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ISSUE 59 • NOVEMBER 2018

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features

regulars

Cover photo: View of the Armadillo Auditorium at the Scottish Events Campus (SEC), Glasgow, venue of the FIP 2018 Congress. Courtesy of SEC and Peter Sandground.

INDUSTRIAL PHARMACY is an official publication of the Industrial Pharmacy Section of the FIP
The FIP represents 4 million pharmacists worldwide

INDUSTRIAL PHARMACY

Issue 59 November 2018

ISSN 1741 4911

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Industrial Pharmacy is published quarterly by:
Euromed Communications
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Liphook, Hampshire
GU30 7SB, UK

Tel: +44 (0)1428 752222
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Email:
publisher@euromedcommunications.com

www.industrialpharmacy.eu
Annual subscription rate £90

Indexed by:
Scopus & Embase

EUROMED communications

editorial

Expanding the horizons of the *Industrial Pharmacy* journal

The world is changing at an increasingly rapid speed. New medicines are more and more specialised (personalised), and this often comes at a higher price. Real world data (RWD) is then required to show that the new medicines produce the health gains promised. And with the high access to information provided by the media and the internet, patients are aware of and demand the new medicines without delay, often before they are approved!

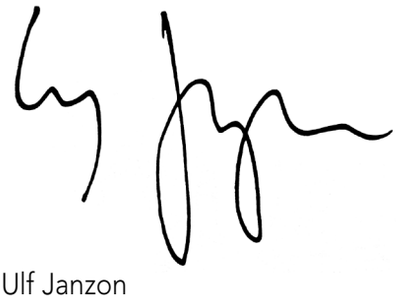
Despite these advances, a lack of essential medicines is still a reality in many parts of the world. Not only is the financial situation in many countries such that it is difficult or impossible to afford all the medicines needed, but also within an individual country it is not uncommon to find that inequalities exist between different sections of the population.

To make it even more complicated the expectations to be healthy are increasing and medical care is seen as a cure to almost everything. The reality is that in many countries large groups live a life that is far from healthy. Smoking, abuse of alcohol/narcotics, lack of physical exercise and obesity are important risk factors to health, resulting in illnesses like diabetes, depression and cancer, and these are risk factors that can be avoided or reduced by the individual.

In whatever way you look at the current situation pharmacists are in a unique position to guide the developments in a positive direction. From research and development of new medicines, to advising on how best to use these medicines, collecting experience (RWD) from patients, and helping patients live a healthier life, including vaccination and other preventive medicines, but also by advising and supporting a healthier life for the individual.

To achieve this ambitious vision of the pharmacist's role we must work across all related disciplines, be it in practice, science or education, community pharmacy, in industry or in regulatory sciences. A first step is to increase the understanding of what other pharmacists do, not only in other countries but also in other parts of the profession. The FIP and the FIP Congress plays an extremely important role.

As incoming President of the Industrial Pharmacy Section I am very happy that the *Industrial Pharmacy* journal will be distributed to all FIP members worldwide, providing an opportunity to improve the understanding of what industrial pharmacists do. The journal also covers other areas of pharmacy and hopefully, this increased shared knowledge will work both ways throughout the pharmacy profession.



Ulf Janzon

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INDUSTRIAL PHARMACY SECTOR REPORT FROM THE 2018 FIP 78th WORLD CONGRESS

by Gabrielle Wiederkehr and Anna Laven

The 2018 annual FIP Congress of Pharmacy and Pharmaceutical Sciences was held at the Scottish Events Campus (SEC) in Glasgow between 2-6 September. This year the Congress hosted two full sessions dedicated to the Industrial Sector of the FIP. We provide reports on each of these sessions by the session chairpersons.

Gabrielle Wiederkehr is Managing Director, ACCESS Regulatory Consulting, Switzerland, and Executive Committee Member of the Industrial Pharmacist Section of the FIP.
Anna Laven is a Researcher and Trainer at Pharmabrain GmbH, Germany, and Executive Committee Member of the Industrial Pharmacists Section of the FIP.

Breaking down barriers to patient access – how to bring stakeholders together

by Gabrielle Wiederkehr

Introduction

There are several barriers to effective access to medicines across the pathway from drug development through regulatory approval to initial treatment and proper patient management. The nature of those barriers differs substantially in various parts of the world. In emerging markets, they include low awareness of patients and healthcare professionals of the right treatments or the benefits of new medicines, inadequate accessibility to care as often there are not enough hospitals, diagnostic equipment or trained medical staff, lack of availability of medicines in local pharmacies or hospitals and affordability.

In the industrialised world, market access used to be assured if a pharmaceutical product was safe, effective and of good quality. Today, as private and government payers grow more powerful, market access to innovative new drugs is far more challenging due to the need to contain rising costs, the proliferation of competing drugs in the same therapeutic area, reliance on evidence-based medicine and health technology assessment which drive payer decisions. In addition, growth of the generics segment and the emergence of biosimilar drugs have given payers additional choices when deciding which products they will cover.

This complex topic was competently addressed by four speakers representing different stakeholders.

Presentations

The first speaker, Sola Solarin, Savanté Consulting, Nigeria, talked about barriers to market access in emerging markets. According to an informed estimate access to medicines globally is 67%. When disaggregated, emerging market have an average of 50%. The WHO definition of "Access to Medicines" reads: "Access to medicines is defined as having essential medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk from the homes of the population". Clearly this is not met in most of the emerging markets. A number of factors have been identified as responsible for poor access to medicines in emerging markets. They include poor infrastructure and accessibility, sub-optimal supply chain management, infiltration of distribution system by falsified medicines, cost/economics aspects as payment for healthcare is often out of pocket and pricing systems are not transparent. Also, policy choices may limit medicines access and long patent protection and exclusivity periods granted to the originator companies, which block availability of generics.

Hermann Schulze, Mallinckrodt Pharmaceuticals Ltd, Switzerland, pointed out that fast access of innovative medicines is not only of big interest to patients – it is also of big interest to the pharmaceutical industry. Drug development and obtaining marketing authorisations are the time-limiting hurdles to pass before medicines become available to patients, which can take up to 10 years or more. Additionally, the time required to provide evidence that a new medicine is safe and effective for treatment up to market approval can take about two years; a time when patients cannot benefit from the new medicine and a time when the pharmaceutical company cannot receive any return on its investment. Various tools were described, which regulators have developed and which help to expedite rapid access of new innovative medicines. For example, the US FDA offers fast-track designation, accelerated approval, priority review and break-through designations and the EMA accelerated assessment, PRIME and parallel EMA/EUnetHTA scientific advice.

Richard Huckle, Pope Woodhead & Associates Ltd, UK, highlighted the benefits and risks of early

Photo: Peter Sandground

Figure: Aerial view of the SEC complex with spire of Glasgow University in the background

market access. The evolving early access pathways require multiple stakeholder interactions (including regulators, HTA bodies/payers and patients) with the aim to facilitate and accelerate development, marketing authorisation and access of medicines to patients in areas of high unmet needs. Early access decisions are particularly challenging due to the limited clinical evidence available on the benefit–risk and relative (cost-) effectiveness of innovative drugs for treating unmet needs. For severe diseases with unmet medical need, regulators increasingly accept clinical trial packages that lack large Phase 3 comparative randomised controlled trial data and use intermediate surrogate endpoints to demonstrate a positive benefit-risk profile. HTA bodies/payers want to see that a new product delivers clinically meaningful benefits (i.e., improvement in quality-of-life and morbidity/mortality endpoints that are directly relevant to patients), as well as in more diverse, real-world settings. Patients and caregivers demand sufficient information to make informed benefit/risk treatment decisions and manage risks effectively. So clearly accelerated access of promising drugs that fulfil an unmet medical need often results in tradeoffs of the current system and ongoing initiatives from patient and other stake-holders perspectives.

The last speaker, Katja Hakkarainen, EPID Research, Sweden, discussed the contribution of real-world evidence (RWE) to faster access to medicines for patients. RWE research and real-world data are used to further investigate a medicine and its effects and use once the medicine is on the market. The used data sources include electronic health records, prescription databases, patient registries, and claims databases. RWE studies are increasing in the pharmaceutical industry, which is reflected in the number of studies registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). RWE studies by the pharmaceutical industry are typically conducted to investigate a safety concern raised from pre-clinical and clinical studies or to study the effectiveness of the medicine in real-world clinical practice. RWE studies also enable investigating medication use in patient groups excluded from trials, such as pregnant women and children. Furthermore, RWE supports health economic evaluations and the development of treatment guidelines. The early access initiatives of the European Medicines Agency (EMA) and the US FDA provide an opportunity to bring new, innovative medicine available to patients faster than through the normal approval process. As part of the early access initiatives, the authorities require RWE to complement evidence from clinical trials.

The overall conclusion of the session was that over the last years all stakeholders have been pursuing many approaches and have made a lot of progress in facilitating global access to medicines in a timely manner. Nevertheless, there was agreement that further efforts are required to improve existing tools and introducing similar programs particularly in developing countries.

Strategies to improve adherence – technology needs communication.

by Anna Laven

Introduction

Life-saving drugs are fully effective only when they are prescribed for the right patient and if patients use

Delegates at one of the sessions answering the question "Do you think that you can influence the patient's adherence to medication?"

them correctly. This includes the responsible use of the drug and often life-long therapy adherence. The reasons why patients are unable to use drugs correctly vary enormously. Additional and individual support, e.g. via patient-centred counselling or appropriate (digital) devices are therefore required to foster adherence. Community pharmacists are not the only pharmacists that can enhance adherence - hospital pharmacists and the pharmaceutical industry also have their contribution. In this session, different and innovative ways and concepts were presented and discussed.

Presentations

The first speaker was Bernard Vrijens from Belgium. He is the founder of the European Society for Patient Adherence, Compliance and Persistence. Bernard stated that ideal adherence might be the goal but is rarely the reality. Even when patients are taking the same percentage of prescribed doses, the reason for missed doses might be very different, such as drug holidays, weekend stoppers, or patients who have problems with evening doses. Depending on whether patients do not initiate the treatment, or have problems implementing it into daily practice, or stop the treatment prematurely, different digital devices might be helpful to support adherence. This is important, as non-adherence leads to treatment failure, disease progression or acute events and subsequently to more complex treatments that would foster even more non-adherence.

Adherence is the key to therapeutic success, as drugs do not work in patients who do not take them. One reason for missing adherence might be drug-related problems that are linked to physiological factors such as age, sex, weight and disease status, or environmental factors such as co-administered drugs, diet, tobacco use and chemicals. They also occur more often if the patients have a corresponding genomic background, as variation in genes are related to drug metabolic enzymes and drug transporters that control the number of active drug metabolites in the system. In that situation, a standard dose could lead to an excess, to inefficacy or ordinary efficacy, depending on the patient's genes. When drugs are not processed at the expected or average rate, it leads to adverse side effects or lack of efficacy. Examples are poor codeine metabolisers, or increased pantoprazole or escitalopram metaboliser.

