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EIPG: Energy, Inclusivity, Professionalism, Growth

EIPG is an active and vibrant organisation representing industrial pharmacists across Europe. This was the first thing I learned about EIPG when I joined by working as a Finnish country delegate back in 2010 in Milan, where we had a wonderful General Assembly, my first one. Ever since, I have been honoured to represent Finland as a country delegate and it has been extremely rewarding at a personal level all these years. Thank you for that!

In 2014, I was elected to the Bureau of EIPG as a Vice-President for Education and Careers. In this position, my responsibility is to collaborate with students and promote self-education, work closely with universities and other stakeholders providing courses and training for self-improvement and continuous education. Learning should not stop with a degree in pharmacy. We all know that. To be “on-board”, one must develop and improve know-how constantly. EIPG provides many good and comprehensive channels for self-development! Scientific journals, active websites and social media, as well as close collaboration with universities and organisations providing courses are some examples to be mentioned. Last, but not least, we have launched webinars over a year ago and this new way to learn from your home or your place of choice makes learning and self-development easy and free-of-charge!

Webinars, organised in conjunction with the European Pharmaceutical Student Association (EPSA), have turned into a success story. We are very proud of this, and of our valuable and fruitful collaboration. EPSA represents students who study pharmacy in Europe. This collaboration brings students and professionals together and, by establishing these connections, facilitates and encourages knowledge-sharing and networking. Collaboration with students is one of our core values. Of course, this is understandable as students are our future!

What have I learned during these years as a member of EIPG? There are many potential points to be mentioned but I will summarise a few I have valued the most. First, as a member of the Finnish Pharmacists Association (Suomen Farmasiaiitto), I am also a member of EIPG as our national organisation is a member of EIPG. This means that I have access to all the benefits EIPG offers, for example, to this excellent journal you are reading at this very moment. This is a valuable member benefit and an easy way to update yourself. Secondly, by being a part of the EIPG family, I have had the opportunity to meet several, top professionals and have had the chance to engage in fruitful talks and meetings with these people. You can easily join our network by contacting us! Also, as a member of EIPG, you get the first seat to the hottest news in the pharmaceutical industry. As this sector is constantly evolving, staying on top of the latest news is important! Thirdly, this organisation wants to do its best to ensure that we have this profession on-going also after 10, 20 and 50 years. Who knows, even hundreds of years! This professional promotion that EIPG undertakes for industrial pharmacists is something to be much appreciated and treasured!

EIPG is having its 50th anniversary this year! I invite you to join our journey alongside us!

Anni Svala
Vice-President Education and Careers

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THE EU-FMD CLOCK IS TICKING!

by Christoph Krähenbühl

The publication of the “Safety Features” Delegated Regulation on 9 February marked the start of the 3-year implementation countdown to the 2019 European Falsified Medicines Directive (EU-FMD 2011/62/EC) deadline. This article examines key requirements in detail and discusses the implications for pharma manufacturers and the other participants in the European pharma supply chain.

Christoph Krähenbühl has been involved in serialisation projects since 2006, including as project manager for the implementation of the global serialisation system for AstraZeneca, one of the early adopters and global leaders in pharma serialisation. In 2012, Christoph founded 3C Integrity, specialising in consulting and training in pharma serialisation, which joined forces on 1 January 2016 with Excellis Health Solutions to form 3C Excellis Europe. 3C’s core business is to support pharma companies – brand owners, generic manufacturers, contract packers, from large enterprises that are active worldwide to small specialised companies – in shaping up, planning and delivering their serialisation programmes. Since 2009, Christoph has also been supporting EFPIA and the EMVO in their work to prepare the industry stakeholder response to the EU-FMD requirements that is now culminating in the roll-out of the EMVS at European level and across all participating Member States.

The “Safety Features” Delegated Regulation

On 9 February 2016, the long-awaited European Falsified Medicines Directive (EU-FMD) “Safety Features” Delegated Regulation was published in the Official Journal of the European Union. This Delegated Regulation sets out the details of the “Safety Features” provisions to be implemented under the EU-FMD, such as the nature of the mandatory safety features and how these are to be used. The Delegated Regulation also confirms the medicinal products that are in scope of the regulations and what the responsibilities of the various stakeholders are in this Europe-wide medicines verification process. Most critically, the formal publication of the Delegated Regulation marks the start of the 3-year implementation timeline to achieve compliance by the early 2019 deadline that comes into force across Europe.

The key provisions of the Directive and the Delegated Regulation are well understood by now, so a brief summary should suffice. Key elements are, firstly, the requirement that in Europe all prescription drugs (with few, clearly defined exceptions, see black-/white-list approach described below) as well as some over-the-counter (OTC) products must carry safety features consisting of a Unique Identifier (UI) on each pack combined with anti-tampering device (ATD). Secondly, that medicinal products will need to be verified routinely at the point-of-dispense as well as – risk-based – in the supply chain (see Figure 1) and, thirdly, that a Europe-wide infrastructure of “repository systems” will need to be established to support this end-to-end process.

EU-FMD scope: products, participants and countries

A few points are worth highlighting, first of all the products, participants and countries that are in scope of this legislation.

To start with, the EU-FMD covers not just the 28 EU Member States but also the three European Economic Area (EEA) members, Iceland, Norway and Lichtenstein (Switzerland is likely to align as well). There is the provision that Member States that already apply serialisation to their packs, such as vignettes or Bollini in Belgium, Italy or Greece, might benefit from a deadline extended by 6 years although it is by no means certain that all three of these Member States will choose to follow this longer deadline, given the complications that would arise by the common use of shared marked packs.

What is clear is that all manufacturers of medicinal products in Europe must be ready to implement serialisation by 2019.

Figure 1: Point-of-dispense medicines verification process.
products supplying the European market are now tasked with upgrading their manufacturing capabilities to apply the UI and ATD, regardless of whether they are brand owners, contract manufacturers, generics companies or repackers/parallel traders. But manufacturers are not the only participants in the pharmaceutical supply chain that are affected: the requirement to carry out risk-based verification in the supply chain puts an obligation on wholesalers and distributors to verify and/or decommission medicinal products in situations where a higher risk is present, such as returns or shipments not directly received from the manufacturer or the manufacturer’s direct distributor. In addition, the Delegated Regulation describes a whole range of use cases where wholesalers may need to verify and decommission packs, for example, those that are exported from Europe, returns that cannot be sold, products intended for destruction, etc.

**Member States empowered**

The need to accommodate the rich variety of processes across the participating markets is reflected in the regulation’s provisions that allow Member States to define additional points in their national supply chains when the verification of the safety features and the decommissioning can be delegated to wholesalers. This includes supply to nursing homes, hospices, prisons, “universities and other higher education establishments using medicinal products for the purposes of research and education”, “armed forces, police and other governmental institutions maintaining stocks of medicinal products for the purposes of civil protection and disaster control”, emergency services, etc. How Member States will interpret this provision is not yet clear but, given the primary aim of the EU-FMD legislation to protect patients by closing all loopholes through which counterfeit medicines might infiltrate the legal medicines supply chain, it would be a safe assumption that national authorities will want to maximise the powers granted them by the European legislation. Similarly, Member States are entitled to refine the scope of application of the UI or the ATD beyond what has been defined by the Europe-wide risk-based approach: by default all prescription medicines are in scope (unless they are white-listed) and OTC medicines are out of scope (unless they are black-listed). The initial white- and black-lists that have been released along with the Delegated Regulation offer no surprises: the list of prescription medicines that are excluded contains radionuclides, medicinal gases, intravenous solutions in ATC (Anatomical Therapeutic Chemical) therapeutic subgroup B05B “blood substitutes and perfusion solutions”, contrast media, as well as homeopathic medicinal products amongst others. The proposed black-list of OTC products that will be subject to the safety features requirements is even shorter and currently consists of two strengths of omeprazole capsules. The inclusion of this product gives a good indication of how the risk-based approach will be administered: this is not only a product that is OTC in some markets but prescription-only in other markets, but omeprazole was also subject of falsification alerts in retail pharmacies in April 2013 (in Germany).

