european
INDUSTRIAL
PHARMACY

features

regulars

ISSUE 26 • SEPTEMBER 2015
www.industrialpharmacy.eu
www.eipg.eu

associate editors

european INDUSTRIAL PHARMACY

September 2015

ISSN 1759-202X

European Industrial Pharmacy
is published four times a year by:
Euromed Communications
Passfield Business Centre,
Lynchborough Road, Passfield,
Liphook, Hampshire GU30 7SB

Tel: +44 (0)1428 752222
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www.eipg.eu/eipg-journal

Indexed by:
Scopus & Embase

european INDUSTRIAL PHARMACY
discussion group:
www.pharmweb.net/gmp.html

european INDUSTRIAL PHARMACY
is the official publication of the European Industrial Pharmacists Group (Groupement des Pharmaciens de l'Industrie en Europe) www.eipg.eu

Cover photo: Muscle fibres (see First-in-Class Innovation in the Pipeline for Treatment of Muscular Dystrophy on page 4).

The journey and the goal

An oft-cited oriental story describes a student who asked his teacher, "How long will it take me to master your discipline?" The teacher replied, "Ten years." The student said, "If I work twice as hard, how long will it take then?" "Twenty years." answered the teacher. Again the student said, "But if I work really hard, night and day, how long will it take me?" The teacher responded, "Thirty years." The student was confused, "How is it that if I work harder, you say that it will take longer?" The teacher replied, "Because when you keep one eye on the goal, you only have one eye with which to find the way."

The moral of the story, namely, that the journey is more important than the destination, is perhaps difficult to apply in the pharmaceutical industry. How else, if not by keeping in mind that the goal of maintaining the highest standards of good practices is to guarantee patient safety, does one find the courage and justification to face the consequences of suspending the marketing authorisations of hundreds of medicinal products due to flawed studies? As I pen this message, the first draft of the Delegated Regulation laying down detailed rules for the safety features appearing on the outer packaging of medicinal products for human use has just been made public. It is a regulation that will require a challenging journey to put into practice, and how else, if not by keeping in mind the goal of protecting patients from the dangers of falsified medicinal products, does one convince all players to embark, without delay, on the steps needed to implement the requirements of this important regulation within the established timeframes?

Similarly, consider the panic of Greek patients unable to purchase their medicines at the height of the economic crisis but a few weeks ago, or the frustration of French patients, hearing once more *"Désolé mais votre médicament est indiqué manquant"*, due to drug shortages that, according to the Agence Nationale de Sécurité du Médicament et des Produits de Santé, have risen by ten times in the last 6 years. How else, if not than by keeping our eye on the goal of solving this perennial challenge in the provision of healthcare, can one continue to bring together all stakeholders at a European level, to go beyond the limited, albeit well-meaning, initiatives of the European Commission as outlined in its recent response to the European Parliament?

Yes, the goal is important. However, this does not in any way diminish neither the importance of the journey that needs to be undertaken, nor the challenges, trials and tribulations that all concerned experience in reaching that goal. Therefore, in the words of Lord Alfred Tennyson, *"Oh yet we trust that somehow good will be the final goal of ill"*.

Professor Claude Farrugia
Vice-President Communications, EIPG

We are sad to announce the death of Arthur Dewelde, industrial pharmacist, technical director Pfizer Jette and Lieutenant-Colonel in the pharmacy reserve of Belgium. Through his professional drive, he shaped the aims, objectives and culture of the European Industrial Pharmacists' Group. Following years of representations to the Commission alongside other healthcare professions, he ensured that pharmacy had its own professional directive appropriate to the industrial pharmacists as well as other areas of pharmacy of that period. We wish to extend our condolences to his friends and family.

FIRST-IN-CLASS INNOVATION IN THE PIPELINE FOR TREATMENT OF MUSCULAR DYSTROPHY

by Angel Wong

Duchenne research has gained momentum recently with the first innovative therapy to treat the underlying cause of a nonsense mutation in the *DMD* gene. The exceptionally high level of innovation and diversity in the pipeline will open up numerous opportunities for more novel products to thrive, creating an encouraging outlook for the vast majority of muscular dystrophy patients, as well as companies and investors in the market.

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Muscular dystrophy is a group of heritable, genetic neuromuscular disorders characterised by progressive muscle weakness and degeneration. The most common types of muscular dystrophy are Duchenne muscular dystrophy (DMD) followed by its milder form, Becker muscular dystrophy (BMD). Both diseases are caused by mutations in the single *DMD* gene on the X chromosome, and as a recessive disease, this means it is exclusive to males.

Dystrophin, which is the protein product of *DMD*, is a rod-shaped cytoplasmic protein expressed primarily in skeletal muscles and cardiac muscles. It associates with various proteins, including α-dystrobrevin and β-dystroglycan, to form the dystrophin-associated protein complex (DAPC) at the sarcolemma (cell membrane of a muscle fibre cell). The DAPC functions as the structural link between the actin cytoskeleton and extracellular matrix, which is crucial for normal muscle function during muscle contraction and relaxation.

Destabilisation of the sarcolemmal a DAPC, which can arise from mutations in *DMD*, leads to increased susceptibility to muscle fibre damage and necrosis. Most DMD-causing mutations shift the reading frame by one or two base pairs, resulting in the addition of incorrect amino acids to the polypeptide. A nonsense mutation, for instance, leads to a premature stop codon, causing early termination of translation and the production of truncated, non-functional dystrophin.

Symptoms such as delay in age of walking generally arise in boys after the age of five. By late childhood, they typically lose the ability to walk, and may develop life threatening cardiac and respiratory complications during their late teens as heart and lung muscles weaken. Despite similar symptoms, the disease progression in BMD is slower, as it is caused by non-frameshifting mutations which retain partial protein function of dystrophin.

It has become increasingly apparent that dystrophin deficiency is not the only factor driving disease progression, particularly when muscle fibre degeneration has been long regarded as a multifaceted process. Following sarcolemmal defects, secondary pathological processes that may contribute to the hallmarks of DMD/BMD include mechanical stress, deregulated calcium homeostasis, impaired vascular adaptation and inflammation. Ultimately, increased muscle necrosis, coupled with the failure to repair damaged muscles, leads to replacement of muscle fibres by adipose and connective tissues, namely fibrosis.

Current treatment

Over the past few decades, generic glucocorticoid treatment, specifically prednisone and deflazacort, remains the mainstay of pharmacological treatment of DMD and BMD. They are glucocorticoid receptor agonists which act by suppressing transcription of inflammatory genes via activation of NF-κB. In clinical studies, prednisone and deflazacort were shown to offer similar symptomatic benefits in improving muscle strength, delaying the loss of ability to walk and stabilising pulmonary function in DMD patients[1,2]. Although the exact mechanism that gives rise to the clinical benefit remains unclear, they are thought to upregulate expression of muscle-specific target genes via the calcineurin/nuclear factor of the activated T-cells pathway, such as utrophin (an autosomal homologue of dystrophin), which has a structural role similar to dystrophin[3].

Like other glucocorticoids, prednisone and deflazacort are associated with significant adverse events, including weight gain and increased risk of vertebral fractures. Studies showed that deflazacort is associated with less weight gain and more preservation of bone mass, making it the preferable treatment over prednisone in patients with pre-existing weight issues[4].

Apart from muscle weakness, secondary complications comprising respiratory, cardiovascular and orthopaedic issues are managed with

	Pipeline product	Company	Molecule type	Stage of development
Myostatin inhibitor	AAV1-foliistatin	Milo Biotechnology	Gene therapy	Phase II (DMD), Phase III (BMD)
	PF-06252616	Pfizer	MAb	Phase II
	BMS-986089	Bristol-Myers Squibb	Protein	Phase II
	Antisense oligonucleotide to inhibit myostatin for DMD and BMD	Sarepta Therapeutics	Antisense oligonucleotide	Preclinical (DMD, BMD)
	OSX-200	Ossianix	MAb	Preclinical
Utrophin activator	SMTC-1100	Summit Therapeutics	Small molecule	Phase I
	Small molecules to target utrophin for DMD	Summit Therapeutics	Small molecule	Preclinical
	SMT-022357	Summit Therapeutics	Small molecule	Preclinical
	RE-001	Retrophin	Recombinant protein	Preclinical
	Small molecule to activate utrophin for DMD	PTC Therapeutics	Small molecule	Preclinical
	Recombinant protein to activate utrophin for muscular dystrophies	University of Wisconsin-Madison	Recombinant protein	Preclinical
Dystrophin activator	eteplirsen	Sarepta Therapeutics	Antisense oligonucleotide	Pre-registration
	drisapersen	BioMarin Pharmaceutical	Antisense oligonucleotide	Pre-registration
	SRP-4045	Sarepta Therapeutics	Antisense oligonucleotide	Phase III
	SRP-4053	Sarepta Therapeutics	Antisense oligonucleotide	Phase III
	BMN-044	BioMarin Pharmaceutical	Antisense oligonucleotide	Phase II
	BMN-045	BioMarin Pharmaceutical	Antisense oligonucleotide	Phase II
	BMN-053	BioMarin Pharmaceutical	Antisense oligonucleotide	Phase II
	Biostrophin	Asklepios BioPharmaceutical	Antisense oligonucleotide	Phase I
	NS-065	Nippon Shinyaku	Antisense oligonucleotide	Phase I
	Gene therapy to activate dystrophin for DMD	Nationwide Children's Hospital	Gene therapy	Phase I
	SRP-4050	Sarepta Therapeutics	Antisense oligonucleotide	Preclinical
	PRO-052	BioMarin Pharmaceutical	Antisense oligonucleotide	Preclinical
	PRO-055	BioMarin Pharmaceutical	Antisense oligonucleotide	Preclinical
	Gene therapy for DMD	Genethon	Gene therapy	Preclinical
	Gene therapy to activate dystrophin for DMD	University of Missouri	Gene therapy	Preclinical
	SRP-4044	Sarepta Therapeutics	Antisense oligonucleotide	Preclinical
	SRP-4052	Sarepta Therapeutics	Antisense oligonucleotide	Preclinical
	Stem cell therapy to activate dystrophin for DMD	Stanford University	Stem cell therapy	Preclinical
	SYN-01	Synthena	Antisense oligonucleotide	Preclinical
	Antisense oligonucleotide for DMD	Daiichi Sankyo	Antisense oligonucleotide	Discovery
	SRP-4055	Sarepta Therapeutics	Antisense oligonucleotide	Discovery
	SRP-4008	Sarepta Therapeutics	Antisense oligonucleotide	Discovery
	Antisense oligonucleotide to activate dystrophin for DMD	nLife Therapeutics	Antisense oligonucleotide	Discovery
	Small molecule to activate dystrophin for DMD	PTC Therapeutics	Small molecule	Discovery

combinations of pharmacological and non-pharmacological interventions.