John Papastergiou from Canada is a community pharmacist specialising in pharmacogenomics. He outlined the basic principles of pharmacogenomics, explained strategies for implementation of pharmacogenomic services into community pharmacy practice and explored real-world case examples that highlighted the improvement in adherence from one of the world's first community pharmacy-directed pharmacogenomic clinics.

Kerstin Neumann from Johnson and Johnson Germany showed how using QR Codes for patient education works. She explained that the pharmaceutical industry plays a significant role in supporting adherence and that this work needs to be reinforced by the community pharmacist to reach the patient.

The next speaker was Sheila Ryder from Trinity College in Dublin. Sheila presented smart devices for adherence, and the do's and the don'ts that pharmacists need to take into account when changing to digital. Many hundreds of apps already exist, but only a few have been evaluated in detail regarding adherence functionality, medication management functionality, connectivity, health literacy considerations and general features. Factors affecting engagement, tailoring content to subgroups and considering health literacy attributes were considered as a clear "Do" as they reduce barriers, connect with the patient's identity and sustain motivation. However, we should not assume that smart devices can replace direct counselling.

Stephen Chapman from Keele University was the next speaker. He introduced the audience to virtual reality. Avatars have been built at

Keele University that can be used in the training of counselling skills. For example, an avatar can mimic a patient with atrial fibrillation who sees his pharmacist in order to get his anticoagulant drug. The pharmacist then needs to decide which questions to ask and what advice to give. The consultation follows a specific algorithm and is built to foster responsible use and adherence. At the end of the consultation, the avatar (representing the patient) gives feedback to the pharmacist on the consultation and suggests improvements for the future.

The last speaker was Anna Laven who presented the structured pharmaceutical counselling process. Due to time restraints, pharmacists all over the world need to develop a strategy to counsel their patients effectively and efficiently at the same time. Anna Laven has developed the "Pharmaceutical Action Plan". The method consists of a) a trust-building phase covering the introduction of the healthcare professional, the identification of the patient and the review of the patient's record, b) the medication history that covers what the physician has already told the patient about the drug and the condition, other drugs that the patient uses, and that may interact with the prescribed one, further medical conditions that could lead to contraindications and c) the drug counselling including the mode of action of the drug, dosage/duration/drug information ("Laven's DDD") and drug-related problems that might occur. It ends with a joint decision making and a reachable goal until the next visit. Depending on whether the consultation is aimed to enforce responsible use in new drug users or to foster adherence in chronic patients, Anna suggests appropriate wordings that lead to a very fruitful short intervention in the everyday practice of a community pharmacist.

The session was very well received by the participants who suggested that a master-class on adherence could be included at one of the future congresses.

BIOSIMILARS – CHALLENGES AND OPPORTUNITIES

by Paul Fleming

The UK is entering a critical period for biosimilar medicines. The biggest savings opportunity for the NHS from the use of biosimilars is about to happen. However, during the current Brexit negotiations, we have continuing uncertainty on the regulatory mechanism for licensing future biosimilars. This article looks at the upcoming challenges and opportunities.

Paul Fleming is Technical Director of the British Biosimilars Association and the British Generic Manufacturers Association and prior to that Chair of its Regulatory Working Group for several years. The role includes close and regular discussions with MHRA, Department of Health, the NHS and other stakeholders. At a European level, Paul is a key member of the regulatory and quality committees of Medicines for Europe. In both these roles, he is involved in the development, influence and implementation of new regulatory and quality guidance.

Paul has more than 15 years' experience from working in the generic sector of the European pharmaceutical industry, in a variety of senior board level roles covering R&D, drug regulation, pharmacovigilance and clinical development. Earlier in his career he spent six years with the MHRA as a pharmaceutical assessor and is an appointed expert to the British Pharmacopoeia. He is a registered pharmacist and holds a higher degree in pharmaceutical technology. Throughout his professional life Paul has maintained an involvement with the science of pharmaceutical development connecting to how medicines can be used for the maximum benefit of patients and the NHS.

The patent expiry of adalimumab, the world's top selling prescription medicine, in mid-October is expected to make the single biggest contribution to reducing the NHS budget. Between £200 million to £300 million per year by 2021 will be saved through the uptake of biosimilar medicines. Building on the experience gained with other recent biosimilar introductions, the NHS is in a strong position to make the most of the opportunity through deep and rapid uptake of biosimilar competition.

As real-world experience has grown with UK patients; very high levels of biosimilar usage are now being achieved (May 2018 NHS data):

- Infliximab (from March 2015) = 89%
- Etanercept (from April 2016) = 89%
- Rituximab (from April 2017) = 73%

It is particularly important that the rapid introduction and take up of the opportunities from new biosimilar medicines is consistent across the NHS. To help achieve that, a monthly briefing update on adalimumab is being rolled out through the coordination of the Regional Medicines Optimisation Committees (RMOCs). The main purpose of the four RMOCs of NHS England is working together as a single system to avoid unnecessary variations in the best use of medicines.

Alongside the budget savings to the NHS from the increased use of biosimilars is the equally important benefit of freeing up resources so that more patients can have access to biological medicines and the significant health improvement benefits they can provide. There is emerging data that when biosimilar introduction leads to a reduction of 50% in price it delivers a 50% increase in the number of patients that can be treated. The higher relative cost of biological medicines both in R&D and manufacturing has tended to place constraints on access and routine use. Therefore, the availability of interchangeable biosimilar medicines gives an opportunity for prescribers to revisit patient treatment pathways and the group of people considered suitable for biological treatments to be widened.

It is vital that the biosimilars following adalimumab are not delayed by uncertainty or disruptions to the licensing system for new medicines. Today, the one and only licensing route for biosimilar medicines in Europe is the Centralised Procedure, operated by the European Medicines Agency (EMA) from their offices in Canary Wharf, London. The uncertainties over Brexit could have major impacts. The relocation of EMA from London to Amsterdam will be disruptive. According to a recent staff survey by EMA of their staff, at least 30% will not relocate to the Netherlands. Therefore, the EMA is already having to strictly prioritise and reduce its range of work. The licensing of new medicines is a core activity for all medicines regulators so it is hoped that impacts in this area will be minimised. However, relocation will inevitably be challenging for systems, processes and timelines. For these reasons, delays in the approval of new biosimilar medicines is a significant risk factor.

Due to the lack of political certainty, the life sciences industry has had to include in its plans the worst case "no deal" Brexit scenario. If that happens and the UK is separated from the EMA and the EU regulatory network then it has not been made clear how the UK

licensing authority, the Medicines and Healthcare products Regulatory Agency (MHRA) would operate. It is hoped that MHRA would review in parallel to EMA for the assessment of biosimilar medicines, taking account of EMA opinions and not duplicate or diverge on scientific issues. It is vital that the same scientific dossier can be submitted at the same time to EMA and MHRA, followed by the same assessment and approval timetable. Some reassurance has come from the technical notices published by the UK Government at the end of August. These indicate that MHRA will continue to reference opinions and decisions coming out of the EMA procedure when a company applies to EU27 and UK in parallel. However no mention is made of national control laboratory testing (National Institute for Biological Standards & Control - NIBSC - in UK) which is an important pillar of the regulatory control of biological medicines. It is important that even if the UK and EU regulatory systems start off in parallel they do not gradually diverge over time.

Overall, we are at an important milestone moment in the history of biosimilar medicines. In the coming months the largest opportunity for saving scarce health resources and treating more patients will take place. However, it is important that this is not the high-water mark for the sector and that it is not then followed by uncertainty on the timely availability of the next wave of biosimilar medicines. The British Biosimilars Association is fully committed to work with its member companies to help navigate this period of challenge.

GROWTH AND GLOBALISATION OF PHARMA PRODUCTS

by John Jolley

Pressures on the cost of public services in regions such as Europe and the US are beginning to restrict growth in pharmaceuticals, forcing companies to compete for limited funds as the current level of pharma business no longer reflects demand when compared with the proportion of their population. Sales in the US market will reach USD 1,430 billion by 2020 and market share increase from 40.3% in 2015 to 41% in 2020, but Europe's share will fall from 13.5% in 2015 to 13.1% in 2020, and sales in Pharma emerging countries will account for 25% of global sales by 2020. Emerging economies will account for 90% of the incremental growth in global pharmaceutical sales over the next five years. Manufacturing sources in emerging markets (India in particular) already account for 15 percent of the medicines sold in US, which will only be improved if companies are prepared to be flexible in their approach to the differing regulatory strategies that might limit market entry.

John Jolley is a Director of PharmaConsult providing technical consultancy and bespoke training solutions to Global Healthcare organisations. John has a degree in Pharmacy and has been awarded fellowships with the Royal Pharmaceutical Society and Chartered Quality Institute. He has held positions in Clinical Research, Product Registration, Manufacturing, Quality Assurance, and General Management and was member of the Council at the RPS 2003-2008. He was Technical Director for Boehringer Ingelheim UK for 15 years before his work in International consultancy and is a practicing Qualified Person (QP) with experience of sterile product manufacture and clinical trials.

This paper identifies some of the socio-economic factors that are influencing growth in the pharmaceutical markets by introducing issues of affordability in both developed and emerging markets and comparing these with the effects of demand to identify the markets that are likely to see high growth. In recent years we have seen increased regulatory controls of raw materials and medicines due to companies seeking low cost raw materials from emerging markets such as China and India that have been responsible for 75% of the adulterated and counterfeit medicines in to the global supply chain. This has resulted in the introduction of expensive controls to implement "pack realization" in developed global markets to attempt to control the quality of pharma products.

As pharmaceutical companies grapple with expiring patents and pricing pressures in developed markets, they are starting to expect more from emerging markets. Although the global economic environment is depressing near-term GDP growth, countries such as China, India, Russia, and Brazil have a bright medium and long-term future as some of the world's largest economies. Rapid growth can also be expected in some smaller economies in Eastern Europe, Southeast Asia, Latin America, and the Middle East. As GDP growth converts into greater personal wealth and higher disposable incomes, spending on health rises disproportionately, and drugs consumption even more so. Even in the near term, large emerging pharmaceutical markets are likely to grow more strongly than developed markets.

