Packaging + Serialisation
**SERIALISATION** Drug makers have only until two years from now to make their drugs and packaging counterfeit-resistant. By 9 February, 2019, every prescription drug pack must carry a 2D data matrix code that can be tracked by wholesalers and pharmacists along each stage of the value chain. Additionally, each pack must be sealed with an anti-tampering device. If companies and the NMVOs that handle national databases can’t manage the task, their drugs cannot be sold after the deadline.

In 2014, a record number of falsified drugs flooded the legal supply chain. Expensive biologics, including Herceptin, Remicade, and Gardasil, were stolen in Italy, repackaged and reimported in 390 cases throughout Europe. However, that same year, the police confiscated nine million falsified medicines in over 100 countries and shut down more than 10,000 illegal online pharmacies. Only rarely, as in the case of the German Pillendienst, the criminals responsible are sentenced to imprisonment, as law firm Dentons and Boehringer Ingelheim reported at the end of January. Counterfeit drugs cost Europe more than €10bn a year, a new report by the European Observatory on Infringements of Intellectual Property Rights estimated last October. However, nobody knows the precise figures, and the WHO stopped publishing estimates on the economic impact in 2012.

According to a global surveillance and monitoring system implemented by the WHO in 2013 to assess the economic impact of counterfeit drugs, over 920 falsified medical products have been reported by member states thus far. “While counterfeit drugs are leaking into the legal supply chain, it’s highly important to secure it from criminal action,” says Dr Reinhard Hoferichter, spokesman for the board of securPharm. Germany’s National Medicines Verification Organisation (NMVO) is the very first early adopter of the EU’s Falsified Medicines Directive 2011/83/EG and its delegated regulation. The regulation, which must be implemented in the EU member states plus Norway, Iceland, and Liechtenstein, fourteen states have founded NMVOs, and two have selected an IT provider. According to the EMVO, all IT systems must be ready for testing by the end of 2017, and fully functional by 02/2019. Belgium, Italy, and Greece, which each have a system that verifies individual medicines, must implement the new system by 2022.

Pharma companies that have already adapted their packaging lines to print an identifier on the pack can upload the code into a national database provided by NMVOs, or directly into the EMVO database. The code can be tracked along the whole value chain.
WE ARE YOUR PARTNER FOR THE IMPLEMENTATION OF THE SAFETY FEATURES ACCORDING TO THE FMD - 2011/62/EU

IN KEEPING WITH:
+ THE DELEGATED REGULATION 2016/161
+ THE STANDARD EN 16679:2014
+ REQUIREMENTS OF THE NMVO AND EMVO
+ ADDITIONAL DRUG REGULATIONS

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SERIALIZED LABELS
Individual positioning on the packaging considering the packaging dimension, labeler and inspection system. Individual formats, shapes, materials and also additional safety features are possible. Labels ensure a permanent application. Manual and mechanical application is possible. There is no need to provide a varnish free area. We guarantee print quality, optimized order processing, just-in-time delivery and a secure supply chain.

TAMPER-EVIDENT LABELS
Individual formats, shapes, materials and also additional safety features are possible. Finishing with perforation or safety die cutting are practicable. Manual and mechanical application is possible. There is no need to provide a varnish free area.

COMBINATION LABELS
2-in-1 label solution allows two process steps in one pass. The multi-purpose solution is suitable for many serialization cases e.g. folding box bundles, special formats, manual packaging, small batch sizes, re-packaging or your special case.

Please get in contact with us to discuss your special serialization case. www.baehren-druck.de - phone: +49 2166 97291 43
tenstein by February 2019, describes exactly what drug manufacturers and prescription med sellers must do to block stolen and repackaged drugs from leaking into pharmacies: print a unique identifier onto every prescription medicine, and seal drug packs with an anti-tampering device.

The NMVOs are responsible for building the appropriate IT-infrastructure. Linked to a central EU data hub, it tracks and verifies the unique identifier along the entire value chain. “It’s a highly complex task. That’s why we already started work in 2011, five years before the EU’s delegated regulation defined the requirements for practical implementation,” Hoferichter says. “Today, this decision has proved to be correct.”

Currently, the EU sees two different speeds of implementation. Early adopters such as Germany and Sweden needed about two years to build their NMVOs with the players of the value chain and establish the technical system required for authentication of a drug. All other countries waited for the publication of the delegated act in February 2016.

Industry lagging behind

According to the European Medicines Verification Organisation (EMVO), two-thirds of EU countries are lagging behind in implementation. The EMVO manages the EU data hub that will pool all data uploaded by NMVOs through their national blueprints to verify pharmacists and hospitals. By February, only 14 NMVOs had been incorporated and two IT providers for implementation had been selected, with Germany and Sweden taking the lead (see map). Four countries had not started technical preparations.

