YOU HAVE REACHED YOUR DESTINATION

How to navigate the differing regulatory routes in Asia Pacific, to achieve success in the world’s third largest pharmaceutical market

PLUS
Meeting report: The EMA’s annual review of the year
Interview: Heidi Marchand, FDA Assistant Commissioner
Consultant Editors for this issue

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Having completed his PhD in Molecular Biology from Imperial College, London, Ivan has worked as a Regulatory Affairs Consultant since 2003. Currently Assistant Vice President, Global Regulatory Affairs at Genpact Pharmalink, Ivan’s experience spans the pharmaceutical, consumer healthcare and generics industries. Recipient of TOPRA Distinguished Service Award in 2014.

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Cover illustration: The city of Xi’an, China, which marks the eastern end of the Silk Road.

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Erratum

The February 2016 issue of Regulatory Rapporteur published an article titled: “A regulator’s guide to the UK Early Access to Medicines Scheme”, which contained an error. In fact, as at October 2015, there have been three scientific opinions issued in the cancer area (two indications for melanoma and one indication for lung cancer), and not four as stated in the article. This error occurred during the production process and the authors highlighted it to the Managing Editor. The online version of this article is correct.

Regulatory Rapporteur is indexed on two Elsevier academic databases, Embase and Scopus. To access these go to embase.com/embase-pharmaceutical-research and info.scopus.com

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If you know of anyone else who may be interested, please pass this information on to them. If you are serious about a career in regulatory affairs, you cannot afford to miss this.
While the exact definition of what comprises the Asia Pacific region tends to differ depending on context, it is an oft-used cliché that the approximately 50 nations comprising the region that spans South Asia, East Asia, Southeast Asia, and Oceania are “united in their diversity”. Beyond this truism, however, is the fact that many of these countries are viewed as emerging markets that are experiencing rapid growth and present significant opportunities. Countries that are expected to experience double-digit levels growth over the coming few years include Vietnam, China, Sri Lanka, Myanmar and Bangladesh.

Indeed, Asia Pacific is the third largest pharmaceutical market in the world after North America and Europe. A steady rise in healthcare expenditure across the region, fueled by a rising middle-class, ageing population combined with the expiry of a number of patented drugs has meant that generics have proven to be a central driving force. Across the region as a whole, combined sales of prescription drugs and over-the-counter (OTC) medicines are forecast to increase from approximately $275 billion in 2013 to approximately $385 billion in 2018, representing a five-year compound annual growth of 7%.

While the diverse cultural nature and economic maturity of Asia Pacific’s markets pose challenges, substantial gains have been made by the Association of Southern Asian Nations (ASEAN), a collaboration of ten nations with a combined population of 621 million. To this end, ASEAN has made significant progress towards harmonisation through technical cooperation between member nations and implementation of guidelines and mutual recognition agreements in order to build a common platform for drug registration. The numerous challenges and opportunities that the ASEAN emerging regulatory landscapes present to us is reviewed in this edition of our journal, providing a comprehensive overview of documentation preparation, submission and post-approval requirements across this harmonised regulatory framework.

In contrast to the emerging and developing markets of the region, Japan, South Korea, Australia and New Zealand represent developed, economically mature markets with established regulatory frameworks. The Australian clinical landscape is also placed under the spotlight this month, with recent developments offering pharmaceutical manufacturers the opportunity to reach patients sooner and at lower cost than in many other Western countries, with the additional draw of significant tax incentives. A further article focuses on the clinical requirements of the East Asia markets of China, South Korea and Japan, which highlights the opportunities for collaboration that lie therein.

Outside of this month’s focus topic, we have in-depth coverage of the Annual European Medicines Agency’s Review of the Year and Outlook for 2016 (held on 19–20 November 2015). This meeting report provides insights into a range of topics including the development and innovation of new medicines, post-approval activities, the new EU Clinical Regulation and the involvement of patients and healthcare providers in the work of EMA and its committees. Presentations were given by an international panel of speakers from a variety of regulatory agencies, as well as industry experts.

Meanwhile, an Interview with Heidi C Marchand (Assistant Commissioner of Health and Constituent Affairs, FDA) provides a fascinating glimpse into the vital role that she performs, building trusted relationships with the FDA’s diversity of stakeholders on public health issues.