Pharma Economics

The share of revenues and profits contributed by emerging countries is lower in pharma than in other global industries, and major multinationals have yet to engage with the emerging middle classes in these countries. At a typical global consumer goods company, emerging markets account for a share 1.5 to 3 times higher than at a typical multinational pharma company. Such figures indicate that emerging markets are still emerging and offer significant opportunities for further growth. Such optimism must, however, be tempered by an awareness of the challenges and volatility that multinational pharma companies face in emerging markets:

a) Government intervention is increasing through both direct actions (such as price setting and compulsory licensing) and indirect measures (such as changes in manufacturing requirements and the terms of government tenders).
b) Promotions are reaching saturation point, especially in

the big cities where multinational and local companies have expanded their sales forces rapidly over the past few years.

c) As some multinationals shift their focus toward specialty products, managing portfolios of drugs with very different commercial needs is becoming considerably more complex.

d) The competition is intensifying in some countries. Looking ahead, we believe that emerging markets continue to offer attractive opportunities for growth, but pharma companies will need to navigate the intricacies of individual markets and tailor commercial models and approaches to their specific needs

Product Innovation

The biggest challenge to the pharma Industry is to recover development costs within the patent period remaining after obtaining Marketing Authorisation, and still meet the fiscal challenges of the market place. The cost of developing a successful medicine now can exceed USD 2.6 billion compared to USD 179 million in 1970s. This huge increase reflects the various technical, regulatory and economic challenges facing R&D pipelines. Companies often experience lost R&D investments (that is, R&D expenditures that do not materialize in a market-approved medicine) because pharmaceutical R&D is marked by high failure rates. An early-phase compound may have a promising outlook, but only preclinical and clinical trials will demonstrate its efficacy, quality, and safety. In addition, lost investments may increase when a failure occurs in later R&D phases. A phase III failure is significantly more costly than a preclinical failure because each phase is associated with a certain amount of required investment.

Market Globalization

The exciting growth forecast in emerging markets come with some key challenges, particularly market segmentation in balancing the differentiated capacity of the super-rich versus low-income consumers, along with pricing and access to public versus private market. Global multinationals have typically focused on the smaller high-end private payer population. The greatest opportunity, however, will come from the expanding middle-class segment, which, with its greater purchasing power, will expect access to the full range of pharmaceuticals and the very best in healthcare. Growth in emerging markets over the last decade has developed with compound annual growth rates (CAGR) of 10-14 % versus 0.6-2 % in many newly developed markets (see **Figure 1**).

The pharmaceutical market is changing. China is now the third largest pharmaceutical market in the world – almost 50 percent larger than Germany — and other emerging markets are working up the ranking. In fact, growth in this sector is forecast to continue for the foreseeable future. Over the next five years, emerging markets are expected to nearly double their spending on drugs, reaching nearly 30 percent of the global pharmaceutical spend (see **Figure 2**).

Improving Healthcare Systems

Emerging markets have seen a rise in the number of individuals who have moved from a subsistence lifestyle to one with an increase in personal net worth and disposable income. These markets have also seen rising numbers of employment opportunities with company health insurance schemes. Experts believe that more people, with greater disposable income, will seek an increasing number of healthcare treatments, thus expanding the markets for medicines. Political pressure and demand from the middle-class to increase availability and access to healthcare has already resulted in significant health reforms designed to provide basic universal healthcare coverage. Examples of recent reforms include:

China – Reforms will provide affordable medical care for all by 2020.

Russia – The Health and Pharmaceutical 2020 reform will extend basic healthcare coverage and reimburse outpatient drugs. Also, 50 % of all generic drugs will be replaced by domestic alternatives by 2017, and 50 % of all innovative drugs will be manufactured domestically by 2020, fuelling domestic and international pharmaceutical investment.

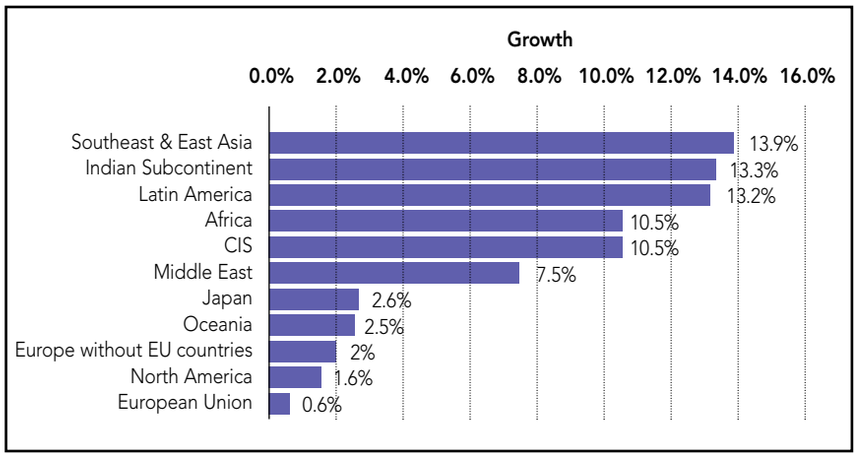

Figure 1. Global pharmaceutical market growth for the period 2011 – 2016, by region (CAGR). Source: IMS Health.

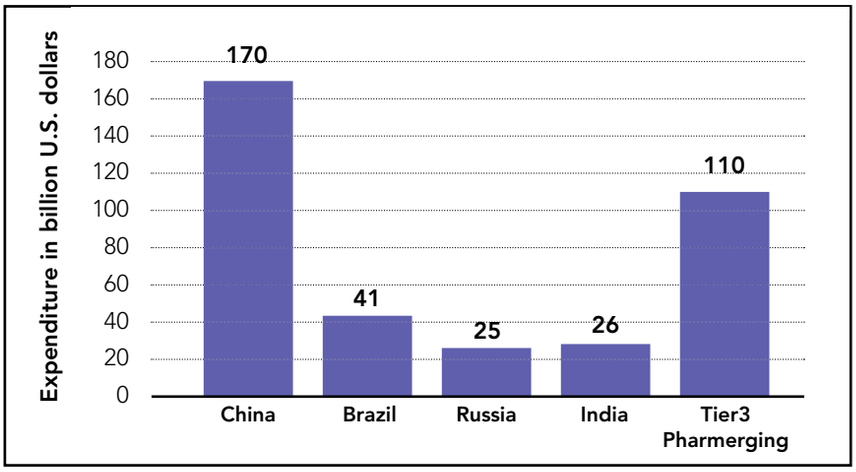

Figure 2. Projected spending on medicine in selected emerging markets in 2018 (in billion U.S. dollars). Source; IMS Health.

India – The hospital sector has grown considerably in recent years, and improving access to healthcare remains a priority for India's Ministry of Health.

Brazil – The Brazilian government pledges universal health coverage for all, although many drugs will still require out-of-pocket payments. Generics account for about one-quarter of all medicines sold in Brazil, making it the largest generics market in Latin America. Analysts believe there is still room for growth in this sector.

Africa – Pharmaceutical expenditure is expected to reach $45 billion by 2020. The sub-Saharan African economy, excluding South Africa, is growing faster than anywhere else in the world – a trend that is expected to continue.

Disease Prevalence

Emerging markets face the challenge of dual epidemiological burden, with high rates of infectious disease, as well as the rising numbers of non-communicable diseases. Increase in "Western diseases" due to changing diet and lifestyle are contributing to this rise, with diabetes reaching epidemic proportions in countries like Indonesia. Seventy percent of all cancer deaths now occur in low- and middle-income countries, which mean the demand for chronic treatments continues to increase. (see **Figure 3**).

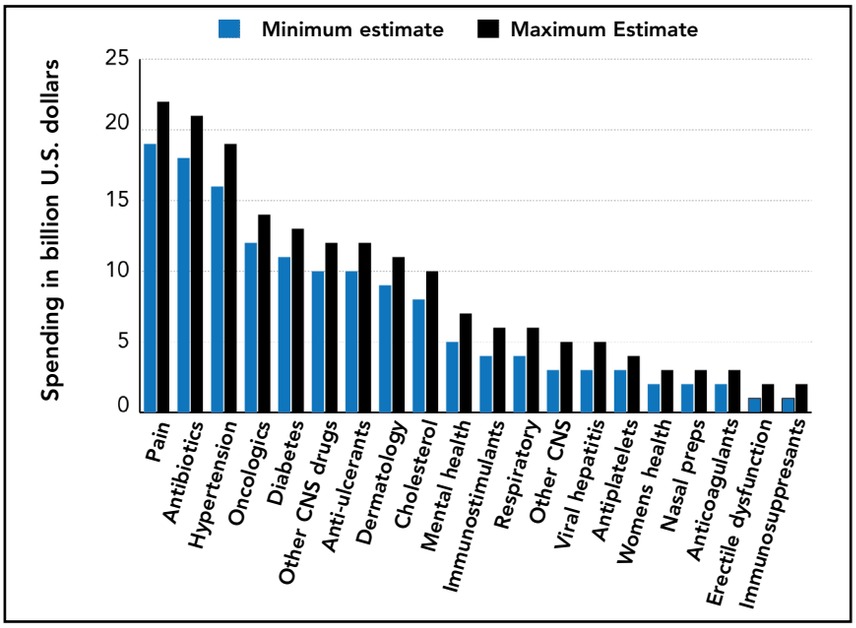

Figure 3. Top therapy areas in pharma-emerging markets in 2018, by spending (in billion U.S. dollars). Source IMS Health.

Policy Supporting Generics and Biosimilar

The final feature contributing to the growth in many emerging markets is the increasing demand for generics and biosimilar, which is encouraged by government policy. Brazil's Generic Medicines Policy of 1999 resulted in generics now having over 60 % of market share by volume. The expansion of the branded generics/biosimilar market may be the greatest opportunity for pharma due to the mass population that requires access to medicines. Countries, such as Saudi Arabia, South Africa, China, India and Russia, are keen to promote and sustain a robust generics industry by implementing policies to encourage use and manufacture.

Factors affecting development in Emerging Markets

Adapting and applying business decisions should be customized for the emerging markets as each country differs in terms of epidemiology, awareness, treatment protocols, compliance and, above all, pricing. Innovator companies will have to customize their strategies when launching into these markets in order to make the product accessible and affordable to the masses. Over the next ten years for example, Russian pharma will more than double in size. Companies seeking to capture a share of this growth must prepare to face the challenges of increasing pharma regulation and intensifying competition. However, the environment will also become much more challenging as the state regulates market access, pricing, and competitive pressure intensifies from both multinationals and local pharma companies.

The Indian pharmaceutical market presents a unique set of opportunities and challenges that arise from its distinctive nature. Branded generics account for a huge share – more than 80 % of the retail market. Local players dominate thanks to their early investments and capabilities in formulation development. Intense competition has kept prices low, which explains why India ranks in the top three markets in the world in terms of volume yet only in the top fifteen in value.

Mexico's health care has improved thanks to recent public initiatives, but rising costs, capacity constraints, and growing disparities pose new challenges. To keep pace with these shifts, pharma companies need to raise their capabilities to global standard and preserve the flexibility to update their plans as often as every quarter. Health care in Mexico is at an inflection point. Recent advances in public policy have helped bring noticeable improvements in health indicators, but the system is under pressure.

