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Cover photo: Serialized medicine packs with 2D data matrix barcodes

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editorial

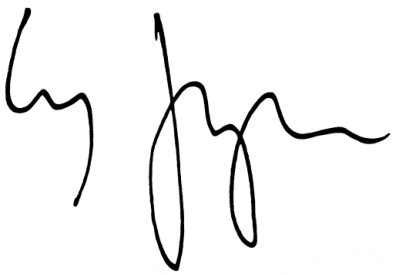
Falsified Medicines Directive – important as we rely on public trust

This issue is the first of a special two-part report on the Falsified Medicines Directive. It is a very timely topic as serialization of new medicine packages became mandatory within the European Union (EU) in February 2019 and the share of serialized medicine packages is rapidly increasing as stocks of old packages are used up.

I'm often asked if the new EU directive was necessary, as there are few incidents of falsified medicines reported. For me there are three crucially important reasons to safeguard the authenticity of medicines. The first, and maybe most obvious, is the risk falsified medicines pose to the individual. The second, and to me the most important, is that diminished trust in medicines would then reduce trust in health care which in the longer run would have a detrimental effect on public health. The third is that the current innovation model for new medicines is built on a system (patents, etc) that provides return of investment during a limited period of exclusivity. Thus, if even an illegal copy were found to be as safe and effective as the original it would reduce the financial input, discourage research and development in life science and bring an end to the innovation model as we know it. Taken together the answer is yes, the new directive is necessary to safeguard continued public trust in medicines!

We live in a time where scientific developments are increasing rapidly, and consequently the need to discuss and debate the issues. You are very welcome to join me and several thousand colleagues in Abu Dhabi at the 79th Annual Congress of Pharmacy and Pharmaceutical Science under the theme; "New horizons for pharmacy – Navigating winds of change", 22nd – 26th September 2019. There will be a full series of Industrial Pharmacy sessions and other pharmacy sessions with many new topics on the agenda including green pharmacy practice, 3D-printing, nanomedicine, anti-microbial stewardship, supply shortages, ethical issues, digitalization and 'Amazonification', and of course the role of the pharmacist in these developments. Topics that we need to discuss and debate together, not only at the country level, and not only between industrial pharmacists, but at the international level and across the pharmacy disciplines.

I look forward to meeting you in Abu Dhabi!



Ulf Janzon
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THE FALSIFIED MEDICINES DIRECTIVE

by Adrian Van den Hoven

The Falsified Medicines Directive (FMD) introduced mandatory serialisation of prescription medicines in Europe in February 2019. This new directive will help ensure that European patients will continue to have safe access to medicines.

Adrian Van den Hoven is Director General of Medicines for Europe, which represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members directly employ 190,000 people at over 400 manufacturing and 126 R&D sites in Europe, and invest up to 17% of their turnover in R&D investment. Medicines for Europe member companies across Europe are both increasing access to medicines and driving improved health outcomes. They play a key role in creating sustainable European healthcare systems by continuing to provide high quality, effective generic medicines, whilst also innovating to create new biosimilar medicines and bringing to market value added medicines, which deliver better health outcomes, greater efficiency and/or improved safety in the hospital setting for patients. For more information see www.medicinesforeurope.com and Twitter @medicinesforEU.

Introduction

The FMD directive was adopted in 2011 (Directive 2011/62/EU). It laid down requirements that aim to prevent falsified prescription medicines from entering the legal supply chain. The law also details the characteristics of the safety features and how medicine authenticity should be verified by healthcare professionals responsible for the dispensing of medicines to patients – mainly pharmacists. The legal supply chain is a distribution network composed of manufacturers, distributors (wholesalers and parallel traders) and dispensers (high street pharmacies, hospital pharmacies and dispensing physicians) whose activities are overseen and regulated by national medicine agencies and inspectorates.

Falsified vs authentic medicines

Falsified medicines are products, (often) disguised as authentic medicines, but which may contain ingredients of bad or toxic quality, or in the wrong dosage. As such, they can pose a real risk to patient health. They represent a serious threat to global health and call for a comprehensive strategy both at European and international level. Luckily, the prevalence of falsified medicines in the European legal supply chain was estimated to be only 0,005%. While small in percentage terms, this could represent up to 750,000 medicinal packs on the European market which is justification enough to take action.[1]

The pharmaceutical industry has been committed and engaged in implementing the FMD serialisation requirements. The law requires the pharmaceutical industry to apply two safety features to the outer packaging of prescription medicines: a 2D data matrix (similar to a QR-code) and an anti-tampering device which should both be verified prior to the medicine being dispensed to a patient. The legislation applies to almost all prescription medicines. The majority of over the counter medicines (medicines not prescribed by a physician) are exempt from the legislation.

In practice, pharmacists and dispensing physicians will check the authenticity of medicines by scanning the 2D data matrix via a secure database and checking that the pack has not been tampered with at the point of dispense of the medicine. If the authenticity of the medicine cannot be verified via the secure database or if the box has been tampered with, it should not be dispensed to a patient. This verification procedure became a legal obligation as of the 9th February 2019 across the EU which has an extended deadline for implementation.

As described, the FMD requires numerous changes to the business of all actors operating in the legal supply chain for pharmaceuticals. For the medicine manufacturers that our association represents, we are committed to a sustainable supply of high-quality medicines to European patients in compliance with FMD. Thus, our members have invested significantly in their manufacturing processes to enable serialisation and are financing the secure database across the EU.

Costs and scope of the operation

For the generic industry specifically, which supplies over 67% of prescription medicines in Europe, this project was a massive undertaking from a manufacturing, IT, regulatory and supply chain perspective.

There are 10,000 packaging lines in efficient operation to supply European patients with generic medicines.[2] To apply serialisation and tamper verification features costs around € 500,000 per packaging line.[3] As the life-span of a packaging line is 5 years on average, the application of safety features adds a cost of € 1 billion per year for generic medicines manufacturers as a whole. The secure database for the verification of medicines which costs €100 million/year will be paid for by manufacturers.

The rough estimate of this cost for medicines can be calculated as follows. Each year in Europe 10 billion packs of generic medicines

are dispensed[4], the application of safety features on packaging adds on average €0.10 to the cost of goods per pack of generic medicines. A Dutch study shows the total cost (including e.g. regulatory procedure changes) can rise to €0.17 per pack.[5] In their impact assessment, the European Commission acknowledges that the financial impact of their legislation can be the greatest for the generic medicines industry and for Small and Medium Sized Enterprises (SMEs).[6] Given the generally low prices of generic medicines in Europe, it is clear that FMD will have an impact on their patients.

These costs simply cannot be absorbed for the majority of generic medicines on the EU market. Consequently, Medicines for Europe will seek to engage with national authorities to review the sustainability of supplying Europe's essential medicines at very low cost while having to invest in massive regulatory compliance projects like FMD. Our industry will strive to avoid the situation arising whereby large numbers of medicines are withdrawn from the market due to unsustainable market conditions. Stock outs and shortages of medicines are now widely reported in the media and it is clear that unsustainable pharmaceutical policies are one of the main causes of supply disruptions.[7]

Conclusions

Patient health and the availability of high-quality medicines are of the utmost importance to the pharmaceutical industry. The FMD will make it more difficult for counterfeiters to bring falsified medicines into the legal supply chain, and this is a positive initiative. The implementation of the directive, as well as maintenance of the secure database have come at a substantial cost. To sustain and secure the safe supply of medicines, we look forward to working with governments and stakeholders to find access solutions together.

Our surveys show that all of our members are connected to the system and have serialised their production lines in line with the legal requirements. We are tackling any technical glitches with the system together with the European and national hubs. According to the European Medicines Verification Organisation (EMVO), there are still many companies which are not connected to the system and therefore their products cannot be verified. We anticipate that national authorities will start to address cases of non-compliance with the rules in the coming months.

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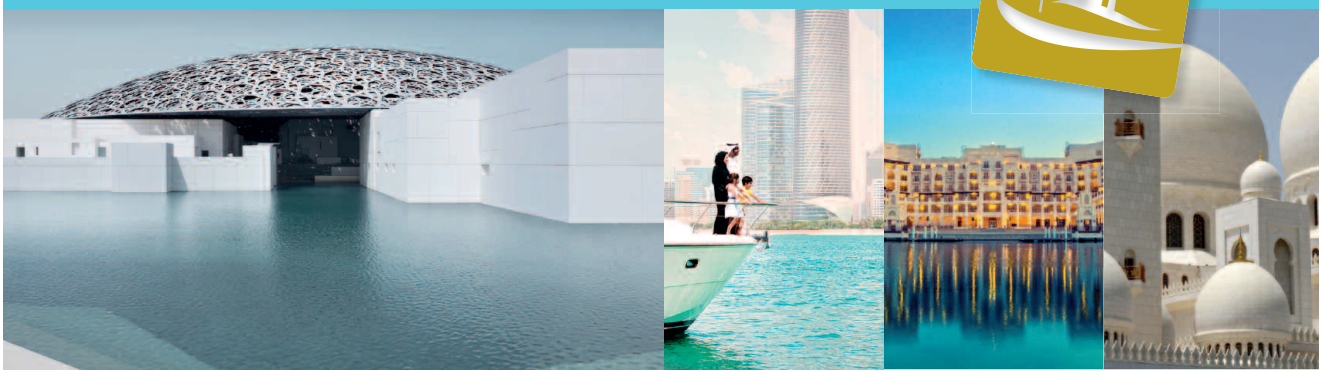

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GETTING STARTED WITH FMD – A PHARMACY PERSPECTIVE

by Jonathan Buisson

With the start of medicines pack authentication under the Falsified Medicines Directive (FMD) now in force, writing on behalf of the UK FMD Working Group for Community Pharmacy, the author, describes what's been happening and what pharmacists need to do.

Jonathan Buisson leads the UK FMD Working Group for Community Pharmacy's communications sub-group and the development of FMD Source. He is International Pharmacy & Policy Manager at Walgreens Boots Alliance and an expert on FMD and its implications for the entire medicines supply chain.

The UK FMD Working Group has produced FMD Source (www.fmdsource.co.uk) to help pharmacy owners and their staff catch up to speed with FMD.

Authentication of medicines under the Falsified Medicines Directive (FMD) [Directive 2011/62/EU and Delegated Regulation 2016/161] started across 32 Member States of the European Union (EU) and European Economic Area (EEA) on 9th February 2019. This followed a hectic three-year implementation period during which an entire system of interconnected European and national databases was developed, pharmacies and wholesalers upgraded their internal systems and processes, and manufacturers began serialising billions of individual prescription medicine packs.