Pharmaceutical companies looking to maximise their return on investment are increasingly considering the region in their portfolios outside of the more mature markets of Australia, New Zealand and Japan, but only by understanding both the similarities and differences in regulatory processes across all individual markets can a truly global expansion strategy be successful.
This one-day workshop features discussions on eCTD topics and comes with an eCTD Workshop Guide that is also a handy reference manual for future use.

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• How the eCTD organises study files, including Node Extensions, Study Tagging Files and the regional requirements for datasets and case report forms
• The lifecycle management advantages of the eCTD
• The challenges and logistics of a submission.

Speakers
Margaret Gait – Submission Manager, Accenture Accelerated R&D Services
Husna Khatun – Senior Project Coordinator, Accenture Accelerated R&D Services

Go to topra.org/ectd1-16 for more information
Challenges and opportunities in the ASEAN emerging regulatory landscape

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Keywords
Association of South East Asian Nations (ASEAN); Asia Pacific (APAC); Emerging markets; ASEAN common technical dossier (ACTD); ASEAN common technical requirements (ACTR); Pharmaceutical Product Working Group (PPWG); Product registration; Lifecycle management; Post-approval variation.

Abstract
The ASEAN region is becoming an increasingly attractive prospect for pharmaceutical companies. ASEAN is experiencing impressive growth across a number of industries, including the healthcare sector, and the region’s regulatory framework is developing. Broad differences in infrastructure, economic stability, language, population size and existing legislation across ASEAN’s ten member states make cohesion within ASEAN challenging. However, efforts have been made and the ASEAN common technical dossier (ACTD) has now been implemented to varying degrees across all of the member states. The official timeframes for product registration, variations and renewals also vary between member states and the guidelines governing the regulatory requirements are more defined in some states than others. If pharmaceutical companies are prepared to meet the region’s challenges, the potential rewards may be great. Planned initiatives like the ASEAN Economic Community (AEC) aim to create a single marketplace for the region to further improve their economic strength through increased harmonisation.

Introduction
The Asia Pacific (APAC) region is currently undergoing a period of rapid growth. Its current population of four billion already constitutes 60% of the world’s population, and this figure is on course to reach five billion by 2050. From the perspective of the pharmaceutical industry, the APAC region represents a large and rapidly expanding market. Between 2001 and 2010, the industry’s sales more than doubled from US$97 billion to US$214.2 billion. To put these sales into context, the world’s largest pharmaceutical market – the US – saw a pharmaceutical sales value of US$325.8 billion in 2012. These APAC figures are not surprising considering the region includes the world’s second and third largest pharmaceutical markets, Japan and China. Global investors are beginning to look in depth at other areas in the region demonstrating potential for new and exciting growth. One such area demonstrating this growth is the Association of South East Asian Nations (ASEAN).

ASEAN was established in 1967 with the aim of promoting regional growth, peace and harmonisation among member states by assisting each other in economic, social, cultural, technical, scientific and administrative matters. Five countries initially signed the ASEAN declaration, founding the association: Thailand, Malaysia, Indonesia, Philippines and Singapore. Over the years, the organisation expanded to include Brunei, Vietnam, Laos, Myanmar (also known as Burma) and Cambodia. As of 2014, the region encompassed a population of over 620 million people and it is expected to grow to approximately 650 million people by 2020.

The ASEAN collaboration is achieved through mutual assistance initiatives in the form of training, education and maintaining close relationships with other similar organisations with a focus on harmonisation. One of the first initiatives by the group was the establishment of the ASEAN Free Trade Area (AFTA), which was designed to promote economic development and improve competitiveness through the elimination of trade barriers. The agreement was established in 1992, by the six-member ASEAN member states at that time, and has subsequently been a joining requirement. Figures suggest that the increased harmonisation is beneficial; if the ASEAN region were to be viewed as a single economy, it would be the seventh largest in the world with a combined GDP of US$2.4 trillion in 2013. In 2013, the five largest ASEAN economies combined – Thailand, the Philippines, Singapore, Malaysia and Indonesia – received greater foreign investment, at US$128.4 billion, than China, which received US$117.6 billion.