Over the past five years, generic and branded generic have continued to grow strongly in emerging markets, often at a pace two to five times faster than branded originals. In those emerging markets where brands are seen a proxy for quality, and where physicians retain considerable control over prescriptions and patients over purchasing decisions, branded generics have been more successful than their unbranded counterparts, and have maintained their prices for longer. Recognizing this opportunity, many global pharma companies have announced plans to boost their emerging market business by investing in branded generics, whether by launching their own portfolios or by acquiring those of other companies. However, the landscape for branded generics is far from uniform, with individual markets evolving in markedly different ways. In some markets, such as Turkey and Saudi Arabia, governments are implementing cost reduction measures. In other markets, such as South Africa, payers are putting pressure on prices. By contrast, some markets, such as Brazil, are continuing to see rapid growth in branded generics as the emerging middle class acquires increasing purchasing power.

Sales growth in the emerging markets will only occur if companies register newly developed products in emerging markets. Price will be a limitation but this will be less than the restrictions imposed by public expenditure in developed markets. Pharma companies will need to take account of appropriate regulatory affairs and marketing strategies that will establish realistic costs for newly introduced drugs tailored to emerging market needs. They will also need advice on the right local partners, and organizational resources necessary to manage partnerships in the emerging markets.

THE RISE OF TRADITIONAL MEDICINE (TM) IN MALAYSIA: POTENTIALS, CHALLENGES AND OPPORTUNITIES FOR ENHANCEMENT

by Ai Ch'i Liew

Traditional Medicine (TM) is gaining popularity in Malaysia and many other countries globally. The adoption of TM may be due to the limitation of conventional treatments. An increasing role for TM could herald great opportunities for pharmacists, researchers and pharmaceutical industries to take up the challenges to overcome the obstacles to ensure better future treatments for patients.

Ai Ch'i Liew graduated at Universiti Sains Malaysia in 2006 and finished her postgraduate study of Master in Science (Clinical Pharmacy) at Universiti Sains Malaysia in 2014. She worked as a Traditional & Complementary Medicine (T&CM) pharmacist and served in the first T&CM unit in Malaysia between 2006 and 2017. She is currently working as a clinical pharmacist in the Clinical Research Centre in Seberang Jaya Hospital, Penang, Malaysia.

The increased worldwide popularity in the use of Traditional and Complementary Medicine (T&CM) has escalated public health policy issues. The WHO has developed the Traditional Medicine (TM) 2014-2023 framework to promote the safe and effective use of T&CM. It aims to regulate products and practices for practitioners to ensure a safe integration of T&CM into national health systems[1].

A 2004 Malaysian national survey on T&CM found that 69.4% of Malaysians used T&CM during their lifetime, an increase of 55.6% from the previous year[2]. Annual sales of T&CM/ alternative medicines were estimated to be MYR 1000 million as compared to MYR 900 million for allopathic pharmaceuticals[3]. This figure is projected to increase in the future.

Malaysia established the National Policy on T&CM to emphasize capacity resources on practice, education, training, raw materials, products and research[4]. On 11th January 2006, the Malaysian government established TCM units within the Ministry of Health Malaysia (MOH) facilities. These units provide choices of Chinese Herbal Medicine (CHM), acupuncture and Malay massage services across three hospitals, namely the Kepala Batas Hospital in Penang, Putrajaya Hospital in Federal Territory of Putrajaya and Sultan Ismail Hospital in Johor. This pioneer project was aimed at integrating T&CM into the pre-existing public healthcare delivery systems. An integrated medical system would promote rationalization in the use of T&CM through the development of technical guidelines, regulatory procedures and standards of T&CM practices[5].

With various ethnicities, Malaysia's rise of T&CM systems is diversified with allopathic medicine, traditional Malay medicine, traditional Chinese medicine (TCM) and Ayurveda, each reflecting the accustomed Malay, Chinese, Indian and indigenous heritage. Other forms of T&CM include homeopathy, aromatherapy and chiropractic.

Malaysians have integrated TM into their daily lives, although the practice correlates with ethnic culture and beliefs. TM treatment mostly depends on the individual practitioner's experience. Albeit, TM in Malaysia is sharing some principles and taboos[6], there are some differences as well across different ethnic groups. TM practice is not solely restricted to one's own ethos or culture, as it has now diversified across to other ethnicities. For example, Malay postnatal massage is popular among the Chinese, while acupuncture and CHM were well accepted by other ethnicities in the country.

As a T&CM pharmacist for the past 10 years, I have found that TM provides numerous benefits to cancer patients when the practices are added to the conventional medical system. However, there is a lack of evidence on the efficacy of TM when it is integrated to allopathic medicine. Many TM modalities are based on beliefs and traditions of the culture. The effectiveness when assessed to date has mainly been based on patients' testimonials with little scientific rigour. Therefore, the practice of TM is still limited due to patient safety concerns.

Safety and efficacy of TM are major concerns. To offset these concerns, more research either *in vivo* or *in vitro*, should be performed. The complex mixture of chemical compounds present in various herbs should also be assessed. Modern medicine and TM postulate different philosophies towards the treatment of illness. Modern medicine has methodologically reviewed the structure and function of organ systems with therapeutic drugs being targeted against pathological diseased cells, tissue and/or pathogens. On the other hand TM advocates the philosophy of holism and the interrelationship with the environment. Variation of research methodologies are needed in order to assess the possible integration

between modern medicine and TM practices. Although randomized controlled trials (RCTs) are considered to be the "gold standard" approach to provide the most reliable and valid results in evidence-based practice, they may not be so suitable for TM therapeutic evaluation.

Observational studies and case reports are often found to be more suitable for the assessment of TM rather than RCTs. RCTs often neglect TM practices as the approach often emphasize a highly personalized therapeutic regimen. An observational approach may be more suitable to generate valuable information through scrutinizing individual patient's outcomes and the factors influencing it. Individualized treatment success was shown by a 14 week follow-up trial that highlighted the continued improvement of patients who received Chinese herbal medicine (CHM) formulations post-treatment as compared to those who received standard CHM formulations[7]. As a result, Evidence-informed practice and Value-based medicine might be more suitable in TM research which integrates research evidence with clinical expertise and patients' value. However, it would be an immense challenge for the pharmaceutical industry to commercialize TM to a large scale.

Integrated objective measurements such as Quality of Life (QOL) instruments for patient reported outcome (PRO) and systems biology technology that provide biomarker measurements during treatment intervention will substantiate the subjective assessment of TM practice, where Reverse Pharmacology practice could be employed. Reverse Pharmacology is defined as the science of integrating documented clinical/ experiential hits into leads by transdisciplinary exploratory studies and further development of drugs by experimental and clinical research[8]. Bioinformatics, pharmacogenomics and systems biology are expected to open new channels for the convergence of TM and modern medicine. Advancement of these approaches will create a building block to measure the mechanism of action of TM formula by modern pharmacology methods without neglecting the common TM practice[9]. This traditional knowledge-inspired reverse pharmacology is able to prove better leads to explore potential herbal drug development. This approach is an important way to elucidate the mechanism of action of TM formulas in clinical management. The efficacy of TM may be reduced when essential factors do not meet certain criteria such as different combinations or pairing in a variety of formulations.

Drug discovery in the pharmaceutical industry should explore the classic herbal formulations which have been used for centuries for therapeutic and prophylactic purposes. Integrated digital databases of TM use in Taiwan for example, would be able to generate safety and efficacy profiles in an integrated medicine practice. This is an easy economical way to discover new drugs through exploring such databases. The incorporation of TM syndrome classification into biomedical disease diagnosis will lead to a new era in the development of medical sciences to provide improved treatment efficacy with specific indications of integrative therapy.

The safety of TM should be taken into consideration. Misconception of adverse effects of TM may limit the therapeutic model potential. Qualitative and quantitative study methods should be applied into research, exploring the safety of TM. Quantitative study is sufficient to determine the seriousness of adverse effects within the routine practice of TM while qualitative study could determine patients' perceptions of TM, and at the same time weighing the perceived costs of adverse effects and/or its perceived benefits.

Authorities should also undertake pharmacovigilance of herbal medicine treatment, to monitor herb-drug safety and identify adverse reactions in humans, assessing risks and benefits and responding to and communicating herb-drug safety concerns with practitioners and the public. This will be an important factor in forming a national herbal medicine safety database to extend knowledge of safety in TM rather than focusing on the harmful side of TM.

In conclusion, the deficiency or insufficient outcomes of conventional medical treatment may lead to the adoption of TM. TM utilization should at the same time undergo quality control procedures to overcome any potential issues in the use of TM.

Acknowledgement:

I would like to thank the Director General of Health Malaysia for this permission to publish this article.

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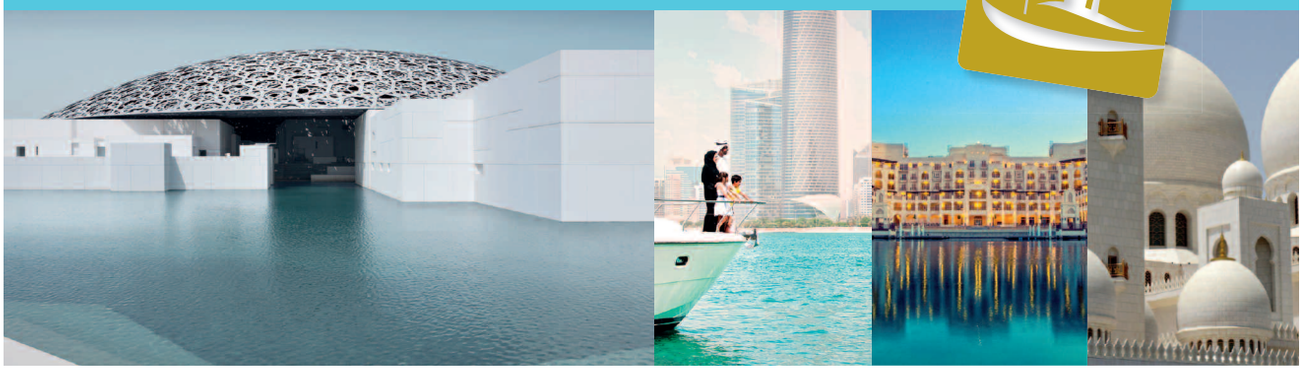

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REGULATORY CONVERGENCE AND GLOBAL TRENDS IN EXPEDITED REGULATORY PATHWAYS

by Marisa Carcione

Regulators in both established and maturing agencies are facing challenges in their effort to provide faster access to medicines to patients who need them.

Marisa Carcione is Partner & Director of IPRAT, a business development, intellectual property & regulatory affairs consultancy firm for Latin America. She has a Pharmacy degree from the University of Buenos Aires and has more than 20-years' service in the Health Industry in Latin America (Pharmaceutical Products, Medical Devices, Cosmetics and Food Supplement).

Prior to joining IPRAT in 2015 to lead the consultancy team, she worked for Boehringer Ingelheim in a broad range of regulatory leadership roles, with global, regional and local scope. Marisa's experience covers strategic, tactic and operational roles, in positions of Head of Regional Regulatory Affairs for LATAM and Head of Local Regulatory Affairs for Argentina, Uruguay, Paraguay and Bolivia, both based in Buenos Aires, Argentina. During a three-year assignment in Germany, she covered international responsibilities as Manager for the Regional Coordinating Centre in Global Regulatory Affairs, supporting other regions like Europe, Middle East and Asia.