With the widespread use of glucocorticoids and improved management of respiratory complications, the life expectance of DMD patients has markedly extended to 27 years, from that of 19 years in untreated patients. Most BMD patients receiving optimised treatment can live into mid-to-late adulthood, or even a near normal lifespan.

A recent breakthrough in DMD research is marked by the conditional approval of PTC Therapeutics' Translarna (ataluren) in the European Union for the treatment of DMD, caused by a nonsense mutation in *DMD*, accounting for 10–15% of all DMD cases. It is thought to interact with the ribosomal translational machinery to enable ribosomal readthrough of the premature stop codon on the dystrophin messenger RNA (mRNA), thereby restoring the synthesis of full-length dystrophin. The conditional approval was based on the Phase IIb trial, where Translarna was shown to slow the rate of the loss of ambulation and disease progression in ambulant patients with nonsense *DMD* mutation[5]. The safety profile was shown to be favourable, with mild and transient gastrointestinal adverse events reported[6]. However, data from the Phase III confirmatory trial that is currently underway will be required for full approval for DMD.

Despite the approval of the breakthrough treatment Translarna which is only beneficial to 10–15% of the DMD population, high unmet needs for disease-modifying treatments remain in most patient segments, given the wide spectrum of *DMD* mutations identified in the DMD population. Additionally, unfavourable adverse events limit the long-term use of glucocorticoids, although it can be used as a symptomatic treatment in patients regardless of their genetic mutation. The DMD/BMD market is still highly under-served and, therefore, presents opportunities for breakthrough therapies. There is market opportunity not only in the non-ambulant patient segment although the critical lack of validated clinical trial endpoints remains a challenge, but also for disease-modifying treatments intended to treat the vast majority of DMD/BMD patients

First-in-class innovation in the pipeline

The DMD and BMD pipeline is small (88 molecules) but contains products targeting a diverse range of molecular targets, such as *DMD*, utrophin, myostatin, integrin α7β1 and extracellular matrix proteins. Analysis also reveals a high level of innovation in the pipeline, with identification of 46 first-in-class products acting on 13 unique targets. The majority of first-in-class molecules are in preclinical development, while the late stage is dominated by products with established targets. The most common first-in-class molecular target is *DMD*, targeted by 24 pipeline products. These drug candidates, mostly exon-skipping compounds, are developed to correct the disrupted reading frame of the dystrophin mRNA and produce an internally truncated but functional protein. Their presence in all developmental stages indicates a strong focus on personalised treatments. Of which, six specific therapies are currently in development for exon 51, which is apparent in 13% of all DMD patients, and by far the largest subpopulation identified compared with other specific exon deletions. Drisapersen (GSK and BioMarin Pharmaceuticals) and eteplirsen (Sarepta Therapeutics) are the two exon-skipping therapies currently in pre-registration for the treatment of DMD. Another approach under early-stage investigation is *DMD* replacement via gene therapy. However, discrepant preclinical findings and the lack of efficacy in clinical trials, due to issues with cellular immunity and insufficient transgene expression in humans, leaves substantial challenges for gene therapy to become a successful treatment.

The rest of the pipeline focuses on alleviating the secondary manifestations of the diseases without correcting the defective *DMD*, such as modulation of proteins that interact with the DAPC, and inhibition of fibrosis. These therapies are designed to promote muscle growth, sustain muscle regeneration and reduce fibrosis in DMD/BMD patients regardless of the genetic mutations, therefore, holding high potential for widespread use.

Many proteins have been shown to interact with the DAPC, of which a few are suggested to act through a functional compensatory mechanism in the absence of functional dystrophin. Utrophin, which has interchangeable functions with dystrophin, is among the most promising first-in-class targets. Animal models of DMD demonstrated that the utrophin modulator SMT C1100 resulted in significant functional improvement in muscle strength and resistance to muscle fatigue by restoring the actin cytoskeleton-sarcolemma link lost in dystrophic muscles, without having unfavourable side effects[7]. SMT C1100 is currently one of the six utrophin modulators under investigation and has progressed the furthest (Phase I) in the pipeline.

Transforming growth factor (TGF)-β signalling, which plays a crucial role in many processes including tissue repair, is of particular interest in DMD due to its role in promoting pathological fibrosis. One of the first-in-class targets that intervene in this pathway is myostatin, a TGF-β superfamily member known to regulate muscle growth and fibrosis. It negatively regulates muscle growth by binding to activin receptor type IIb localised on the muscle cell surface, and subsequently promotes transcription of pro-fibrotic genes through activation of the Smad transcription complex. Myostatin inhibition in *mdx* dystrophic mice was shown to reduce fibrosis and

improve muscle regeneration, alongside the benefits of increasing muscle mass and force *in vivo*, despite a lack of effect on muscle necrosis[8,9]. Experimental approaches, including myostatin-neutralising antibodies and gene delivery of an antagonist, have progressed to human trials, but there have been setbacks due to efficacy issues and adverse immune response in clinical trials. An approach currently being investigated in earlier stages is knockdown of myostatin expression through antisense oligonucleotide-mediated exon skipping, which prevents synthesis of functional myostatin. Additional to its improvement in muscle mass *in vivo*[10], the low risk of provoking immune response makes it an attractive anti-fibrotic approach to slow disease progression in DMD.

Poor disease prognosis and significant unmet needs in the market has been the driving force for the high level of first-in-class innovation. The diverse array of first-in-class targets in development which, closely aligned to the disease pathophysiology, presents a positive outlook for the future market. However, despite their potential disease-modifying effects, growing evidence suggests that correcting the mutated *DMD* gene alone is insufficient to cure the disease, creating combination opportunities for first-in-class molecules targeting secondary disease pathways to preserve muscle function and transform the future treatment algorithm.

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CHILD RESISTANCE IN PHARMACEUTICAL PACKAGING

by Hung Le

The best solutions in child-resistance come from a deep understanding of consumer insights and a dedication to innovation. In order to achieve both child safety and a positive consumer experience, insights should be gathered and applied to packaging design and the development of any communications or instructions accompanying the packaging.

Hung Le (hung.le@westrock.com) is Vice President of Innovation Engagement for WestRock's Home, Health and Beauty Group. An engineer by training, Hung leverages a deep understanding of the development and commercialisation of consumer packaging to lead the creation of package design concepts that are connected to business, brands and consumers. Hung previously served as Vice President of Global Design for WestRock, as well as Senior Director of Innovation and Product Line Management for WestRock Healthcare (healthcare@westrock.com).

"Packaging Matters," a recent international packaging satisfaction study, commissioned by WestRock, found that the packaging usage experience is extremely important to consumers' overall experience with a product. Study results showed that 37% of consumers have purchased something again because of packaging functionality. However, if consumers find the experience of using medication packaging frustrating, they are not inclined to take the medication as often as they should, delaying refill or repurchase.

What are consumers looking for in their medicine packaging, ultimately? The following packaging attributes were ranked as most important.

1) Keeps the product safe
2) Prevents spilling, leaking or breaking
3) Keeps the product fresh/effective
4) Easy to reclose or reseal
5) Easy to get the right amount out and Designed to keep me and my family safe (tie)

The study found 34% of consumers strongly agreed that "packaging designed to keep the product safe and/or protect me and my family" would make them more likely to purchase products from that manufacturer or brand. The study also noted the importance of ease of use. This tells us that innovation in child-resistant (CR) packaging, to ensure it is both user-friendly for adults and resistant for children, can improve consumer satisfaction and boost sales.

There are two approaches to CR packaging: (1) the use of strength and force to access medication, or (2) the use of cognitive abilities, such as sequential motions like a pushing then pulling to access medication. A subsequent consumer preference study conducted by WestRock found that when using the latter approach, there is sometimes a learning curve or educational element that is needed, but the overall opening experience is much better. Ultimately, this study affirmed that consumers preferred cognitive-based approaches, and package designs were modified based on these findings.

Developing innovative packaging starts with understanding that the best designs emerge from the strongest insights, which almost always come from the consumer. One example is WestRock's CR nasal pump that was developed in preparation for new Consumer Product Safety Commission (CPSC) regulations in the United States. In December 2012, the CPSC passed a new regulation requiring CR packaging for any over-the-counter or prescription drug product containing the equivalent of 0.08mg or more of an imidazoline in a single package. This "special packaging" must be designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance within a reasonable time, and not difficult for normal adults to use properly. The affected products included commonly used eye drops and nasal sprays, which can cause serious adverse reactions in children when accidentally ingested.

During the development of the nasal pump, WestRock tested three concepts with consumers and refined the preferred design based on their feedback. Specific features that were incorporated into the final package, the HiMark® CR Nasal Pump (see Figure 1), as a result included the following.

- On-pack visual and tactile cues that communicate how to use the CR package.
- Use of a simple range of motions to open the pump, without requiring extreme precision, making the package truly senior-friendly.
- Audible indication, so the product locks and seals tightly without any wiggling.
- Integration of the child-resistance feature into the pump versus the over cap; this ensures the highest level of protection for children by preventing access to the medication even if the over cap is left off or lost.

***Figure 1:** The HiMark® CR Nasal Pump.*

These modifications to design yielded a consumer-preferred package that meets the needs of both children and seniors, including flexibility and cognitive skills.

A second example is WestRock's Dosepak® Express with Optilock® technology design (see Figure 2). Optilock technology is a locking mechanism that transforms adherence packaging by enabling a significantly smaller CR package. It was developed based on insights from experts in the field of patient medication adherence, customers and consumers.

Dosepak Express with Optilock technology is part of WestRock's line of proven adherence-enhancing solutions. It includes a calendared medication blister and flat panels on the outer carton, providing a format for readable medication information and links or QR codes that connect to additional adherence programs. Overall, the package incorporates insights-based innovations.

- An integrated calendar that allows patients to easily track and monitor their medications, increasing their adherence.
- Its small size is discreet and portable, making it convenient to use and easily fitting into patients' lifestyles.

It is important to keep consumer insights at the heart of innovation and remember that when consumers have a positive experience, it can help create a better overall healthcare experience, including the possibility of improving adherence to medication regimens. That is why when choosing a packaging supplier, drug manufacturers should consider the benefits of using CR packaging that not only minimises risk, but is also based on consumer insights and matches consumer preferences.