In the industry, implementation of serialisation is also lagging behind, particularly among smaller companies that do not belong to pharma industry associations. According to a recent study of TraceLink among 200 drug makers, nearly 80% of respondents were concerned about hitting the deadline. As serialisation efforts are currently implemented on a worldwide scale, drug makers, CMOs, and Contract Packaging Organisations must adapt all packaging lines to be able to print machine-readable unique identifiers on the pack and seal it. “Printing and tracking the identifier is a big challenge,” says Hoferichter. “Costs for technical adaption of a single packaging line are estimated to be in the range of €100,000–200,000, or 3–5 cents per pack. If you take the German market alone, with its more than 700 million packs of prescribed medicines annually, implementation cost will be about €21m–€35m per year.” Other estimates are up to four times higher.

Intensive training required

SecurPharm’s system is currently the only one throughout Europe that can already feed its database with 2D matrix codes provided by drug makers. They include a randomised Unique Serial Number, the manufacturer product code, the batch number, and the expiry date. Each time a drug is dispensed, data is sent to another database used by pharmacists to authenticate the drug as legal. “Providing one database for drug makers and another for the pharmacists and wholesalers improves data protection,” explains Hoferichter. However, it takes almost a year to make the process run perfectly, because without proper training mistakes can occur from the manufacturer’s side. That’s why the EMVO is pushing NMVOs to start the training phase early in 2018, at the very latest, to prevent gaps in the system.

The switch to the new serialisation and traceability requirements could become expensive, particularly for midsized companies. They not only must retrofit packaging lines and adapt manufacturing and IT systems to the new requirements, but also train operators, which comes on top of the annual EMVO/NMVO service costs based on the number of countries in which a drug is authorised. For small enterprises, this can be a substantial expenditure affecting product margins. For biopharmaceutical companies that have outsourced manufacturing and packaging, the challenge is to align their IT systems with those of their partners in order to appropriately transmit batch numbers etc. covered by the unique identifier. As securPharm’s system is in the advanced stage, 25% of German manufacturers of Rx medicines have already joined it for practical testing. However, for most companies, it’s time to act now.

t.gabrielczyk@biocom.eu
Pharma labelling with foresight

UPM Raflatac has developed a range of labelling products to support compliance with the Falsified Medicines Directive on packaging for prescription drugs and high-risk, over-the-counter medicines. The tamper-verification functionality of the RP62 EU adhesive is available with a range of clear film and paper-based label face materials. Few solutions offer the same ease of adoption for meeting the February 2019 deadline. UPM Raflatac’s innovative pharma and healthcare labelling solutions are backed by comprehensive support, an established supply network and a worldwide presence you can rely on.

Details on our Pharma pages at www.upmraflatac.com
Disposable pens – a unique offer for clinical testing

**SELF-INJECTION DEVICES** Driven by the aging of Western societies, the market for self-administration auto-injectors currently grows at 20% annually. European Biotechnology spoke with Konrad Betzler, CPO at pen specialist Haselmeier, who is preparing a completely new application field: clinical trials.

EuroBiotech_Self-administration of injectable drugs in diabetes treatment and hormone replacement therapy is a growing market. Where does Haselmeier see further growth opportunities? Betzler_The market for injection pens in Europe is almost covered. However, the Asian markets are still growing. Accordingly, Haselmeier recently opened manufacturing facilities in India to serve this market. In Europe, we are focused on sophisticated, high-margin solutions for convenient daily self-application, i.e. in hormone replacement therapy at home. Medicines packed into and administered by auto-injectors or pens help reduce visits to the doctor and thus can enable health systems to work more cost-effectively. For drug developers, sophisticated solutions, which are the focus of Haselmeier’s offerings, can significantly reduce the time-to-market and CAPEX.

EuroBiotech_What's your market expectation in the new field? Betzler_Our vision is to expand with market demand. In the short-term, we can deliver up to one million pens per year using existing manufacturing facilities; in the long-term, the market could grow to 5-10 million pens annually.

Konrad Betzler has been Chief Pharma Officer at Haselmeier GmbH since 2016. He is responsible for setting up and directing the drug-device assembly and packaging business. Previously he was the Head of Quality Governance at Celesio AG and spent more than 10 years working as quality leader and Qualified Person for Catalent’s German Clinical Supply Services facility, the global no. 1 CDMO. He is a registered pharmacist and started his career at Roche and Schering AG, now part of Bayer. Betzler has a strong background in global GMP and GDP, including the supply chain peculiarities of clinical trial supplies.