This article aims to give an overview of the ASEAN region’s current regulatory framework and efforts to harmonise regulatory objectives. Consideration will also be given to the numerous challenges and potential for future opportunities within the region.

ASEAN current regulatory affairs landscape
In 1999 ASEAN established the Pharmaceutical Product Working Group (PPWG) in an effort to develop a more sophisticated regulatory framework, which is at varying stages of implementation across the region. PPWG is comprised of representatives from each of the ten member states’ respective regulatory bodies (or government factions responsible for the regulation of pharmaceuticals), with attendance of each country being voluntary. The role of the PPWG has been to incorporate elements of the International Council for Harmonisation (ICH), relevant to ASEAN, into regional guidance. The PPWG is tasked with creating committees to assess the opportunities for regional regulatory harmonisation and to develop common guidelines; the findings of these committees are then reported back through the ASEAN Consultative Committee for Standards and Quality (ACCSQ).

Dossier preparation and submission process
A key area of focus for the PPWG is the inclusion of the ASEAN common technical dossier (ACTD) and the ASEAN common technical
requirements (ACTR) into the necessary requirements for product registration in the region. The ACTR provides guidelines for the compilation of a submission, in accordance with the CTD structure, and is comparable to the notice to applicants (NtA) Volume 2C in Europe. The CTD incorporates ICH guidelines and is comparable with the common technical document (CTD), as described in Table 1. Currently the ACTD is utilised in all of the member states to varying degrees, for example the health authority in Singapore, Health Sciences Authority (HSA), will accept submissions in either the CTD or ACTD format. Many of the ASEAN national health authorities require new registration submissions to be made using their own specified regional documents alongside elements of the ACTD. For example, a new registration submission in Laos requires the safety and efficacy documents outlined in parts I–IV of the ACTD and the health authority specific “LP2” form.12

There are multiple registration categories for new products throughout ASEAN, and the applicable categorisation will vary based on the member state in which the product is to be registered. For example, Thailand currently has just two major distinctions for new drug applications, “modern” or “traditional”. Modern products are then divided further into four sub-categories: household remedies whose sales require no licence; ready-packed drugs that can be sold in drugstores by nurses or other medical professionals; dangerous drugs; and specially controlled drugs.13 There are plans to replace the existing Thai sub-categories, with prescription-only, pharmacy-dispensing and home remedies, through the “New Drug Act of B.E.2546 (2003)”. The anticipated reclassification of the drug categories in Thailand would align them more closely with the categories used in Singapore: Prescription Only Medicines (POM), Pharmacy Only (P) and General Sales List (GSL).14 However, these categories are based on the assumption that patients will receive their medicines via a pharmacy and this is not the case in all of the member states. In Malaysia, drugs are often dispensed to patients directly by their physician, eliminating the need for the intermediary step of visiting the pharmacy.15

Approval timelines, following the submission of a product registration application, vary between the individual member states. The timelines can also vary within each state based on the type of product being registered. In Indonesia for example, orphan drugs have an approval period of 100 days; products which have been already been approved in countries with respected regulatory evaluation systems have an approval period of 150 days, and new products not covered by the previous two options have an approval period of 300 days.16 The respective product approval times for each of the ASEAN member states have been summarised in Table 2.

Traditional medicines are still widely used throughout ASEAN, predominantly in the rural populations where, as previously discussed, access to modern healthcare services can be limited. Traditional medicines are considered to be an important part of the culture in Asia and the Product Working Group for Traditional Medicines and Health Supplements (TMHSPWG) was established in 2004 as part of economic initiatives designed to make the ASEAN region more competitive. Among other things, the TMHSPWG has been tasked with: harmonising technical requirements for traditional therapy registration; creating guidelines regarding good manufacturing processes (GMP); substantiation of therapeutic claims; and labelling requirements.17

National online submission portals are beginning to be used for submissions in some member states, for instance, registration applications in Singapore can be made via its online submissions platform, PRISM.18 In Malaysia, Part I and II of the ACTD must be submitted to its regulatory authority via its online platform, QUEST3, but Part III and IV can be submitted locally in a hard copy.19 Currently there is no centralised submission portal to facilitate a simultaneous dossier submission across multiple ASEAN member states.