FMD is not a "track-and-trace" system. Instead, it was developed on the "bookends" principle. Unique identification codes are produced and uploaded by manufacturers at one end. These codes are verified and decommissioned when the packs leave the supply chain at the other end. This decommission is normally undertaken by community or hospital pharmacies as part of the dispensing process, but can also be undertaken by dispensing medical practices, pharmaceutical wholesalers (in some circumstances) and a range of other healthcare institutions that supply medicines to patients.

The aim of FMD is to make it more difficult to introduce falsified products in to the European medicines supply chain. Serialised packs and a process of verification and decommissioning should help identify any potentially falsified products before they reach patients. The introduction of machine-readable 2D barcodes on all packs should also help with stock ordering, stock rotation, accuracy checking, product recalls and reimbursement.

FMD and verification systems

The European FMD system is based on National Medicines Verification Systems (NMVSs) in each Member State. These are connected to and by the European Medicines Verification System (EMVS). The EMVS acts as the central portal through which manufacturers upload unique identifier codes for distribution to relevant NMVSs (see **Figure 1**). It also allows checks of packs intended for sale in more than one market (on a regional or language basis).

Pharmacies, wholesalers and other healthcare institutions make a secure connection to their local NMVS and use this to verify the authenticity of packs in their possession by scanning the 2D barcodes.

Each NMVS is run by a National Medicines Verification Organisation (NMVO). These are normally formed by representatives of the main stakeholders in the supply chain – branded medicine manufacturers, generic manufacturers, parallel traders, wholesalers and dispensing entities (pharmacies). The three categories of manufacturers pay fees for the costs of running of the NMVS. The European Medicines Verification Organisation (EMVO) is a similar stakeholder body that controls the central EMVS and sets the rules for connections and data uploading.

FMD progress so far

The EMVO was established in 2015 and between 2016 and 2019 all 32 NMVOs were established. They have all set up their NMVSs and been connected to the central hub at the EMVS. They are currently in the process of completing the registration and connection of many thousands of "end users" (pharmacies, wholesalers and others), including conducting strict identity checks to ensure the security of the system.

Manufacturers have been changing their packaging to incorporate the new 2D data matrix barcodes and accompanying human-readable data. This began during 2018 and FMD-compliant packs can now be seen appearing in wholesalers and pharmacies, (see **Figure 2**) especially among fast-moving branded and generic lines. Uploads of data are now occurring on a large scale, with millions of identifiers being added every week.

Verification and decommissioning of packs by pharmacies has now begun, but is currently at a low level in most markets, mainly due to the time taken for new packs to move through the supply chain.

In addition, most Member States are now operating FMD in a "stabilisation" or "implementation" phase, or – as the Irish have dubbed it – taking a "use and learn"

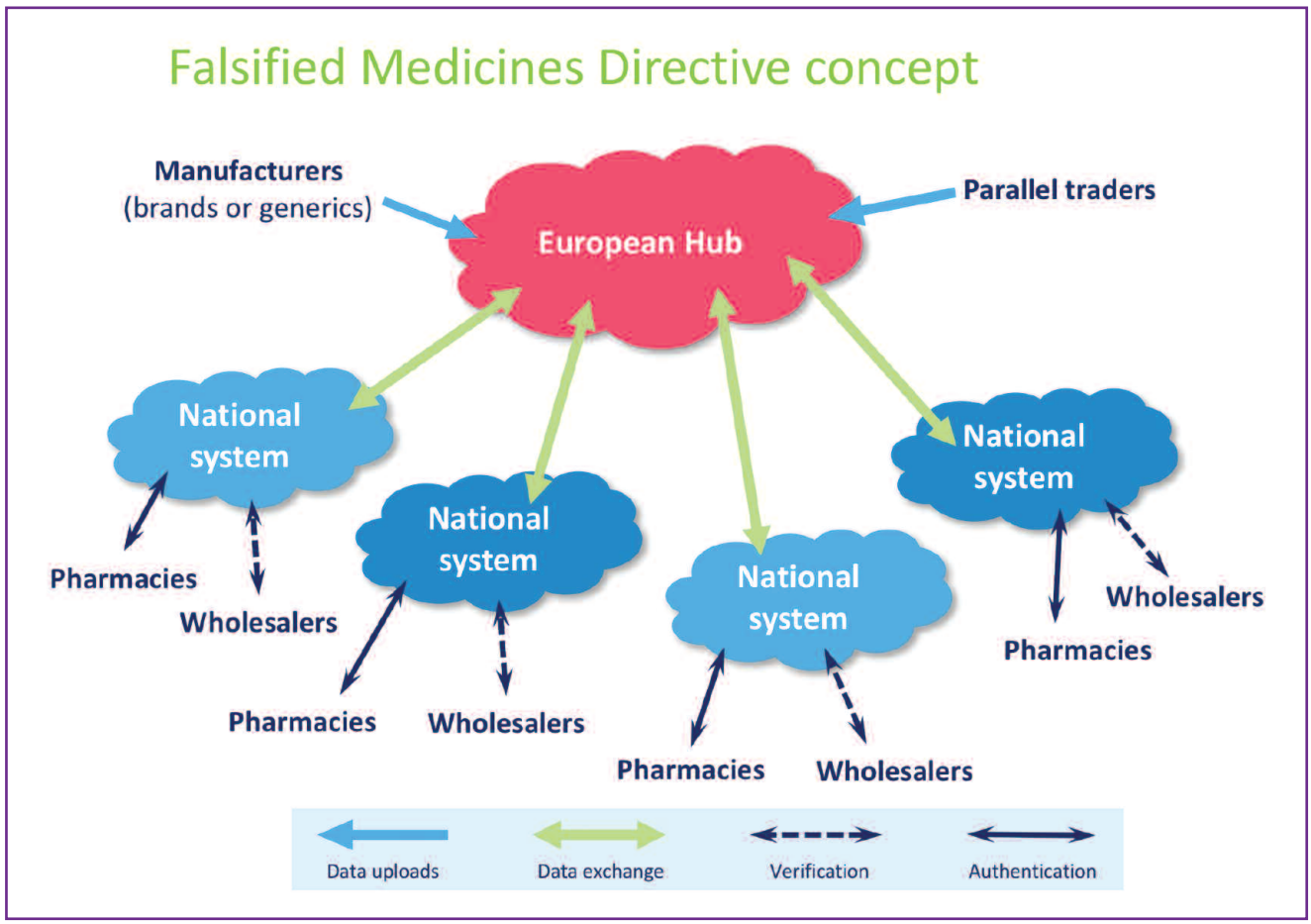

Figure 1 – The FMD concept is based around manufacturers and parallel traders uploading unique product identifiers which are then distributed to relevant national medicines verification systems by the European Hub. The unique identifiers can be used by wholesalers, pharmacies and other dispensing entities when they need to verify and authenticate (dispense) medicines in their possession. The European hub can be used to synchronise pack statuses across multiple markets and to verify products from other markets, if necessary.

approach. Regulators are waiting for the system to come up to full speed and for early issues to be resolved before considering any moves towards formal enforcement. This is expected to last well in to 2019.

Key issues so far

Not unexpectedly, a number of issues have arisen with the complex, multi-country FMD system in its early days. Some of these were expected, like low availability of compliant stock, but others relate to how the system operates in under real-world conditions. In addition, especially for the UK, there is the unforeseen and seemingly never-ending complication of Brexit.

- *Non-compliant packs* Packs that were produced before February 2019 do not need to carry FMD safety features. They can be supplied and dispensed up until their expiry dates. They will gradually be replaced by new packs but some could remain on shelves for several years. An added complication in the early days has been that many generic products produced in India already carry 2D barcodes to meet local legislation (but not anti-tampering devices). Scanning these under FMD will produce an "unknown pack" error message. Guidance is being issued to help end users recognise packs that meet FMD requirements.
- *Expiry dates* FMD requires packs to have expiry dates encoded in a DD/MM/YYYY format. Some manufacturers previously reported expiry dates as being "End of Month/Year" and these were encoded as 00/MM/YYYY. This has led to false alerts about packs having expired due to a mismatch with data uploaded. This is being addressed through additional guidance to manufacturers
- *Alerts and reporting* In its early stage, the FMD system is generating large numbers of alerts, many of which relate to the "unknown pack" or "expiry date" issues mentioned above. There are

Figure 2 – Serialised packs are now appearing in wholesalers and pharmacies across Europe

also issues relating to pack data that has failed to upload or to reach its intended market. False alerts increase the time taken to complete the dispensing process and can be off-putting for users. A lot of work is being done to address this and to make the overall system more stable.

- *Brexit* The uncertainties relating to Brexit, and when (or if) the UK will leave the EU, with or without a Withdrawal Agreement, have cast a shadow over FMD implementation in the UK. Despite this, the UK has successfully implemented its NMVS and remains one of the leading countries in developing FMD processes and understanding. As long as the UK remains an EU Member State it will continue to undertake FMD authentication. This would probably continue under any transitional arrangements.

Benefits of FMD

As well as the stated intentions of FMD to reduce the risk to patients from falsified medicines, there are other benefits that should become clear as experience builds up and more packs become compliant.

By scanning the machine-readable codes on each pack, pharmacies should be able to gain more detailed insights into the stock they are handling, especially in markets where scanning has not been part of the normal dispensing routine. Being able to read expiry dates straight off packs just by scanning them should help reduce the risk of stock going out of date, leading to savings. Similarly, being able to scan batch information should help with handling recalls or product withdrawals. If packs are scanned when they first enter the pharmacy, it should be possible to have a system that automatically alerts pharmacy teams to products that are becoming short-dated or which have been recalled, even before dispensing.

In the longer term, the ability of manufacturers to mark packs or batches as having been stolen will add a further level of security of supply.

Information and support

There are now many sources of information about FMD. One of the first places to start is the EMVO website (emvo-medicines.eu) and its extensive knowledge hub. Each NMVO also has information relating to its own market, especially in relation to getting registered and connected as well as any local operating issues. National Governments and medicines regulators have also added guidance and resources to their own websites. In the UK, the FMD Working Group for Community Pharmacy has produced FMD Source (www.fmdsource.co.uk) as a central resource for pharmacy owners. It has a range of articles, guidance and diagrams, including what to look for when scanning FMD packs.