Her current responsibilities are business development, management and leading of technical teams for international, regional and local companies in consultancy, including regulatory strategy development for innovative products and new technologies, regulatory management system and compliance. She actively participates in public health and regulatory intelligence forums and working groups, supporting FIFARMA and other industry associations in convergence initiatives and regulation development.

Why do we need alternative expedited registration pathways?

Among the most relevant causes are the following:

- Medical needs which are not met by medicines available in the market.
- More information for patients, even in early stages of the development of products, demanding faster access to them.
- Developing alternative ways to conduct reviews in a rapid manner, without compromising the safety, efficacy, and quality of the medicine.
- Alternative registration pathways are needed to expedite access, but must be established within a framework that is sustainable for all stakeholders.
- Improved allocation of local resources, improved patient access, and increased equity of access are urgent global needs.

Key points to consider to accelerate access to medicines

Regulatory agencies focus on:

- applying the principles of WHO draft guidelines on Good Regulatory Practice and Collaborative Registration Procedures when establishing expedited regulatory pathways;
- focussing on submission documents on what is absolutely required for purposes of local assessment;
- consider allowing face-to face meetings with applicants to discuss the overall filing strategy, especially for products addressing unmet medical needs.

Main global regulatory advances

In the US, companies have regularly been using available expedited pathways such as Priority Review, Breakthrough Designation, and Fast Track for many years.

FDA Regulatory advances have impact outside the US, showing a wide readjustment of priorities in the European Medicines Agency (EMA) and in Japan (PMDA). This effect has also been emulated in other agencies such as Health Canada, China FDA, and Korea MFDS with their recent establishment of pathways to accelerate the review of certain types of products or to establish conditional approval based on a more limited clinical data package.

Many agencies are assessing the outcomes of the medicines reviews previously conducted by other agencies and then ensuring that any additional work conducted by the local agency adds value to prior work. This approach centres on the use of two related but different concepts:

"RELIANCE" (Dependence based on trust), whereby a regulatory authority in one jurisdiction may give significant weight to work performed by another regulator or

other trusted institution in reaching its own decision.

Recognition, the routine acceptance of the regulatory decision of another regulator or other trusted institution.

Reliance pathways to facilitate regulatory decisions

Recognition procedures: authorities review medicinal products intended to be marketed in countries or regions other than their own.

Verification review procedure: is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorized by one or more SRAs (Stringent Regulatory Authorities). Review on the basis of CPPs, GMP certificates, and/or the assessment reports of reference authorities.

Abridged review procedure: assessments of data that have been already reviewed and approved by SRAs but includes an abridged independent review of a certain part of the dossier relevant to use under local conditions.

Expedited regulatory pathways for medicines targeting unmet medical need

Expedited review: regulatory authorities speed up the review of certain products to enable faster approval.

Expedited submission (rolling submissions): information and data-packages can be submitted and reviewed as they become available.

Expedited development: earlier submission and approval with a data set which may be less complete than from a standard development program (e.g., surrogate endpoints, phase 2 data only).

"**RELIANCE**" models in Central America and the Caribbean, and equivalence agreements in Mexico, provide the benefit of moving approval times from nine months to three to four months.

Other emerging market countries, such as Saudi Arabia, Egypt, Jordan, and the UAE, have recently approved accelerated pathways with review timelines ranging from 60 to 90 days. Recently, "Priority Review" criteria for products that meet at least one of the eligibility criteria have been established in Brazil, for example medicines for neglected diseases, and vaccines to be incorporated in the national immunization program.

Likewise, expedited procedures for clinical trial applications, certificate of good manufacturing practices, and registration of new drugs intended for diagnosis, prevention, or treatment of rare diseases have been established.

Recently, ANVISA published two new guidelines with the purpose of accelerating the approval of medicines in Brazil:

Resolution 204/2017 establishes "Priority Review" criteria for products that meet at least one of the eligibility criteria; for example, medicines for neglected diseases, and vaccines to be incorporated in the national immunization program. This guidance also addresses priority review processes for post-approval applications when there is a public health risk of drug shortages. Publication of a special procedure for registration of drugs intended to treat rare diseases was another effort to expedite drug approvals.

Resolution 205/2017 establishes expedited procedures for clinical trial applications, certificate of good manufacturing practices, and registration of new drugs intended for diagnosis, prevention, or treatment of rare diseases.

Service Orientation 45 is another recent (February 2018) regulatory advance from ANVISA, which establishes optimized review for registration and post-registration changes for biological products. According to the agency, this is also being considered a "Reliance Pilot Project" open for one year. Products already approved by the FDA and EMA with same indications, dosage, adverse reactions, and precautions are eligible. Applicants must submit reports containing the criteria used by both agencies to review and approve these applications.

Conclusion

Progress has been remarkable and has not been limited to the SRAs of developed countries, but also to those of emerging countries. Looking to the future, where tailored therapies will gain special prominence, we still have a way to go. The evolution of regulation, accompanying the development of science, will be the key to guarantee the access of patients to new health technologies.

Although FDA was a pioneer in providing expedited approval pathways, other established and emerging markets agencies have joined by incorporating the recognition and reliance concept in previous evaluations performed by other health authorities. Regulatory agencies attempt to facilitate review and approvals, simplifying procedures, and reducing timelines and backlogs in reviews and decisions. Collaboration among regulatory agencies, and the support of the industry and the academy, make it possible to build upon existing frameworks, deepen local needs aligned with global standards, building trust and sharing resources and experiences. The ultimate goal is to provide faster access to medicines for the population, ensuring their safety and efficacy.

PHARMA IN PLENARY

A Manufacturing Waiver for Supplementary Protection Certificates in the EU

by Nicola Davies

An initiative to amend the legislation (Regulation (EC) No 469/2009) on Supplementary Protection Certificates (SPCs) is in motion.[1] SPCs afford companies an extended patent protection of up to five years on top of the typical 20-year market exclusivity period for innovative medicines.[2] In particular, SPCs disallow the manufacturing and selling of generic versions of a patented medicine in the European Union (EU) during the SPC term.

While SPCs are granted to compensate drug makers for the lengthy development stage and reward them for their efforts at research and innovation, SPCs reportedly have given rise to unintended consequences that disadvantage small to medium-sized drug makers of generic and biosimilar products.[3] To facilitate investment, job creation, and growth in pharmaceutical companies based in the EU, the European Commission has proposed to adjust the intellectual property rules contained in SPCs.[4]

At risk: The EU's global competitiveness in generics and biosimilars

One of the unintended consequences of SPCs is the loss of opportunities in the export market for medicinal products that are experiencing global growth.

In 2017, the global demand for medical products reportedly reached €1.1 Trillion.[4] The Commission also acknowledges that there is an increased demand for affordable alternative treatments such as generics and biosimilars. Indeed, the European Parliament estimates that these products would represent 80% of the global volume of medicines by 2020.[1] A significant number of pioneering biologics are also set to lose their market exclusivity starting 2020, which would open up massive opportunities for investments and job creation in relation to biosimilar manufacturing.[1]

However, since SPCs preclude the early manufacturing of generics and biosimilars, EU-based manufacturers can only begin production after the SPC for the related product expires. This delay places EU-based manufacturers at a competitive disadvantage to non-EU-based manufacturers that can market their products in Member States immediately after a certificate expires.[1]

The original SPC legislation is also no longer relevant to the current state of the pharmaceutical marketplace. It was implemented almost three decades ago; it does not reflect the rapid pace of technological advancements applied in pharma research and the emergence of novel products such as biosimilars.[1]

The risk of a having an SPC legislation that is lacking in industrial relevance is that manufacturers might move their facilities outside of Europe where they can manufacture and market sooner. This exodus of manufacturers might lead to losses in investment and employment opportunities in Europe.

The manufacturing waiver for exported medicines

To boost the competitiveness of manufacturers in the EU, the Commission has proposed to adopt an SPC manufacturing waiver for generics and biosimilars. Under the waiver, manufacturers can begin the production of generics and biosimilars within the EU even during the SPC protection period.[1] However, the waiver only applies to products that are intended for export to countries outside the EU, countries without an SPC in place, or countries where an SPC has already expired.[5]

In addition, the waiver will enable "Day-1 entry" of EU-made generics and biosimilars. The waiver enables stockpiling, where manufacturers can make and store their product so that they can readily market their medicine to EU Member Nations on the first day following a certificate's expiry.

According to the Commission, the Day-1 entry provides added incentive to small- and medium-sized manufacturers to retain their production within the Union borders rather than relocate to non-EU countries.[4,5] With the expected growth in the global demand for generics and biosimilars, the Commission expects that the manufacturing of these products (within the EU) will generate between 20,000 and 25,000 direct jobs.[1] Moreover, EU-based manufacturers can deliver their products to patients in Member States in a timely manner, enabling them to more effectively compete with global competitors.[5]

The implications of Brexit on SPCs

The UK Parliament might need to consider the potential impacts of the proposed adjustments on SPC legislation. The granting of these certificates is under EU regulation.

So, while the certificates granted prior to the date of Brexit shall remain in force, the UK may be required to develop an equivalent legal framework that would replace EU-granted SPCs. The EU (Withdrawal) Bill, which is still being assessed by the UK Parliament, is set to introduce domestic legal equivalents of EU-directed laws and regulations.[2]

Safeguards in the proposal

To avoid abuses of the manufacturing waiver, the proposal includes a notification requirement. Manufacturers are required to inform the national public agency in their Member State that is designated to monitor SPC manufacturing waivers. In addition, manufacturers must meet certain product labelling requirements for export and supply chain requirements to demonstrate due diligence.[1]

The Commission has developed the proposal as part of numerous stakeholder consultations. In February 2017, an inception impact assessment (an in-depth roadmap of the initiative) was published. Between October 2017 and January 2018, the Commission also held many public consultations.[1] In a response to a question posed to the Commission, a Commission representative revealed that they analysed a total of 231 contributions from public and private stakeholders during the consultation period.[5]

Consultations were important for the Commission to ensure limited, targeted, and balanced content in the proposal.[1] The amendments are designed to be limited in that the exception to the SPC rights only relates to manufacturing products for export. The legislation adjustments are also targeted because they are designed to remedy the specific unintended consequences of Regulation (EC) No 469/2009 on the EU's manufacturing competitiveness. Lastly, the legislative changes are balanced; the initiative shall promote the competitiveness of EU-made generics and biosimilars without undermining the market exclusivity afforded to drug innovators and certificate holders in the EU.[1]

According to the Commission, a careful consideration of the need for safeguards and stakeholder involvement can help to diffuse the threat on the EU's drug manufacturing sector.[1] The timely adjustment of SPC-related intellectual property rules may provide an intervention that does not simply lead to growth but also maintains Europe's status as a key competitor and innovative leader in the global pharma industry.