Member States, however, can extend (but not reduce) the scope of application of the UI or the ATD as follows. For the purpose of reimbursement or pharmaco-vigilance, any medicinal product subject to prescription or reimbursement can be included or – for the purpose of patient safety – the scope of application of the ATD can be extended to any medicinal product. How this provision will play out in practice remains to be seen, although what is clear is that this will, in practice, affect mainly OTC products (given that prescription drugs are by default already subject to the Europe-wide UI/ATD requirement).

**Getting ready: manufacturers, wholesalers, pharmacists**

There are several areas of activity that need to be undertaken to ready the pharmacy supply chain into Europe. The first of these has already been mentioned, the work that needs to be completed by all pharma manufacturers to establish their in-house capabilities to apply serialisation and ATD to their products. Experience from early adopters has shown that it is not a trivial adopt to equip pharmaceutical manufacturing lines with the necessary technology which is, moreover, only part of the picture: complying with the EU-FMD’s data reporting and data retention requirements means, in practice, that every manufacturer will be looking at establishing a serialisation data repository to manage this vital data securely and reliably. After all, once the EU-FMD has come into force across Europe, the definition of quality product changes fundamentally – a pack in the market without a corresponding “high quality” UI available for validation, for the duration of its shelf-life, is no longer a “good pack” and cannot be sold. But manufacturers are not the only participants in the pharmacy supply chain who will need to establish additional technical capabilities. The requirement on distributors and wholesalers that has been mentioned before, in particular, will demand investment in new technology and the introduction of additional process steps presenting a challenge that should not be underestimated.

Similarly, the key players at the other end of the medicinal supply chain, the pharmacists, are now taken to task to scan every pack of medicines that is dispensed to the public. The role that comes first to mind is that of community pharmacists where scanning technology and additional process steps now come into play, but let us
not forget that there are a plethora of other situations where similar system interactions will become part of daily operations.

**Getting ready: Europe-wide infrastructure of “repositories systems”**

All these process steps are linked to the Europe-wide infrastructure of “repositories systems” required by the FMD that will be needed to support the routine verification of all medicinal products at the point-of-dispense. The bitter pill that manufacturers have had to swallow has been the provision in the original directive stating that it is the pharma manufacturers who have to fund the establishment and ongoing operation of this infrastructure. The spoonful of sugar to help that particular medicine go down is the European Commission’s support of the approach embodied by the European Medicines Verification System (EMVS) which is currently being rolled-out across Europe by the European Medicines Verification Organisation (EMVO) that was set up in February 2015 as a collaboration between the organisations representing the main stakeholders in the European pharmaceutical supply chain – the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Medicines for Europe (formerly the European Generic Medicines Association), the European Association of Euro-Pharmaceutical Companies, the Groupement International de la Repartition Pharmaceutique (the European Healthcare Distribution Association) and the Pharmaceutical Group of the European Union.

The central piece of this infrastructure, the European Hub that the manufacturers will connect to in order to upload the UI data, was implemented in 2014 and is now in ramp-up mode, connecting an increasing number of pharma manufacturers via a standard interface to the manufacturers’ internal serialisation data repository (see Figure 2).

The companion pieces, the national repositories, are following, with the first national system – Germany’s SecurPharm – live since 2014 and connected to the European Hub since mid-2015. In order to help the remaining markets make the tough 2019 deadline – and to achieve consistency and interoperability, as well as cost-efficiency – the EMVS has selected three providers of so-called ‘blueprint’ systems (i.e. national system solutions that are fully compliant with the EMVS user requirements) that are strongly recommended to be selected as the basis for the national systems.

**EMVO and NMVOs**

So who will choose, establish and operate these national systems? This is the – formidable – task of the National Medicines Verification Organisations (NMVOs) that will need to be established in every European country. The process of setting up the NMVOs has started across Europe and will gather pace through 2016. While the detailed steps and the process of how these NMVOs will be set up will vary between countries to reflect their specific circumstances, it will generally follow a similar course.

The national representatives of the key pharma supply chain stakeholders are coming together, supported by the EMVO and the preparatory work that has been done at European level over the last few years, to reach a common understanding. In line with the legislation, the NMVO – and later the national systems – will be set up and managed by the industry stakeholders, with National Competent Authorities playing a hands-off supervisory role.

Following the establishment of the legal entity, a technical project team will be appointed that will engage with the vendors and select the most suitable technical solution. In parallel, the NMVO will need to set up an organisation to take over ownership of the national system, to manage the day-to-day operation and provide the support to the involved pharmacists, wholesalers and manufacturers who are going to rely 100% on the functioning of this infrastructure of interoperable systems that are going to be essential to the provision of safe medicines to each and every European citizen.

**Figure 2: The European Medicines Verification System (EMVS).**
NEW PERSPECTIVES FOR GENE DETECTION

by Birgit Oberleitner and Antonio Manetto

The term click chemistry, introduced by the nobel laureate K.B. Sharpless in 2001, refers to the possibility to synthesise complex molecules in a simple and rapid way. The copper(I) catalysed azide-alkyne cycloaddition (CuAAC) is the most prominent example of this group of reactions. baseclick GmbH, a member of the European training network “ClickGene” (Horizon 2020), set out to develop a new click chemistry-based assay to improve current gene detection approaches.

Introduction

Click chemistry was developed to provide an easy method to join two organic molecules with high yields in mild conditions. Probably, the best example among this class of efficient chemical reactions is the copper(I) catalysed azide-alkyne cycloaddition (CuAAC) reaction (Figure 1).

Since its discovery by M.P. Meldal and K.B. Sharpless in 20021,2, the CuAAC forming 1,2,3-triazoles became the epitome of click chemistry due to its reliability, specificity and biocompatibility. Click chemistry is largely used in different scientific areas, such as drug discovery, bioconjugation, polymer and supramolecular chemistry3. The triazole ring formed by this reaction is more than just a simple linking unit; it has shown its potential as a very important pharmacophore, widely used in medicinal chemistry4,5. This particular Cu(I) catalysed cycloaddition reaction has a great impact on, for example, chemical transformations as it allows the production of new classes of materials and libraries of molecules with applications in biological systems. Main advantages of the CuAAC over traditional bioconjugation methods can be found in its unique properties.

- The functional alkyn and azide groups are biorthogonal and, therefore, ensure pure, side product-free conjugates in biological environments.
- These regio- and stereospecific reactions are high yielded, very fast and allow for mild working conditions and tight control.

In addition, this chemical modification strategy can be used to attach novel functionalities to the nucleic acid molecule opening the way to innovative studies of unsolved biological questions. Such applications include, but are not limited to, molecular diagnostics, for example, the synthesis of DNA microarrays6, molecular probes7, antisense oligonucleotides8,9, and short-interfering RNAs10. Furthermore, synthetically modified nucleic acid derivatives are constantly used as antiviral and anti-tumour agents, and for the regulation of gene expression.

In next-generation medicine, gene therapy will play an important role by correcting the genetic causes of disease, consequently facilitating a personalised approach. Current gene therapy methods, such as viral vectors, often suffer from undesirable side effects, including insertional mutagenesis, toxicity, low efficiency and off-target cutting11. Another unsolved issue is the optimal method for delivering nucleic acids into cells and tissues. The aim of these strategies is to achieve the stable expression of transgenes in cells or tissues for the period required, in a specific region, without side effects, such as toxicity or carcinogenic transformation.

Click chemistry and the European Commission

The above described limitations will be thoroughly studied within the unique and innovative approach of the European training network ClickGene, a research project in the field of click chemistry and gene therapy. The modification, activation, modulation and repression of DNA functional domains holds an immense potential for human health applications. The main research focus of this network is to develop new knowledge and methods for genetic engineering while training a new class of young scientists in this field. To reach these ambitious goals, ClickGene bases its research on three different pillars.