CR packaging is critical because it has the potential to improve and, in certain situations, even save lives. Poisoning is the third leading cause of unintentional injury deaths in children in the European Region – 3000 deaths per year[1,2], according to the World Health Organization. Non-fatal poisonings are even more numerous and an important cause of ill health and long-lasting disability. One of the most successful ways to prevent the unintentional poisoning of children is through CR medication packaging[3] – which helps prevent children from gaining access to medications, even after they have their hands on the package. However, that package will only work if consumers understand how to use it and welcome the innovation, adding even greater value to deep consumer insight(s).

While CR regulations have existed in the United States and the European Union (EU) for quite some

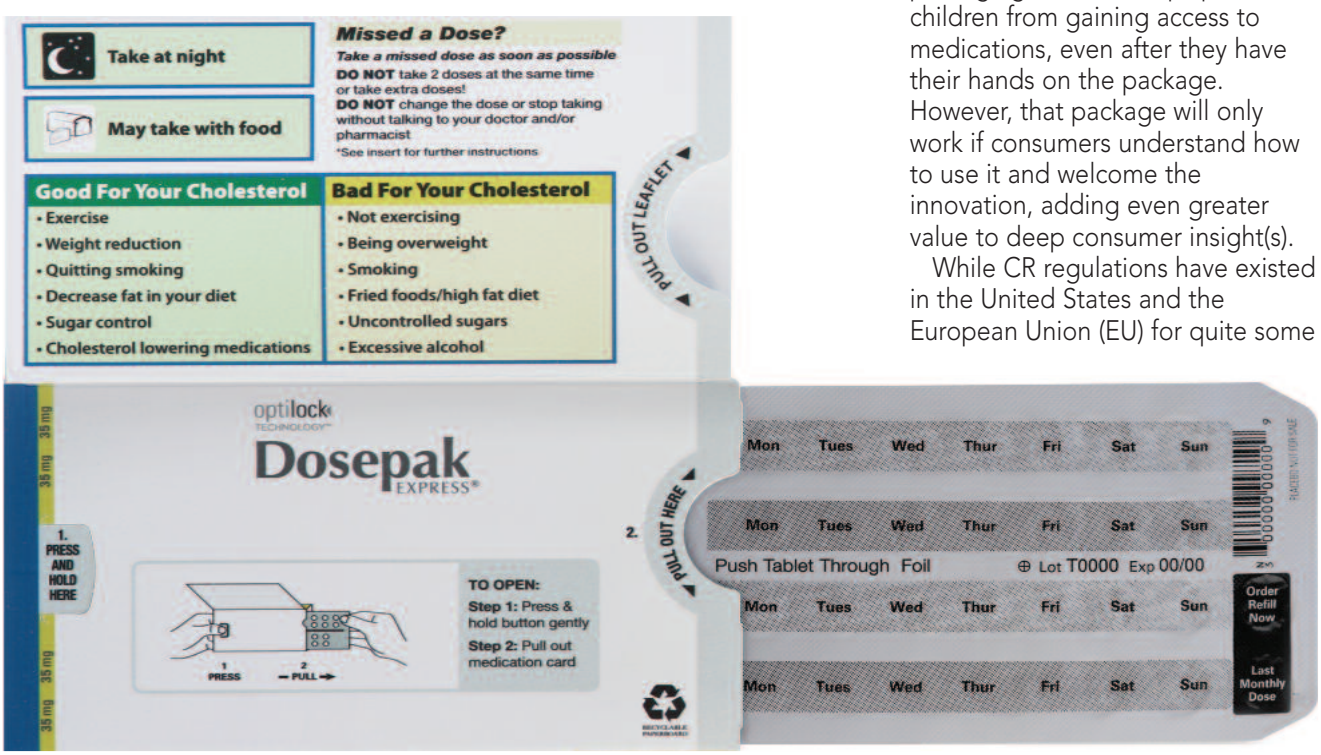


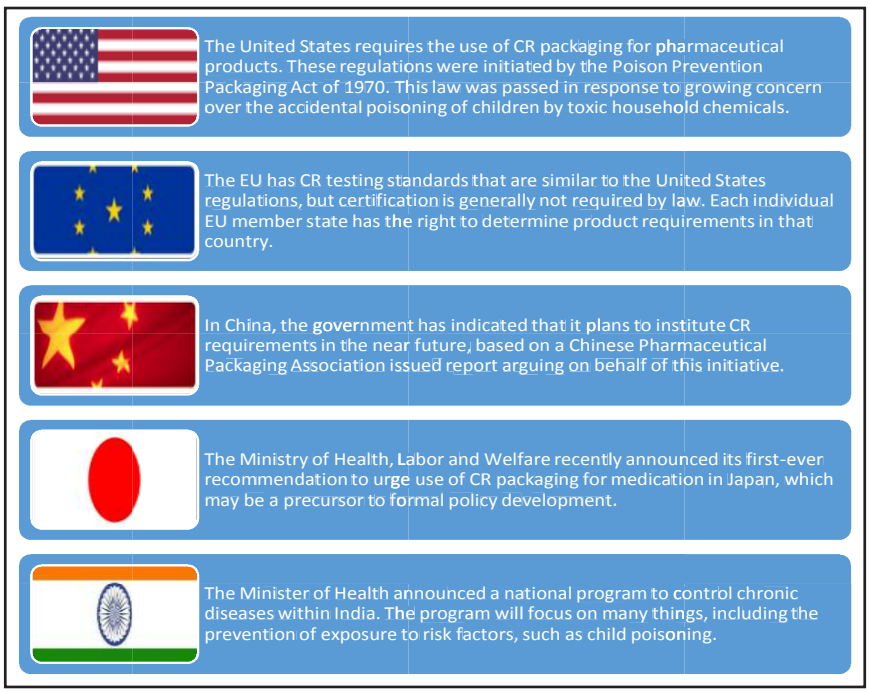
***Figure 2:** WestRock's Dosepak® Express with Optilock® technology design.*

time, these requirements vary in other countries around the world and are surprisingly non-existent in many. Most would agree, however, that since accidental child poisonings are a global problem, the responsibility to consider CR packaging for medication goes beyond regulations. Clearly, CR packaging is the new best practice or standard of excellence, rooted in the desire to keep children safe. If a medication toxicity issue warrants the use of CR packaging in one region, then drug manufacturers are responsible and smart to consider integrating CR packaging in other locations as well – even if formal guidelines have yet to be put in place.

Research demonstrates that CR packaging saves lives, and many leaders in the space are choosing not to wait until mandates are in place to implement change. For those leaders, change starts right now.

Further information

Global CR trends



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GETTING TO HIGHER QUALITY PROCESSES SOONER – NEW GUIDE HELPS YOU MAKE A BETTER CHOICE OF BIOLOGICAL MATERIALS

by Patrick Ginty and Ben Sheridan

The BSI (British Standards Institution), the UK's National standards body, has worked collaboratively with the Cell Therapy Catapult and a wider group of cell therapy experts, to develop *PAS 157:2015 Evaluation of Materials of Biological Origin Used in the Production of Cell-Based Medicinal Products – Guide*. This document supports the evaluation of biological materials used in the production of cell-based medicinal products for human use. It will help developers of high quality cell-based medicinal products to select the biological materials in a consistent manner. The aim is to reduce the probability of minimising both variation in product characteristics and the introduction of unwanted agents, thus potentially reducing the barriers to eventual successful commercialisation of the products. The background and key benefits of PAS 157:2015 are discussed, along with any previous guidance in this area as well as methods in which to mitigate risks associated with procurement of biological materials.

Patrick Ginty is currently working as the Regulatory Affairs Manager at Cell Therapy Catapult Ltd in London. He gained his PhD in tissue engineering and drug delivery in 2005 and has since spent 10 years working in both industry and academia pursuing a career in the regulation of cellular therapies and medical devices. During this time, he has received a certification from the Regulatory Affairs Professionals Society, has worked on over 20 different cell therapy products, and gained over 25 publications/patents in regenerative medicine and cellular therapy.

Ben Sheridan leads on the development of standards to underpin innovation in high value manufacturing at the BSI. He spent a number of years at the National Physical Laboratory, supporting the long-term development of measurement research programmes in support of emerging technologies, and before this worked in the semiconductor industry.

Background

Cell-based medicinal products are complex and their therapeutic benefits are often derived from mechanisms that are not fully understood, thus making it challenging to demonstrate the safety and efficacy of these medicinal products. As such, during the manufacture of these products, there is a strong requirement to minimise both sources of risk and process variability in order to maximise the quality of the final product. The choice of biological materials used in the production of cell-based medicinal products has a strong impact on important biological characteristics of the final product, such as viability, purity and potency, but can also have an adverse effect on product variability and also be potential sources of contamination.

The BSI has worked with the Cell Therapy Catapult, as well as a wider range of cell therapy experts, to create a guide with the intention of helping those people looking to develop high quality cell-based medicinal products. The guide intends to help these developers select the biological materials in such a way that reduces the probability of minimising both variation in product characteristics and the introduction of unwanted agents, thus potentially reducing the barriers to eventual successful commercialisation of the products.

This guide, with the title *PAS 157:2015 Evaluation of Materials of Biological Origin Used in the Production of Cell-Based Medicinal Products – Guide*, is a document that supports the evaluation of biological materials used in the production of cell-based medicinal products for human use.

What does the PAS cover?

The PAS covers all biological materials that come into contact with the cellular active substance during the manufacturing process for cell-based medicinal products, such as those found in cell culture media components, e.g. cytokines, animal-derived sera, proteins, etc. The scope of the knowledge contained within the document includes guidance on the following.