What pharmacies have to do

Under FMD, community pharmacies are required to authenticate all prescription medicines bearing the safety features "at the time of supplying them to the public". Authentication involves two steps:

- Checking that the anti-tampering device (ATD) sealing the bottle, pack or carton is still intact at the start of the dispensing process. This is a simple visual check
- Scanning the 2D barcode on the pack, comparing the unique identifier data contained in it with data originally uploaded by manufacturers, and decommissioning the pack. This involves connecting to the NMVS through either a stand-alone interface or through an integrated pharmacy system

If the data from the pack scan matches that held in NMVS then the decommissioning scan will change the pack's status to "inactive—supplied". This will prevent other packs that might have the same unique identifier from being dispensed, thereby reducing the risk that falsified products are handed to patients.

However, if the NMVS returns a negative message, such as that the product in question has been recalled by the manufacturer, then the pharmacy will need to take appropriate action in response.

UKFMD
Working Group for Community Pharmacy

The FMD Working Group was established in 2015 to bring together all the bodies representing community pharmacy owners in order to discuss the practical implementation of FMD within community pharmacies across the UK, and to influence the Government to seek cost-effective solutions to the issues raised by it.

The Working Group consists of representatives from pharmacy trade bodies and negotiators. It meets regularly with representatives of UK Government and regulators and with the main IT system suppliers for pharmacies in the UK.

The Working Group has produced FMD Source (www.fmdsource.co.uk) to help pharmacy owners and their staff to come up to speed with FMD.

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FMD: HOW HAS THE INTRODUCTION OF FMD IMPACTED PHARMACIES?

by Oliver Pittock

The biggest change to the medical and pharmaceutical industry across Europe, the implementation of the Falsified Medicines Directive (FMD), came in to force in February 2019. So, four months later, what is the status of the directive across and what are the next steps for success?

Oliver Pittock is Managing Director at the pharmaceutical packaging expert company Valley Northern, Astonfields, Stafford, UK. Valley Northern supplies pharmacies and other healthcare establishments with a range of medical dispensers, medical disposables, packaging and other equipment from its headquarters in Staffordshire. The company website can be accessed at: https://www.valleynorthern.com/latest-news

Introduction

FMD is a legal framework that was introduced by the European Union to improve the protection of the public against counterfeit, falsified and tampered medicines.

The directive orders that the more than 2,200 pharmaceutical companies that hold marketing authorisations to supply prescription medication to countries across the European Economic Area, must upload unique identifier codes for each pack of medicine manufactured or repackaged.

However, even back in August 2018, reports suggested that almost half of companies that hold marketing authorisations would miss the deadline, with only 841 companies having completed the first stage of connection to the new system.

The directive in effect

FMD came into effect for pharmaceutical suppliers and healthcare providers, including community and hospital pharmacies, on 9 February, 2019. From this date, market authorisation holders were required to place two safety features on all new packs of prescription medication placed on market across Europe.

These safety features include a unique identifier (UI) in the form of a 2D data matrix, or barcode, which can be scanned at the various points across the supply chain to determine the medication's authenticity. The UI must contain the product details, including name, pharmaceutical form, strength, pack size and type, a serial number, a national identifying code, a batch number and an expiry date.

Prescription packs must also include an anti-tampering device (ATD), which allows visual checks as to whether the pack may have been tampered with since its manufacture. There are no stringent regulations as to what constitutes an ATD, however typical methods include glued down packaging flaps, seals or labels that must be broken when opening, shrink or film wrap, or foil blister packs.

The aim is for wholesalers and pharmacies to scan the UI and compare the data on the pack with the data stored in the National Medicines Verification System (NMVS), which is a digital system that holds all information and UI for medicinal products that are subject to the FMD in each EU Member State.

In the United Kingdom, SecurMed, the UK Medicines Verification Organisation (UKMVO), was established to implement the UK Medicines Verification System to enable FMD compliance across the nation. Other countries have their own version of the UKMVO. For instance, Germany uses securPharm, France MVO supplies France and Sistema Español de Verificación de Medicamentos (SEVEM) provides the FMD drug verification service for Spain.

Going live

Since the FMD was implemented in February 2019, there have been some reports of issues that are affecting its success both in the UK and overseas.

On 21 March, 2019, it was reported that a number of UK pharmacies were still not compliant with the new regulations and that there had been a number of delays as a result of a lack of clarity, slow roll out of required technology and external factors such as the uncertainty as a result of Brexit.

A further update was issued on 25 March, 2019, which suggested that pharmacies across the UK were struggling to deal with false counterfeit alerts, despite 167,000 packs of medication being dispensed without issue since the launch 44 days prior.

At the time, the National Pharmacy Association reported that nearly 9,000 community pharmacies across the UK, around 62 per cent of the total number operating, had registered with SecurMed and that many had experienced minimal disruption to dispensing services.

Yet, the UK FMD Working Group for Community Pharmacy, which is continuing to manage the rollout of the FMD across the community

pharmacy sector, claimed, even before the FMD came in to effect, that 'false positive' alerts would be problematic — and they were correct.

Many pharmacy systems displayed 'false alerts', including 'unknown product code' and 'failed to find batch' error codes, which were reportedly caused by manufacturers not uploading the relevant data to the system. The UK FMD Working Group for Community Pharmacy issued guidance on managing false alerts on its website, including a flow chart intended to support compliance.

It's good to talk

A roundtable event entitled 'Improving patient safety with the FMD in the hospital pharmacy, status of implementation' took place on 19 February, 2019 at the EU Parliament, and brought together representatives from hospital pharmacies, patient safety organisations, EU Commission officials, European and national agencies, as well as other industry personnel. The event aimed to help debate solutions that are in support of the implementation of the FMD across the hospital pharmacy setting.

The head of the IT solution, whose responsibilities include all of the bar-coding data, stated that while the system had been built in all 28 Member States, there is a need for a period of stabilisation and inspection to ensure everything is running smoothly.

The roundtable reported a number of challenges to the new FMD regulation including the delayed procurement of new IT systems, the volume of packs being processed, the complexity of distribution pathways specifically within hospitals as well as staff training delays.

However, a number of successes were also identified including support from national bodies, communication between stakeholders, third-party automation providers support, as well as the handling of the aforementioned false alerts.

Following the roundtable, the European Medicines Verification Organisation (EMVO) launched a bi-weekly newsletter informing Member State organisations, such as SecurMed, securPharm, France MVO and SEVEM, of any technical updates as well as general news.

In the first edition of the e-newsletter, published on April 26, 2019, EMVO provided technical updates on a number of issues, including medication packaging expiry dates not matching the European Medicines Verification System (EMVS).

The newsletter also announced an update of the centralised router, or EU Hub, which transfers the data between the pharmaceutical manufacturers and the wider supply chain. The update will include additional functionality including simplification of the serial number randomisation test, bulk activity capabilities and mandatory national codes, when applicable.

The future of FMD

So, four months on, what does the future hold for FMD?

The regulation isn't going anywhere, particularly considering the time it took to implement it across the majority of Europe. In fact, Italy and Greece are still scheduled to go live with the regulations before 2025.

Reports also suggest that the loom of Brexit will not affect the regulation either, as the Withdrawal Bill will convert any existing EU law, including the FMD, into UK law. This means that the duties and requirements of the regulations would continue to apply, unless specifically revoked.

While pharmacists on the public front lines may have struggled with the implementation of the FMD with technology delays and minor technical issues, as highlighted in the EMVO newsletter, integration of the FMD into day-to-day pharmacy life has been welcomed, if somewhat delayed.

One leading UK pharmacist commented before the FMD came in to play that they were working on a standalone solution that would form part of the new pharmacy management and record system, which would have an integrated FMD solution. It stated that this new system would provide additional patient safety checks along with FMD compliance, however it would be rolled out to high-street stores later than the February deadline.

The vast change in process will require pharmaceutical manufacturers, suppliers and pharmacy staff to work collaboratively to help ensure everything runs as smoothly as possible.

As Hugh Pullen, president of EMVO comments, "The EMVS has a unique structure that really makes [FMD] one of a kind. It will connect around 2,000 pharmaceutical companies, around 6,000 wholesale distribution authorisation holders, 140,000 pharmacies, 5,000 hospital pharmacies and around 2000 dispensing doctors in 28 countries". He adds; "It would not have been possible to reach this landmark without a strong EMVO team and the substantial collaboration between all stakeholders in the pharmaceutical supply chain."

So, in what is described as the largest verification system initiative in the world, the overall disruption to patient services and impact on pharmaceutical supply across the EU has been minimal. While some high-street pharmacists are still working to implement the full FMD regulations, the future is promising.

There is certainly opportunity for those across the industry to look back in decades to come, once the regulations have taken full affect across the region, with a sense of pride and satisfaction, particularly if it reduces counterfeit and dangerous medication reaching patients.

OPTIMIZED CYCLONE SYSTEMS IN POWDER RECOVERY AND EMISSION CONTROL

by Julio Paiva and Romualdo Salcedo

The design of new high efficiency cyclones is facilitated by using proprietary developed optimization algorithms and simulation software that can produce the best solutions for each industrial process. These solutions have been tested at pilot and industrial scales, both for particulate emission control and high-added value products, allowing the software to continuously monitor and improve the real functioning of cyclones. These compete favorably both with bag filters and electrostatic precipitators.

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Júlio Paiva has a PhD in Biological and Chemical Engineering from the University of Porto, Portugal. Since 2010 he has worked as Head of R&D and his research involves modelling innovative cyclone systems and the development of the PACYC computer model for fine particle capture taking into account particle agglomeration in cyclone systems. Furthermore, the competences have been broadened with a wide vision range of automation/logic programming and non-linear systems, especially in the field of component of automated information management applications. Email: julio.paiva@fe.up.pt

Introduction

One of the challenges of an industrial pharma production site, is not only the formulation and scalability of the production, but the 'simple' fact of not losing part of the product obtained in the process, which often manifests as a dispersion and/or aerosol (ie solid dispersed in a gas stream). The different approaches to gas-solid separation have their own set of Pros/Cons but a new approach to a common technology (ie gas cyclone) in a typical procedure (e.g spray drying) may help promote an almost perfect product capture.

This new gas-cyclone equipment promotes separation inside a specially designed chamber, that usually is constituted by a cylindrical part where the aerosol flow enters tangentially, on top of a cone from whose base the particles are discharged. The separation is physically obtained by accelerating the particles towards the wall, promoting their separation due to impact and slide down the wall, dispensing any physical barrier in this separation.

