IN THE HOME

As home-managed disease states, medical devices and user groups diversify and proliferate helping ever more people, Ian Scrimgeour, MEng, User Centred Designer, Shore Design Consultancy Ltd, explores the growing role of the trainer device, and shows how the right trainer can greatly help reduce adverse events, improve adherence and build user satisfaction and confidence.

## INTRODUCTION

Progress in modern medicine and device design increasingly means we are able to monitor, manage and treat our ailments at home. As discussed in the October 2013 Association for the Advancement of Medical Instrumentation (AAMI) summit on Healthcare in Nonclinical Settings (Herdon, VA, US), this is a laudable trend. Moving treatment out of the clinical environment has many advantages<sup>1</sup> but places greater emphasis on the patient or carer to use drugs and devices as intended. As

“Moving treatment out of the clinical environment has many advantages<sup>1</sup> but places greater emphasis on the patient or carer to use drugs and devices as intended”

home-treatable disease states, devices and their users diversify, ensuring effective and safe device deployment is an increasingly complex challenge for the industry. Device design must consider these diverse user groups and always, training plays a vital role. How can training methodologies advance to ensure each user has the opportunity to learn, becoming comfortable and confident with the safe use of their device? The value of the training device is becoming increasingly apparent.

## ADVANCING HEALTHCARE AT HOME

With current and projected growth in home healthcare, increasing numbers of chronic and acute medical conditions are being managed in the domestic non-clinical environment. In the US, it is estimated between 8.6 and 12 million people currently receive home healthcare, increasing to 27 million in 2050.<sup>1</sup> Advances in technology and medical care systems are enabling this

shift, lowering the cost of healthcare whilst improving patient quality of life and independence.<sup>2</sup> This trend is global as technology advances and populations grow.

As the medical devices driving this paradigm shift devolve and diversify, home device user groups and disease states become similarly diverse. Where once home-use medical devices were restricted to a select group of indications and patient groups, they are now used for an ever expanding range of treatments and conditions. Adding further complication, devices used in the home are subjected to significantly different environments and user

profiles than in the more controlled environment of hospitals, surgeries and clinics. As extolled in usability engineering standards,<sup>3</sup> robust user-centred design identifies user groups and provides device designs that attempt to understand and accommodate the users, their habits, expectations and capabilities. A device's risk profile is anticipated during

development and monitored through the products lifecycle. However, sometimes such diverse user abilities and expectations pose hazards which seem difficult to resolve in the device design alone. A good risk assessment can identify issues which can leave development teams head-scratching for solutions, such as the following:

- Users can have an established mental model of use based on a similar or drastically different device, creating unanticipated expectations and actions.
- A user may not be capable of absorbing all information from the training session provided
- A user's anxiety can impede their ability to follow seemingly simple usage steps. Emotion can overwhelm cognitive reasoning.<sup>4</sup>

## TRAINING IS ESSENTIAL

No matter how effective the device design, training is an essential element in overcoming risks like those just described

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and, as such, fulfils a fundamental role in the application of modern medicine. There are many reported cases where adverse events are attributed to poor training. For example, a retrospective review of adverse events associated with adolescent use of insulin pumps identified poor education (device training) as the cause in 47 out of 102 cases, the majority of which led to hospitalisation.<sup>5</sup>

Currently the medical device, pharmaceutical and healthcare industries use the following training methods to impart learning to the user or patient:

1. Written Instructions for Use (IFU) – a regulatory bare minimum, often augmented with:
2. Visual stimuli, diagrams and pictures – pictorial representation of what to do
3. Video instructions – via DVD, website or mobile app
4. Instructor-led learning – a healthcare professional (HCP), such as a nurse or other clinician, who introduces the device and method of use
5. Peer learning – a fellow patient provides a demonstration or guidance on device use.

There is another training tool available to industry: training devices.

Training devices are growing in popularity as a way of enhancing learning and mitigating use error issues. To explore how these support medical device use we need to consider the different ways through which one might learn.