- Unique gene silencing tools that interact with DNA in a fundamentally different way compared to state-of-the-art technology.
- New liposomal nanoparticles as drug delivery agents.
- Novel fluorogenic probes for epigenetic base detection in high-throughput polymerase chain reaction (PCR) assays.

Figure 1: Schematic representation of CuAAC reactions.

Dr. Birgit Oberleitner is the Head of Business Development and Marketing at baseclick GmbH, Neuried, Germany (www.baseclick.eu).

Dr. Antonio Manetto is the company’s Chief Scientific Officer and PhD supervisor in the ClickGene program.
What baseclick will add to this program

Already awarded with an international EU Initial Training Network grant in 2013 that is focused on the application of DNA nanotechnology in life sciences and biomedicine (EScoDNA), baseclick is again a full partner in such a privileged network, the Horizon 2020 Innovative Training Network. The so-called ClickGene consortium brings together leading scientists in the field of click chemistry and gene therapy. baseclick fits perfectly in this list of outstanding members, as its core technology is the click reaction, and it holds an exclusive worldwide license for the use of this click chemistry technology in the field of nucleic acids.

Gene therapy and molecular diagnostics are nowadays regarded as revolutionary tools in personalised medicine.

The cells in all organisms regulate gene expression by adjusting the gene transcripts (messenger RNA (mRNA)): the level of gene expression in a cell can be measured by the number of copies of mRNA transcript of that gene present in a sample. To detect and quantify gene expression from small amounts of RNA, an amplification of the gene transcript is usually needed. The PCR is a common method for amplifying DNA; for mRNA-based PCR the RNA sample is first transcribed into cDNA with reverse transcriptase. baseclick GmbH aims to develop a new click chemistry-based assay capable of facilitating, speeding up and improving the sensitivity of the detection of gene/transgenes in tissue. Such new methods could eventually allow the development of point-of-care methods or devices for rapid, reliable and easy detection of (trans-)genes. The main approaches followed at baseclick include the following.

Gene/transgene detection via fluorescence in situ hybridisation (FISH) assay

Active genes/transgenes are expressed through the transcription of the DNA sequence into mRNA.

These mRNA strands can be selected by their complementary DNA (e.g. PCR products or synthetic oligonucleotides), which are labelled generally with fluorescent dyes, biotin and others. Using this fluorescence in situ hybridisation (FISH) technique, it is possible to visualise mRNA synthesis within cells by fluorescent microscopy, fluorescence-activated cell sorting, fluorescent reader, etc. However, this technique still lacks from low labelling rates, low sensitivity and low selectivity of the probes. baseclick GmbH will investigate the use of multi-labelled oligonucleotides prepared by click chemistry as efficient FISH probes. Using these probes, RNA molecules will be simultaneously detected, localised and quantified at the subcellular level in fixed samples, using wide field fluorescence microscopy.

In a first approach, a pool of multi-fluorescent-labelled oligonucleotides will be designed as complementary strands of the target sequence. They will then be used in a standard FISH experiment in target cells followed...
Gene/transgene signal-amplification/detection via chromogenic in situ hybridisation (FISH) assay

In a second approach, the detection of gene activity will be achieved by simple signal amplification. Herein, a pool of multi-labelled oligonucleotides will be hybridised to their target (mRNA) before the click reaction will be performed. The signal amplification will be a result of azide derivatives of enzymes (such as peroxidase, alkaline phosphatase or horseradish peroxidase), undergoing a colour change by the addition of its substrate (ELISA-like assay), visualised under a standard bright-field microscope or ELISA reader (Figure 2).

The project ClickGene officially started in January 2015 and will continue until the end of 2018. It gave 14 Masters students the opportunity to perform their PhD thesis in another EU country. Since August 2015, a Masters student from the University of Rome Tor Vergata, Stefano Croce has been conducting his PhD project at baseclick, working on exploring the options mentioned above.

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IMMUNO-ONCOLOGY: THE NEW WEAPONS FIGHTING CANCER

by Peter Murphy and Kelly Lambrinos

There has seldom been a word used in the biotechnology space that has generated quite as much excitement as the word immuno-oncology (IO). Recent developments in anti-programmed death (PD-1)/anti-programmed death ligand 1 (PD-L1) checkpoint inhibitors, chimeric antigen receptor T cell (CAR-T) therapies and cancer vaccines have given oncologists more weapons in their often underpowered arsenal. It is apparent we could be on the verge of a treatment paradigm shift in medical history as new innovations hone the ability to harness the power of the body’s own immune system. Investigating the current developments in the field, we talk to experts in IO to give a brief overview of the current drug candidates in developments.

Peter Murphy is a senior healthcare analyst at BioPharm Insight, and is based in London. He has a first-class honours BSc degree in chemistry from Newcastle University, UK. He also undertook 3 years of medical school training before joining the BioPharm Insight healthcare analyst team. Peter has obtained the CFA Society’s Investment Management Certificate and is an associate member of the Chartered Institute for Securities and Investment.

Kelly Lambrinos is a healthcare analyst at BioPharm Insight and is based in New York. Prior to joining BioPharm Insight, Kelly held a researcher position at Innovative Science Solutions, a full-service scientific and strategic regulatory consulting firm. Kelly has a BSc in biology from the University of Athens, Greece and earned a Master’s degree in biotechnology from Columbia University. Her Master’s thesis focused on comparing the established guidelines, approval rates and length of the approval process for biologics between the US and EU.

PD1 /PD-L1

Anti-programmed death (PD-1) inhibitors and anti-programmed death ligand 1 (PD-L1) inhibitors are immunomodulators designed to inhibit the interaction between PD-L1, found on the surface of tumour or antigen-presenting cells, and PD-1, found on the surface of activated lymphocytes. This interaction blocks the negative regulation of T-cell activation and allows the immune system to attack the cancerous cells.

In 2014, Bristol-Myer’s Squibb (BMS) saw the approval of its metastatic melanoma drug, Yervoy (ipilimumab), the first checkpoint inhibitor to receive US Food and Drug Administration approval. This was followed by the approval of another BMS drug Opdivo (nivolumab), again for metastatic melanoma and then later for non-small cell lung cancer (NSCLC). It is widely regarded the largely unrivalled treatment effects seen in melanoma and lung cancer so far could be just the tip of the iceberg. The push is to not only find effective treatments for cancers with no current therapeutic options but to continually improve on those cancers already benefitting from having PD-1/PD-L1 checkpoint inhibitors on the market.

PD-1/PD-L1 inhibitors in combination with platinum doublet chemotherapy have oncologists encouraged for future potential in first-line NSCLC. One oncologist said the combination may offer a potential route for “PD-L1 negative” patients to receive first-line treatment with checkpoint inhibitors. Both Roche and Merck presented Phase 1 data for their PD-1 and PD-L1 inhibitors, MPDL3280A and Keytruda (pembrolizumab), respectively, in combination with platinum doublet chemotherapy. Both Roche and Merck have been using PD-L1 expression to enrich clinical trials as patients with higher PD-L1 expressions are more likely to respond to these drugs, said one investigator in the ongoing MPDL3280A trial. One oncologist noted future patients considered “positive” for PD-L1 expression, are likely to get single agent PD-1/PD-L1 inhibitors in the first-line setting. For low expressers of PD-L1, PD-1/PD-L1 inhibitors in combination with chemotherapy may be necessary for the cancer immunotherapy to be used in the first-line setting.