- Identifying, assessing and controlling risks associated with materials of biological origin.
- The evaluation of all materials of biological origin.
- Applying the fundamental principles of risk management to both materials of human and animal origin, and also to reagents derived from a wider range of biological sources.
- Legislation for developers of cell-based medicinal products

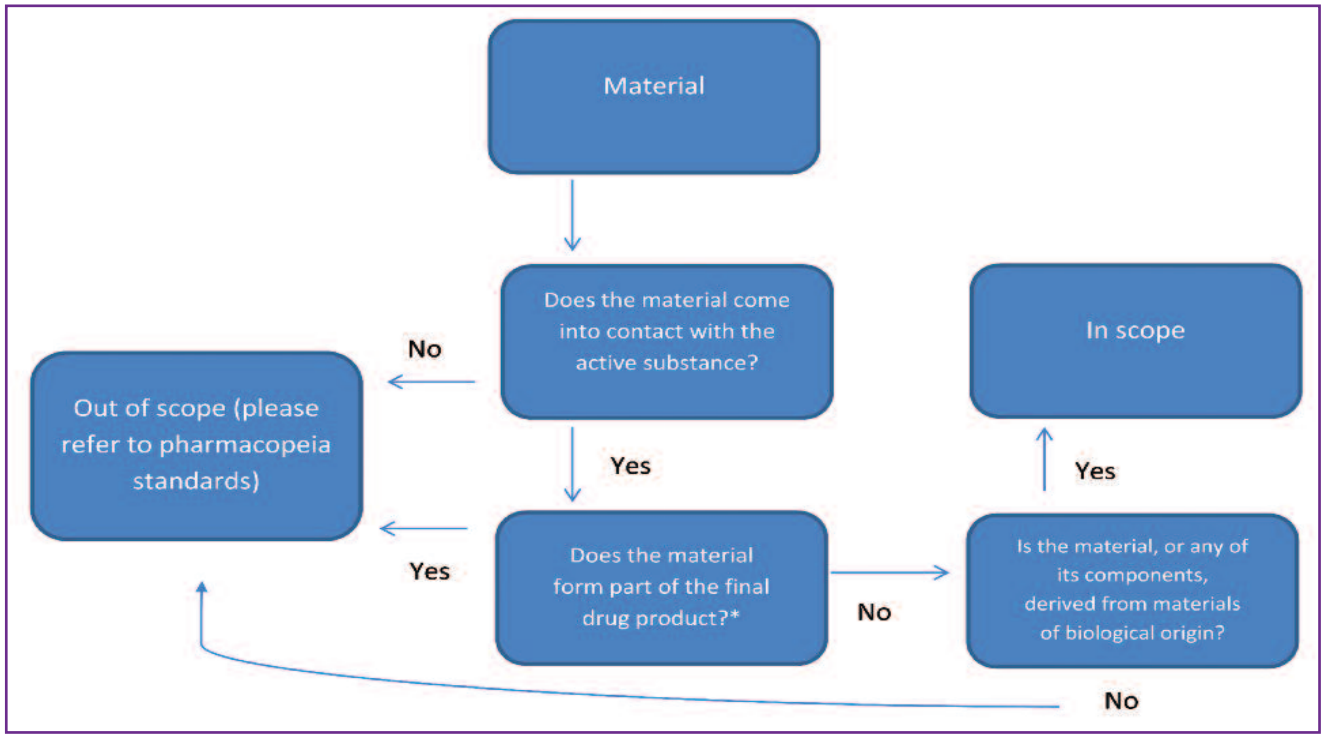


***Figure 1:** Decision chart demonstrating the rationale applied to the scope of PAS 157. *Starting material or excipient as defined in Directive 2001/83/EC and, therefore, out of scope of PAS 157.*

in both the European Union (EU) and the US.

It is important that we also identify what the PAS is NOT intended to do. It does not cover the selection, assessment or control of cellular active substances, nor starting materials as defined in Directive 2001/83/EC and excipients. Additionally, it also does not cover biological materials that are used in the development of any other biological medicinal product.

Previous guidance

This is not the first guidance published by the BSI that is relevant to developers of cell therapy products. Recent years have seen the following documents also published by the BSI in collaboration with cell therapy experts.

- *PAS 83 Developing Human Cells for Clinical Applications in the European Union and the United States of America – Guide.* This document gives a description of the development pathway and relevant regulatory regimes in the EU and US that is applicable to cell-based medicinal products.
- *PAS 84 Cell Therapy and Regenerative Medicine – Glossary.* This is a glossary of terms for use in the cell therapy and regenerative medicine industry.
- *PAS 93 Characterization of Human Cells for Clinical Applications – Guide.* This is a guidance document helping developers of products containing human cells for clinical applications to characterise their products and processes.

A fundamental part of PAS 157 is deciding whether or not a particular application is in or out of scope of the guidance. The document contains Figure 1, which helps users make this assessment.

What is in PAS 157?

Quality considerations for biological materials used in the production of cell-based medicinal products

There are a number of considerations related to the quality of biological materials that are used in the production of cell-based medicinal products, and it is these considerations that provide the context to the PAS. For example, the use of biological materials brings with it the potential for the transmission of adventitious agents, such as the risk of transmissible spongiform encephalopathy (TSE) from human or bovine material. Therefore, when sourcing a new material for use in a manufacturing process, a number of key questions should be asked. For example, if using bovine material, is the material sourced from non-TSE countries such as Australia or New Zealand?

It is equally important to ensure that the manufacturing process used to produce the material does not introduce any risk of contamination with adventitious agents, i.e. processing in an environment where materials of animal or human origin are present. In cases where there is no suitable alternative to a material of human or animal origin, it is important to know that the supplier has taken steps to eliminate risk and that they

have tested the material in compliance with international and regional regulatory requirements.

Equally, it is valuable to know if any downstream purification or inactivation measures have been taken by the supplier of the material. Beyond the mitigation of safety risks, it is also essential to know if the material in question provides the functionality that is required for its intended use. Therefore, it is important to know if the material has been used for other similar processes and/or that the supplier can provide assurances over the consistency of the quality of the material. One such method is to ask the supplier to provide a detailed specification and evidence that the material is manufactured under a recognised quality system. Equally, the developer should make sure that they carry out any characterisation, the level of which being dependent on the criticality of the material and the potential impact on final product quality if the material does not meet its specification.

Applicable regulatory requirements and other sources of guidance

PAS 157 contains a great deal of useful information that is intended to help developers to develop high quality processes and products. For example the difference in regulatory requirements in the EU and US relating to biological materials selection is highlighted, including, for example, the potential for using a Drug Master File in the US, but not in the EU.

One major source of confusion that can occur is the differing usage of terminology in the EU and the US, and this is highlighted in PAS 157, for instance, when using the terms 'raw materials' and 'ancillary materials'. The intention is to make it clear to the developer where differing usage of terminology occurs, and to go some way to helping the reader deal with this situation.

The document also contains more detailed information relating to the existence in the EU and US of specific regulatory requirements and guidance applicable to the manufacture of cell-based medicinal products. It highlights recurring themes that occur within each territory, and also the use of the risk-based classification system used for ancillary materials in the US.

Manufacturers of biological materials available on the market can make various quality declarations about the materials in question, and it is important that the product developer is aware of what these mean, and the limitations of what useful information can be inferred from such statements. PAS 157 identifies commonly used examples of such quality declarations and explains their meanings/implications from both a technical and regulatory perspective.

Evaluating supplied materials and mitigating potential risks

Most developers of cell-based medicinal products will be procuring biological materials from a third party supplier. Each of these suppliers will have their own quality management regimes when demonstrating control over their processes, and there is, therefore, no single means of using supplied information to evaluate the materials and establishing potential risks associated with them. PAS 157 identifies certain criteria that can be used to evaluate such supplied materials, and also steps that can be taken to mitigate risks that are identified during this process.

The document also gives particular guidance on how to undertake an audit of a biological materials supplier, and also on how to use all of the information gathered to form the basis of a risk assessment.

Characterisation

Whilst there is shared responsibility for sufficient characterisation to demonstrate the quality of a biological material between the supplier and the developer, once the developer accepts the material, the responsibility for control and characterisation of the material lies with the developer themselves. PAS 157 guides the developer on the kinds of characteristics they will need to be aware of. Commonly, this may include testing to establish the identity, purity and biological activity of the material in question, in addition to more simplistic measurements such as pH and osmolality.

Changes to materials

PAS 157 demonstrates that changes to the supply of biological materials gives rise to certain responsibilities to the developer to ensure their processes remain acceptable to the regulator. Changes in quality of the biological material can lead to adverse consequences on the quality of the final product, and these changes can be as a result of changes to the manufacturing process, the manufacturing site, or if the supplier stops manufacturing the product altogether.

The document guides the developer in how to manage such potential changes in advance of them happening, particularly through dialogue with the supplier, and also in establishing other potential sources of the material.

How was PAS 157 developed?

A PAS is developed to address a particular market need. This may be a request from an individual sponsor for a standardisation document that serves an emergent market, technology, service or public policy interest. The approach used in the development of a PAS is a means of quickly introducing a standardised approach. It often acts as the basis for further development towards more formal standardisation at a European or international level through international standards bodies, such as the International Standards Organization or the European Committee for Standardization.

The true value of a standardisation document is that if it is often optimised, it is more widely

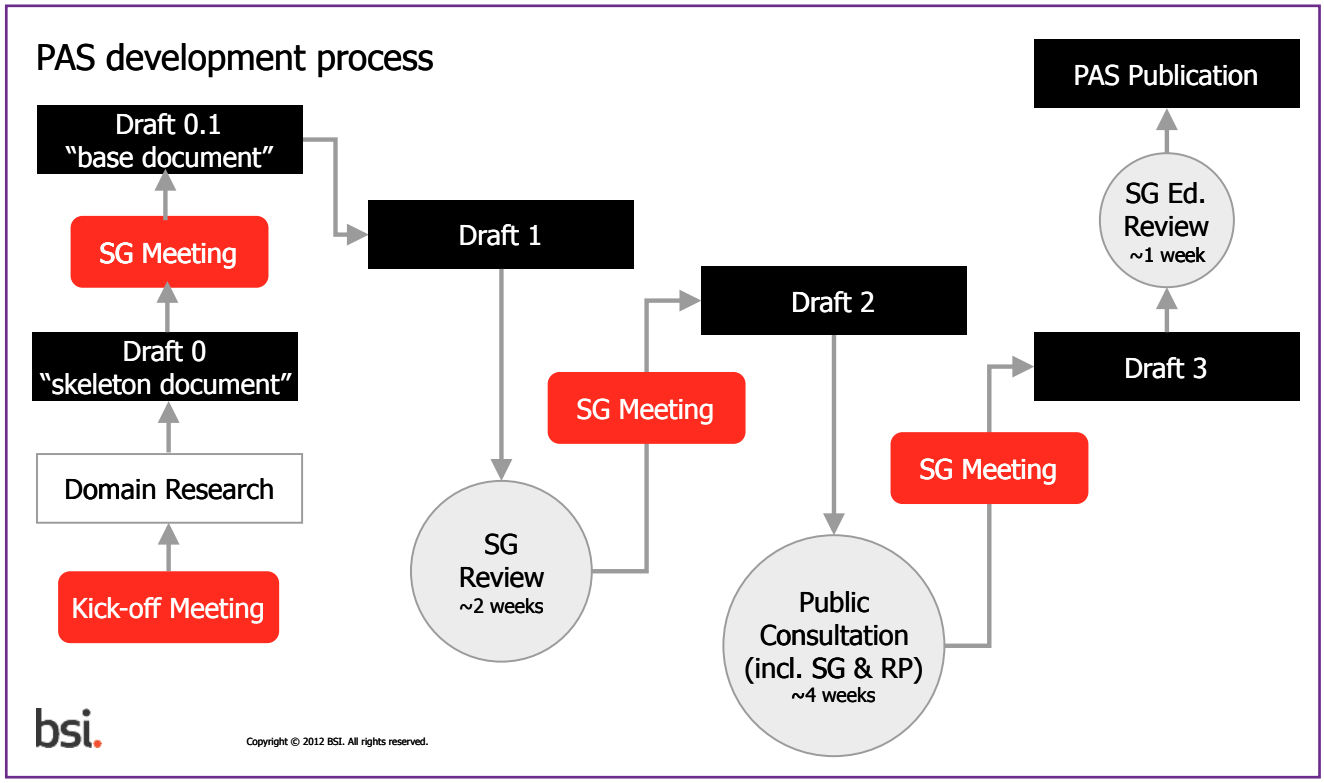


***Figure 2:** PAS development process. SG: Steering Group; RP: Review Panel.*

adopted. As such, a PAS is generally not only applicable within the UK, nor is its development model restricted to UK stakeholders. The process for developing a PAS is described in Figure 2. The work is led by a technical author, who is assisted by a Steering Group and a Review Panel.