## LEARNING STYLES

Different people have different learning styles, as summarised in Fleming's well-known VARK model of learning which divides learners into four categories of learning preference.<sup>6</sup>

1. Visual learners (looking at images and pictures)
2. Auditory learners (hearing instruction)

## BOX 1: TEN BENEFITS OF HOME-USE TRAINING DEVICES

1. Promotes kinaesthetic learning through practice and experience
2. Promotes repetition at home leading to enhanced learning
3. Reduces anxiety. Giving the user a chance to get used to the device and activity promotes the alleviation of concerns. Especially important prior to the first "real" device use
4. Improves compliance. Not being comfortable with a medical device and being unsure as to how to use it effectively can have a significant impact on patient compliance
5. Prevents waste of high-value drugs - non-adherence costs US\$100-300 billion (£62-£185 billion) each year<sup>8</sup>
6. Provides additional risk mitigation for risk analysis e.g. failure modes and effects analysis (FMEA)
7. Creates competitive advantages – users look favourably at pharmaceutical companies which they perceive to care enough to provide trainer devices
8. Mitigates curtailed or missed introductory training sessions. Current training is often less than that mandated by the drug company. They may recommend 30 minutes training, but in reality healthcare providers sometimes don't have that time with patients.
9. Prevents "training erosion" where information is diluted or changed when passed on, for example, from device company to drug company, to distributor, to healthcare provider, to patient. A training device allows the device company direct contact with the user.
10. It allows device training to take place in the correct usage environment and promotes private learning, for example, in the bedroom at home, not the consultation room at the health clinic. Training at home in private allows the user to explore the device and usage experience.

"Especially for kinaesthetic learners, training devices are increasingly being used. These trainer devices are non-functional, containing no drug or needle and are ideally configured to feel the same as the real device"

3. Reading-writing preference learners (reading instruction)
4. Kinaesthetic learners or tactile learners. (doing and practicing).

It is well understood that a combination of these learning styles will usually be more effective than reliance on a single style. For example, somebody with an innate

visual learning preference will learn best from visual infographic rather than written instructions, and will learn even more quickly if their learning is supported with a secondary stimulus such as kinaesthetic learning – practicing the activity.

Mixed learning styles are often utilised to maximise learning during the initial introduction to a new medical device. Pharmaceutical



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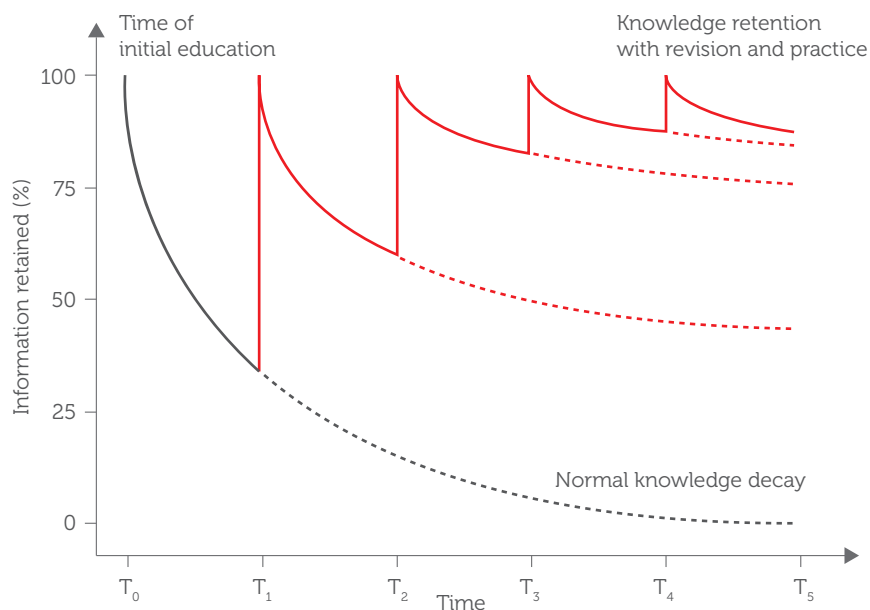


Figure 1: Representation of Ebbinghaus forgetting curve, knowledge degradation chart.