Checkpoint inhibitors in combination with radiotherapy have oncologists feeling encouraged about future lung cancer treatment potential. Oncologists noted the complimentary mechanisms had potential to improve upon current efficacy standards. As radiotherapy has an immunomodulatory effect, other types of cancer immunotherapy could also have potential in combination with radiotherapy. Experts told BioPharm Insight, the hypoxic niche, i.e. the tumour environment, suppresses the immune system, however, irradiating the tumour stimulates the immune system against the tumour by increasing dendritic cell production. By destroying lesions, radiotherapy is able to increase the expression of antigens, which in turn is likely to enhance the efficacy of the immune checkpoint inhibitors.
Strong efficacy data backing IO drugs has oncologists excited for future clinical potential in small-cell lung cancer (SCLC). However, according to some, considerable toxicities observed with combination IO therapies could limit their applicability in frailer patients. The combination appears to increase response rates as Yervoy primes T-cells, allowing them to infiltrate the tumour more effectively and generate the inflammatory phenotype that makes Opdivo more active. There is particular concern about the combination’s synergistic toxicities, particularly for patients who are performance status 2 or 3, said one expert. Whilst in melanoma it may be tolerable, the SCLC patient population is older and tend to be heavier smokers so are unlikely to tolerate the combination. Despite some early efficacy potential in NSCLC, Merck and AstraZeneca’s IO combinations face significant tolerability issues. Autoimmune toxicities in both trials made oncologists hesitant about these combinations. While there have been no fatal toxicities with Keytruda/Yervoy, the aforementioned autoimmune toxicities for both combinations would be challenging to manage. MEDI4736/tremelimunab had slightly better tolerability but not a dramatic improvement, experts

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* NDA: new drug application; Source: BioPharm Insight
adduced. As these trials have very small, carefully selected groups of patients, tolerability could even be worse in the general population, one oncologist noted.

Prior to the unprecedented fast approval of Opdivo in second-line NSCLC, BioPharm Insight reported the approval of Opdivo could spell the end for docetaxel in the second-line setting and hamper uptake of Eli Lilly’s Cyramza. Although Cyramza is unlikely to be used in patients that have received first-line Avastin due to the similarities in mechanisms, there is no doubt that Cyramza improves upon the efficacy of docetaxel when used in combination. However, there is only a marginal efficacy increase, noted one oncologist. By comparison, Opdivo greatly improves upon the efficacy of docetaxel, all experts noted.

BMS’s Phase III Checkmate 214 trial of Opdivo with Yervoy has good chances of showing significant improvement in progression-free survival in renal cell carcinoma, experts told BioPharm Insight. Yet, demonstrating an overall survival benefit will be difficult, they added. The true impact of the combination of these checkpoint inhibitors is seen in the longer response observed in a smaller proportion of patients, experts noted. Median overall survival will not be as impressive, if this subset is the minority of patients. The field for PD-1 and PD-L1 inhibitors in ovarian cancer is still nascent, experts told BioPharm Insight. Despite this, Merck’s KGAa and Pfizer’s PD-L1 inhibitor avelumab has experts cautiously optimistic about immune checkpoint inhibitors in ovarian cancer, with the hope that combinations might increase response rates. Better responses in less heavily pre-treated patients indicate that the PD-L1 inhibitor may be more efficacious earlier in the treatment process. The relatively good side-effect profile of the drug also offers encouragement, experts noted.

Table 1 gives a breakdown of various anti-PD-1/PD-L1 therapies and details the indications in which the therapies are being trialled. The stage of development and the date the results of each trial are expected are also given.

**CAR-T**

Chimeric antigen receptor T cells (CAR-Ts) are genetically engineered T-cell receptors that redirect specificity and enhance T-cell function. T-cells are extracted from the patient, modified and grown in the laboratory until there is a sufficient number for reinfusion. These CAR-T cells bind to specific surface antigens on the patient’s own cancerous cells and multiply in number to mount an immune response.

Data from several studies of the eagerly anticipated CAR-T therapies in haematological malignancies were presented at ASCO 2015. Data from a Phase I study of Juno Therapeutics’ JCAR015 in relapsed/refractory acute lymphoblastic leukaemia and in non-Hodgkin’s lymphoma, was presented, as well as JCAR014 in acute lymphoblastic leukaemia, non-Hodgkin’s lymphoma and chronic lymphoblastic leukaemia. Novartis presented CTL019 data on non-Hodgkin’s lymphoma and multiple myeloma, while Kite Pharma presented data on KTE-C19 in patients with diverse B-cell tumours. Despite very promising early stage efficacy signals, the sentiment from experts is that CAR-T therapies have become more predictable in terms of toxicity, but challenges still remain. There are some toxicity predictors, such as more cytokines, to which physicians can respond by giving patients prophylaxis, for example with steroids. However, while steroids can be used to mitigate some of the toxicity, they can also reduce the CAR-Ts’ activity because they kill T-cells. Experts highlighted cytokine release syndrome (CRS) as being the main toxicity that worries physicians, and the various

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Indications</th>
<th>Stage of development</th>
<th>Data expected/ NDA* filing date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL019</td>
<td>Novartis</td>
<td>– Adult acute lymphoblastic leukaemia</td>
<td>Phase II</td>
<td>June 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Paediatric acute lymphoblastic leukaemia</td>
<td>Phase II</td>
<td>November 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Diffuse large B-cell lymphoma</td>
<td>Phase II</td>
<td>October 2021</td>
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<td></td>
<td></td>
<td>– Multiple myeloma</td>
<td>Phase I</td>
<td>2016</td>
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<tr>
<td>JCAR015</td>
<td>Juno Therapeutics</td>
<td>– Acute lymphoblastic leukaemia</td>
<td>Phase II</td>
<td>December 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Adult non-Hodgkin’s lymphoma</td>
<td>Phase I</td>
<td>April 2016</td>
</tr>
<tr>
<td>KTE-C19</td>
<td>Kite Pharma</td>
<td>– Diffuse large B-cell lymphoma</td>
<td>Phase II</td>
<td>March 2017</td>
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<td></td>
<td></td>
<td>– Mantle cell lymphoma</td>
<td>Phase II</td>
<td>September 2017</td>
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<td></td>
<td></td>
<td>– Acute lymphoblastic leukaemia</td>
<td>Phase I/II</td>
<td>March 2017</td>
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<tr>
<td></td>
<td></td>
<td>– Chronic lymphocytic leukaemia</td>
<td>Preclinical</td>
<td>March 2016 (start)</td>
</tr>
<tr>
<td>bb2121</td>
<td>bluebird bio</td>
<td>– Relapsed/refractory multiple myeloma</td>
<td>Phase I</td>
<td>December 2016</td>
</tr>
<tr>
<td>BPX-601</td>
<td>Bellicum</td>
<td>– Prostate cancer</td>
<td>Phase I</td>
<td>June 2016 (start)</td>
</tr>
</tbody>
</table>

* NDA: new drug application; Source: BioPharm Insight
therapies appear pretty similar in that regard except for when CRS begins. CRS starts early with CD28 CAR-Ts like Kite’s KTE-C19 and Juno’s JCAR015, whereas CRS starts later with 4-1BB-based therapies such as Novartis’ CTL019 and Juno’s JCAR014. In addition, 4-1BB CAR-Ts’ greater persistence can lead to B-cell aplasias, which in turn leaves uncertainty as to whether patients will become more susceptible to infections, experts noted.

CAR-T toxicity concerns are prompting expert discussion on their potential use in the treatment of glioblastoma multiforme (GBM). One expert told BioPharm Insight, the 4-1BB co-stimulatory domain produces lower cytokine production than the CD28 co-stimulatory domain, while another said the lack of CRS or other major toxicity nevertheless seen with CD28 CAR-Ts in GBM could be due to the cells having less room to grow and multiply than they do in blood cancers like acute lymphoblastic leukaemia, given the ample space and abundance of B-cells for them to attack.

Aurora Biopharma of Cambridge, Massachusetts, is the commercialisation partner for one study of “living drug” CAR-T agent AU-105 taking place at the Baylor College of Medicine, while City of Hope in Duarte, California, is sponsoring another study of IL13Ra2-specific CAR. Fortress Biotech division Mustang Bio is the partner for the City of Hope program.

Table 2 gives a breakdown of various CAR-T cell therapies and details the indications in which the therapies are being trialled. The stage of development and the date the results of each trial are expected are also given.