In the case of PAS 157, the technical author was Patrick Ginty from the Cell Therapy Catapult, and the Steering Group consisted of representatives from the following.

- Cell Medica
- CellData Services
- Cell Therapy Catapult
- GlaxoSmithKline (GSK)
- Consulting on Advanced Biologicals Limited
- Miltenyi Biotec
- National Institute for Biological Standards and Control (NIBSC)
- Roslin Cells
- University College London

Further reading

1 British Standards Organisation. *PAS 83 Developing Human Cells for Clinical Applications in the European Union and the United States of America – Guide*. London, UK: BSI; 2012.
2 British Standards Organisation. *PAS 84 Cell Therapy and Regenerative Medicine – Glossary*. London, UK: BSI; 2012.
3 British Standards Organisation. *PAS 93 Characterization of Human Cells for Clinical Applications – Guide*. London, UK: BSI; 2011.
4 European Directorate for the Quality of Medicines and HealthCare. *European Pharmacopoeia 8th Edition*. Chapter 5-2-12. Raw materials for the production of cell-based and gene therapy medicinal products (draft). Strasbourg, France: EDQM, Council of Europe; 2014.

IN SILICO CLINICAL TRIALS: DREAM OR CERTAINTY?

by Marco Viceconti, Adriano Henney, Edwin Morley-Fletcher and Martina Contin

The astronomical cost of bringing medical products to market has stalled the development of drugs, crippling healthcare budgets and, for rare diseases, making new treatments the preserve of the rich. However, this September the Avicenna Consortium, tasked by the European Commission to investigate how computer modelling might mitigate the cost of clinical trials, released its Roadmap – '*In Silico* Clinical Trials: How Computer Simulation Will Transform The Biomedical Industry'.

Marco Viceconti is Professor of Biomechanics in the Department of Mechanical Engineering at the University of Sheffield, UK and Professor Associate at the Department of Human Metabolism. He is the Scientific Director of the University of Sheffield's Insigneo Institute for *in silico* Medicine, a joint initiative between the University of Sheffield and the Sheffield Teaching Hospital NHS Foundation Trust.

Adriano Henney, Director of Obsidian Biomedical Consulting Ltd, worked for 13 years in one of the top five multinational pharmaceutical companies before becoming Programme Director of the German Virtual Liver Network, the largest Virtual Physiological Human (VPH) project running in Europe (http://www.virtual-liver.de). Dr Henney has directed this major German national flagship research programme focusing on modelling human liver physiology since 2010.

Edwin Morley-Fletcher is President of Lynkeus srl, Italy and has over 25 years' experience in ebusiness. In the last 10 years, he has progressively focused on information and communications technology for health, managing some of the largest VPH projects, including MD-Paedigree, one of the three integrated projects funded in call 9.

Martina Contin worked as Communication Manager in various VPH initiatives at the VPH Institute, Belgium, before taking the helm of the not-for-profit organisation that coordinates all VPH research worldwide. The organisation aims to ensure the VPH is fully realised, universally adopted and effectively used.

Introduction

The Roadmap is the culmination of 2 years' work involving contributions from over 500 international experts at five events held across Europe. It promises huge cost reductions in medical product development through the use of computer simulation.

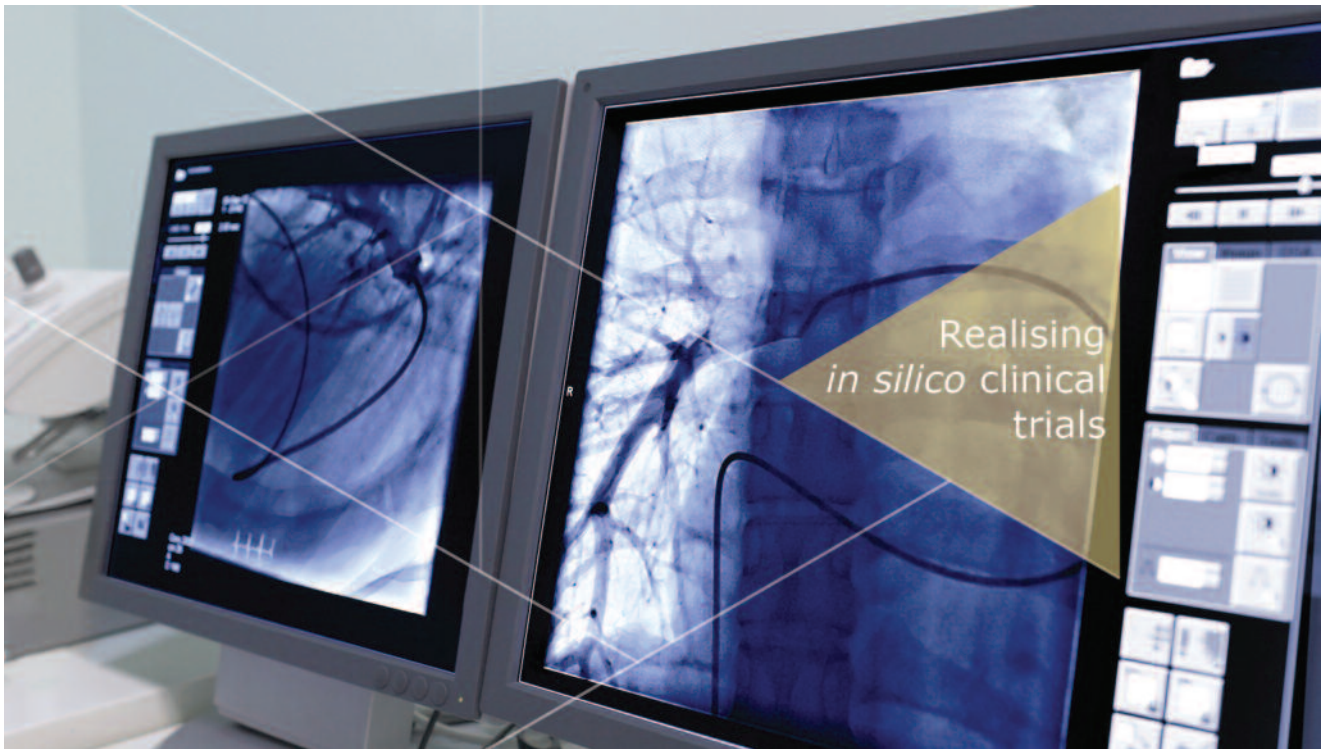
With the release of the Roadmap, the Avicenna project officially comes to an end. However, to ensure the ideas contained are taken forward and making its recommendations become a reality, a new organisation has been formed: the Avicenna Alliance – the Association for Predictive Medicine. This first partnership of pharmaceutical industrialists, medical device manufacturers, academic researchers and regulatory experts will aim to revolutionise the healthcare industry through the use of computer simulation.

This September, the Avicenna Consortium, tasked by the European Commission to investigate how computer modelling might mitigate the cost of clinical trials, released its Roadmap: '*In Silico* Clinical Trials: How Computer Simulation Will Transform The Biomedical Industry'. This article describes the process and the future of the Avicenna vision.

The Roadmap

Approaching the investigation of the potential impact of *in silico* clinical trials, the Avicenna Consortium brought together a range of experts from around the world – academics, clinicians, industrialists, patients' advocates, computer experts, regulators and safety experts. Over 2 years, the consortium organised five events in different European cities, conducted dozens of experts' interviews, and used state-of-the-art online technologies to collect hundreds of individual opinions and align them around agreed statements, in order to arrive at a consensus on how to introduce computer simulation into the clinical trials process.

Why go to such efforts to discuss computer simulation in clinical trials? Professor Marco Viceconti, Coordinator of the Avicenna Project explains: "Developing a new medical product, whether it is a new medicine or a new medical device, is becoming prohibitively expensive and can take anything up to 12 years. The latest industry figures estimate that the costs of developing and bringing a new medicine to market are approaching US $3 billion. All analysts agree that this situation is unsustainable, and that the biomedical industry must quickly find alternative and more effective ways to develop and assess new medical products."



The huge cost of developing new medical products has many consequences. Countries with universal healthcare struggle to afford the best new products, and in countries with private healthcare only the wealthy can afford the best treatments. Many conditions are ignored by the biomedical industry because they cannot return the significant investment needed for clinical trials – because the groups of people affected by the conditions are too small (e.g. Sanfilippo Syndrome) or too poor (e.g. Chagas disease).

The Avicenna Consortium believes computer simulation is one solution that will contribute to revolutionising the clinical trials process. In all other industrial sectors, computer simulation plays an essential role in the design and assessment of new products. Given recent advances in medical imaging and other analytical technologies, the Avicenna Consortium asked if we have collected enough knowledge to start using computer simulation in the development of medical products. Could we use the computer simulation of individual patients' bodies in the development or regulatory evaluation of a medicinal product, medical device or medical intervention? If we could, what would be the barriers to its widespread adoption?