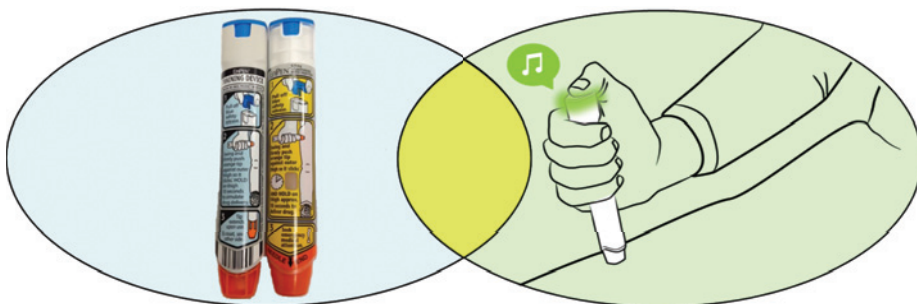


Figure 2: Replication and enhanced educational training device options.

companies, hospitals, clinics or support groups often provide a HCP led instructional session for the new patient. During such a session the patient is able to hear from the HCP, read the training material, look at charts and photographs and observe a device like the one they will be using. By such meth-

Medical device companies will construct training materials and requirements and the patient is presented with visual, auditory, written and tactile information. However, what happens to the patient's knowledge after their initial introductory consultation?

and full learning is usually not achieved for the following reasons:

- Insufficient time available. Time for training session is often reduced or eroded. The HCP will often have other pressures on their time and a 30-minute training session may be cancelled or reduced.
- Information overload. Being introduced to a new medical device is often a very emotional, abstract or alien experience for the patient, all of which can increase patient stress significantly and inhibit learning.
- Learning degradation. Learned knowledge degrades rapidly over time. A patient can leave an instructional session feeling confident that have absorbed adequate knowledge, but without reinforcement the knowledge will degrade, as described first by Ebbinghaus.<sup>7</sup>

Figure 1 is a representation the Ebbinghaus forgetting curve, describing how information degradation is diminished with repeated repetition and practice. At each time point, the learner practices and reviews device use, resulting in improved long-term retention.

In summary:

1. Knowledge can be better retained if it is reinforced repeatedly after the initial introduction.
2. Multi-style learning promotes better retention.
3. Kinaesthetic learning is a valuable but often overlooked learning style.

A way to leverage these three key learning mechanisms is by providing training devices that users can take home. In Box 1 we identify ten benefits of home-use training devices.

## ASSIGNING VALUE TO TRAINING DEVICES

Investing in a training device can provide significant added value to both device company and user. When done smartly the development and manufacturing costs can be a fraction of the parent device cost and, whilst assigning monetary value to some of the softer benefits outlined above can be challenging, the cost of non-adherence is well documented. This is especially true of the more expensive drugs and treatments currently being prescribed. If the confidence and knowledge provided by a training device prevents users missing their \$1,000 dose of medicine, then the return on investment can occur very rapidly.

“What should a training device be? There are two methodologies available: deploying the precise replication of the parent device experience or deploying a multi-sensory enhanced educational device”

ods visual, auditory and reading learners are given means to learn. To support learning further, especially for kinaesthetic learners, training devices are increasingly being used. These trainer devices are non-functional, containing no drug or needle and are ideally configured to feel the same as the real device so the patient can role play device use.

## LEARNING RETENTION

Using mixed learning styles in the initial consultation, the patient is given all the information they require to understand the correct use of the device. Of course once the patient has left the consultation room, the reality is quite different

Figure 3: West's SelfDose® device, for which a replication training device was created.

## TRAINING DEVICE STRATEGY

So what should a training device be? There are two methodologies available: deploying the precise replication of the parent device experience or deploying a multi-sensory enhanced educational device (Figure 2).

A replication device seeks to match the parent device user experience as precisely as possible. For example, a complex force profile from the parent device shall be engineered into the trainer device ensuring the user has the opportunity to run through the precise tactile experience.

Alternatively, a multi-sensory enhanced educational device does not rely on precise replication (though replication to some extent plays a part), rather audio, visual and tactile enhancements guide the user through the usage experience. These give clear positive reinforcement for the correct actions and correspondingly highlight incorrect actions.

These options are not mutually exclusive and a hybrid solution may be the most effective. Selecting the preferred option or combination of options depends on issues such as parent device complexity, the nature of anticipated failure modes and the projected training device complexity and cost.

The SelfDose® from Janssen / West Pharmaceutical Services (shown in Figure 3) is a single-use injection device intended for user groups with reduced dexterity, for example the aging population.<sup>9</sup> Based around a 1 ml prefilled syringe, it's ergonomically designed and allows the user to control injection speed, as quickly or slowly as they like, which also means it is suitable for a variety drug and biologics over a wide range of viscosities. A training device was created to enable the users to overcome anxiety and become familiar with the tactile response felt during a real injection. It accurately recreates the progressive resistance felt by the user during an injection without having any needle or drug product, it feels just like the real thing, allowing multiple "dry-runs" before using the real device.