### Vaccines

Cancer vaccines are intended to promote tumour antigen specific immune responses amongst the patient’s own T-cell population. Many vaccine strategies are being tested, including autologous and allogeneic tumour cell vaccines, protein/peptide-based cancer vaccines and genetic vaccines.

The Phase II overall survival benefit observed with Celldex’s Rintega in EGFRVIII-mutated glioblastoma (EGRVRVIII+ GBM), has experts believing it may demonstrate similar Phase III efficacy. However, the heterogeneity of glioblastoma raises scepticism regarding the effect magnitude, since the vaccine only targets cancer cells expressing the EGFRvIII antigen thus leaving behind a portion of the tumour without the mutation. Experts told BioPharm Insight, use of the vaccine in the frontline - when tumours are generally more homogenous before extensive genetic modifications – has a good chance of improving overall survival.

Bavarian Nordic’s vector-based vaccine for metastatic castrate-resistant prostate cancer (mCRPC) patients has triggered restrained optimism regarding the success of the Phase III trial. Expert confidence was largely based on the encouraging Phase II Prostvac efficacy and safety outcome in which the overall survival benefit was significant and on par with approved therapies. Nonetheless, they highlighted the need for appropriate biomarkers – currently lacking in mCRPC immunotherapy studies – which would enable assessing the improvement in progression-free survival. One expert also explained prior patient exposure to recently approved anti-androgen drugs in the Phase III study could improve overall survival for both treatment and placebo groups and subsequently decrease the Phase III overall survival advantage compared to Phase II.

VentiRx Pharmaceuticals’ toll-like receptor (TLR) agonist VTX-2337 (motilomod) which targets TLRs, or TLR8 in particular, has a scientific rationale to demonstrate beneficial synergistic anti-tumour effects when combined with pegylated liposomal doxorubicin in platinum-resistant ovarian cancer, according to oncologists. While they agreed it

| Table 3: BioPharm Insight’s top five cancer vaccines in development |
|---|---|---|---|
| **Drug** | **Company** | **Indications** | **Stage of development** |
| Rintega (rindopepimut) | Celldex Therapeutics | – EGFRVIII-positive glioblastoma | Phase III |
| Prostvac (Rilimogene Gafolivec) | Bavarian Nordic | – Asymptomatic or minimally symptomatic mCRPC | Phase III |
| GVAX Pancreas + CRS-207 | Aduro Biotech | – Metastatic adenocarcinoma of the pancreas | Phase II |
| Axalimogene Filolisbac | Advaxis | – Recurrent/refractory cervical cancer – HPV+-associated squamous cell carcinomas of the head and neck – HPV-associated anal cancer | Phase II/II |
| INO-3112 | Inovio Pharmaceuticals/MedImmune | – HPV-associated cervical cancer – HPV-associated squamous cell carcinomas of the head and neck | Phase II/II |

* NDA: new drug application; † HPV: human papilloma virus; Source: BioPharm Insight
was too early to comment on the Phase II efficacy outcome, they see the trial sufficiently powered to show a clinically meaningful overall survival improvement, and the side-effect profile seen so far is manageable.

Combining vaccines with a PD-1 checkpoint inhibitor reflects a sound scientific rationale which can augment the vaccine’s immune stimulatory potential in various cancers, according to experts. The concept of pairing Agenus’ Prophage vaccine with a PD-1 checkpoint inhibitor has triggered expert interest who characterised the combo as a “double-killer” with potential to improve overall survival in glioblastoma. While patients with low PD-L1 expression seemed to benefit the most from the vaccine in an investigator-sponsored Phase II study, experts believe the combo can provide benefits to patients with high PD-L1 expression as well.

Despite some concerns that the duo can lead to an immune overreaction and subsequent autoimmunerelated side effects, the Phase III trial should demonstrate an improvement in overall survival.

Combining Inovio Pharmaceuticals and MedImmune’s INO-3112 vaccine with a PD-1 checkpoint inhibitor can enhance the immune system in human papilloma virus-causing cancers, according to oncologists. Past vaccine monotherapy studies have not demonstrated adequately strong immune responses. The combination with PD-1 checkpoint inhibitors – which allow the induction of prolonged T-cell proliferation – could potentially change that, one expert added. However, he stressed the importance of establishing the vaccine’s effectiveness as a monotherapy prior to examining its potential in combination with another agent. According to another expert, administering INO-3112 following chemoradiation could trigger a subsequent immune reaction which the vaccine would further reinforce.

Table 3 gives a breakdown of various cancer vaccines and details the indications in which the therapies are being trialled. The stage of development and the date the results of each trial are expected are also given. This analysis was based on investigative news articles by Hamish McDougall in London and Manasi Vaidya and Alaric DeArment in New York.

Further reading
TRANSFORMING BIG PHARMA FORTUNES BY REPLACING PATENTS WITH PATIENTS

by Hedley Rees

Big Pharma is receiving unprecedented attention from governments, regulators, payers and patient advocacy, over such issues as sky rocketing drug prices, poor levels of research and development productivity, shortages of life-saving drugs and a general lack of consideration for the patient. This paper cuts to the chase by homing in on the underlying cause – the crack of the patent gun. The contention is that an unyielding focus on conserving remaining patent life has led to behaviours that have undermined Big Pharma’s ability to develop properly differentiated drugs.

As an alternative, the paper proposes a new model for product development, based on tried and tested methods adopted by sectors that have made massive transformations. Finally, suggestions are made as to how each key stakeholder in the industry can contribute to meaningful change for the better.

Hedley Rees is author of “FIND IT, FILE IT, FLOG IT: Pharma’s Crippling Addiction and How to Cure It” (December 2015) and "Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticals and Biologics” (February 2011). He holds a degree in production engineering from the University of Wales and an executive MBA from the Cranfield University School of Management.

After working as an industrial engineer, Hedley held senior positions at Bayer UK, British Biotech, Vernalis, Ortho-Clinical Diagnostics and OSI Pharmaceuticals before becoming the managing consultant at Biotech PharmaFlow Limited, a UK-based consultancy specialising in operations and supply chain management in the life science sector.

How is it looking for Big Pharma these days?

Big Pharma is not in good shape, neither by reputation nor in the business sense, if you listen to the media. Even taking much of it with the customary pinch of salt, the balance of evidence, certainly from a patient perspective, seems to support a damning picture.

The recent much criticised Big Pharma advertisement for opioid-induced constipation, during the Super Bowl, is a recent example of how Big Pharma companies are being vilified. Many saw the advertisement as an attempt to capitalise on the opioid epidemic that is plaguing the United States – apparently fuelled by the industry itself.

This is just one of many examples. Recent eye-watering prices being charged for new drugs, such as the Gilead hepatitis C drug, has received broad criticism from patient groups and governments alike. A search engine trawl of the pharma press will list numbers of other drugs, often for orphan indications, with hefty price tags.

US legislation is now pushing for a breakdown of the cost to develop drugs, as reported in the Los Angeles Times1. The article highlights a crucial policy idea in President Obama’s $4 trillion budget plan, labelled “Establish Transparency and Reporting Requirements in Pharmaceutical Drug Pricing2”, which the report suggests is a bureaucratic way of saying that drug companies should have to justify their high prices. The report concludes that certain drugs “cost a small fortune because drug companies can get away with charging that much”.

Less obvious, but still of great concern, are the unscrupulous businessmen, such as Martin Shkreli, CEO of Turing Pharmaceuticals and J. Michael Pearson, CEO at Valeant Pharmaceuticals, who have been snapping up out-of-patent products discarded by Big Pharma and ramping up the prices by astronomical proportions.

If we add to this the fact that estimates suggest ever-decreasing returns on investment on research and development in the pharmaceutical industry3, then something must have gone wrong somewhere, mustn’t it?

What is behind it all?