In its conclusions, the Avicenna Roadmap states that, in the opinion of the Consortium and the contributors to the Avicenna Research and Technological Roadmap, the use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device or medical intervention (generally referred to as "*in silico* clinical trials") is one of the most important strategic priorities in biomedical and technological research, if we want to make the development and assessment of new biomedical products simpler, cheaper, faster and safer, whilst at the same time minimising those activities such as animal or human experimentation that pose ethical concerns. It recommends that all public and private research funding agencies across the world do the following.

a) Acknowledge the significant socioeconomic relevance that research and technological development, assessment and adoption of *in silico* clinical trials technologies pose. The mounting needs of universal healthcare provision in developed countries exceed our ability to innovate quickly and efficiently, and *in silico* approaches are the best possible route to address those needs.

b) Progressively increase the expenditure in this area in the next 5 years, so that by 2020 at least 1% of the total public and private expenditure in biomedical research and development worldwide (estimated as US $268 billion in 2012) is dedicated to the development and adoption of *in silico* clinical trials technologies used to translate biomedical research discoveries into new products and services more quickly, safely and efficiently. This should be initiated with a dedicated programme in the 2016/17 European Commission Work Programme of the European Union Horizon 2020 programme, with a budget of at least €50 million per year.

c) Ensure that such public and private research and technological development funding is dedicated in equal parts to the core scientific and technological development of predictive models, to their pre-clinical and clinical validation, including the necessary regulatory science aspects, and to support their early adoption in industrial and regulatory practice.

As the Avicenna consensus process has demonstrated, in a globalised economy the discourse of *in silico* clinical trials must develop globally. Thus, it is recommended that all agencies remove as many barriers as possible to developing and prototyping these approaches, and actively support pre-competitive research and technological development across international boundaries.

The consensus process adopted in the project has shown that there is a strong will to ensure these messages are acted upon, and it has resulted in the first tangible step being taken: the creation of the Avicenna Alliance – the Association for Predictive Medicine. This will be an association of industry and research organisations who have a commercial or research interest in *in silico* medicine. While there is a great number of policies that impact on the *in silico* market, there is currently no one organisation that is dedicated to this field. The Avicenna Alliance will advocate for the creation of policy and regulatory environment that is favourable to the uptake of *in silico* models and promote the interests of its members in this field.

The Avicenna Consortium has broadened its focus to promote *in silico* medicine in general, i.e. using computer simulation to revolutionise healthcare. The Consortium has been urging the European Commission to support research that will allow clinical trials to be run in computer simulations, reducing the need for animal testing and helping to cut down the astronomical cost of testing new medical products. This pressure appears to have been effective, as the early drafts of the 2016/17 European Commission Work Programme indicate support for *in silico* clinical trials.

As the Avicenna Consortium comes to an end, the newly founded Avicenna Alliance will take up the cause of *in silico* medicine, as the first platform for research and industry organisations with an interest in *in silico* medicine to impact the political environment for the emerging *in silico* market. Following a recommendation from the European Commission, the Avicenna Alliance will work towards drafting and submitting a proposal to form a public–private partnership which will raise the profile of *in silico* medicine, create new funding streams for research, and provide evidence of genuine impact on healthcare.

The time is now, the challenge is huge; only if we all work together will we be able to address and overcome that challenge.

Funding

The project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 611819.

Reference

[1] Chakma J, Sun GH, Steinberg JD, *et al.* Asia's ascent – global trends in biomedical R&D expenditures. *N Engl J Med* 2014 Jan 2;**370**(1):3–6. doi: 10.1056/NEJMp1311068.

For further information

Avicenna website: http://avicenna-isct.com

Avicenna Alliance website: http://www.avicenna-alliance.org

700 GÉNÉRIQUES RETIRÉS DU MARCHÉ: CONCRÈTEMENT, ÇA CHANGE QUOI?

by Hugo Jalinière, for Sciences et Avenir

Isabelle Adenot, présidente du Conseil national de l'Ordre des Pharmaciens, revient pour *Sciences et Avenir* sur les conséquences du retrait massif de médicaments génériques du marché européen.

On the 21 August, an EU-wide suspension of the marketing authorisations of 700 medicinal products entered into effect, and the products withdrawn from the markets. Mme Isabelle Adenot, President of the French Conseil national de l'Ordre des Pharmaciens, a member of EIPG, was interviewed by the journalist Hugo Jalinière, of the French periodical *Sciences et Avenir*, on the impact of this withdrawal. *european Industrial Pharmacy*, by kind permission of M. Jalinière and *Sciences et Avenir*, is pleased to bring to its readers a reprint of the article that appeared on the periodical website sciencesetavenir.fr, reporting the interview.

Vendredi 21 août 2015, 700 médicaments génériques à travers l'Europe ont été retirés des officines. Un retrait des autorisations de mise sur le marché décidé en juillet 2015 par l'Agence européenne du médicament (EMA). Une décision prise après plus d'un an passé à réévaluer quelque 1000 génériques dont les tests de bioéquivalence menés en Inde avaient révélé des entorses aux bonnes pratiques cliniques. Ces tests sont conçus

> *« Il y a des alternatives pour chacun des génériques retirés du marché" – Isabelle Adenot »*

pour évaluer la conformité pharmacologique du générique avec le médicament princeps. Une procédure dont *nous vous expliquions les tenants et les aboutissants à l'annonce de l'Agence européenne du médicament.*

Mais concrètement, comment ces retraits vont-ils se traduire pour les patients concernés? "En France, ce n'est vraiment pas un souci", explique Isabelle Adenot, présidente du Conseil national de l'Ordre des Pharmaciens (CNOP). "Il y a des alternatives pour chacun des génériques retirés du marché. Par ailleurs, il y a déjà eu une première alerte il y a quelques mois, à la suite de laquelle les laboratoires concernés avaient agi", précise-t-elle, confirmant ainsi les dire de l'Agence nationale de sécurité du medicament (ANSM) qui avait prévenu qu'en France, ces retraits n'auraient pas d'impact. Par ailleurs, "sur cette liste de 700 génériques retirés, la France n'est concernée que par une infime partie, une trentaine je crois", ajoute-t-elle.

La présidente du CNOP voit même un motif de satisfaction dans ces retraits successifs l'année passée (25 génériques retirés en décembre 2014, puis 8 en janvier 2015 et, donc, 700 en août 2015): "Je me réjoui d'une chose: c'est que les grandes agences du médicament (Etats-Unis, Australie, Europe, Canada...) fonctionnent main dans la main et se font mutuellement confiance. Ce qui me rassure, c'est que le mode de contrôle a fonctionné. Tout n'est pas parfait bien évidemment, mais cet épisode montre que les génériques sont surveillés de la même façon que les princeps; et c'est plutôt rassurant", fait-elle valoir. Une façon peut-être légitime mais optimiste de voir les dysfonctionnements survenus dans les tests de

> *« Cet épisode montre que les génériques sont surveillés de la même façon que les princeps" – Isabelle Adenot »*

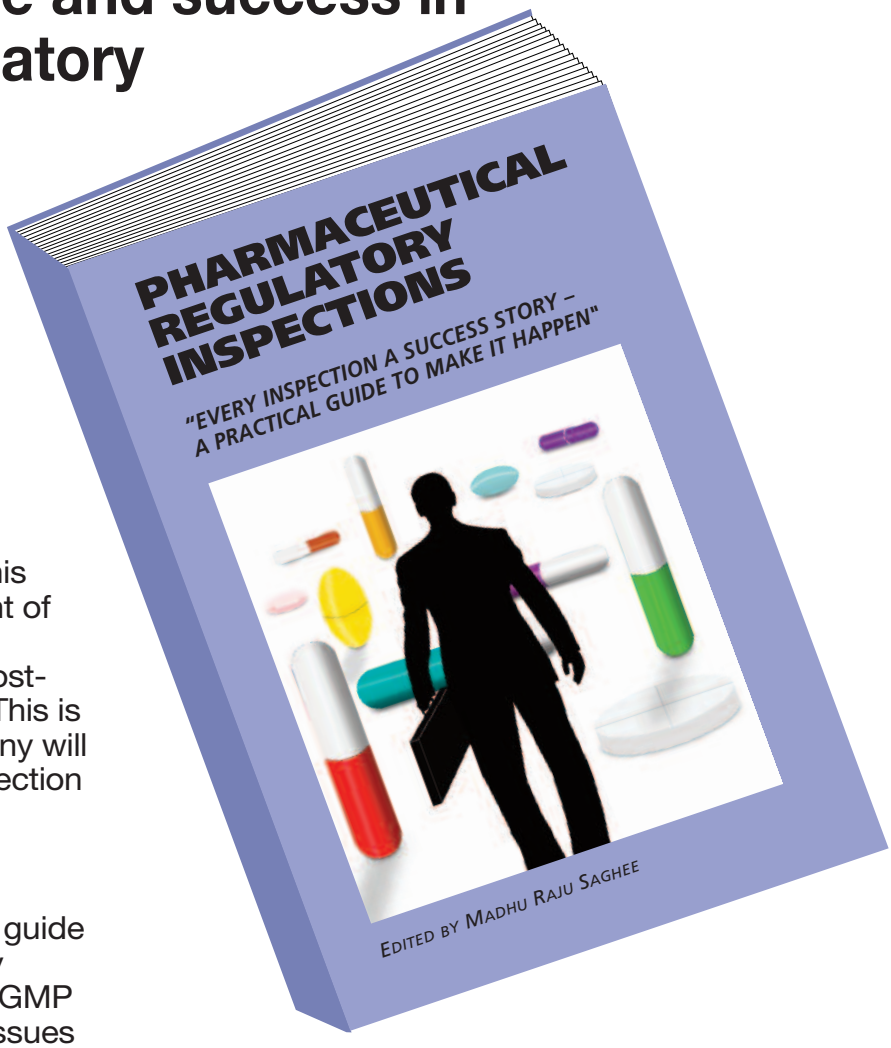
bioéquivalence menés en Inde.

Dans le reste de l'Europe, certains pays sont néanmoins touchés à plus grande échelle par ces retraits: "En Angleterre ou en Allemagne, ce sont entre 100 et 200 médicaments qui sont concernés", précise Isabelle Adenot. Mais même là, "la possibilité de continuer à recevoir un des traitements retirés est envisageable sur dérogation si jamais il existait des cas sans alternative", ajoute-t-elle. Les dysfonctionnements constatés dans les tests de bioéquivalence ne mettant pas en jeu une éventuelle dangerosité des produits.

A unique and comprehensive guide to ensure regulatory compliance and success in pharmaceutical regulatory inspections

Edited by Madhu Raju Saghee
Quality Assurance, Micro Labs, and Director of PHSS, India

Foreword by Peter D. Smith
Vice President, Strategic Compliance, PAREXEL Consulting, USA



In over 500 pages and twelve chapters this unique book provides a focussed account of regulatory issues from pre-approval inspections and the inspection itself to post-inspection and maintaining compliance. This is a book that every pharmaceutical company will wish to study before and during any inspection process to ensure a successful outcome.