Technical drawbacks

In pharmaceutical manufacturing there is a general view that cyclones are inefficient powder collectors. The problems are generally found within the areas of emission control and powder recovery. In spite of the physical phenomena involved being the same, the drivers for each of the two problems are quite different.

In Emission Control the major drivers are as follows:

- Increasingly strict Particulate Matter (PM) emission limits are being enforced worldwide. Poor air quality is the number one environmental cause of premature death in the EU
- The majority of combustion processes are associated with PM Emissions. Cleaning hot gases is mandatory for heat recovery and to improve plant efficiency.
- Many other processes in large industrial plants are sources of PM – for example steel, cement, paper and glass.

In Powder Recovery the major drivers are the high economic added value:

- 60% of the world chemical related industries handle products in the fine powder form and a significant share is taken by the Pharmaceutical, Food Ingredients, and Mineral industries.
- Virtually all powder processing industries need gas-solid separation
- Many of these industries are actively seeking to optimize the yield of their processes and reduce powder losses.

There are several different kinds of gas-solid technologies such as cyclones (multicyclone, straight through and reverse-flow), bag filters and wet scrubbers (venturi). **Table 1** summarizes the main characteristics for each approach.

Despite numerous advantages (robust, absence of maintenance, no pressure and/or temperature constrains, no moving parts , working

Table 1: Technology comparison on secondary collectors.
Performance of different equipment for the collection of a Demineralized Whey Powder.
Median Particle Size in Volume (MVD) = 20µm; p = 1,000 kg/m^3; Inlet concentration: 154 mg/m^3

Comparison of Fine Powder secondary collectors	Wet Venturi Scrubbers	"CIPable" Bag Filter	Typical Cyclone
Efficiency (%)	85-95	99+	60 to 70
Emissions (mg/Nm^3)	10-25	<10	45-60
Quality of separated product	Waste	Second grade	First Grade
Contamination risk (sanitary conditions)	Very high	Considerable	Minimal
Cleaning perfection with CIP	Bad	Reasonable	Very Good
Investment Costs	Low	Very High	Suitable for CIP
Maintenance & Operation Costs	High	High	Reasonable

on a dry basis, no electrostatic components, no barrier filters) , regular cyclones are associated with *low efficiency for particles <5-10µm*, and typically, traditional "non optimized" cyclones have to be complemented with other separators due to their low efficiency. Specifically, in Powder Recovery, this type of separation presents challenges that the incumbent technologies fail to address.

Usual Sources of Powder:

The main applications in Powder Recovery are Dryers, Millers & Reactors

Spray Dryers which are used in the manufacture of pharmaceuticals, fine chemicals and food ingredients, have problems with the typically associated technologies of cyclones and bag filters. High efficiency cyclones have low efficiency for fine particle and bag filters lead to product degradation and/or contamination, production downtime and cleaning costs. See **Figure 1**.

By being aseptic and easy cleanable, cyclones are mandatory in several drying processes. Nevertheless, their low efficiency results in significant losses for many plants where powder recovered from downstream bag filters is not considered as first grade.

Thus, there is a requirement for more efficient cyclones to increase the recovery of first grade products and the question is *How can we improve cyclone efficiency?*

Understanding How Cyclones Work

Cyclone separation dynamics is very difficult to model and as a result cyclones have usually been designed empirically or, less often, according to models which can be found in the literature that do not consider the inter-particle interaction/agglomeration/clustering inside the cyclone.

Since cyclones have a wide range of operating conditions real on-site conditions and constraints must be imposed on the design as follows:

- Operational constraints:
  - …- 85°C < Temperature < 120°C (negative T for cryogenic micronizers)
  - …mg/Nm^3 < powder concentration < …kg/Nm^3
  - …25 Nm^3/h < flowrate < …150,000 Nm^3/h

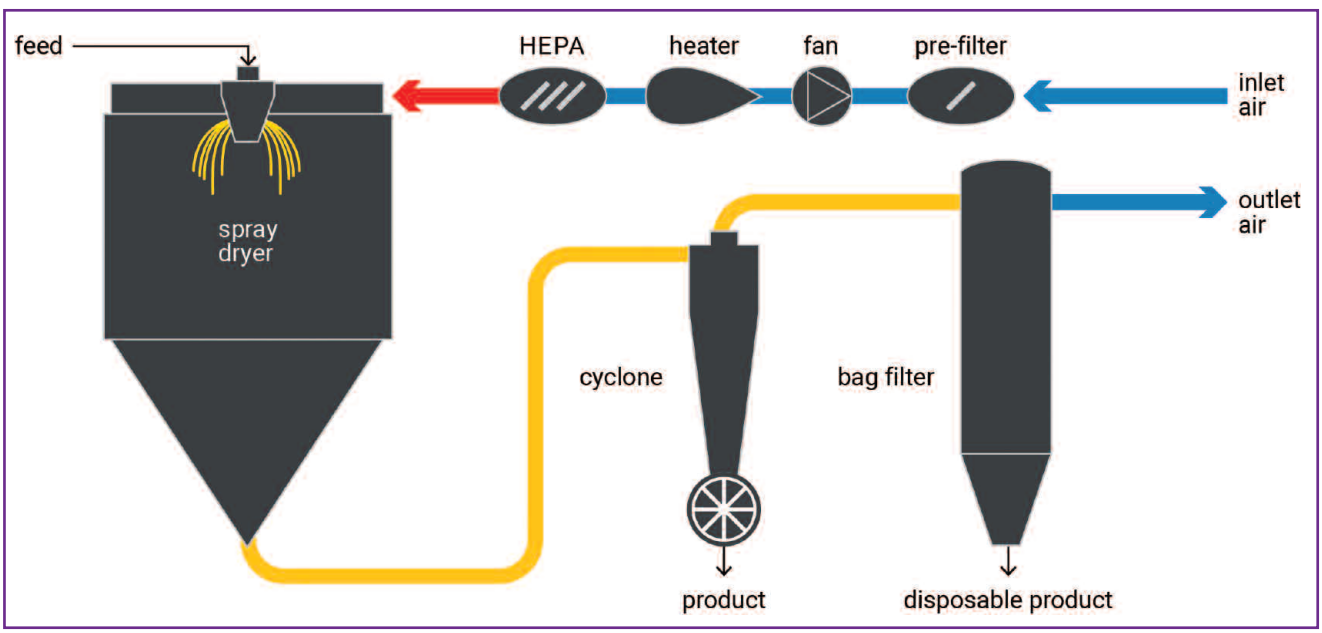

Figure 1 – Typical Spray Drying scheme

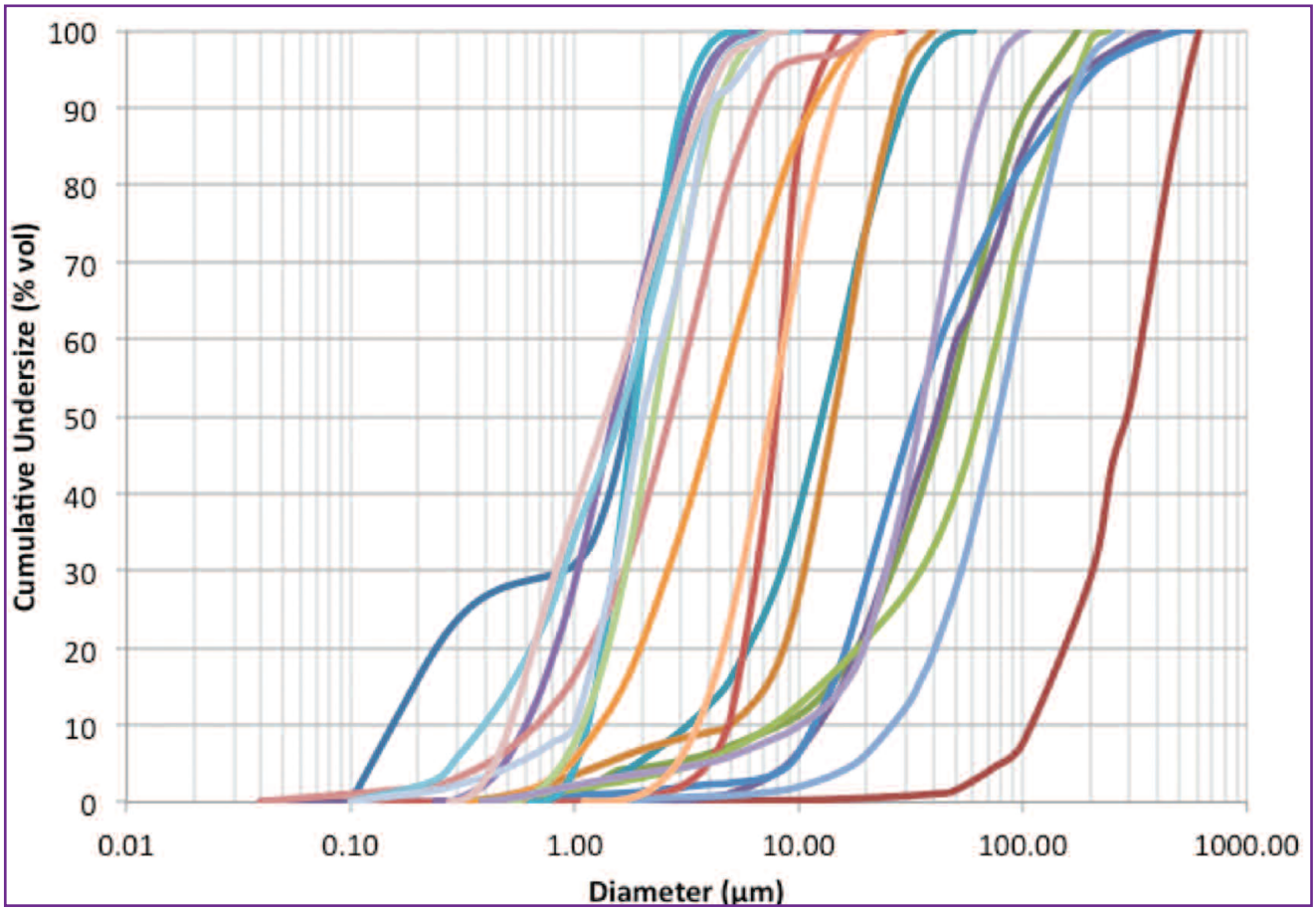

Figure 2 – Particle size distributions obtained by Laser Particle Sizer in the Pharmaceutical Industry.