## TRAINING DEVICE DEVELOPMENT

Training device development can be initiated at any point during the parent device devel-



opment programme, it's never too late, though of course earlier is better. In itself a non-intrusive training device with no sharps, active drug ingredient or diagnostic capability is not a medical device, which means that a full GMP or 13485 programme may not be required and a more rapid development programme is possible, providing it fits with and supports the parent device development and regulatory requirements. Careful consideration needs to be given to the impact on the use of the parent device of course, and care needs to be taken not to create additional failure modes. (For example, it is crucial to avoid the scenario where the trainer device is confused with the real device at times of need.)

In order for medical device companies to achieve the rapid and flexible development required, often third-party developers can help. A training device development team studying the parent device development, function and modes of use, can provide rapid, clearly resolved training device solutions. Using partners with sound basis in

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"In itself a non-intrusive training device with no sharps, active drug ingredient or diagnostic capability is not a medical device, which means that a full GMP or 13485 programme may not be required"

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medical device development, engineering and usability will help the training device development programme effectively and efficiently create the training device to suit.

## CONCLUSION

As home-use medical devices come to the fore, training devices provide means to educate and train diverse and complex user groups, by allowing them the chance to role-play, practice and prepare at home. In providing such training devices, medical and pharmaceutical companies can improve learning, improve adherence and reduce patient/user anxiety. Together this creates a more robust home-use medical device proposition, which should smooth the regulatory approval route and ultimately reduce adverse events.

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## COMPANY PROFILE: ZAHORANSKY AG SYSTEMS TECHNOLOGIES



Written by Harry Pruner, Freelance Journalist, Pruner Marketing Services (info@pruner-marketing-services.de)

As automation systems supplier for drug delivery devices, ZAHORANSKY provides the Z.BLIZZARD system for the glueless production of staked-needle prefillable syringes (PFS). This system combines complete needle isolation, injection mould and automation into a single unit.

The new Z.BLIZZARD system (Figure 1) for the production of staked-needle syringes is an integrated automation solution in module design, allowing the isolation and glueless sheathing of cannulas. The Z.BLIZZARD system features both the needle feeding system, Z.NFS (see Figure 2), and the injection moulding machine (Figure 3) with tool. The integrated Z.NFS is also modular in structure, with the effect that different design variations of cannulas



Figure 2: The Z.NFS needle feeding system.

can be processed within the specification. The Z.NFS is capable of handling needles, cannulas and piercing aids in various lengths and diameters. Optionally, even needles and cannulas with grinded or shaped sections can so be aligned automatically and then carried to downstream processing.



Figure 1: The Z.Blizzard full-range automation system.

One invaluable advantage of plastic syringes compared with glass syringes is that there is almost no risk of breakage during handling, storage and transport. Another benefit compared with the conventional way of making PFS from glass is in the much greater design freedom for the components to be made. Technical function features can be designed and added directly to the plastic part. With optimised construction, this results in highly cost-effective overall systems. These may be design-related, technical or safety features which are integrated directly onto or into the syringe body. Every conceivable freedom in design is possible in line with the customers' ideas and specifications, with the ultimate solution in terms of design and functionality found in the dialogue among the pharma company, the plastic processor and the filler. Fillers should ensure, however, that existing filling systems can cope with new products.

## THE COMPANY

For more than 110 years, the name ZAHORANSKY has stood for reliability, precision and fully evolved engineering for machines for automation, mainly in the production of brushes. Today, ZAHORANSKY AG is a full-range supplier in mechanical engineering, sophisticated, innovative injection moulds and automation equipment. The company's Systems Technology division is based in Freiburg (see Figure 4) and operates with more than 600 associates at production sites in Germany, Spain, China, India and the US.

ZAHORANSKY offers across-the-board systems and solutions for the whole process chain, including the integration of tools and moulds, packaging engineering, handling, programming and robotics in the production of fully automated production and assembly plants. Automation systems are made for the industrial sectors Oral Care, Medical Engineering, Cosmetics, Consumer Goods, Household and Industrial Brushes, and Packaging. Systems for medical are available in medical classes 1 to 3.