EuroBiotech_How is that? Betzler_Currently, we are preparing to roll-out a completely new application: the very first disposable pen for clinical testing in Europe. In contrast to existing pens, our D-Flex system can be used in dose-escalation trials, because it offers unique flexibility. Up to today, different pens would be required to apply the diverse fixed doses of a biologic drug administered in dose-escalation studies. D-Flex can be flexibly configured before assembly to eject different preset fixed doses, but subsequently, the system does not permit any other amounts. So, patients cannot select an unintentional dose by mistake. On the other hand, the system has built-in dose-correction that allows companies to reduce overstock of injectable meds set to be clinically tested. This advantage over syringes translates from early-stage clinical studies to series production, thereby reducing time-to-market and CAPEX.

EuroBiotech_When will the new option be available to the industry? Betzler_In Europe, a combination of a medical device – the pen – and a cartridge that contains the API – the capsule – is considered a drug. That means you need to fulfil GMP requirements. We expect an inspection by October 2017 and to receive EU manufacturing authorisation in Q4/2017. After that, we will be the only company in Europe offering such a combined service.

EuroBiotech_For which purpose do you need a manufacturing authorisation? Betzler_Pen use in clinical trials is a very specialised business. Pharma majors have the infrastructure to manufacture pens on their own – but mainly at large-scale. On the other side of the spectrum, there are companies willing to outsource packaging completely. We won’t offer sterile filling, but we wanted to be able to organise a seamless supply chain of small to midsize batch packaging – from clinical studies to commercial supply.
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We provide a unique range of products and services including the most advanced elastomer formulations, coatings, aluminum seals, and processing technologies.

Partnering up with the world’s top pharmaceutical and medical companies, we stand by our mission to improve patients’ lives.

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Please visit us at Interphex, NY March 21-23, 2017 Booth No. 1546
Falsified Medicines Directive: ready for 2019?

CODING  UPM Raflatac has developed a range of pharmaceutical labelling products to support compliance with the Falsified Medicines Directive (2011/62/EU) on packaging for prescription drugs and high-risk, over-the-counter medicines. An estimated 30 billion drug packs are sold and handled annually in Europe. Few solutions offer the same ease of adoption for meeting the February 2019 deadline.

Markku Pietarin, Business Segment Manager, Pharmaceutical Labelling, UPM Raflatac EMEIA

The Falsified Medicines Directive requires that all prescription (white list) or high-risk OTC (black list) drug packs must carry a unique serial number to identify and authenticate individual products. In addition, packs should be sealed in a tamper-evident way which visibly exposes attempts to open them.

While the delegated regulation (EU) No 2016/161 stipulates that an anti-tampering device should provide verification of package tampering, it does not specify how. The European Commission Directorate-General for Health and Food Safety recommends consulting the new CEN standard EN 16679:2014 entitled “Tamper-verification features for medicinal product packaging.” UPM Raflatac used this standard as a guide to develop tamper-verification labelling products to meet an urgent market need for Directive-compliant solutions.

Irreparable tamper-verification

UPM Raflatac’s tamper-verification products are based on the RP62 EU adhesive, which exploits the properties of the cardboard wrapper printed with water-based varnish typically used in pharmaceutical packaging. RP62 EU enhances tearing between the bleached chemical pulp and BCTMP layers in the cardboard construction – lifting or removing the label causes highly visible and irreversible damage that indicates package tampering. The labels cannot be smoothed back down.

RP62 EU is available for both clear film and paper-based label faces. Pharmaclear PP Seal visibly stretches on removal, and Pharmaclear PP Tear TC displays the surface torn from tampered packs. Pharmatight paper label face is relatively fragile and suffers irreversible damage or breaks when tampered with. Attempted removal of the Pharmatight label will also cause surface damage to cardboard pharmaceutical packs. An RP62 EUL adhesive variant allows a missing label to be detected by luminescent detectors.

Inherent ease of adoption

For many pharmaceutical product lines, these self-adhesive label solutions are the preferred option due to their simplicity of implementation.

Ease of adoption is particularly a strong point when the tamper-evident functionality of the RP62 EU is combined with a clear, filmic label face, which has little effect on the graphic design of the package. Pharmaceutical manufacturers achieve the tamper-evidence required by the Falsified Medicines Directive, while continuing with their existing package layouts and packaging stocks.
Valuepack: at the forefront of outsourced Serialized packaging services for SME’s
We are an assembling and packaging service provider (Contract Packaging Organization) for the Medical industry. We are currently implementing our print and verification systems, including level 4 repository software in order to offer Serialization as a service. It is essential for anyone in the supply chain! However it seems that not many organizations, especially SME’s, have easy grip on this matter.