- Type of product:
  - …solid dispersions, inhalable, injectable, microcapsules, tablets' waste recovery, …
  - …wide range of densities (non-porous, porous) …
  - Very different particle size distributions occur in any process (Eg: Spray Drying in **Figure 2**).

Considering all the different realities, it is quite understandable that it is impossible to have a single cyclone geometry to effectively deal with all cases. A new approach as proposed by Paiva *et al* (2010)[1] has extended the models of Salcedo *et al* (1993)[2], Mothes and Löffler (1988)[3] and Ho and Sommerfeld (2001, 2002)[4,5] to generate fine particle clustering in turbulent cyclone flows, which led to good agreement between experimentally observed grade-efficiency curves and those predicted by the new model.

With a good agreement between predicted and experimental global collection efficiency, there is now a theoretical framework on which to base the hypothesis that clustering inside the cyclone may be responsible for the very high collection of fine particles.

Numerical optimization vs. Empirical trial-and-error

Traditionally, and since the first patent was issued in 1886, cyclones have been designed and improved by empirical means. There has always been a difficulty in having a good prediction method due in part to the complexity of the modelling, since these kinds of equipment handle both multiphase and highly turbulent flows. Considering the overwhelming number of prototypes that would have to be built in order to explore the effect of changing dimension ratios on cyclone performance, it is no wonder that hundreds of so called high efficiency (HE) cyclone geometries have appeared, despite the fact that they are all sub-optimized.

The new optimizing algorithm can rapidly generate millions of virtual prototypes and, through numerical optimization, select the best geometry to each given cyclone application, and this optimization approach has resulted in multiple cyclone patents, since it is possible to design the best cyclone system for each application.

Sequentially, the cyclone optimization process is described below:

Setting up the relevant mathematical problem

Objective function: ***Maximize efficiency*** or ***Minimize surface area*** or ***Maximize efficiency/cost ratio***

Table 2: Cyclone comparison on secondary collectors
Performance of different equipment for the collection of a Demineralized Whey Powder
Median Particle Size in Volume (MVD) = 20µm; p = 1,000 kg/m^3; Inlet concentration: 154 mg/m^3

Comparison of Fine Powder Recovery Technologies	Standard Cyclone	Advanced Cyclone
Efficiency (%)	70	96
Product Losses (%)	30	4
Use of Separated Product	First Grade	First Grade
Sanitary Conditions	Very Good	Very Good
Restricted Applicability due to Temperature?	No	No
CleaningSuitable for CIP	Suitable for CIP	
Investment Costs	Reasonable	Reasonable
Maintenance & Operating Costs	Minimal	Minimal
Auxiliary Equipment Needed?	None	None

or ***another suitable objective*** within the following parameters:

Equality constraints

- Relevant design equations (cyclone modeling)
- Particle size distribution and density
- Gas flow rate and dust load
- Gas temperature, density and viscosity

Inequality constraints

- Maximum pressure loss
- Non-ideal effects minimized
- Geometric constraints

Efficiency estimation of the new advanced models & experimental validation

Numerically optimized cyclones systems have been designed by solving appropriate optimization problems. The abnormal high collection of fine submicrometric particles often observed with these systems is attributed to particle agglomeration within the turbulent cyclone flow field. The interparticle agglomeration leads to good predictions of overall efficiency of all these systems.

The new advanced models were developed based on the Ho and Sommerfeld particle agglomeration model, superimposed on the Mothes and Löffler particle collection model in isolated cyclones or on the Paiva *et al* PACyc model[1] for mechanical recirculation systems. Coupling these with electrostatic precipitator classical models enables the predictions of these recirculation systems with a superimposed electric field.

On average, these new cyclones can reduce emissions of between 40% and 95%. Their effectiveness has already been shown at laboratory, pilot and industrial scales for a variety of very fine dusts (relevant for mineral and chemical industries), including dusts as pharmaceuticals/chemical of high added value, white slag recovery or emission control from biomass boilers.

Table 2 evidences show not only all the common positive characteristics of cyclones, but also the performance difference between each type of cyclone.

Conclusions

Cyclones are well established and widely used in many industries, but usually associated with low efficiency which results in high product losses and high emissions in many plants. An efficiency increase in cyclones can be achieved with a new approach to cyclone design and customized numerically optimized cyclones can significantly reduce losses. Optimized cyclones with a wide application range can ensure emission limits compliance in various processes such as Spray Drying, Dryers and Millers.

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PHARMA IN PLENARY

A Call to Review EU Orphan Drug Legislation and Enforce Competition

by Nicola Davies

The purpose of Regulation (EC) No 141/2000 of the European Parliament and Council is to provide incentives for the research and development of medicines with an orphan designation.[1] However, reported price manipulations of orphan drugs have led to monopolistic and abusive practices that are limiting patient access to critical treatments. The question is whether the European Commission is taking action to prevent such abuses.[2]

Regulation (EC) No 141/2000 grants a 10-year exclusivity on the manufacturing of an orphan product to incentivize companies to invest in orphan drug research and development despite the associated high costs. However, the same regulation also allows currently marketed medicines to be used to treat rare diseases and be granted an orphan status. Manufacturers of existing drugs can therefore leverage an orphan drug status and raise the price of an existing medicine.[3]

Reports of orphan designation abuse

Price increases have already been reported on at least two occasions within the orphan drug space. The first involved an existing drug called CDCA [cholic acid and chenodeoxy cholic acid], manufactured by Leadiant Biosciences, which is used to treat a rare genetic metabolic disease known as Cerebrotendinous Xanthomatosis (CTX). The Italian manufacturer also purchased competitor producers and slowly closed down each one, giving rise to a monopolistic condition.[4] Since CDCA was granted an orphan drug status in 2017, the drug's price has gone up 500 times in the Netherlands.[5] In Belgium, the same pricing issue was reported, with the price of CDCA increasing more than 300 times over the last 10 years – in 2009, the price for a month of treatment was only €38, but today it is priced at €12,750.[6] This increased price has contributed to the inaccessibility of CDCA, as many payers have become unwilling to cover the drug and many patients can no longer afford it.[7]

Another reported occasion of abuse involved Lutathera (lutetium Lu 177 dotatate), which is a treatment for a rare cancer type called gastroenteropancreatic neuroendocrine tumors. The European Medicines Agency (EMA) approved the orphan product in 2017.[8] Novartis, the manufacturer, then acquired Advanced Accelerator Applications (AAA) for $3.9 billion [€3.49 billion] in late 2017.[9] The price has since increased from €4,000 to €23,000 per infusion of the medicine; and one course of treatment consists of four infusions.[10]

Abuse of rules governing orphan drugs

Honourable Members of the Commission point out that the practice of price increasing does not align with the intended purpose of Regulation (EC) No 141/2000 and is a blatant exploitation of a loophole in the legislation that has placed patients at a disadvantage.[11] These Members are asking whether the Commission is aware of such abuses. One Member specifically asks if the Commission is aware that pharmaceutical companies are abusing the rules governing orphan drugs to drive up the prices of existing medicines.[12] Another Member asks if the Commission plans to take action on the situation and whether it will amend the legislation to prevent such abuses.[13]

A response from the Commission states that the agency is aware of the issues surrounding orphan drug pricing.[14] However, pricing controls are beyond the Commission's authority and are within the remit of individual European Union (EU) Member States. Nonetheless, the Commission is currently evaluating the functioning of the orphan dug regulation, how its incentives are used in practice, and what financial consequences have resulted from this. The Commission also continually shares information on pricing policies across Member States to minimise inaccessibility of medicines. Furthermore, there is the European medicine price database, Euripid, to facilitate the sharing of best practices and strengthen region-wide cooperation for ensuring the affordability of medicines.[15]

The enforcement of EU competition rules

With reports of the abuse of rules governing orphan drugs, the non-profit group Foundation for Pharmaceutical Accountability requested the enforcement of the Netherlands' Authority for Consumers and Markets in 2018 to penalise the Italian company Leadiant Biosciences for its monopolistic practices with CDCA.[16] Consequently, another Honourable Member posed a question on the enforcement of competition rules, asking if the Commission has launched a competition inquiry pursuant to Article 102 of the Treaty on the Functioning of the European Union (TFEU). If not, the Member wanted to know what is holding the Commission back from taking such action?[17]

Article 102 of the TFEU states, "Any abuse by one or more undertakings of a dominant position within the internal market or in a substantial part of it shall be prohibited as incompatible with the internal market in so far as it may affect trade between Member States."[18] This article also applies to abusive practices in relation to regulatory exclusivity and patent protections.[19]

The Commission's response on the enforcement of its competition policy explains that the agency constantly monitors drug markets and investigates possible violations, some of which may involve high prices. However, they also enforce competition in a way that they consider significant in providing incentives to innovate. The agency's role is to support the national competition authorities in Member States that are tasked to investigate the reported breaches of competition rules at a national level.[20] As the Dutch and Belgian competition authorities are currently running analyses of the situation, the Commission is limited to cooperating with the national authorities before taking action.[21]

A national and European level assessment of incentives for orphan drug development

On a broader perspective, an Honourable Member has asked whether the Commission is taking measures to enact national and regional level assessments of the incentives for orphan drug development to ensure affordability and treatment access.

The Commission reiterates that the purpose of Regulation (EC) No 141/2000 is to stimulate research and development of orphan medicines to provide the same quality of care to patients with rare diseases. The agency is currently evaluating the functioning of the regulation at the EU level and cooperating with national authorities to gain insights at the national level.[22] This evaluation and cooperative approach to dealing with the orphan pricing issue is expected to bring to light some best practices for the prevention of monopolistic behaviour and to ensure a reasonable balance between affordability and innovation.[23]

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The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, International markets and the USA.

RECENT DEVELOPMENTS IN GMP AND REGULATORY REQUIREMENTS

United States of America

The US Food and Drug Administration (USFDA) Considerations in demonstrating interchangeability with a reference product

This final guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)). Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations in demonstrating interchangeability of a proposed therapeutic protein product with a reference product.

FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient" and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

This draft guidance describes the Agency's recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product licensed under section 351(a) of the Public Health Service Act (PHS Act).

Submitting documents using real-world data and real-world evidence to FDA for drugs and biologics

This guidance document is being distributed for comment purposes only.

This guidance is intended to encourage sponsors and applicants who are using real-world data (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format. FDA will use this information for internal tracking purposes only. This guidance applies to submissions for investigational new drug applications (INDs), new drug applications (NDAs), and biologics license application (BLAs) that contain RWE used to support regulatory decisions regarding safety and/or effectiveness.