## GLUELESS PRODUCTION OF DISPOSABLE SYRINGES

First, the needles to be sheathed are taken or isolated from a magazine (see Figure 5), using the first-in-first-out principle. The components to be sheathed are then brought together and provided at a defined handover



Figure 3: View into injection moulder.



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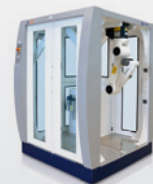
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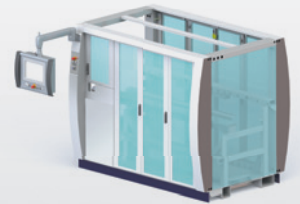
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Figure 4: Zahoransky AG, Systems Technology plant in Freiburg, Germany.

point between the Z.NFS and the further downstream automation. In the process step, the components are placed by a gripper system developed in-house into the injection mould also developed and patented by ZAHORANSKY. The full hot-runner valve gate injection mould is an integral and essential part of the value added chain. Before insertion, checks are carried out at various points to make sure that the following injection moulding process proceeds without any rejects. In line with the number of cavities in the injection mould, the needles are aligned and transferred to a handling system which first checks whether they are in place and in correct position. Using a numeric controlled axis robot, the needles are then placed in a parting line of the injection mould. Suitable devices hold the needles in the correct position. Parallel to equipping the needles, the finished parts are removed out of the second parting line by a six-axis robot. This reduces the cycle time to a substantial degree, because feed-in and removal take place almost simultaneously. After feed-in the needles and removal of the finished parts, the mould closes again. All open cavities and areas, in particular those of the needle bore, are closed by the appropriate functions of the injection mould. Plastic material is then injected into the cavities of the injection mould.

The high-grade technical polymer used is, for example, Zeonex cyclo-olefin-polymer (COP) from Zeon, or cyclo-olefin-copolymer (COC) from Ticona or similar alternatives. When using the glass-like COP, processing recommendations instructions say that the screw feed-in of the injection moulding machine should be nitrogen flooded to ensure that almost no so-called black spots or defects come up at the plastic parts. Using full hot-runner valve gate moulds means that there is no, or only very little, particle contamination, caused by a mass guidance system in the production area. To keep the particle contamination on the surface of the plastic part as low as pos-



Figure 5: Detailed view of needle isolation.

sible, it is recommended to cover the area of the injection zone (the mould) and maybe also the handling and downstream automation system with one or several additional laminar flow units.

### OPTIONS FOR SUBSEQUENT PROCESSING

After removing the staked-needle syringes (Figure 6) with a suitable removal system (in this case a Kuka s-axis robot), the parts are placed on a sight or transport line to prepare them for further processing. Some of these subsequent processing steps can be, for instance, a visual inspection, siliconisation, various checks and inspections for best possible patient use, plugging on a sealing cap and handing over to standardised trays (100/160) as carrier system for further processing or filling the PFS. To ensure that no silicone seeps in or contaminates the injection moulding area during subsequent processing, these areas are separated from each other by the above-mentioned sight or transport lines. Visual inspections and siliconisation are possible in the downstream



Figure 6: Plastic staked-needle prefilled syringes.

automation independent from the actual injection moulding process. Other options are also feasible between the pick-up from the sight line and placing the parts in the standardised 100 or 160 trays. Options are for example, covering and sealing the disposable syringes (PFS) with a fleece and a covering film, an optical camera control of the needles in the sheathed zone, siliconising the needles, an lubrication check

of the needles, if necessary, siliconising the inside of the barrel and maybe one more quality check. There is also the option to use a plunger to be able to generate a so-called zero-bubble filling situation.

### OUTLOOK – WHAT'S NEXT?

In the future, ZAHORANSKY will build more in-house downstream automation units on a modular platform (Z.MISTRAL). Basically, this automation platform relies on a larger number of approved components, allowing the customer to build up a total automation concept from a range of standardised function units. From the range of ZAHORANSKY AG there will also be a tray loader (Z.LODOS), as interface to a downstream automation. Tray loaders are used to place parts in industry trays that are usable for automation or in trays for staked needle syringes, for example.

The glueless production of prefilled syringes is relatively new and already enjoys a high level of acceptance. But, according to ZAHORANSKY's investigations, well over 95% of all cannulas are still being glued in Europe. If new developments and interrelations of all parties consider design, engineering and technical safety features, the future will certainly belong to glueless plastic syringes.

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