Complete Remit

The book is a fully detailed and practical guide containing advice and insight to help any pharmaceutical organisation prepare for GMP Inspections, understand key regulatory issues and review inspectorate trends and findings.

Expert Advice

The authors, with a wealth of regulatory experience behind them, express their views and provide useful and practical tips for succeeding in vital regulatory inspections

International Applications

The book includes chapters covering FDA Inspections, EU Inspections, Japanese Inspection and International Inspection processes.

Global Health Training

Training and guidance is vital for pharmaceutical firms especially those who are hoping to trade overseas

Consultants are vital to healthcare companies looking to operate globally, especially in the areas of distribution, training and product development. PharmaConsult is an international consultancy and bespoke training provider.

Working with clients across the full spectrum of healthcare services in Europe, USA, Middle East and Asia, from blue-chip multinational Pharmaceutical companies (GSK & Novartis), biotech start-ups (Julphar UEA) to generic companies (Activas), Regulatory Authorities (SFDA), and Local Ministers of health (UAE). Pharma Consult offers a consultancy service to companies operating in all pharmaceutical markets, helping to develop their portfolio of products and to achieve high performance and best cost effective practice from their operating systems.

Services range from advice on product registration, specialist product development, regulatory compliance auditing, quality management systems for medicines supply chains and pharmacovigilance.

On the international front this year the company will provide national conference briefings in Delhi, Istanbul, Riyadh, Dubai, Brazil and The Netherlands.

PharmaConsult claims it differs from other companies in that it provides a personalised consultancy service tailor-made to needs and appropriate to the markets in which clients operate. This can be compliance audit services to survive a regulatory GXP inspection, or a turnkey solution to commissioning a new factory or laboratory site.

For companies looking to operate

PHARMA CONSULT
Pharma Consult Global Ltd

overseas, it provides the opportunities to register products through the National Regulatory Authority provided by its associate organisations in the Indian Gulf States and Latin America, providing a unique global networking opportunity.

Firms might be given advice on the development of their medical products (either large or small molecule) or medical devices to meet the latest international regulatory requirements by its various affiliates. Leading local agents can be proposed to distribute products through local representation provided by PharmaConsult's associate organisations in the Indian Gulf States and Latin America, providing a unique Global networking opportunity.

Client's staff are provided with the opportunity to develop their skills and competencies though comprehensive training services which can include online training, or onsite training solutions, comprising of over 40 online eLearning, and 25 Workshop courses. PharmaConsult is the only training provider who can translate courses in to the language appropriate to the region, so that all employers will be able to access training, which encourages a lifelong approach to learning and career development.

In addition the company will be populating automated Quality Management software to ensure the product and process training will be provide to those persons as appropriate which will be documented in accordance with GXP regulatory requirements.

Training

PharmaConsult is an International Training provider of high quality courses based on the latest published technical and regulatory requirements. Method of training delivery is by:

Online training: There are 40 eLearning and webinars on 8 specialist topics. These include: Pharmaceutical Product Development, Clinical Research, Pharmaceutical Product Registration, Pharmaceutical Quality Management systems, Pharmaceutical Manufacture, Pharmacovigilance, Pharmacoeconomics and Pharmacy Practice containing current issues (contain only new regulatory and technical requirements) Presentation (including video/graphics with minimum PowerPoint slides) and include Course notes (copy of slides, reading material, &case studies), candidate Assessment Questionnaire, and CPD Accredited Proficiency certificate.

Professional Training courses are provided over 6-12month periods consisting of a combination of 2-4 day workshops held at regional centres, and online eLearning, conferences and webinars.

Certificate/diploma qualification courses for membership of the professional Group available are;

'Services range from advice on product registration, specialist product development, regulatory compliance auditing, quality management systems for medicines supply chains and pharmacovigilance.'

King's College London is in discussion with PharmaConsult Global to create a new Certificate course in Biopharmaceutics which will comprise 5 modules on:

- **Clinical Pharmacology**
- **Clinical Assessment**
- **Product Discovery**
- **Product Development**
- **Manufacturing.**

The course will be available from Summer 2015. Further details of this important new concept in CPD will be available on www.pharmaconsultglobal.com or contact john.jolley@pharmaconsultglobal.com to register your interest in the course.

Product development: The major focus of the program is to develop the knowledge and understanding for teams to devise a good regulatory strategy for continuous project assessment to promote regulatory and PharmacoEconomic acceptance of the developed product.

Course Leader: Professor Luigi Martini – Kings College University London

Chartered Quality Institute Certificate in Quality Management:

This Certificated course establishes the principals of quality management systems allowing use of well-known quality tools and risk assessment techniques. It provides an ideal basis for any person employed in Healthcare, wishing to take the exams for a Certificate in Quality Management Practices (QMP), providing the first step to qualifying for entry on the CQI Diploma Couse and becoming a CQI Chartered Quality Professional.

Medicines Procurement and Supply Chain management: This introductory qualify course establishes the wide range of causes for medicine supply shortages, dealt with by government agencies, medicines' regulatory authorities and manufacturing organisations. And provides strategies for managing changes in procurement practices, avoiding falsified medicines and defective medicines entering the supply chain (such as insistence on World Health Organization prequalification status or registration with a stringent regulatory authority) may invalidate a previous supplier).

Workshops: A range of 25 specialist subjects relevant to the region and/or company for a basis for presentation, which can vary in duration from half a day up to five days, public seminars are usually are of 2-4 days in duration, and always in small groups so as to allow for detailed discussion on the topic in question.

'PharmaConsult is the only training provider who can translate courses in to the language appropriate to the region, so that all employers will be able to access training, which encourages a lifelong approach to learning and career development.'

Further information

www.pharmaconsultglobal.com

regulatory review

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. Incidents are reported of medicines being suspended in the EU because of flawed studies and also of companies being fined for serious breaches of good manufacturing practice (GMP) in the manufacture and supply of products in the UK.

USA

Request for Quality Metrics

This draft guidance includes an explanation of how the Food and Drug Administration (FDA) intends to collect data and use quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry.

These metrics can be used by the FDA: to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers; to improve the Agency's ability to predict and, therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing.

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals

As a result of chemical synthesis or subsequent degradation, impurities reside in all drug substances/drug products. International Conference on Harmonisation (ICH) Q3A and Q3B provide guidance for qualification and control for the majority of the impurities. Limited guidance is provided, however, for those impurities that are DNA reactive. This guidance provides a practical (safety and quality risk management) framework that is applicable to the identification, categorisation, qualification and control of mutagenic impurities to limit potential carcinogenic risk from mutagenic impurities that reside or are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use.

Reportable CMC Changes for Approved Drug and Biologic Products

This draft guidance addresses the lack of clarity with respect to what chemistry, manufacturing, and controls (CMC) information in a marketing application constitutes an established condition or a "regulatory commitment" that, if changed following approval, requires reporting to the FDA. Such clarification, should lead to a better understanding that certain CMC changes can be made solely under the Pharmaceutical Quality System without the need to report to the FDA. The result should be a more effective post-approval submission strategy over the lifecycle of the product by the regulated industry.

Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules

Generic drug products are required to be both pharmaceutically and therapeutically equivalent to a reference listed drug (RLD). The FDA is also concerned that differences in physical characteristics (e.g. size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors. The FDA recommends that generic drug manufacturers consider physical attributes when they develop quality target product profiles for their generic product candidates.

Europe

Concept paper on new guidance for importers of medicinal products

The GMP/GDP [good distribution practice] Implementation Working Group agreed to draft a specific guidance for import authorisation holders. This document most likely would take the form of a new annex (annex 21). The scope of the project will focus on importation activities not addressed in detail in the current GMP guide and annexes.

Fast track routes for medicines that address unmet medical needs

The European Medicines Agency (EMA) has revised its guidelines on the implementation of accelerated assessment and conditional marketing authorisation, two key tools in European legislation to accelerate patients' access to medicines that address unmet medical needs.

EMA confirms recommendation to suspend medicines over flawed studies

The EMA originally suspended a number of medicines for which authorisation in the EU was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India. Following a re-examination requested by marketing authorisation holders for seven of the medicines concerned. Around 700 pharmaceutical forms and strengths of medicines studied at the Hyderabad site remain recommended for suspension. For around 300 other pharmaceutical forms and strengths, sufficient supporting data from other sources had been provided; these medicines will therefore remain on the market in the EU.

Medicines and Healthcare Products Regulatory Agency *(MHRA)*

Companies sentenced for supplying hospitals with defective pre-filled syringes

A major healthcare company and a sister company that sold a range of ready-to-use pharmaceutical products it manufactured have been sentenced for supplying hospitals with defective pre-filled syringes that in one case contributed to the

death of a diabetic patient after being treated with a batch of intravenous insulin syringes that actually contained no insulin. The faulty syringes were supplied by Fresenius Kabi Ltd as a licenced wholesaler for Calea UK Ltd, which manufactured the product.

Both companies, based at the same address in Runcorn, Cheshire, were fined at Sheffield Crown Court after being prosecuted by the MHRA.

These two incidents followed a series of previous inspections by the MHRA officials that highlighted deficiencies. Fresenius Kabi Ltd was fined a total of £500,000 plus £5900 in costs after pleading guilty to breaching Sections 64(1) and 67(2) of the Medicines Act 1968. Calea UK Ltd was fined £50,000 with £5900 costs after pleading guilty to similar breaches.

MHRA Inspectorate blog

This blog is aimed at organisations that are inspected by the MHRA and need to keep up to date with the latest thinking and guidelines. It will give the MHRA inspectors a chance to speak directly to the organisations they inspect and get feedback from them on topics they would like to hear more about.

MHRA helps to future-proof mammalian cell culture manufacturing facility

Fujifilm involved the MHRA early on to meet regulatory expectations to reduce risk of any late or costly changes. They wanted to include as much feedback from the MHRA into the design of the facility as possible.

International

ICH

ICH Q7 Q&As

Experience gained with the implementation of the ICH Q7 Guideline since its finalisation in 2000 shows that uncertainties related to the interpretation of some sections exist. Technical issues with regard to GMP of active pharmaceutical ingredients (APIs) and also in context with other new ICH Guidelines are addressed, in order to harmonise expectations during inspections, to remove ambiguities and uncertainties, and also to harmonise the inspections of both small molecules and biotech APIs.

Pharmaceutical Inspection Cooperation Scheme (PIC/S)

Strengthening of international regulatory cooperation in the field of GMP

The aim is to encourage PIC/S members to accept inspection findings on a voluntary basis, by relying on mutual trust and confidence building, based on the PIC/S accession process.