### Post-approval variations

ASEAN have produced a central guidance document, “ASEAN Variation Guideline for Pharmaceutical Products”20 which sets out the post-registration variation categories and their parameters. Variation applications can be categorised as a “major variation” (MaV) or a “minor variation” (MiV). MaVs cover any changes to a registered product that may significantly impact its quality, safety or efficacy, and MiVs relating to administrative changes, or changes that will have little effect of the quality, safety or efficacy of the product. MaVs require prior approval from the national regulatory bodies and the variation applications require extensive documentation to substantiate the proposed change. According to ASEAN guidelines MaVs will be approved “within a duration subject to country-specific proposal”. For example, in Singapore MaVs are

### Table 1: Comparison of the ASEAN ACTD and ICH CTD component structure.

<table>
<thead>
<tr>
<th>Components</th>
<th>ASEAN ACTD</th>
<th>ICH CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive table of contents and</td>
<td>Part I</td>
<td>Module 1</td>
</tr>
<tr>
<td>regionally specific administrative documents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality, nonclinical and clinical overall</td>
<td>Included in Parts II, III &amp; IV</td>
<td>Module 2</td>
</tr>
<tr>
<td>summaries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality documents</td>
<td>Part II</td>
<td>Module 3</td>
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<tr>
<td>Nonclinical study reports</td>
<td>Part III</td>
<td>Module 4</td>
</tr>
<tr>
<td>Clinical study reports</td>
<td>Part IV</td>
<td>Module 5</td>
</tr>
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Minor variations are further sub-divided into “minor variation – notification” (MiV-N), and “minor variation – prior approval” (MiV-PA). MiV-Ns are so called “Do and Tell” variations – where the market authorisation holder (MAH) may implement the necessary change and notify the relevant health authority thereafter – which are appropriate for small changes such as change of address for the MAH. The MiV-N variations are comparable to EU Type IA variations. MiV-PA variations require prior approval from the relevant health authority before the change can be implemented; similarly to MaVs the period of time associated with the approval of MiV-PA variations will vary depending on the approval timelines associated with member states. Examples of MiV-PA variations include labelling changes, an additional site of product manufacture, or changes to the excipients of a registered product. The MiV-PA variations are comparable to Type IB variations in the EU.

Renewal applications in ASEAN are required to be submitted every five years in almost all of the member states. The renewals process is particularly sophisticated for products registered in Singapore; renewal applications can be submitted via an online platform, “Renew@PRISM”, and more than one product renewal can be included per application. A key benefit of Singapore’s online submission platform, PRISM, is that it will generate an automatic notification to the MAH two months before and again one month before the expiry of a product licence. Each successful renewal in Singapore extends the licence of the product for a year, at which point a new renewal application is required.23

Additional post-approval activities
The harmonisation of adverse event reporting and pharmacovigilance (PV) in ASEAN presents a real challenge due to the previously discussed differences between the member states. As PV activities are also a relatively new concept in the region there is a shortage...
of qualified persons with the necessary expertise to support the function.\textsuperscript{24} One example of a harmonised initiative which has seen successful implementation in ASEAN is the post-marketing alert (PMA) system. The PMA system is designed to facilitate knowledge sharing between the ten member states’ regulatory authorities regarding any post-marketing safety concerns that have led to the suspension or withdrawal of a particular product. The PMA system can also be used to circulate notifications on new restrictions and product safety. However, the PMA system is not widely utilised by all ASEAN members, perhaps in part due to a lack of regional awareness on the importance PV plays in continually improving drug safety.\textsuperscript{25}

ASEAN member states have similar restrictions in their legislation covering the advertising of medicinal products. No member state permits pharmaceutical advertising aimed directly at consumers; however, they allow advertising aimed at healthcare professionals. In some member states, pharmaceutical companies can publicly advertise the sale of products which are available as over-the-counter drugs, or their equivalent. For instance, in Thailand it is possible to promote products registered in the “Household Remedies” category, once they have received approval from the Thai regulatory body.\textsuperscript{26}

**Challenges facing ASEAN**

One of the largest challenges facing ASEAN is the harmonisation of a diverse group of countries. The ten member states have large contrasts in a number of key fields, for example, different languages and vast ranges in population.