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How Data Integrity Issues Sunk a $4.3 Billion Drug Company Acquisition – Lessons Not Just for Quality Professionals, But Also Their Top Management

by Michael Swit

Astute quality professionals know that the U.S. Food & Drug Administration (FDA) has markedly increased its focus in the past few years on issues relating to data integrity (DI). Indeed, when FDA suspects/identifies data integrity issues at a regulated company, it now uses a warning letter format specifically dedicated to DI remediation. Paradoxically, however, the most recent detailed discussion of DI issues comes to us not from FDA or the Department of Justice, or a federal judge, but from a 247-page October 1, 2018 decision by a judge from a chancery court in Delaware.[1]

What's a Delaware Judge Got to Do With It?

A little background – in April 2017, Germany-based Fresenius Kabi AG ("Fresenius") entered into an agreement to buy Akorn, Inc., an Illinois-based generic drug maker specializing in sterile parenterals, topicals, and other less common formulations. At the time, Fresenius management hailed the deal as representing a great opportunity for Fresenius to expand its presence in North America, especially the United States.

The deal valued Akorn at $34 per share for a total price of $4.3 billion and was subject to many typical conditions prior to closing, which was scheduled to occur no later than one year later, or by April 24, 2018. On April 22, 2018, Fresenius informed Akorn in writing that it was terminating the agreement and pulled out of the deal. The next day, Akorn sued in Delaware Chancery Court (the locus of many corporate legal battles due to Delaware's pro-business corporations laws) seeking to have the court force Fresenius to consummate the deal – and at the original $4.3 billion price. What ensued was an accelerated schedule that led to a week-long trial in July before a single judge, leading to the October 1 decision.

About the Deal and the Due Diligence Conducted by Fresenius Prior to Contracting

Prior to entering the agreement, Fresenius conducted detailed due diligence regarding Akorn, its operations, and its future business prospects. However, even the most extensive due diligence effort cannot examine every potential issue impacting an FDA-regulated company. To address potential unknowns, deals such as the Fresenius/Akorn agreement contain a number of contract clauses that, among others, require that, in the period between entering the deal and closing:

a) the seller (Akorn) continue to operate its business in "the ordinary course;"
b) that the seller continue to make information available to the buyer (Fresenius); and
c) that there be no changes in the business of the seller that would equal a "material adverse event" (i.e.., substantially undermine the value of the deal).

In addition, in the merger agreement, Akorn made certain representations and warranties as to its operations, including its compliance with applicable law, especially those relating to its adherence to FDA's varied requirements governing the manufacture and marketing of drugs. If any of those representations or warranties turned out to be untrue, then the buyer potentially could void the deal.

Why Did Fresenius Cancel the Deal?

Unexpectedly, beginning in the autumn of 2017, Fresenius received the first of three anonymous letters alleging, in increasing levels of detail, that serious DI issues existed at Akorn. As the level of detail increased, Fresenius reached out to Akorn for explanations and, ultimately, both Akorn and Fresenius initiated investigations – using both outside counsel and independent quality experts with deep experience in DI issues. Because the October 1 Decision goes into great detail as to the conduct of those investigations, I will not repeat them here, although I will review some key findings from those investigations and what we can learn from those efforts. Suffice it to say that, by early April, Fresenius was convinced that significant DI issues existed at Akorn that arguably raised questions about virtually Akorn's entire product line. In addition, in the 9 months after the April 2017 signing of the deal, Akorn sales had plummeted. Thus, a deal that potentially had a value estimated as high as $5 billion had degraded to being worth less than $3.5 billion, meaning Fresenius would be paying, absent a renegotiation of the purchase price, $4.3 billion for a deal that potentially was worth almost one third less than originally contemplated.

What Were the Data Integrity Issues?

The DI issues ran the gamut and, as will be discussed, how Akorn approached them also impacted the judge's decision in the case. Here are key Data Integrity issues highlighted by the decision:

- A senior executive submitted stability data to FDA in response to a complete response letter that he knew (or should have known) had been falsified;
- Falsified data was later found in a number of other submissions;
- FDA inspectors witnessed Akorn employees retrospectively modifying laboratory notebooks;
- Some Logbooks were missing and other contained data on Post-it notes or data that were entered late or not at all;
- Many computerized systems lacked passwords and, with other systems, any user could change the time/date setting on the computer;
- Akorn "invalidated" negative test results in more than 70% of cases between January 2017 and July 2017 without adequate support;
- Akorn quality control personnel often "tested" products into compliance, a practice that is unacceptable at an FDA-regulated company and first publicly highlighted over 25 years ago in the seminal U.S. drug GMP legal case, *U.S. v. Barr Laboratories*;[2] and
- In August 2018, during an FDA inspection of Akorn's Somerset facility –*after Fresenius had terminated the deal and the subsequent July trial was held to review the evidence relating to data integrity and whether Fresenius had grounds to kill the deal, but before the judge issued his decision* – an unidentified Akorn employee intentionally deleted a database of a stand-alone high accuracy liquid particle counter, along with the backup file and electronic security logs. This deletion may have been done with an "electronic shredding utility." In response to this, the court's opinion commented:

> *"Given the timing of the deletion, it is reasonable to infer that the perpetrator may have been trying to hide information from the FDA, or from personnel who would follow up on the deficiencies that the FDA identified in its Form 483."*[3]

In commenting on Akorn's data issues as a whole, the opinion was very blunt:

> *After hearing the evidence at trial, I did not have any confidence that Akorn would be able to support its data if the FDA called upon Akorn to do so. Based on developments since trial, Akorn's situation has grown even worse.*[4]

How Did Akorn End Up With So Many DI Issues?

The Opinion contains a lengthy discussion of Akorn's approach to DI issues that is a roadmap for what not to do. Although DI concerns had been raised at various times prior to the Fresenius deal being signed, Akorn failed to address them both before and after the merger agreement was signed in April 2017. Among the questionable DI management approaches were:

- Akorn's Information Technology function, which is crucial to sound DI practices, failed to support efforts to improve DI. Indeed, once the deal was signed, IT deferred all DI-related projects and effectively regarded DI issues as something that Fresenius could address – after the agreement closed.
- After the deal was signed, rather than perform formal audits as would be appropriate in the quality arena to follow up on findings from prior audits, Akorn decided to instead perform "verifications," which involve a much more abbreviated approach to probing quality issues such as those that constitute DI concerns.
- Management at the highest levels of Akorn displayed little concern for ensuring that quality issues, including DI, were properly handled, a conclusion reached by the judge in his opinion, where he stated:

> *Rai*[5] *made claims about quality, but having considered his answers and evaluated his demeanor while he was being cross-examined about his commitment to quality, I am forced, to conclude that he does not regard it as a priority.*
>
> In fact, testimony at trial revealed that, although Akorn CEO Raj Rai received copies of audit reports, he never had read any of them.[6]

What Are the Lessons of the Fresenius-Akorn Merger Demise?

The Opinion's discussion of the pervasive deficiencies in Akorn's quality culture are extensive and worth a careful review by quality professionals as an exemplar of what not to do. The Opinion also raises questions as to how a seller can adequately protect themselves from similar DI issues arising in the future. A few suggestions follow:

- Ensuring DI issues don't arise (or properly addressing them

when they do) is the responsibility of senior management. It is essential that a compliance culture not only emanate proactively from the CEO, but that those efforts are supported actively by the Board of Directors. Indeed, a commitment to complete compliance should be a specific obligation of all company personnel (including contractors) and memorialized in writing and ratified by the Board (e.g., in a Code of Conduct).

- You can't put a bandage on DI issues. When they are discovered, they must be addressed promptly, proactively, thoroughly, and pervasively throughout the organization.
- And, ideally, the discovery of DI issues should arise in the context of an active and effective internal audit program, supported, when necessary, by outside experts.
- Training on proper data management and record keeping must be vigorous, comprehensive, validated, and reinforced periodically.

What does a potential acquirer do to not end up in Fresenius' position?

It is fairly clear from the Opinion that Fresenius conducted a vigorous due diligence campaign, although it is not stated how Fresenius approached quality issues in general and whether they had any specific due diligence tactics relating to DI matters. Thus, with the benefit of hindsight, an acquirer should consider these additional efforts[7] in conducting quality[8]-related due diligence in acquiring an FDA-regulated company:

- Read everything relating to the target company's quality history – inspection reports (FDA and other regulatory agencies), warning and untitled letters, audit reports (both internal and those by third parties such as customers of the target), etc.;
- Conduct your own audits of the target's operation, including all facilities;
- Talk to not only senior management and middle management, but also a sampling of line workers (whether on the manufacturing floor or in a QC lab, etc.) to get as candid a picture of the target's compliance culture.

Mergers are unique scenarios. The business drivers often can override other concerns in the "heat of the deal." However, as Akorn/Fresenius illustrates, quality issues, especially those that are key elements of the very value underlying a transaction such as data integrity concerns, cannot be ignored. While not all issues are easily found, especially ones such as data integrity violations, the acquirer must be aggressive and vigilant, preferably before signing a deal, but particularly prior to closing, as Fresenius was able to do here (with a little help from one or more anonymous whistleblowers).

References

1 https://courts.delaware.gov/Opinions/Download.aspx?id=279250 (hereafter referred to as "Opinion")

2 https://law.justia.com/cases/federal/district-courts/FSupp/812/458/1762275/

3 Opinion at 110.

4 Opinion at 113.

5 Akorn CEO Raj Rai.

6 Opinion at 32, Footnote 112.

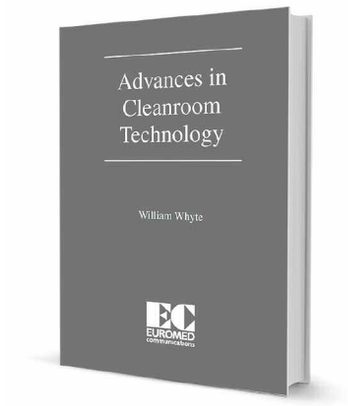
7 To facilitate these efforts, the merger agreement should grant the acquirer broad powers to probe the inner workings of the target company. Of course, the target will insist upon confidentiality in the process, all of which can be addressed in a properly drawn merger agreement (by the way, while I use the term "merger," not all corporate acquisitions are technically mergers. I am using that term for convenience here).

8 This article focuses primarily on quality issues that can unwind a deal involving an FDA-regulated transaction. Care also needs to be given to regulatory concerns such as whether a drug or device maker has made changes to the approved manufacturing processes and has failed to secure FDA approval (when needed) for the change. Several examples of this occurring in the early days of the generic drug industry resulted in companies facing situations where they were marketing multiple products that did not comply with approved manufacturing processes, many of which had to be recalled as they were unapproved new drugs.