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@euromedcommunications.com

bottled brown

Target over heart

Utah, USA has a problem. Citizens cannot obtain drugs required for capital punishment by lethal injection. The alternative firing squad (five anonymous police markspersons) fire four live bullets and one blank onto a target pinned over the heart. Lethal injections contain chemicals, commonplace in industrial pharmacy but so elderly that they have grown whiskers. Sodium thiopental was first used clinically in 1934; pentobarbitone in 1930; curare, akin to the potentially lethal muscle relaxant pancuronium, in 1948. Humphry Davy discovered potassium chloride in 1817.

Apparently some injections were "botched". Observers noted the condemned took hours to die. An American manufacturer, such as *Hospira* for thiopental, will not supply such medicaments to prisons. Moreover, the EU, under "torture regulations" (Council Regulation (EC) No 1236/2005) bans export of certain drugs. That is despite lethal injection being deemed not a medical procedure. That by-passes doctors' concerns.

At that point, Brown's nose twitched. I felt like a small pig detecting a whiff of mouth-watering truffle underneath forest litter. What brutalising and barbaric nonsense and delicious ironies did my snout detect?

Way to go

My starting reflection was that, had I been a particularly undesirable citizen of Utah condemned to death, my preferred exit would be by efficiently-administered injection. I remember experiencing intravenous barbiturates as precludes to gaseous general anaesthesia. I drifted into sleep. If longer than desired, there could be worse ways to exit. It seems preferable to the Gaelic Guillotine (fraction of a second), hanging (second or two) or electrocution (dozens of seconds). Maybe that exposes my bias because medicines have been my life. In salad days, dispensing wonderful-smelling Brompton cocktail with heroin, honey, brandy, chloroform water and so forth, I reflected that, if ever I required it, I hoped some pharmacist would be available to compound. That would be more human than the clinically efficient *MST* and *Oramorph* – and more tasty.

I then wondered whether I would be willing to certify a batch of lethal injections fit for release onto the EU market, as a qualified person; Netherlands citizens use similar cocktails for euthanasia. I have left that fray but, were I still involved, my answer would probably be "Yes". Indeed, I would strain every sinew to ensure that it was made, as our American cousins might say, "real good".

Medicine safety

Those reflections deposited me within the Medicines and Healthcare Products Regulatory Agency (MHRA) website. That informed "what you need to know" about medicine safety. Before licensing, medicines should be "thoroughly trialled on thousands of people", the "advantages" must "outweigh the disadvantages of taking the medicine" and, for the people taking the medicine (condemned criminals), "do the most good for the least harm". I sensed a mismatch between those aims and the prisons in Utah containing human beings whom some staff labelled as "monsters". For example, I am unaware of thousands of clinical trials testing "superdoses" of lethal agents resulting in death. In fairness, package inserts and label exclude that outcome.

Scrutiny of the MHRA website exposed it as glaringly anthropocentric. Humans (not say, salmon; they require medicines, also: I have made them) are its taken-for-granted reference species. It is fascinating that octopi are deemed so intelligent that the UK considers them honorary vertebrates for the purposes of animal cruelty laws. Presently, I am ingesting for bronchitis – thankful to be a patient in the rich West – clarithromycin. Hopefully, that is "harmless" to my mammalian cells but will kick-the-ass of *Haemophilus influenzae, Streptococcus pneumoniae* and *pyogenes* and any other unfriendly interlopers.

I end with a final twitch in viewpoint. Most of humankind accepts the scientific evidence base that capital punishment is ineffective.

Malcolm E Brown

news from the EIPG

European Medicines Agency

(a) EIPG comments on the Concept Paper for Guideline on Topical Products have been submitted to the European Medicines Agency. For a copy of the comments, see the EIPG website under "News" from the Bureau.

(b) EIPG comments on the Draft Guideline on the Chemistry of Active Substances are being consolidated by Georgina Gal (Hungary) and Marianne Anderson (Sweden).

European Commission

A draft Commission Delegated Regulation has been published on the Unique Identifier and includes the details of the rules for the safety features appearing on the outer packaging of medicines. It will apply 3 years from publication of the final text.

The 34 pages of main document and 5 pages of annexes can be found at http://ec.europa.eu/growth/tools-databases/tbt/en/search/?tbtaction=search.detail&num=306&Country_ID=EU&dspLang=EN&BASDATEDEB=&basdatedeb=&basdatefin=&baspays=EU&basnotifnum=306&basnotifnum2=306&bastypepays=EU&baskeywords

If any reader wishes to submit comments on the draft, they should be sent to Piero Iamartino (pieroiamartino@gmail.com).

News from the European Parliament

A new section under "News" has been added to the EIPG website called "European Parliament Pharma Watch". It collects questions and answers, statements, etc at the European Parliament on matters relating to the pharmaceutical industry. See http://eipg.eu/eurparlpharm/

EIPG awards

Fellow of EIPG

The purpose of this award is to recognise individuals who have exhibited strong leadership internationally, have distinguished themselves in the pharmaceutical sciences and/or practice of industrial pharmacy, who have contributed to the advancement of pharmaceutical sciences and/or practice of industrial pharmacy, and who have served the EIPG. Nominations for next year's award should be submitted by any EIPG Full Member Association not later than 1 January 2016.

EIPG Emerging Industrial Pharmacist Award

The purpose of this award is to recognise significant intellectual contributions by emerging industrial pharmacists within EIPG that promote state of the art in industrial pharmacy and the pharmaceutical sciences. Nominations for the award may be submitted by any EIPG Full Member not later than 1 January of the year in which the award is to be made. At the time of nomination, the nominee should be a person who is within 10 years of having started a career in industrial pharmacy.

Education

A new publication on the Phar-In project has been published: A European competence framework for industrial pharmacy practice in biotechnology. *Pharmacy* 2015;**3**(3):101–128; doi:10.3390/pharmacy3030101

A new course on Personalised Medicine prepared by Drs Claire Thomson and Felicity Sartain is available on the PharmaConsult website. This can be found at http://www.pharmaconsultglobal.com/course_detail.html?id=31

MOGLYNET Project

EIPG has been invited to join as a partner in an important European educational project addressed to master students willing to achieve a doctorate level degree. This project, called MOGLYNET, involves five European universities (Milan, Antwerp, Leiden, Aberdeen and Barcelona) and the participation of a few industrial partners and professional association partners, who have offered their support in terms of consultancy, training and assistance to the development of the research and educational activities of 12 doctorate candidates.

In particular, EIPG will be involved in the recruitment phase of students for this project and in the assistance for setting up appropriate training courses promoting an integrated knowledge between university research and pharmaceutical industrial expectations. Anni Svala, EIPG Vice-President Education and Careers and Finnish delegate, is in charge of representing EIPG in this project.

European Pharmaceutical Students Association

Two further successful webinars have been held, each with an audience of 50 participants. The speaker on Pharmacovigilance Audits and Quality Systems was Susanna Heinonen, PV manager, Algol Pharmaceuticals, and the Importance of Continuing Professional Development was presented by Claire Johnson, EBI, LifeTrain.

Jane Nicholson, Executive Director EIPG jane@nicholj.plus.com

events

SEPTEMBER

13–14 September 2015 – Birmingham, UK
Annual Conference 2015
www.rpharms.com

15–16 September 2015 – Munich, Germany
Pharmaceutical Freeze Drying Technology
https://europe.pda.org

28–30 September 2015 – Las Vegas, NV, USA
2015 Pharma EXPO
www.ispe.org

28–30 September 2015 – Washington, DC, USA
2015 PDA/FDA Joint Regulatory Conference
www.pda.org

29 September–3 October 2015 – Düsseldorf, Germany
75th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2015
www.fip.org

OCTOBER

5–7 October 2015 – Loughborough, UK
APS 20th Anniversary International Pharmaceutical Photostability Conference 2015
www.apsgb.co.uk

6–7 October 2015 – Amsterdam, The Netherlands
Pharmaceutical Cold & Supply Chain Logistics
https://europe.pda.org

7–8 October 2015 – London, UK
Pharma Compliance Europe 2015
www.terrapinn.com

8 October 2015 – London, UK
What's new in the approval and conduct of clinical trials in Europe?
www.jpag.org

13–15 October 2015 – Madrid, Spain
CPhI Worldwide
www.cphi.com

14–15 October 2015 – Dublin, Ireland
BioProduction 2015
http://www.informa-ls.com

21 October 2015 – Cambridge, UK
MIBio 2015: Stability of biopharmaceuticals – From molecular interactions to successful products
www.apsgb.co.uk

21–23 October 2015 – Washington, DC, USA
16th Annual Pharmaceutical Regulatory and Compliance Congress
http://pharmacongress.com

22 October 2015 – London, UK
APS Stimulating Antimicrobial Innovation
www.apsgb.co.uk

26–28 October 2015 – Hyderabad, India
4th International Summit on GMP, GCP & Quality Control
http://gmp-gcp-quality-control.pharmaceuticalconferences.com

NOVEMBER

3–4 November 2015 – Vienna, Austria
The Universe of Pre-filled Syringes and Injection Devices
https://europe.pda.org

4–6 November 2015 – Amsterdam, The Netherlands
18th APIC/CEFIC European Conference on Active Pharmaceutical Ingredients
www.gmp-compliance.org

8–11 November 2015 – Philadelphia, PA, USA
2015 ISPE Annual Meeting
www.ispe.orge

9–10 November 2015 – Basel, Switzerland
World Biosimilar Conference
www.terrapinn.com

10–11 November 2015 – Dusseldorf, Germany
PharmaLab Congress 2015
www.pharmalab-congress.de/ple_home.html

11 November 2015 – Basel, Switzerland
HPAPI World Congress
www.terrapin.com

11–13 November 2015 – Geneva, Switzerland
6th Annual World Orphan Drug Conference
www.terrapin.com

17–18 November 2015 – Copenhagen, Denmark
Outsourcing/Contract Manufacturing
https://europe.pda.org

25–26 November 2015 – Berlin, Germany
10th Qualified Person Forum
www.gmp-compliance.org

DECEMBER

1–2 December 2015 – Berlin, Germany
Vaccines
https://europe.pda.org

8 and 10 December 2015 – London, UK
GDP Symposium
www.gov.uk/government/news/mhra-symposiums-good-manufacturing-practice-gmp-and-good-distribution-practice-gdp

9 and 11 December 2015 – London, UK
GMP Symposium
www.gov.uk/government/news/mhra-symposiums-good-manufacturing-practice-gmp-and-good-distribution-practice-gdp

10 December 2015 – London, UK
Maximising Productivity in Pharmaceutical QC and Stability Testing
www.jpag.org