Figure 1 overleaf, reveals some stark facts. The US Government Accountability Office diagram depicts the sickening attrition rates in drug development – for every 250 compounds entering the development pipeline, only one makes it to market. Overlaid on the diagram is the underlying cause of such a failure rate – the crack of the patent gun.

Once a new molecular entity enters the development pipeline, with a robust patent lasting up to 20 years behind it, the skids are put under it. Figure 2 overleaf, is a cartoon (courtesy of Dr Graham Cox, expert witness in Find It, File It, Flog It: Pharma’s Crippling Addiction and How to Cure It), somewhat tongue in cheek, but illustrating the principle.

This haste to gain a regulatory approval to market results in the devastating failure rates. I have resorted to calling this the ‘File It’ stage of drug development, part of the industry’s overall approach to
development of medicines I have christened “Find It, File It, Flog It”. This approach involves finding a promising patented compound (Find It), placing it into a development pipeline intended for regulatory approval to market (File It), and then marketing the approved product with the utmost verve and vigour (Flog It). In mathematical terms, we have:

F1 + F2 + F3 = $\$$

Where:

- F1 = Drug discovery (Find It)
- F2 = Regulatory review and approval (File It)
- F3 = Marketing (Flog It)
- $\$$ = Megabucks

This is the equation that has driven the industry ever since the battle of the stomach ulcer drugs Tagamet and Zantac, in the 1980s, where superior marketing muscle was reported to have won the day for Glaxo’s Zantac over SmithKline French’s Tagamet.

**So how does this relate to the issues we see today?**

This modus operandi has resulted in a very clear chain of events. The rush to register a pipeline of products for market, maximising remaining patent life, results in what we now know as the valley of death. That has spawned the patent cliff, whereby significant revenues are lost once the patent runs out. This, sadly, is not the end of it. Dependence on the crack of the patent gun has also driven two crippling behaviours that have been endemic in Big Pharma for over three decades; dropping out-of-patent products and outsourcing critical assets, both people and facilities.

The former has resulted in eighty percent plus of products sold today resting in the hands of generic companies, which have been growing like topsy. The large, research and development-based pharma companies are now having to target increasingly shrinking patient populations, charging swinging prices in an attempt to maintain blockbuster returns. Hence, we have the commotion from US politicians and many other industry stakeholders.

This would not have been so damaging if the Big Pharma companies had held onto the people and facilities involved in developing new products for market; but that hasn’t been the case. Fuelled by blind optimism over the power of the patent, these critical assets were allowed to go and the consequence, Big Pharma companies now have to depend heavily on third parties to develop their products. Professional as these third parties are, they do not have the skin in the game that clinical trial sponsors and product license holders have.

Some readers may be thinking at this point that other sectors have successfully used an outsourced approach with good results; but in the words of that well-known song “it ain’t what you do, it’s the way that you do it”; and pharma hasn’t done it very well.

This is what Professor Andrew Cox, world renowned expert in procurement and outsourcing best practice, has to say on the matter.

> “Unfortunately for the major Pharmaceutical companies that used to be the ‘channel captains’, who controlled the industry and all of its major supply chains through a judicious control internally of critical assets, there has been considerable evidence of very poor practice in outsourcing in recent years.”

We also have the example of Boeing, which dabbled with increased levels of outsourced development for the Dreamliner and suffered a reported 18-month delay, as well as much pain and suffering, for its troubles. This is what Peter...
Cohan, author of “You Can’t Order Change: Lessons from Jim McNerney’s Turnaround at Boeing” had to say in his book.

“But by outsourcing both the design and the manufacturing, Boeing lost control of the development process.”

At this point, I am drawing the conclusion that for Big Pharma to reverse its fortunes, massive change is required.

**What should change look like?**

We must turn product development on its head, as other sectors did very successfully in the 1950s and 1960s. They had similarly been throwing their products ‘over the wall’ into the system consuming their goods, until the Japanese revolution took place. Companies, such as Toyota, Honda, Nissan and Matsushita led the charge to place end-user value at the forefront of their missions in life. The results were startling as we all now know.

The same has to happen in Big Pharma, the alpha male of the industry. Healthcare professionals and the patients they serve have to become the central focus of development activities – they must be deeply involved and consulted on the indication under consideration, at the earliest stage, even before pre-clinical assessment takes place. It is not sufficient to involve only a small number of investigators, appointed by the pharma company, in trialling drugs; attrition rates in the industry prove that.

Once this engagement takes place and the value proposition established, prototypes must be built and pressure tested before progressing into commercial development. Maximum use of predictive technologies must be employed, using in silico and ex vivo technologies. These methods have moved on unrecognisably in recent years, but the industry is reluctant to apply them in any meaningful way.

To achieve the above, discovery research scientists need to stay and help develop the prototypes, rather than move on to ‘discover’ new compounds, oblivious to any issues arising from their previously orphaned offspring. Only those prototypes passing muster under the scrutiny of a multi-disciplinary review team (including the healthcare professionals), would move forward into development for end-user markets. Figure 3 overleaf, shows a schematic comparing the current and proposed new approach.

Readers will notice the iterative nature of the proposed approach, whereby candidate compounds are designed, tested and optimised and then subjected to clinical validation using predictive technologies. The power of this approach is the depth of scrutiny each compound receives, weeding out potential failures at the starting gate.

Once on the road to development for commercial markets, a ‘production system’ approach must be taken, whereby the target destination is a product in end-users’ hands, not the statistical end-point of a clinical trial, as it is today.

This means that a much broader range of skills, including those derived from the world of engineering, must be recruited and applied; also leadership in taking the product to market will be a single continuum, rather than a two-tier approach as it is currently. This severely challenges the industry’s historic tendency to withhold allocation of resources until the later stages of clinical trials. However, this has only come about because attrition rates are so high. The solution is to reduce the attrition, as suggested here, rather than withdraw the resources.

**What can stakeholders do to help?**

It would be naïve to think this level of change would be easy; it certainly was not for the other sectors discussed above. There is also no sign of one such as Toyota’s Taiichi Ohno emerging from the ranks of Pharma CEOs. We, therefore, contend that it is incumbent upon key stakeholders to catalyse the change. Below are some suggestions, radical in part, that may be considered as a useful starting point.

**Governments**

The underlying root cause of the issues lay in patent laws, as applied in pharma. Patenting a molecule with no evidence that it can be converted into a medicine is ridiculous. Along with changing these laws to require more evidence for patent registration, governments should also seek post mortems on failed drugs to prevent predictable ‘no hopers’ being pursued. The Italian Medicines Agency is already showing innovative thinking by...
focusing on success in drug development, by asking for its money back if drugs do not meet the potential claimed, as reported in BloombergBusiness\(^5\).

If these things were developed, it would encourage drug developers to collaborate with healthcare professionals to gather the necessary evidence and avoid the failures.

**Regulatory authorities**

Regulation is vitally important to patient safety, but there is a risk that it can sometimes confuse the interface between healthcare professionals and those developing drugs. We should bear in mind that a ‘highway code’ for medicines is essential, but it does not automatically lead to safe drivers. Regulators should increasingly become facilitators of interaction, rather than enforcers of rules.

**Healthcare professionals**

Healthcare professionals must begin to view themselves as the ones in control and start with a proactive rejection of sales representatives at the door, if they have not already done so. They must cease dependence on pharma-derived statistical evidence supporting one-sided marketing claims, and anything else that detracts from the patient/provider interface. They should then push for early involvement in development of the drugs they prescribe, if not themselves personally, then their professional bodies.

**Patients**

Patients should ask their doctors the dumb questions and expect sensible answers. If the answers don’t work, they should keep on with the questions. As is often said, there is no such thing as a stupid question and the few minutes of embarrassment in asking the question could avoid decades of suffering by remaining silent. They should also support their healthcare professionals in pushing back on pharma sales speak.

**Pharma CEOs**

The final message is for CEOs of Big Pharma companies. Your predecessors discovered a wonderful way to build businesses, which could not be summed up better than by repeating the words of George W. Merck, founder of Merck:

“We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been!”