The ASEAN region has a population of more than 600 million,\textsuperscript{27} however, distribution is uneven across the individual nations. For example, with a population of 252 million, Indonesia represents a potential market 610 times the size of Brunei Darussalam, which has a population of just 413,000 people.\textsuperscript{28} There is also broad economic diversity; in 2014 the most urban member state, Singapore, had an average GDP per capita of US$82,800, one of the highest in the world,\textsuperscript{29} whereas Laos had an average GDP per capita of just US$5,000.\textsuperscript{30}

The economic inequalities between the countries extend to differences in healthcare spending at both the individual and national level. In 2013, the total healthcare expenditure in Indonesia was US$26.6 billion, equating to approximately US$106 per capita, whereas Myanmar had a total healthcare expenditure of US$1.1 billion, which equated to approximately US$20 per capita.\textsuperscript{29}

Consideration should also be given to the fact that the level of health insurance coverage is not uniform across the region. In most member states, a large proportion of the healthcare bill is paid for by the individual, rather than the state.\textsuperscript{30} More than 50% of healthcare spending in Cambodia, the Philippines and Singapore is paid for by the individual, rather than the state.\textsuperscript{30} More than 50% of healthcare spending in Cambodia, the Philippines and Singapore is paid for by the individual, rather than the state.\textsuperscript{30} More than 50% of healthcare spending in Cambodia, the Philippines and Singapore is paid for by the individual, rather than the state.\textsuperscript{30}

The WHO responded to the claims by sub-dividing the ASEAN region, and the trend towards increased healthcare spending in many of the member states, would suggest that ASEAN’s regulatory affairs will continue to develop through increased industry awareness and investment.

In 2007, ASEAN member states committed to the creation of an integrated economic region known as the ASEAN Economic Community (AEC). The ASEAN pharmaceutical sector falls under the jurisdiction of the new AEC, through the AFTA, and the aim is that a single market would further increase the region’s ability to compete globally, through improving its economic development. However, it has become evident that the original implementation date of 2015 was unrealistic and the move towards economic harmonisation will need to be more of a gradual transition.\textsuperscript{31}
Conclusion

ASEAN must now focus on increased harmonisation of the regulatory framework, implemented equally across all member states, to ensure every individual has access to genuine, safe and efficacious medicine, irrespective of their location or demographic. The challenge facing ASEAN is how they can achieve their aims, while accommodating the varying stages of development of each member state, without becoming entrenched in bureaucratic systems which would lead to delays in product registration, and ultimately in patient care.

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34. Focus – Asia Pacific
Clinical trials in East Asia: Requirements, collaboration and considerations

It is important to continually bear in mind that any difference in ethnic factors (intrinsic factors and extrinsic factors such as local clinical practice and socioeconomic conditions) may impact a drug’s efficacy and safety, including within and across countries in Asia. During the design of clinical trial programmes, a review and evaluation of available data on the effect of ethnic differences must be carried out. Time invested in this review can add significant value to any subsequently-submitted bridging evaluation package.

Economic statistics and demographics for China, Taiwan, South Korea and Japan are highlighted in Table 1. Information on each country’s regulatory setting and their requirements for drug registration are given below.

China
The China Food and Drug Administration (CFDA) is the national authority that reviews and approves clinical research. The key challenge for performing clinical trials in China is the relatively long regulatory approval timeline of clinical trial applications, which can be up to 12 months from submission. Additionally, CFDA approval and ethics committee/institutional review board (EC/IRB) approval are not in parallel. This is due to the high volume of regulatory applications, with up to 8,000 or more applications each year for investigational new drug/c clinical trial applications (INDs/CTAs), new drug applications (NDAs), renewals and variations. In 2015, China’s central government urged CFDA to take action to reform drug evaluation. CFDA’s mission includes the encouragement of new drug innovations and multinational global trials with the US and the EU.

In terms of clinical trial requirements for drug registration, full Phase I–IV clinical trials are required for new drugs developed locally. Based on the current legislation for new drug registration and administration (CFDA order #28 in 2007), the CFDA has established the requirements on minimum sample size:

- Phase I study: At least 20–30 subjects
- Phase II study: At least 100 subjects in testing arm
- Phase III study: At least 300 subjects in testing arm
- Phase IV study (post approval): At least 2,000 subjects

However, for new foreign drugs that are already approved outside China, the clinical trial requirements for import drug registration are as follows: a pharmacokinetic (PK) study in China and a Phase III study with at least 100 pairs (100 subjects in the testing arm and 100 subjects in the control arm) in China. If a foreign-developed new drug already has a global or regional Phase III trial including China, and meets the minimum sample size requirement, these Chinese data can be used for Chinese registration.