Michael A. Swit, Esq., has been tackling critical FDA legal and regulatory issues since 1984. His private FDA regulatory law practice included service as Special Counsel in the FDA Law Practice Groups of several major law firms. Michael has lectured and written on a variety of subjects relating to FDA law, regulation and related commercial activities, and is a former member of the Food and Drug Law Journal Editorial Board. He can be reached at mswit@fdacounsel.com

Euromed books

Books on pharmaceutical management and clinical research



Advances in Cleanroom Technology

William Whyte

ISBN 978-0-9956666-5-8

This book is based on the author's work, published over the last sixteen years to advance knowledge of cleanroom technology. Thirty-four articles are collected and divided into seven sections that cover common themes, with helpful introductions. The themes include the history of cleanrooms and operating theatres; risk assessment; ventilation design and air supply rates; required cleanroom standard for specified product contamination; and the dispersion, transfer and deposition of contamination.

At over 500pp, this book is a comprehensive and valuable source book for anyone involved in the design, testing and operation of cleanrooms.

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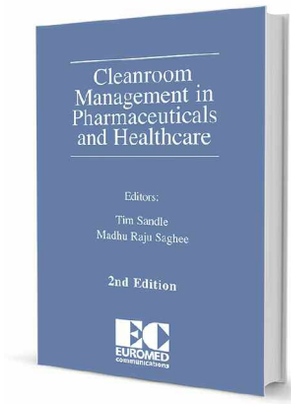

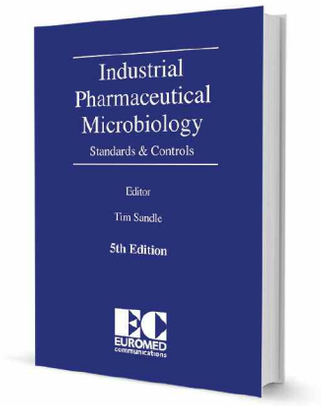

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*Foreword by Peter D. Smith**

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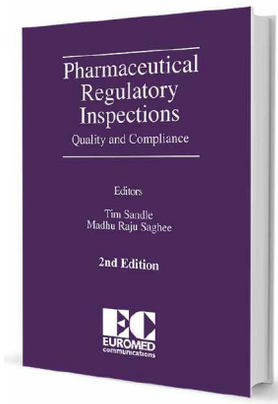
*Vice President, Strategic Compliance, PAREXEL Consulting, USA



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

United States of America

Field Alert Report (FAR) submission - Q&A

This draft guidance provides the agency's current thinking regarding the requirements for submission of FARs by applicants of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) and outlines FDA's recommendations for FAR submissions to help increase their consistency and relevancy. The guidance also addresses certain frequently asked questions.

Dissolution testing and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drug substances

This guidance is developed to provide manufacturers with recommendations for submission NDAs, INDs, or ANDAs, as appropriate, for orally administered immediate-release (IR) drug products that contain highly soluble drug substances. The guidance is intended to describe when a standard release test and criteria may be used in lieu of extensive method development and acceptance criteria-setting exercises.

Elemental impurities in drug products

This guidance provides recommendations regarding the control of elemental impurities of human drug products marketed in the USA consistent with implementation of ICH guidance for industry *Q3D Elemental Impurities* This guidance will also assist manufacturers of compendial drug products in responding to the issuance of the USP requirement for the control of elemental impurities.

Quality Attribute considerations for chewable tablets

This guidance provides manufacturers of chewable tablets for human use with the CDER current thinking on the critical quality attributes that should be assessed during the development of these drug products. It also provides recommendations for sponsors / applicants regarding the submission of developmental, manufacturing, and labeling information for chewable tablets in applications.

Chewable tablets are an oral dosage form intended to be chewed and then swallowed by the patient rather than swallowed whole. They should be designed to be palatable and be easily chewed and swallowed. Chewable tablets should be safe and easy to use in a diverse patient population of pediatric, adult, or elderly patients who are unable or reluctant to swallow intact tablets due to the size of the tablet or difficulty with swallowing. The availability of safe, easy-to-use dosage forms is important in clinical practice. Chewable tablets are available for many over-the-counter (OTC) and prescription drug products. The USP recognizes and differentiates between two types of chewable tablets:

- those that **may be chewed** for ease of administration, and
- those that **must be chewed or crushed** before swallowing to avoid choking and/or to ensure the release of the active ingredient.

The concepts in this guidance are applicable to both types of chewable tablets.

This guidance describes the critical quality attributes that should be considered when developing chewable tablets and recommends selection of acceptance criteria that are appropriate and meaningful indicators of product performance throughout the shelf life of the product.

Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management

FDA has issued this ICH document as a draft Guidance.

A harmonised approach regarding technical and regulatory considerations for lifecycle management will benefit patients, industry, and regulatory authorities by promoting innovation and continual improvement in the biopharmaceutical sector, strengthening quality assurance and improving supply of medicinal products.

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the firm's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation. The extent of operational and regulatory flexibility is subject to product and process understanding, application of risk management principles, and an effective pharmaceutical quality system.

Europe

Shortages of Medicines

The Commission met with experts from EU countries to discuss shortages of medicines. Shortages occur when supply cannot meet the demand for a specific medicinal product at national level. This

serious problem affects many patients across the EU and represents a threat to the wellbeing of all citizens.

The meeting was a response to the calls from the Council and European Parliament for the Commission to monitor the obligation of marketing authorisation holders to ensure continuous supply of medicines laid down in EU legislation. A summary of Member States measures to ensure continuous supply and a paper on the obligation of continuous supply to tackle shortages were agreed at the meeting.

EDQM publishes a new section dedicated to biotherapeutics on its website

The new biotherapeutics section summarises Ph. Eur. Commission activities and achievements in this field. In addition to clarification of the role of Ph. Eur. monographs in the biosimilars regulatory pathway, it describes the recently concluded P4-BIO pilot phase and the ongoing pilot phase on monoclonal antibodies ("MAB pilot phase"), explaining the strategy followed by the Ph. Eur. when setting requirements for the quality of this important class of biotherapeutics. It also describes various levels of flexibility integrated into Ph. Eur. texts, including those introduced recently to address the structural complexity, heterogeneity and compound diversity derived from different manufacturing processes of complex biotherapeutics.

New EDQM guideline "How to read a CEP"

This document is intended to give Industry and Competent Authorities clarification on the meaning of the statements laid down on the CEPs.

EMA identifies gaps in industry preparedness for Brexit

A recent EMA survey shows that marketing authorisation holders for more than half (58%) of the 694 centrally authorised products (CAP) with an important step in their regulatory processes in the United Kingdom (UK), are on track with their regulatory planning to ensure that their marketing authorisation remains valid once the UK leaves the European Union (EU).

However, for 108 (88 human products and 20 veterinary products), or 16%, of these medicines with manufacturing sites located in the UK only, there are serious concerns that the necessary actions will not be carried out in time.

For 10% of the products included in the survey, EMA received no feedback from companies.

EMA is liaising directly with the marketing authorisation holders who either did not reply to the survey or have indicated in the survey that they do not plan to submit the changes required by 30 March 2019 and have manufacturing sites in the UK only, as this could potentially lead to supply disruptions.

EMA has analysed feedback from the survey and is now looking in detail at those medicines where there are risks of supply shortages and will assess how critical these are.

International

ICH

New ICH Guidelines Q13 & Q14

The ICH Assembly agreed to begin work on two new Q topics for ICH harmonisation:-

- Continuous manufacturing (Q13)
- Analytical Procedure Development and Revision of Q2(R1) Analytical Validation (Q2(R2)/Q14)

ICH prepares for future new topics

The Assembly agreed to begin work on three new topics for ICH harmonisation:-

- Analytical Procedure Development and Revision of Q2(R1) Analytical Validation (Q2(R2)/Q14);
- Continuous manufacturing (Q13);
- Clinical electronic Structured Harmonised Protocol ('CeSHarP') (M11).

The Assembly also discussed future strategic areas for harmonisation by endorsing a strategic reflection paper entitled Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches. *(clearly ICH supports continuous manufacturing however there are some worries particularly in industry that such manufacturing is being held back because of lack of understanding / expertise in certain markets making global registrations and supply uncertain – mh)*

Products

First two marketing authorisations for chimeric antigen receptors (CAR) T-cell therapies in the EU:

The EMA Committee for Medicinal Products for Human Use (CHMP) at its June 2018 meeting recommended granting marketing authorisations for the first two chimeric antigen receptors (CAR) T-cell therapies in the European Union: **Kymriah** (tisagenlecleucel) and **Yescarta** (axicabtagene ciloleucel) are both advanced therapy medicinal products (ATMPs) intended for the treatment of certain blood cancers. Both were designated as orphan medicines during their development. They are also the first medicines supported through EMA's PRIME scheme to receive a positive opinion from the Committee.

USFDA approves first generic version of EpiPen

USFDA has approved the first generic version of EpiPen and EpiPen Jr (epinephrine) auto-injector for the emergency treatment of

allergic reactions, including those that are life-threatening (anaphylaxis), in adults and pediatric patients who weigh more than 33 pounds. Teva Pharmaceuticals USA gained approval to market its generic epinephrine auto-injector in 0.3 mg and 0.15 mg strengths.

Recall of porcine thyroid API from Sichuan Friendly Pharmaceutical Co., Limited, China

FDA is alerting active pharmaceutical ingredient (API) repackagers and distributors, finished drug manufacturers, and compounders that Sichuan friendly Pharmaceutical Co. LTD China, is recalling certain lots of porcine thyroid API due to inconsistent quality of the API. FDA recommends that manufacturers and compounders not use Sichuan Friendly's porcine thyroid API received since August 2015. This thyroid API comes from porcine (pig) thyroid glands and is used to make a non-FDA approved drug product, composed of levothyroxine and liothyronine, to treat hypothyroidism (underactive thyroid).

FDA placed Sichuan Friendly on import alert (66-40) on March 22, 2018, based on current good manufacturing practice (CGMP) deviations observed during an FDA inspection.

Ranier's Rx Laboratory issues voluntary recall of all sterile compounded products

Ranier's Rx Laboratory is now voluntarily recalling all sterile compounded drug products within expiry to the hospital or consumer level.