Framework for the Regulation of Regenerative Medicine Products

The U.S. FDA has published four final guidance documents that are part of a comprehensive policy framework to address how the agency plans to support and expedite the development of regenerative medicine products, including human cells, tissues, and cellular and tissue-based products (HCT/Ps). These guidance documents underscore the agency's commitment to help bring new and innovative treatment options to patients.

Application of statutory factors in determining when a REMS is necessary

This final guidance is intended to clarify how the FDA applies the factors set forth in section 505-1 of the FD&C Act (21 U.S.C. 355-1) in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.

FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market and updates on angiotensin II receptor blocker (ARB) recalls

As well as updating the list of products recalled FDA has posted new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.
To ensure patient access to losartan, FDA will not object to certain manufacturers temporarily distributing losartan containing N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the interim acceptable intake limit of 0.96 parts per million (ppm) and below 9.82 ppm until the impurity can be eliminated.

Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.

Bispecific antibody development programs
This draft guidance provides recommendations to assist industry and other parties involved in the development of bispecific antibodies. Discussion includes general considerations and recommendations for bispecific antibody development programs, as well as regulatory, quality, nonclinical, and clinical considerations in the context of bispecific antibody development programs. This guidance does not discuss development considerations for other multitarget therapies that are combinations of monoclonal antibodies or are antibody cocktails or polyclonal antibodies. Although this guidance is specific to bispecific antibodies, the principles discussed in this guidance may also be applicable to the development of other types of bispecific protein products.

Since the first therapeutic monoclonal antibody was commercialized in 1986, monoclonal antibodies have become a vital component of therapy for various diseases and conditions including, but not limited to, cancer, autoimmune and infectious diseases, and inflammatory conditions. The regulatory pathway for evaluation of monoclonal antibodies is well established, but additional guidance is needed regarding antibody-based products that target more than one antigen. This guidance focuses on general regulatory and scientific considerations for bispecific antibodies, not on development of a particular bispecific antibody. Industry and other stakeholders are encouraged to engage FDA to discuss their individual bispecific antibody development program.

CBER FY 2018 Report
One of the highlights of FY 2018 was the approval of two gene therapies: Luxturna, the first directly administered gene therapy for a specific genetic disorder, an inherited retinal disease, and Yescarta, a cell-based gene therapy for certain types of adult, large B-cell lymphoma.

The report highlights these and other CBER accomplishments that reflect its responses to new and ongoing scientific and regulatory challenges, such as those posed by advanced therapies, emerging infectious diseases, and threats to the blood supply.

Nonproprietary naming of biological products: update
This draft guidance is issued for comment only. It describes FDA's current thinking on nonproprietary names of biological products licensed under section 351 of the PHS Act that do not include an FDA-designated suffix. FDA is also reconsidering whether vaccines should be within the scope of the naming.

Pediatric information incorporated into human prescription drug and biological product labelling
This final guidance is intended to assist applicants in determining the appropriate placement and content of pediatric information in human prescription drug and biological product labeling as described in the regulations for the content and format of labeling for human prescription drug and biological products.

The goal of this guidance is to provide recommendations to help ensure that information on the use of prescription drugs in pediatric populations (whether positive, negative, or inconclusive) is consistently placed in the proper sections and subsections within labeling so that the information is clear and accessible to health care providers.

Special 301 Report on Intellectual Property Protection and Review of Notorious Markets for Piracy and Counterfeiting
The Office of the United States Trade Representative has released its annual Special 301 Report on the adequacy and effectiveness of trading partners' protection of intellectual property rights and the findings of its Notorious Markets List, which highlights online and physical markets that reportedly engage in and facilitate substantial copyright piracy and trademark counterfeiting.

The Special 301 Report identifies trading partners that do not adequately or effectively protect and enforce intellectual property (IP) rights or otherwise deny market access to U.S. innovators and creators that rely on protection of their IP rights.

Trading partners that currently present the most significant concerns regarding IP rights are placed on the Priority Watch List or Watch List. USTR identified 36 countries for these lists in the Special 301 Report:

These trading partners will be the subject of increased bilateral engagement with USTR to address IP concerns. Specifically, over the coming weeks, USTR will review the developments against the benchmarks established in the Special 301 action plans for countries that have been on the Priority Watch List for multiple years. For such countries that fail to address U.S. concerns, USTR will take appropriate actions, such as enforcement actions under Section 301 of the Trade Act or pursuant to World Trade Organization or other trade agreement dispute settlement procedures, necessary to combat unfair trade practices and to ensure that trading partners follow through with their international commitments.
(A little surprising to see some EU Member States and countries such a Switzerland and Canada on the Watch List [mbh])

Europe

EDQM

European Pharmacopeia 10th Edition 10.0-10.2
The 2020 subscriptions are now available. They comprise of either an

electronic version, (for 1 computer and 1 USB stick, for online / offline use [Windows and Linux compatible, Mac coming soon]) or a conventional print version. Both comprise the first 3 volumes (10.0) and 2 non-cumulative updates, 10.1 and 10.2. and are available in the English or French languages.

EDQM inspections and trends of GMP deficiencies: Overview 2006 to 2018

A review of data from API inspections conducted by the EDQM between 2006 and 2018 is now available. This document summarises the trends of deficiencies observed in EDQM inspections with reference to EU GMP and to the corresponding CEP dossiers.

EMA

EU /USA MRA Q&A"

EMA has published an updated Q&A on impact of EU-USA Mutual Recognition Agreement on marketing authorisation applications and relevant variations.

There are 3 Q&As

- Q1: How does the EU-USA Mutual Recognition Agreement (MRA) affect marketing authorisation applications or variations? *(Revised January 2019)*
- Q2: Where can I find more information on the MRA?
- Q3: Shall I discuss with the regulatory authorities the possibility of inspections when planning to file an EU marketing authorisation or variation? *(NEW January 2019)*

EU authorities working to avoid shortages of medicines due to Brexit (Q&A)

This latest version of the Q&A explains that in case of a withdrawal agreement, there will be a transition period during which EU law will continue to apply in the United Kingdom. This means that access to medicines will not be affected.

If the UK leaves without a withdrawal agreement or deal ('no-deal scenario'), EU law will cease to apply in the UK. In this case, in order to be able to continue to supply medicines in the EU, companies carrying out certain activities in the UK will need to make changes to comply with EU law.

[As the situation remains fluid, readers should regularly check for updated guidance on the consequences of Brexit - mbh]

The role of regulators in establishing added benefit of novel therapies

The main conclusions of an article entitled Added therapeutic benefit and drug licensing (which is available through open access in Nature Reviews Drug Discovery) are that regulators have a role to play in ensuring that there is a solid evidence base to support the assessment of added therapeutic benefit of novel treatments compared with existing and potentially cheaper therapies. To help health technology assessment bodies, payers, clinicians and patients to separate merely new from truly better medicines, the regulators, firstly, should provide explicit reasoning on a medicine's added benefit compared to other treatments at the time of approval. Secondly, they should insist on 'evidence by design'. This means they must make companies aware of the need to plan the development programmes of medicines upfront, so that they are suitable to address the evidence needs of all relevant healthcare decisions-makers.

EMA facilitates early engagement with medicine developers to combat antimicrobial resistance

EMA is opening up the early dialogue available through its Innovation Task Force (ITF) to all medicine developers who work on therapeutic approaches for the treatment or prevention of bacterial and fungal infections. ITF is usually reserved for innovative medicines. Given the growing threat to public health caused by antimicrobial resistance and the need for new treatments, EMA is inviting all developers working on medicines for the treatment or prevention of life-threatening microbial infections to enter into early dialogue with the Agency to help strengthen the drug development pipeline for new antimicrobials.

20 years of sampling and testing programme for EU medicines

The number of centrally authorised medicines tested every year has steadily increased and now totals over 700 products. Most of the issues identified during the testing resulted in EMA requiring companies to amend the registered manufacturer's control methods for their medicines. In a small number of cases, the tested samples were not compliant with the authorised quality specifications for the medicine and required other regulatory actions such as re-testing *(hopefully following a documented / formal OOS procedure-mbh),* inspections, recalls or suspension of supply. The programme is an important part of the supervision of the quality of centrally authorised products (CAPs) for human and veterinary use in all parts of the distribution chain.

The selection of medicines for sampling and testing follows a risk-based approach and considers specific criteria such as products with a narrow therapeutic range, a complex manufacturing process, poor stability or a high exposure, as well as the pharmaceutical forms and patient profiles.

The programme will be expanded from 2019 to include testing of biosimilars, and testing of CAPs from the parallel distribution chain. Additionally, the generics programme started in 2011 will be expanded to increase the coverage of market surveillance. Finally, a new *ad hoc* programme for active

pharmaceutical ingredients (APIs) will allow the testing of APIs for CAPs sampled during GMP inspections.

New EudraVigilance system improves reporting of side effects and detection of safety signals

The new and improved EudraVigilance, the European system for managing and analysing information on suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the EU, received more than 2 million reports of suspected side effects in 2018. This is an increase of 37% compared to 2017.

EMA now operating from Amsterdam

EMA is now operating from Amsterdam after leaving its London premises' Overall, EMA still anticipates losing approximately 25% of its total workforce (of around 900 staff members) as a result of the move.

MHRA

GDP Office Based Evaluation and Risk Assessment programme (OBERA)

The GDP Inspectorate is embarking on a pilot of a new inspection approach that will impact holders of a Wholesale Dealer's Licence (WDA(H)) whose main activities operate from a head office supplied from a number of 'satellite' facilities. For the companies selected, their satellite sites will be assessed remotely using information provided by the company in a standardised format.

Who will be affected?

- OBERA is targeted at companies that operate from a single head office location, where the majority of the wholesale activity takes place, with a number of satellite sites which perform a very limited range of GDP activity.
- Inclusion in the programme will be dependent upon the head office of the company passing an on-site 'Gateway Inspection'.
- For the purposes of the pilot, companies with over 100 sites on their Wholesale Dealer's Licence will be allocated a Gateway Inspection first. Inspections scheduled to commence during spring 2019.

Once the OBERA process has been proven through the pilot, it is anticipated that it will be applied to other companies operating applicable business models. MHRA will publish a follow-up blog post towards the end of 2019 on the findings from this pilot phase.