Taiwan
In Taiwan, approval of clinical trial protocols must be obtained from both an IRB and the Ministry of Health and Welfare (MOHW). The IRB or ethics committee of the individual hospitals will review the protocol for any ethics concerns and the clinical trial protocol must also be reviewed and approved by the Taiwanese FDA (TFDA, part of the Ministry of Health and Welfare). Full Phase I–IV clinical trials are required for new drug development.

Abstract
Asia Pacific has become an increasingly important region for the clinical trials industry. In particular, East Asia (comprising China, including Taiwan and Hong Kong, South Korea and Japan) with more than 20% of the world’s population, plays a very important role. This article summarises clinical trial requirements for drug registration in each East Asian country, with updates on collaborations and considerations for regulatory success in the region.

Introduction
Over recent years Asia Pacific, one of the world’s fastest-growing pharmaceutical markets, has become an increasingly attractive region for the conduct of clinical trials. It offers many benefits: research costs are considerably lower; there is a genetically diverse, often treatment-naive, population; pharmaceutical manufacturing competence is increasing; and healthcare infrastructures are being embedded in developing Asian countries. However, there are several hurdles to overcome to successfully conduct clinical trials in the region, including ethical, clinical, scientific and regulatory issues.

The number of multi-regional clinical trials that involve Japan, China and South Korea has grown in recent years as companies become increasingly aware of the requirements, expectations and possibilities. This environment will also continue to be influenced by available knowledge on the types and frequency of metabolic enzyme polymorphisms and genetic profiles which, among the various ethnicities in Japan, China and Korea are thought to be similar. Some medicinal products have recently been approved based primarily on data originating from pivotal global clinical trials with a significant contribution of patients from East Asia. Over the past few years Japan’s Pharmaceutical and Medical Devices Agency (PMDA) has increasingly accepted data from global clinical trials which have included patients from East Asia for review within new drug applications.

Keywords
Asia Pacific (APAC); East Asia; China; South Korea; Japan; Pharmaceutical and Medical Devices Agency (PMDA); China Food and Drug Administration (CFDA); Taiwan FDA (TFDA); Korean Ministry of Food and Drug Safety (MFDS); Ethnosensitivity; Clinical trial; Global trial; Pharmacokinetics (PK); Pharmacodynamics (PD); Bridging data.

Authors
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of the MOHW). Submissions to both the IRB and the MOHW can be made in parallel.

The timelines for IND review/approval are a minimum of four weeks. In cases where a review meeting is required, the timeline for regulatory authority approval could be at least three to five months, depending on the sponsor’s response to TFDA comments or queries.

For the IND of a global clinical study (same protocol number) which has been approved by at least one of the listed ten countries (Germany, US, UK, France, Japan, Switzerland, Canada, Australia, Belgium, Sweden), the IND approval may be completed within 15 days if TFDA has no comments on the study.

In terms of clinical trial requirements for drug registration in Taiwan, there are four scenarios for the NDA review process:

- Abbreviated review with two certificates of pharmaceutical product (CPPs): Both US FDA CPP and EMA CPP are required, with the NDA approval reliant on foreign clinical data.
- Accelerated review with one CPP: TFDA requests a pivotal clinical trial in Taiwan, pivotal study involvement: Phase I with at least ten valid Taiwanese patients; Phase II with at least 20 valid Taiwanese patients; Phase III with at least 80 valid Taiwanese patients or Phase III with at least 30 valid (or 5%, N>200) or 10 (N<200) in total if the Phase III study report will be reviewed by FDA/EMA for NDA registration.
- Standard review with no CPP available: TFDA requests early phase studies involvement, Phase I plus Phase III or Phase II plus Phase III. Phase I with at least ten valid Taiwanese patients, Phase II with at least 20 valid Taiwanese patients and Phase III with at least 80 valid Taiwanese patients.
- Other studies with no Taiwanese patient data: A bridging study evaluation (BSE) is required, either before NDA submission or in parallel. TFDA will determine if a bridging study is required or not after BSE.