These drug products are being voluntarily recalled due to concerns that practices at the pharmacy have the potential to pose a risk of contamination to products that are intended to be sterile. These concerns arose following a routine inspection of the pharmacy by FDA. *(yet another worrying example of lack of sterility assurance in product from a compounding pharmacy.- how much longer will this go on?- mh)*

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

gmp review

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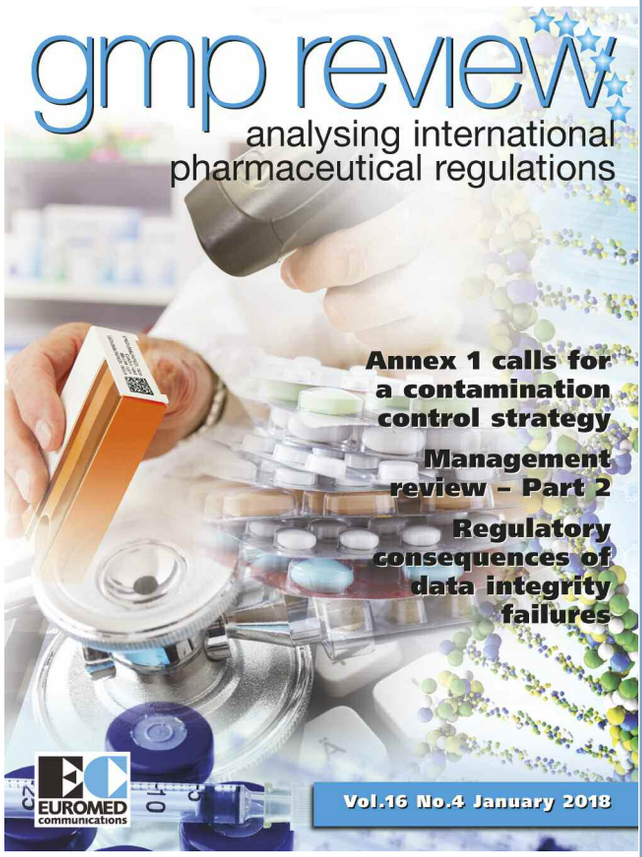
Summary

GMP Review provides information and informed comment on Good Manufacturing Practice and provides in-depth analyses of international pharmaceutical manufacturing regulations.

The journal also keeps readers up to date on the latest Directives, Regulations and Guidelines applicable to the pharmaceutical industry including the latest details on such important documents as Directives and Regulations from the FDA, EU, CPMP and ICH positions. Each item comes with analysis and comment on its effect on pharmaceutical manufacturers and their company.

In addition GMP Review provides the following information:

- News and commentaries on the implementation of new annexes to the Guide to Good Manufacturing Practice.
- Advanced warning on any proposals for further annexes.
- Informed discussion on revisions or additions to the FDA and other key regulatory and reference documents.



A selection of readers' comments:

"This journal has filled a gap in the market and is consequently very useful. I find it readable and accessible and hope that it continues in the same vein for the foreseeable future".

"We all find GMP Review the most useful publication about Quality Systems".

"Generally the issues are interesting, easy to read, understandable and informative – links are good".

"GMP Review is a very useful source of information, particularly for FDA issues. It covers a broad range of countries and gives just the right amount of information".

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We provide standard and bespoke cleanroom microbiology solutions to help you effectively manage your controlled environments and processes.

Founded in 1971, Cherwell Laboratories has evolved into a manufacturing and distribution company offering a range of products for environmental monitoring (EM), cleanroom bio-decontamination and validation of sterilisation processes. Located in Oxfordshire, our site includes a 1000m2 clean room manufacturing suite, warehousing, quality control, engineering and administration. Our business is built on the principles of ISO 9001 and a willingness to always help our customers.

Cherwell has strategically focused on building knowledge and expertise to service pharmaceutical and biotech manufacturing, compounding and the associated markets. We tailor our products and offers to meet the exacting demands within GMP manufacturing environments. We aim to build strong partnerships with QC microbiologists, laboratory managers and senior technicians responsible for delivering EM and sterility testing programs.

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How to use pharmaceutical excipient supplier GMP certification to reduce the qualification and audit burden

CORPORATE PROFILE

Today, Regulators expect that pharmaceutical companies verify that the excipients they use are produced to an appropriate level of GMP. Historically this has been done by auditing only some suppliers. However, today's audit burden required of both suppliers and pharma company users is impractical and unsustainable.

One way of verifying suitable GMP is the use of certifications schemes which must be independent and of demonstrable credibility. Regulators have indicated that such approaches would be acceptable provided the certification scheme met certain requirements that determine the scheme's credibility.

The EXCiPACT initiative, launched in 2012 was designed to fulfil these requirements. EXCiPACT asbl is a not-for-profit organisation comprised of a number of industry associations with members from both the manufacturer and user communities. As an 'association of associations' its independence is assured. EXCiPACT owns the published standard and has oversight of registered auditors and Certification Bodies. The scheme is finding great favour with the industry with all parties, including Regulators, and has already taken the place of many potential individual customer audits.

In 2018, EXCiPACT is organising a series of educational, one-day, free-to-attend seminars in Europe, India and N. America to which interested parties are invited to attend to learn the important facts that determine the credibility of independent certification schemes and how EXCiPACT certification can benefit both manufacturers and pharmaceutical users of excipients, whilst at the same time saving costs in supplier qualification. Speakers will include EXCiPACT certificate and audit report holders, a registered Certification Body, pharma company users and Regulatory expertise.

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Interested parties who wish to receive full details of these seminars as they become available should click on seminar@excipact.org.
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bottled brown

Beware the Black Box

Understanding

"What I cannot create, I do not understand.," said Richard Fenyman (1918 – 1988), Nobel Laureate physicist.

Do you understand how you create your medicines? I am sure you understand your part: development, pharmacovigilance, production, quality control, research, or whatever. However, I wager that you do not understand every part of the endeavour. You rely on a team of specialists. They do understand their specific areas. An example is qualified persons, with different areas of responsibility, trusting each other's certifications. You are comfortable with that because others are trained, competent and bound by financial, legal and moral responsibilities. I will return to that theme. What if your team member was an intelligent machine?

Progress

Automatons mimicking human behaviour have been designed. Clockwork was commonplace during the Renaissance. Edison's talking doll (1877) mechanically amplified sound from bumps in a grove of an internal gramophone record. We have, according to the philosopher and cognitive scientist Daniel Dennett (1942 -), developed all sorts of "clever tricks" (artefacts and thought-tools). These act as "cranes" to give our culture abilities that it lacked. General examples are computers, double entry bookkeeping and language; the pharmaceutical industry favours the CRISPR–Cas 9 technique, double-blind clinical trials and cGxP. Broadly, these lift humans' peripheral intellectual power. They help us do whatever we have chosen to do such as recognise patterns for new therapeutic uses for established marketed medicines in gargantuan data sets. The development of computers has been explosively rapid. Witness that the computer memory on Voyager (1977 technology) now travelling between the stars, is probably less than that in your car's *key fob*.

Until recently computers worked by brute number crunching. Now, cleverer algorithms and deep learning enable computers to solve problems that were previously insoluble, at least within one short human lifetime.

Buy me

New, equipment off-the-shelf entices us. We can buy something that tells us what we want to know but no longer fully understand how it does so. Moreover, as time passes, equipment proves reliable and tumbles in price. We undertake the task less ourselves, even while the warning "use it or lose it," niggles us. We know what goes into the box, what comes out and we check. Output is so useful, increasingly, that we cease to care that we are not sure about everything going on inside. Are you not part of a human team while not understanding what others are doing?

I now lay bare the danger. The black box vendor may over-hype the black box because that increases sales. It may be trusted to give opinion that facilitates choice of action. That is not a peripheral but a central human intellectual power. Humans may cede to the black box competence that it does not possess – *yet*. Adverse effects could be imaginable such as a substandard batch being released or not yet imaginable. Remember, too, that machines, like people, go wrong. If the default remedy of pressing the reset button fails, is a human repairer to hand? Is buying a new black box cheaper?

It is probably too late to avoid black boxes. Maybe, shortly, my caution will seem as quaint as a man with a red flag walking ahead of any self-propelled vehicle. But, arguably, humans should design in robust safety precautions to black boxes just as, in a sword, a guard separates grip from blade. We should use black boxes with eyes wide open, full training on limitations and risks, financial bonding and after signing a compulsory legal agreement accepting full moral and financial strict liability for the black box outputs.

Malcolm E Brown

events

DECEMBER

4–6 December 2018 – Amsterdam, The Netherlands
Cell Therapy Manufacturing & Gene Therapy Congress
https://lifesciences.knect365.com/celltherapy/

10–11 December 2018 – Rome, Italy
23rd International Conference on Pharmaceutical *Biotechnology*
https://biotech.pharmaceuticalconferences.com/

10-12 December 2018 – Huntington Beach, California
2018 ISPE Biopharmaceutical Manufacturing Conference
http://isp.org/conferences/

JANUARY 2019

21-22 January 2019 – London, UK
Pharmaceutical Microbiology 2019
www.smi-online.co.uk

23-24 January 2019 – Washington, DC
14th Biosimilars Summit
www.biosimilardevelopment.com

23-24 January 2019 – London, UK
Festival of Genomics
www.festivalofgenomicslondon.com

28-30 January 2019 – Washington, DC, USA
9th Annual Pharmacovigilance and Risk Management Strategies Conference
www.diaglobal.org/pharmacovigilance

28-31 January 2019 – Twickenham, UK
7th Annual Cool Chain Temperature Controlled Logistics Conference
www.coolchaineurope.com

FEBRUARY 2019

6-7 February 2019 – Prague, Czech Republic
Cleaning Validation
www.jpag.org

7 February 2019 – London, UK
Accelerated Development and Approval
www.jpag.org

12-13 February 2019 – Munich, Germany
Software Design for Medical Devices Europe
www.sdmdglobal.iqpc.co.uk

19-21 February 2019 – Amsterdam, Holland
Disposable Solutions for Biomanufacturing
www.disposablebiomanufacturing.com

21-22 February 2019 – Manchester, UK
14th Annual Biomarkers Congress
www.biomarkers-congress.com

25–26 February 2019 – Berlin, Germany
19th World Congress on Pharmaceutical Sciences and Innovations in Pharma Industry
https://industry.pharmaceuticalconferences.com/

25-28 February 2019 – Toronto, Ontario, Canada
Cold Chain Global Forum 2019
www.coldchainpharm.com

27-28 February 2019 – Rome, Italy
Parenteral Packaging
www.pda.org

MARCH 2019

5 March 2019 – Preston, UK
Dissolution testing: current and future considerations
www.jpag.org

11-13 March 2019 – San Diego, California
2019 PDA Annual Meeting
www.pda.org

13-14 March 2019 – Milan, Italy
20th Annual Clinical Trial Supply Europe
www.arena-international.com/ctseurope

18-19 March 2019 – Paris, France
15th International Conference on Nanomedicine and Pharmaceutical Nanotechnology
www.osa.org

18-20 March 2019 – Edinburgh, UK
17th International Conference and Exhibition on Pharmaceutics & Novel Drug Delivery Systems
www.novel-drugdelivery-systems.pharmaceuticalconferences.com

20-21 March 2019 – Houston, USA
9th Int Conference on Pharma Audit, GMP, GCP and Quality Control
https://gmp-gcp-quality-control.pharmaceuticalconferences.com/

25-26 March 2019 – Bologna, Italy
3rd European Conference on Pharmaceutics
www.europeanmeeting.org

APRIL 2019

3-4 April 2019 – Knutsford, Manchester, UK
Aseptic Processing Workshop
http://phss.co.uk

JUNE 2019

17-18 June 2019 – Stockholm, Sweden
7th European Biopharma Congress
www.biopharmaceutics.pharmaceutical conferences.com

SEPTEMBER 2019

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