**References**

January Bureau meeting
The arrangements for the 50th Anniversary General Assembly were discussed. The meetings will be held in the headquarters of the Ordre National des Pharmaciens. A Friday Symposium will be held with the title “1965–2015 – How medicines have changed over 50 years”. Working groups at the General Assembly will discuss: “The impact of the Delegated Act on Falsified Medicines Systems in the Pharmaceutical Supply Chain” and “The job of the industrial pharmacist in 2026”.

Implementation of the Delegated Act on Falsified Medicines
Maurizio Battistini (EIPG Vice President European Affairs) and Frank Peeters (President UPIP-VAPI) represented EIPG at a stakeholder meeting organised by the European Commission to discuss the Commission Delegated Regulation No 2016/161 published in the Official Journal on 9 February. The main speaker was Dr Patrizia Tosetti, the Policy Officer of Unit B4 in Directorate General for Health and Food Safety. The document sets out the characteristics and technical specifications for the unique identifier to be applied by manufacturers and re-packagers and its verification by pharmacies/retailers and wholesale distributors. The unique identifier, the tamper evident devices, the repository system to be used by stakeholders and the use of the bar code scanners that will trace and identify each pack of medicinal product released into the European market were discussed. Hospital and community pharmacies will have the obligation to decommission packs on the repository system at the time of dispensing. The safety features will be mandatory for products listed in Annex I and II of the Regulation, effectively all prescription products and omeprazole but excluding some hospital only products.

In response to a question from EIPG, the European Medicines Verification Organisation confirmed that the repository system will automatically block each batch at its expiration date. The European Hospital Pharmacists Association indicated their concern over the amount of time that will be involved with decommissioning, which will significantly impact work practice. In response to a question on how the Regulation will be applied to medicinal products considered “over the counter” in some countries and “prescription only” in others, the reply was that the law regulating the product in individual Member States will be applied.

The provisions apply to all Member States from 9 February 2019 except Belgium, Italy and Greece (where there are existing measures applied to medicinal products) who must comply by 9 February 2025.

A link to the slides presented at the stakeholder meeting is given on the EIPG website under News – From the Bureau.

Claude Farrugia (EIPG Vice-President Communications) presented an EIPG perspective on the Verification of Medicinal Products in Europe at the UPIP-VAPI Seminar on the Implementation of the Act on Falsified Medicines. His comprehensive slides are published on the EIPG website under Media Library – Presentations.

Moglynet (European joint doctorate project)
The student recruitment phase of this 3-year project has been completed and twelve PhD students have been selected and enrolled in their home institutions from 1 February.

The summer school time-table and potential speakers have been discussed. Anni Svala, EIPG Vice-President Education and Training, is a member of the project’s supervisory board and is advising on the industrial expectations of students and the dissemination of the project results. Anyone interested in assisting with this project, for example by lecturing to the postgraduate students at a summer school, should contact Anni Svala (anni.svala@gmail.com).

February joint webinar
EIPG/European Pharmacy Students’ Association
Minna Matikainen, GSK’s Commercial Manager for Respiratory Business Unit in Finland, and Marien Rouchon, MSD’s former Product Manager for Oncology in France, discussed marketing in the pharmaceutical industry. Seventy participants were on-line from various European countries.

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

Visit the website: www.industrialpharmacy.eu for PharmaTV and Quality by Design videos, Regulatory Review, Financial Pharma News and other current items concerning Industrial Pharmacy

www.industrialpharmacy.eu
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.

**USA**

Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants – Guidance for Industry

This final guidance reflects a unified approach to all formal meetings between sponsors or applicants and the Food and Drug Administration (FDA) for biosimilar biological products. This guidance is intended to assist sponsors or applicants in generating and submitting a meeting request and the associated meeting package to the FDA for biosimilar biological products.

Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base

This draft guidance provides recommendations to pharmaceutical companies interested in participating in a program involving the submission of chemistry, manufacturing and controls (CMC) information containing emerging manufacturing technology to the FDA. While the implementation of emerging technology is critical to modernising pharmaceutical manufacturing and improving quality, the FDA also recognises that innovative approaches to manufacturing may represent challenges to industry and the Agency. Companies may have concerns that using innovative technologies could result in delays while FDA reviewers familiarise themselves with the new technologies. The FDA’s Emerging Technology Team will facilitate the review of submissions involving manufacturing technologies likely to improve product safety, identity, strength, quality and purity.

**New Requirement for Electronic Submission of Drug Master Files (DMFs)**

This requirement was first published on 5 May 2015 and comes into force on 5 May 2017. The following should be noted.

- There is no requirement to resubmit anything that has already been submitted in paper.
- If you choose to resubmit your entire DMF upon conversion to an electronic common technical document (eCTD), this is acceptable but it is not required.
- You may choose to use either version of eCTD Module 1 (DTD version 2.3 or 3.3).

**Europe**

Safer use of medicines by preventing medication errors

Medication errors can occur for many reasons at the time of prescribing, dispensing, storing, preparation or administration of a medicine. It is estimated that among hospitalised patients, 18.7% to 56% of adverse events are caused by medication errors.

This good practice guide on medication errors complements other existing guidelines published by the European Medicines Agency (EMA). It consists of two parts.

- How suspected adverse reactions that are caused by medication errors should be recorded, coded, reported and assessed. The goal is to improve reporting and to learn from medication errors for the benefit of public health.
- Key principles of risk management planning in relation to medication errors. It describes the main sources and types of medication errors and proposes options to minimise the risk of medication errors throughout the lifespan of a medicine.

In parallel, the EMA has launched a webpage highlighting measures recommended by the Agency to prevent medication errors for specific medicines.

**New strategy to fight antimicrobial resistance**

The EMA has released for public consultation a new strategy on antimicrobials which has been adopted by its Committee for Veterinary Medicinal Products. Antimicrobial resistance is a global problem affecting both animal and human health. This strategy sets clear objectives to help combat the threat of resistance which may arise from the use of antimicrobials in animals.

Guidelines for using the test for bacterial endotoxins

The European Directorate for the Quality of Medicines (EDQM) has published a document Comments Concerning Revised Texts Published in Supplement 8.8 to the European Pharmacopoeia.

The general chapter on bacterial endotoxin has undergone a general revision with the following scope.

- A section has been added to include aspects to be considered when establishing an endotoxin limit for a specific substance or product.
- Reference to General Chapter 2.6.30. Monocyte-Activation Test as an alternative to the rabbit pyrogen test.
- Reference to the use of alternative reagents to the limulus amoebocyte lysate, such as recombinant factor C (this practice avoids the use of animal species).

A number of additional specific points have been included and the structure of the general chapter has been modified to improve its clarity.
Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

This new chapter will be published in the 9th Edition of the European Pharmacopoeia and will become effective on 1 January 2017. The chapter is, however, for information only and is not legally binding. It includes sections on the risk, origin, production of and quality requirements for raw materials of biological origin used for the production of cell-based and gene therapy medicinal products for human use.

Changes in contact details to be notified to EDQM

It is important to keep the details of the official contact person up-to-date. It is the responsibility of applicants and holders of certificates of suitability (CEPs) to ensure that this is done.

The EDQM communicates only with the official contact person appointed in a CEP application and, to protect confidentiality, does not share information with other people. Not receiving communication from the EDQM may lead to the closure of an application or to the cancellation of a CEP.

Optimising the presentation of medicines for Alzheimer’s disease

The Medicines and Healthcare Products Regulatory Agency is working with the pharmaceutical industry to optimise the way medicines for the treatment of Alzheimer’s disease are presented. All these medicines will include the days of the week clearly on the blister packs. This may enable patients to retain independence in taking their medicines.