What does qualification of suppliers mean to you? Risks to patients and to your business

MHRA continues to note concerted efforts to falsely obtain stock by some parties from suppliers, and has undertaken targeted inspections of supply chain integrity, resulting in cases of regulatory and enforcement action. Further emerging trends have been observed by MHRA around criminal attempts to sell falsified and stolen stock into the legitimate supply chain by a variety of methods. This creates the prospect of patients being supplied with substandard medicines, by way of gaps in the qualification processes of suppliers.

Several recent cases have exposed weaknesses in some supplier qualification processes, with individuals stealing the identity of legitimate companies and purporting to be someone they are not. In this instance, validation via EudraGMDP and Competent Authority sources would not detect a fraudulent supplier. There have been further examples of fake websites created in order to mimic legitimate companies, with the intent to deceive prospective businesses into purchasing from them. Obtaining a licence and checking on EudraGMDP may not be enough in these instances to protect licensed entities from fraudulent approaches.

There have also been instances of companies' wholesale dealer licences being purchased outright and new directors and personnel appointed. Such cases are hard to spot as the licence details do not change. Here the newly purchased company supplies falsified medicines to customers who do not notice that contact details have changed or that the company is now offering product types not previously seen.

International

Australia

TGA instructions for disinfectant testing

The TGA has made the new TGO104 to replace the previous TGO 54 which sunset on 1 April 2019.

The TGA has incorporated stakeholder feedback from consultation, about the proposed new TGO and its associated Guidance documents for Listed and Exempt disinfectants. TGO 104 incorporates:

- Updated sections of the previous TGO 54 and clarifies the requirements for hard surface disinfectants;
- The labelling requirements of the previous TGO and TGO 37 'general requirements for labels for therapeutic devices' (which sunset on 1 October 2018); and
- Standards and requirements within the guidelines for the evaluation of disinfectants.

As a result, these regulatory requirements are now contained within one TGO.

TGO 104 March 2019 is designed to support the quality, safety and efficacy of therapeutic goods that are

disinfectants, sterilants and sanitary fluids and powders.
An 'outcomes from consultation' document sets out for the purpose of identifying and explaining the testing requirements, {TGA Disinfectant Test (Part 1) and specific testing requirements (Part 2)}, principally for the purposes of the Order.

Risk management plans for medicines and biologicals
This guidance is for sponsors of prescription medicines and biologicals making applications to enter or vary Australian Register of Therapeutic Goods (ARTG) entries. It describes the risk management plan (RMP) requirements.

Guidance for TGO 101 – (Standard for tablets, capsules and pills
This guidance is to help sponsors and manufacturers of medicines understand the role of the Therapeutic Goods Order No. 101 - Standard for tablets, capsules and pills in ensuring that these types of therapeutic goods are of appropriate quality.

The requirements that applied to tablets and capsules under Therapeutic Goods Order No. 78 Standard for tablets and capsules (TGO 78) have been adopted into TGO 101. This means that, generally, a transition period is not needed for these medicines. Sponsors can elect to move to alternative testing requirements, where this is permitted under the Order, at any time. Details on how to request this type of change are provided later in this document.

The TGO 101 requirements that apply to pills commence on 31 March 2021. Pills were not subject to TGO 78. The delayed commencement allows sponsors two years to update their manufacturing documentation and ensure that their goods will comply with the new requirements by the end of March 2021.

A two-year transition period has also been specified in relation to section 16 of the Order. This allows sponsors time to review the manufacturing documentation for their medicines and update them in line with the requirements for elemental impurities and residual solvents.

Medicine Shortages in Australia: Reporting obligations and the TGA's compliance framework
Medicine shortages have become an increasing problem in recent years for a number of reasons, including a decrease in the local manufacture of prescription medicines, and the increasingly globalised nature of supply chains.

A Medicine Shortages Information Initiative and website was launched in 2014 by the TGA. This was a voluntary notification scheme. Under that scheme, however, a significant number of medicine shortages of critical impact on patients had not been reported, despite encouragement from the TGA for greater industry engagement.

A Medicine Shortages Working Party developed a revised protocol for the management and communication of shortages. This involved mandatory confidential reporting of all shortages to the TGA, the publication of those shortages that are of particular impact on patients and the development of a more transparent and action-oriented approach to the management of confirmed and serious medicines shortages.

Canada
Changes to regulations to help prevent illegal production and trafficking of controlled substances
The crisis of opioid overdoses continues to be one of the most serious public health issues in Canada's recent history. Illegal drugs tainted with highly toxic opioids such as fentanyl and carfentanil continue to be behind the majority of opioid-related overdose deaths.

New regulatory amendments to help tackle the illegal trafficking and production of controlled substances have been announced under the *Controlled Drugs and Substances Act* (CDSA). They come into force immediately and control specific precursors from being imported and used in the illegal production of fentanyls and amphetamines, such as methamphetamine and MDMA (commonly known as ecstasy).

In recent years, law enforcement identified novel chemicals not controlled under the CDSA that were making their way across the border and being used in the illegal production of fentanyls and amphetamines. Before these regulatory changes, law enforcement could take action only once illegal substances were produced using these chemicals, or if there was evidence that the chemicals were intended to be used to produce an illegal substance. With today's changes, law enforcement officers can now take action against illegal activities involving precursor chemicals, such as benzylfentanyl, derivatives and analogues of 4-anilino-N-phenethylpiperidine (ANPP) and norfentanyl. Specifically, officers can detain and seize these chemicals to prevent them from entering Canada.

PIC/S
PIC/S meeting April 2019 (Geneva Switzerland)
The meeting was attended by 45 out of 52 PIC/S Participating Authorities as well as by a number of Applicants, Pre-Applicants, Associated Partners and Guests. Highlights included

- PIC/S Inspection Reliance Initiative: PI 048-1. Further to the entry into force of this guidance members have been invited to collect statistics on desk-top assessments as from 1 January , 2019 based on a template including metrics. The purpose of these statistics is to document the efforts made by members to rely on

existing inspection reports rather than duplicate foreign GMP inspections. Results will be collected at the end of 2019.

In order to apply PI 048-1 some Members will need to adapt their inspection strategy to a risk-based strategy. In this perspective, the Committee was updated on successful examples of processes used by some of its Members in identifying instances where an onsite inspection of an overseas facility is not necessary. In particular, Australia / TGA and Health Canada presented on their active desk-top assessment procedures and implementation as well as on current statistics.

The interest of Industry in PI 048-1 and its implementation is key, in particular as it is up to manufacturers to proactively share reports if they wish to avoid duplicate inspections.

- Updates on future revisions to PIC/S GMP Guide: Annexes 1 (sterile), 2 (biologicals and ATMP), 13 (IMP) and 16 (certification by an AP & batch release).

  The revision of Annex 1 will be the focus of the PIC/S 2019 Seminar which will be hosted by Japan / MHLW & PMDA

  The PIC/S Working Group established with WHO on the *Revision of Annex 2* of the PIC/S GMP Guide has drafted a new annex, Annex 2A for Manufacture of Advanced Therapy Medicinal Products (ATMP) for Human Use. This new Annex takes into account the EU Guidelines on ATMP while addressing the concerns of PIC/S, as expressed to the European Commission (EC) during the drafting process of the EU Guidelines. Annex 2B for the Manufacture of Biological Medicinal Substances and Products for Human Use will be the revised version of EU Annex 2 for biologics (excluding ATMPs). The Committee also decided to carry-out a targeted stakeholder consultation on the development of revised Annex 2.

  The Committee was updated outcome of step 1 of the draft adaptation for PIC/S purposes of *Annex 16* (Certification by an Authorised Person & Batch Release). One major difficulty in the adaptation of Annex 16 was that neither the PIC Scheme nor the PIC/S GMP Guide deal with import or import controls. As a result, there was some discussion on whether to allow for the voluntary implementation for import-related activities. The Committee decided that the question of whether to include or exclude release aspects associated with importation should be further addressed by PIC/S experts of non-EEA Participating Authorities in order to clarify this issue prior to proceeding with step 2
- New working group established to develop a PIC/S Aide Memoire on Tissues and Cellular Therapy Products Inspections (excluding ATMP). This future Aide Memoire is intended for inspection of minimally manipulated human tissues and cells for human applications (ATMPs will not be within its scope).
- Progress in amendment of PIC Scheme.
- PIC/S 2019 Seminar to be hosted by Japan / MHLW & PMDA in Toyama and updates on PIC/S Inspectorates' Academy and future training activities.
- Completion of pre-accession of Saudi Arabia / SFDA and new PIC/S pre-accession application received from Bangladesh / DGDA.
- Bilateral meetings with China / NMPA and ICH.

Russia

Compliance Deadline for 12 Nosologies (diseases)-Products must be Compliant by Oct 2019

Previously pharmaceutical products sold in Russia would need to be in compliance with the announced serialization and aggregation regulations by 1st January 2020, but at the end of 2018, Russia published an update to Federal Law No. 425-FZ. This update included guidance for manufacturers of medicines to treat 12 specific conditions, specifying an earlier deadline of 1st October, 2019. This gives manufacturers of these products very little time before they must be in complete compliance with the new serialization requirements. The medications which are used in the treatment of 12 rare medical conditions.: All medicines aimed at these medical conditions must be labelled, serialized and reported in order to be compliant.

Switzerland

Switzerland now also uses EudraGMDP

The Swissmedic has started to enter information on GMP compliance as well as on manufacturing authorisations related to Swiss manufacturers into the EudraGMDP database. This will allow replacing the current practice of issuing paper documents, i.e. GMP certificates for certain regulatory procedures and therefore should lead to easier information-sharing and efficiency gains for all stakeholders.

EMA offers 'read and write' access to EudraGMDP to the regulatory authorities of all countries with which the EU has an MRA.

WHO

The 53rd ECSPP report (WHO Technical Report Series, No. 1019)

The following guidelines, as contained in the Annexes to the ECSPP's 53rd report, are now recommended for use:

Annex 1-Procedure for the development of World Health Organization medicines quality assurance guidelines

Annex 2 Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

- Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

Annex 3-GMP: guidelines on validation

- Appendix 1 Validation of heating, ventilation and air-conditioning systems
- Appendix 2 Validation of water systems for pharmaceutical use
- Appendix 3 Cleaning validation
- Appendix 4 Analytical procedure validation
- Appendix 5 Validation of computerized systems
- Appendix 6 Guidelines on qualification
- Appendix 7 Non sterile process validation

Annex 4 - Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver

Annex 5 - Guidelines on import procedures for medical products

Annex 6 - Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products

- Appendix 1 An example of information to applicants for registration via the WHO collaborative registration procedure
- Appendix 2 Verification for product submitted under the WHO collaborative procedure
- Appendix 3 Abridged/abbreviated review for product submitted under the WHO collaborative procedure
- Appendix 4 Additional information to be included in the screening checklist
- Appendix 5 Example of a national regulatory authority reliance model approach: information, documentary evidence and assessment activity
- Appendix 6 Model acknowledgement or approval letter for variations of products registered through the WHO collaborative procedure

The newly adopted specifications and general texts will be included in the 9th edition of *The International Pharmacopoeia* which is currently in preparation.