Advantages of outsourcing serialization
- No direct investments
- Capacity on demand
- Expertise
- Cost efficiency

Serialization as a service: a different approach suitable for SME’s
A common practice for organizations to apply serialization involves the incorporation of significant technology in existing in-line production processes and the dedication of personnel to its operation, troubleshooting, and management. Thus, the amount of resources needed for serialization can be significantly demanding for SME’s.

Valuepack’s Serialization as a service aims to relieve the SME’s from the above mentioned investments. Valuepack owns and maintains the serialization equipment and has the knowledge and software to serialize and provide the report of the ready-for-distribution products.

“We serialize your product! Contact us.”

Serialization solutions for
PRE PACKING:
- Flat, unfolded cartons
- Labels
- On-site
- Specials
- Commissioning

AFTER PACKING:
- Folded cartons
- Bottles
- On-site
- Specials
- Aggregation

Contact details
Valuepack B.V.
De Vlotkampweg 4
6545 AG Nijmegen
The Netherlands
theo.snoek@valuepack.nl
+31 (0) 24 642 43 68

Valuepack company profile
Industry
Medical Devices & Pharmaceuticals
Services
Contract assembling, packaging, & labelling services
Unique Selling Point
Serialization as a Service
The evolving needs of biologics packaging

**PACKAGING** Barrier properties alone are no longer sufficient to address the needs of biologics packaging. Changing requirements and expectations of syringe components indicate a growing demand for fluoropolymer coated elastomeric closures, primarily to mitigate risks related to drug stability and compatibility. Datwyler’s First Line facility standard is the most advanced manufacturing concept in the industry, assuring commitment to the highest level of quality.

† Megan Williamson, Vice President Injection Systems, Datwyler Sealing Solutions

Datwyler Sealing Solutions offers a wide range of specialised, complex, and unique coatings, elastomer formulations, and aluminium seals that allow customers to effectively package and administer drug products of the highest quality in the most efficient manner. Datwyler’s parenteral components offer maximum flexibility and provide a full spectrum of packaging solutions including RFS (ready for sterilisation), RTU (ready to use) and RTP (rapid transfer port) packaging components used in clean rooms, isolators, and RABS (restricted access barrier systems). The validated RTU concept comprises a wide variety of plungers, stoppers, and aluminium seals ready for immediate use. All Datwyler RTU closures are double-packed for easy introduction into aseptic filling areas. Additionally, the vacuum packaging technique between the outer bags makes it easy to check for sterility at the point of use.

**State-of-the-art advanced manufacturing**

Requirements and expectations for syringe components are ever-changing, driven by the constant development in drug product complexity and manufacturing, particularly with respect to biologics and biosimilars. This includes a rising demand for reduced particle, endotoxin, and bioburden loads in pharmaceutical containers to reduce risk. Additionally, interaction with leachables and extractables from primary packaging components can lead to chemical and/or conformational changes in therapeutic proteins, possibly rendering the protein and drug ineffective. The majority of biologics manufacturers therefore opt for fluoropolymer-coated closures. Datwyler is answering this demand by manufacturing lubricious barrier coatings (Omni Flex) which do not require siliconisation. Omni Flex Coated Plungers are manufactured using a proprietary, flexible, fluoropolymer spray coating technology that is designed to:

† provide an inert barrier and
† impart a low coefficient of friction without siliconisation.

This method ensures that the entire plunger surface is covered, in contrast to the partial coverage of most film coatings. It also has the benefits of providing a full barrier and eliminating the need for siliconisation of the plunger ribs. A study of Felsovalyi et al. [J Pharm Sci, 2012, Vol 101(12), p 4569] shows that the plunger is the larger source of free silicone. The absence of siliconization thus eliminates the largest source of subvisible particles and translates into only ultra-low subvisible particle loads from the plunger.

Datwyler exclusively produces all components of the Omni Flex family of vials and syringe components in its facilities that operate under the First Line standard. All pharmaceutical rubber components, such as vial stoppers or syringe plungers, are manufactured in a fully integrated Good Manufacturing Practice (GMP) environment. The First Line standard is designed to operate under a zero-defect philosophy. The process flow, gowning protocols, personnel, and material flow, and state-of-the-art automation all result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry.
You need just one. The new D-Flex.

- **Just one** pen that delivers one or more preset doses.
- **Just one** pen with dose correction in order to avoid injection errors or loss of the drug.
- **Just one** pen which does not permit any in-between values besides the doses set.
- **Just one** flexible platform which enables the customer to easily adapt to a wide variety of dose values.
- **Just one** strong platform from the initial clinical study to series production.

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