International

Japan Data Integrity

Following the discovery in late 2015 that Chemo-Sero-Therapeutic Research Institute (Kaketsuken), a manufacturer of blood products and vaccines, had been adding unauthorised ingredients to its products and falsifying data, an investigative panel found that the institute had been doing so for more than 40 years. As a result, Japan’s Ministry of Health Labour and Welfare (MHLW) has issued a demand to marketing authorisation holders for them to confirm that the current actual manufacturing process complies with the approved regulatory files in Japan.

All manufacturers (drug products, active pharmaceutical ingredients, intermediates) listed in the regulatory files in Japan are in scope.

Confirmation should be completed by reviewing manufacturing batch records and interviewing operators, etc. This review should be made by an independent department from manufacturing, such as a quality unit.

Confirmation at domestic manufacturing sites should have been completed by 18 February 2016 and should be completed by 22 March 2016 at foreign manufacturing sites. If there are clear reasons, the due date may be extended subject to MHLW agreement.

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

CALL FOR ARTICLES

Dear Colleague

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We are currently seeking new articles for future issues of the journal and would like to invite you to contribute an article or review paper on any aspect of industrial pharmacy to the journal. All issues of European Industrial Pharmacy are indexed by both Scopus and Embase and thus are available through the listings for any other industrial pharmacist internationally.

Please contact the Managing Editor, Sue Briggs (suze.briggs@sky.com) for further information or submissions.
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** modified EN 13697 sporicidal surface test - log 2 reduction achieved

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Cheering on qualified persons

Qualified persons (QPs) enjoy high status and salaries. The demand for QPs is urgent; more QPs are retiring than are qualifying.

Of course, being an industrial QP is not every pharmacist’s cup of tea. But other roles have their disenchantments: the same four walls surrounding a community pharmacy, “frozen” hospital salaries, company regulations, diabolically low fees as an independent community locum or “heart-sink” patients. Would they prefer more variety and global travel as, effectively, an EU “quasi-governmental” official? Before retiring, my colourful portfolio included medicines for Atlantic salmon, sheep, goats, rabbits, chemical manufacturing and human lyophilised antibiotics and investigational medicinal products. Would such variety compensate pharmacists for reduction in face-to-face patient contact, prescribing, injecting ‘flu’ vaccines and so on?

After, say, a decade’s employment, industrial pharmacists could consider going into consultancy: being their own bosses – or become “poachers turned gamekeepers”, working for the Medicines and Healthcare Products Regulatory Agency or the Veterinary Medicines Directorate. As medicine inspectors, they would gain pensions, security and sufficient clout to close factories. Being sent all over the world, all expenses paid, is probably not a problem, on balance.

I am puzzled why, especially with so many more MPharm graduates, more pharmacists do not become QPs. That possibility remains their birth right. Good quality medicines are any pharmacist’s raison d’être.

The QP viva has assessors from the Royal Pharmaceutical Society, Royal Society of Chemistry and the Society of Biology. The application fee is £600; pass rate is about 70%. Pharmacists gain a certificate and join the eligibility list of the Royal Pharmaceutical Society.

The door is open

You will know that pharmacists only need 1 year of practical industrial experience; chemists and biologists need 2. Chemists and biologists, of course, make splendid QPs. Indeed, there is much mutual collegial respect and positive synergy from having somewhat different background strengths. A pharmacist QP, for example, reviewing the efficacy of cleaning between batches and possible cross-contamination, will instantly spot active pharmaceutical ingredients that, for example, have low therapeutic doses or are teratogenic. His or her antennae will quiver.

Experience in hospitals (even in a specials manufacturing unit) seldom counts. Pharmacists must practise at a site that requires a marketing authorisation for at least one medicine.

However, the pharmaceutical industry is difficult to enter. One entrance route is to first work in National Health Service hospital production (including aseptic) and/or (non-clinical) quality control/quality assurance for, say, 5 years. That will turbo-boost chances of success.

Use it or lose it

But one statistic astonishes me and even leaves me a little sad. Only 6% of viva candidates are pharmacists. Wait much longer and actually approving medicine batches will become something that pharmacists just no longer do; biologists and chemists certify instead. An analogy is that some Australian aboriginal tribes are reluctant to “go walkabout” in their desert. Their reason is that they have not, as caretakers, looked after their land well enough and the spirits – which are real to the tribe – have become stronger. Some spirits may kill travellers.

My fear is that industrial knowledge among pharmacists is becoming so rare that pharmacists may lose their confidence to follow a career in the pharmaceutical industry, let alone become QPs.

Another threat looms. A referendum about whether the UK should remain a member of the EU or leave the EU is scheduled for 23 June 2016. Suppose the vote were to leave. Although, presumably, exit would take quite some time to affect British QPs and negotiations would be detailed, my hunch is that, sooner or later, British QPs could, effectively, cease to exist. That is perhaps worth bearing in mind when you cast your vote.

Malcolm E Brown
**events**

**APRIL**

4–7 April 2016 – Glasgow, UK
10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
www.worldmeeting.org

11–12 April 2016 – Ware, UK
APS Industrial Insights 2016
www.apsgb.co.uk

12–13 April 2016 – Venice, Italy
Parenteral Packaging
www.pda.org

12–13 April 2016 – Dusseldorf, Germany
2016 Pharma Congress: Production and Technology
www.pharma-kongress.com

17–21 April 2016 – Phoenix, AZ, USA
RDD 2016
www.rddonline.com

19–20 April 2016 – Chicago, IL, USA
12th Annual Medical Device Compliance Congress
www.cbinet.com

20–21 April 2016 – Chicago, IL, USA
World Drug Safety Americas 2016
www.healthnetworkcommunications.com

20–22 April 2016 – Washington DC, USA
7th Annual The Global Orphan Drug Conference & Expo USA

22–23 April 2016 – London, UK
The Clinical Pharmacy Congress – The Future of Clinical Pharmacy
www.pharmacycongress.co.uk

**JUNE**

1 June 2016 – Leeds, UK
Symposium of Digital Design of Drug Products - Joint meeting with the British Association of Crystal Growth
www.pda.org

1–2 June 2016 – Vienna, Italy
World Pharma MES Congress 2016
www.healthnetworkcommunications.com

5–6 June 2016 – Bethesda, MD, USA
2016 ISPE Quality Metrics Conference
www.ispe.org

6–8 June 2016 – Bethesda, MD, USA
2016 ISPE Quality Manufacturing Conference
www.ispe.org

7–8 June 2016 – Berlin, Germany
Advanced Therapy Medicinal Products
www.pda.org

13–15 June 2016 – Istanbul, Turkey
EUFEPS Annual Meeting 2016
www.eufeps.org

14–17 June 2016 – Boston, MA, USA
15th Annual World Preclinical Congress
www.worldpreclinicalcongress.com

20–21 June 2016 – Baltimore, MD, USA
2016 PDA Biosimilars Conference
www.pda.org

22–23 June 2016 – Basel, Switzerland
Pharmaceutical Packaging and Labelling Summit
www.pharmapackaginglabelling.com

23 June 2016 – London, UK
Practical implementation of ICH Q3D; challenges and solutions
www.jpag.org

27–29 June 2016 – Valencia, Spain
5th European Biosimilars Congress
http://biosimilars-biologics.pharmaceuticalconferences.com/europe

28–29 June 2016 – Berlin, Germany
1st PDA Europe Annual Meeting
www.pda.org

**JULY**

18–20 July 2016 – Berlin, Germany
5th Annual European Pharma Congress
http://europe.pharmaceuticalconferences.com

**AUGUST**

4–6 August 2016 – Manchester, UK
2nd World Congress on Biopolymers
http://biopolymers.conferenceseries.com

15–16 August 2016 – Toronto, Ontario, Canada
5th International Summit on GMP, GCP & Quality Control
http://gmp-gcp-quality-control.pharmaceuticalconferences.com

**MAY**

2–5 May 2016 – Athens, Greece
3rd Annual International Conference on Pharmaceutical Sciences
www.atiner.gr/pharmako

12 May 2016 – London, UK
Sterility assurance best practice for aseptically manufactured products
www.jpag.org
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