Products

Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic USA Stockpiles

Stockpiles of doxycycline tablets or capsules are held for post-exposure prophylaxis or treatment of inhalational anthrax in the event of an anthrax emergency. States have asked FDA what would be necessary to provide confidence that stockpiled doxycycline tablets and capsules have retained their original quality (purity / potency) beyond the manufacturer's labeled expiration date so the replacement of stockpiled product could be deferred.

This final guidance document provides guidance to government stakeholders on testing to extend the expiration date of stockpiled doxycycline tablets and capsules for public health emergency preparedness and response purposes for an anthrax emergency. *(Many antidote medicines end up not being used before their expiry date. To my mind it is a sensible use of Quality Risk Management to allow expiry date extensions as long as the effectiveness of the antidote is not affected, that the supply chain remains secure and as defined and that the ability to create new supplies as and when needed is maintained. mbh)*

EU withdrawal of marketing authorisations for fenspiride medicines

EMA's safety committee (PRAC) has recommended that the marketing authorisations for fenspiride medicines be revoked, so the medicines can no longer be marketed in the EU. This follows a review that has confirmed that these cough medicines could cause heart rhythm problems. The recommendation will now be sent to the Co-ordination Group for Mutual Recognition and decentralised procedures – Human (CMDH) to make a decision about its implementation. Fenspiride medicines are available as syrup or tablets and used in adults and children from the age of 2 years to relieve cough resulting from lung diseases. In the EU, fenspiride medicines have been authorised via national procedures in Bulgaria, France, Latvia, Lithuania, Poland, Portugal and Romania and are available under various brand names

For further information on these and other topics we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications. To subscribe to this monthly news service contact info@euromed.com

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A Curious Formula

The world of industrial pharmacy and antecedents seem to contain a curiosity. Broadly, one aspect contracts, another expands while yet another remains the same. Over time, the physical mass viewed as the dose of active medicament has tended to reduce while the medicament's visibility has increased; the amount of medicine containing a dose remained the same.

Smaller

For example, the early materia medica mainly used herbs. Even after the drying of leaves or animal glands, the dose was in the gram range. Then active ingredients were identified. For example, a dose of 0.6 gram of Belladonna herb contained about a percent of alkaloids, notably hyoscyamine. Later, a range of chemicals such as penicillin was made by fermentation and, later, synthesis. A typical dose was 250 milligram. By 1969, a typical oral dose of salbutamol was 4 milligram, or just 200 microgram by inhalation.

Today, drugs to change the genome of patients have even smaller doses. For example, for voretigene neparvovec, the dose is around 0.9 micrograms. Note that the very names commonly used for the masses have changed from grams to milligrams to micrograms, each being a thousandth of its predecessor. Indeed, for the genome-changing drug, literature does not mention micrograms but "vector genomes". I am indebted to Dr Christopher Morris, Lecturer in Molecular Pharmaceutics, University of East Anglia, for the calculation.

A practical implication for cross contamination between batches during manufacturing is that, if the same equipment is used for a low dose API and then a higher dose API, between batches, extremely rigorous cleaning is essential. Industry needs to accustom itself to miniscule doses and, perhaps, anticipate further reduction. I speculate that doses will tumble down the scales that materials scientists consider valuable for materials to reveal themselves: human, miniature, macro, micro and nano to atomic. If that occurs, equipment manipulating APIs may have to shrink in size.

Bigger

However, an increase, rather than decrease, strikes me in the immaterial world of the human perception or *visibility* of manufactured medicines.

Centuries ago, the nostrum seller would sell medicaments by flaunting on stages in market towns. Local newspapers, bookshops and billboards carried advertising. Later, chemists displayed window posters. Such local publicity was exuberant but of limited efficacy. However, following electrical telecommunication, the reach exploded. Commercially practicable telegraphs operated from around 1844; Morse's message "What Hath God Wrought?" perhaps a pale harbinger. Telephone, radio and television followed. In the 1960s, systems were developed with multiple pathways to transmit data: redundancy, so that telecommunication could continue even if nodes such as cities had been nuked. The internet followed from around 1989. Today the pharmaceutical industry capitalises upon websites, search engines and social media. They achieve a torrent of visibility in the freshly-constructed domain of cyberspace.

In tandem with that, centuries ago, ingredients were often not as advertised. A UK example is "Beechams Pills"; the British Medical Association exposed the analytical results of many secret remedies in 1909; ingredients were often pedestrian. Before 1976, prescription medicine labels contained no names of ingredients but only, for example, "The Mixture" or "The Tablets", although professional magazines carried advertisements. For about two decades, informative package leaflets must be included. Recently, the Falsified Medicines Directive 2011/62/EU demanded information on the origin of each batch. Therefore, information, discourse, about them grew.

Same

Yet over that period, the size, shape and dexterity of humans changed little, so unit dose packaging sizes remained similar. Examples are earthenware pot, woodchip box and plastic jar for ointment; all those containers must fit the human hand. That applies in the future — if the administer remains human, not robot.

Malcolm E Brown

Has your Company started to plan a Brexit Strategy

Many large companies with EU/UK subsidiaries have already prepared contingency plans to ensure their ability to continue supplying the markets. However, the EU Commission have expressed concern that many Marketing Authorisation Holders have still not begun any preparations for Brexit. While recognising the complexity of some of these procedures they have observed that there are still a number of companies adopting a "wait and see" approach.

PharmaConsult will not only establish legal entities for companies in either the EU or UK, so they can hold Marketing Authorisations (MA) for the products they need to market in the EU or UK, but will also provide the means to:

- Obtain Manufacturing/ Importation approval and wholesale dealer's licences to enable companies to import and to distribute products in the EU or UK.
- Outsource ISO 17025 accredited analytical testing facilities for testing the imported commercial product.
- Provide local QP certification for batch release for Commercial and/or Investigational Medicinal Products (IMP) too either the EU or UK markets or Clinical Research Organisations (CRO).
- Outsource GMP/GDP compliant storage facilities for any product awaiting distribution.
- Provide local QP Vigilance monitoring and reporting to Edra Vigilance.

Please contact us to discuss your BREXIT contingency plan

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12–13 July 2019 – Yokohama, Japan
3rd International Conference and Exhibition on Pharmaceutical Development and Technology
https://pharmatech.pharmaceuticalconferences.com/

15–16 July 2019 – Abu Dhabi, UAE
6th World Congress on Drug Discovery & Toxicology
https://drugchemistry.pharmaceuticalconferences.com/

26–27 July 2019 – Melbourne, Australia
13th Asian Biologics and Biosimilars Congress
https://biosimilars-biologics.pharmaceuticalconferences.com/asiapacific/

29–30 July 2019 – Stockholm, Sweden
7th European Biopharma Congress
https://biopharmaceutics.pharmaceuticalconferences.com/europe/

AUGUST 2019

2–3 August 2019 – Chicago, IL, USA
9th International Conference on Pharmaceutical GMP, GCP &Regulatory Affairs 2019
https://regulatoryaffairs.pharmaceuticalconferences.com/

2–3 August 2019 – Chicago, IL, USA
2nd International Conference on Pharmaceutical Analysis &Analytical Chemistry
https://analysis.pharmaceuticalconferences.com/usa/

2–3 August 2019 – Chicago, IL, USA
14th International Conference on Biologics and Biosimilars
https://biosimilars-biologics.pharmaceuticalconferences.com/

12-14 August 2019 – Cambridge, MD, USA
24th Annual GMP by the Sea Conference
www.pharmaconference.com

14–15 August 2019 – Boston, MA, USA
Data Integrity Validation
http://www.cbinet.com/conference/pi19123

20–21 August 2019 – Alexandria, VA, USA
340B Manufacturer Summit
http://www.cbinet.com/conference/pc19378

20–22 August 2019 – Philadelphia, PA, USA
Cleaning Validation
http://www.cbinet.com/conference/pi19040

SEPTEMBER 2019

9–10 September 2019 – Zurich, Switzerland
23rd European Biotechnology Congress
https://www.biotechnologycongress.com/europe/

10–11 September 2019 – Amsterdam, The Netherlands
World Drug Safety Congress
https://www.terrapinn.com/conference/world-drug-safety-congress-europe/index.stm

11–13 September 2019 – London, UK
10th APS International PharmSci Conference 2019
www.apdgb.co.uk

12–13 September 2019 – Cambridge, MA, USA
5th Annual Compliance Congress for Specialty Products
http://www.cbinet.com/conference/pc19389

16–17 September 2019 – Washington, DC, USA
PDA–FDA Joint Regulatory Conference 2019
http://www.pqegroup.com/blog/2018/01/pda-fda-joint-regulatory-conference-2019/

22-26 September 2019 – Abu Dhabi, United Arab Emirates
79th FIP World Congress of Pharmacy and Pharmaceuticals
https://abudhabi2019.congress.pharmacy

25–26 September 2019 – Brussels, Belgium
2019 ISPE Europe Biotechnology Conference
https://ispe.org

25–26 September 2019 – Hong Kong
17th World Congress on Drug Formulation & Drug Delivery
https://drugformulation.pharmaceuticalconferences.com/

26–27 September 2019 – Bangalore, India
2019 ISPE India Pharmaceutical Manufacturing Conference
https://ispe.org

30 September–1 October 2019 – Singapore
2019 ISPE APAC Pharmaceutical Manufacturing Conference
https://ispe.org

30 September–3 October 2019 – Boston, MA, USA
Global Forum Annual Temperature Controlled Life Sciences Supply Chains
https://www.coldchainglobalforum.com/

OCTOBER 2019

15-17 October 2019 - Basel, Switzerland
Festival of Biologics
www.terrapinn.com/conference/festival-of-biologics/index.stm

21–22 October 2019 – Hong Kong
4th Annual Congress on Nanomedicine and Drug Delivery
https://nanomedicine.annualcongress.com/

21-23 October – Bethesda, MD, USA
PDA Global Conference on Pharmaceutical Microbiology
www.pda.org