South Korea

The Korean Ministry of Food and Drug Safety (MFDS), formerly the Korean FDA (KFDA), is the competent authority for drug and medical device regulations. In order to conduct a clinical trial in Korea, the sponsor must obtain both regulatory and IRB approval in parallel. The MFDS generally recommends that sponsors engage in pre-IND consultations as best practice for new chemical entity (NCE) and new biological product evaluations. The requirements for local bridging data to global clinical data packages are as per MFDS legislation and ICH E5, and are as follows:

- In addition to foreign clinical data, PK study data, pharmacodynamic (PD) study data or dose-response study data, or safety/efficacy data from a confirmatory trial in Korean patients (living inside/outside Korea) will be required.
- There are no official requirements or patient sample sizes stated in the regulations. However, according to the bridging study casebook published by MFDS in January 2015, the ratio of Korean subjects who participated in global Phase III studies was 15.9% (min: 0.6%, max: 50.5%) of the total subjects included in the clinical data submitted as bridging data for new drugs from 2009 to 2013.
- If the clinical data from Korean patients in a global clinical trial are considered insufficient, a local bridging study is required, in which case a PK/PD study, dose-response study, or confirmatory study for safety/efficacy would be needed.3,4

Regulatory approval for an IND typically takes around one to two months, especially if MFDS asks for supplementary information. This request will usually include study design and rationale, nonclinical/clinical safety and efficacy, and in the latter case this is often due to limited information in an application package (e.g., investigator’s brochure only) compared with the package for INDs in China and the US. The Korean government has made efforts in recent years to

Table 1: Economic statistics and demographics for China, Taiwan, South Korea, and Japan.

<table>
<thead>
<tr>
<th></th>
<th>China</th>
<th>Taiwan</th>
<th>South Korea</th>
<th>Japan</th>
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</thead>
<tbody>
<tr>
<td>GDP (PPP)</td>
<td>$18 trillion</td>
<td>$1 trillion</td>
<td>$1.8 trillion</td>
<td>$4.8 trillion</td>
</tr>
<tr>
<td>Per capita GDP (PPP)</td>
<td>$13,000</td>
<td>$47,000</td>
<td>$36,000</td>
<td>$38,000</td>
</tr>
<tr>
<td>Real GDP growth rate</td>
<td>7.0%</td>
<td>3.6%</td>
<td>3.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Population (millions)</td>
<td>1,370</td>
<td>23.4</td>
<td>50.5</td>
<td>127.3</td>
</tr>
<tr>
<td>Ethnic diversity</td>
<td>92% Han; 8% minority groups</td>
<td>Taiwanese (including Hakka) 84%, mainland Chinese 14%, indigenous 2%</td>
<td>Very homogenous</td>
<td>98.5% Japanese, 0.5% Korean, 0.4% Chinese, 0.6% other</td>
</tr>
<tr>
<td>Pharmaceutical market size</td>
<td>$100 billion</td>
<td>$5.5 billion</td>
<td>$22 billion</td>
<td>$120 billion</td>
</tr>
<tr>
<td>Projected growth rate</td>
<td>15.0%</td>
<td>4.0%</td>
<td>4.0%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>
decrease approval times by maintaining consistency and increasing transparency in terms of good review practice (GRP). For Phase I studies in healthy volunteers, MFDS accepts English protocols, and if the pre-review is as per the “Rules of Safety for Drugs”, MFDS review only takes 14 days. The IRB approval process can be performed in parallel to the regulatory approval process. Typically, IRB approval takes one to two months.

Japan

In almost all cases, non-Japanese sponsors will need to conduct at least some clinical trials in Japan in order to obtain product approval to market medicinal products or medical devices in Japan. More often than not, foreign clinical data by itself will not suffice for Japanese product approval.

The Ministry of Health, Labor, and Welfare (MHLW) oversees the regulation and safety of pharmaceuticals, medical devices, cosmetics and food. Since the passage of the revised Pharmaceutical Affairs Law (PAL) in 2002, the MHLW has undergone substantial restructuring. One of the most significant changes was the establishment of the independent PMDA in April 2004. The PMDA was formed by merging three separate organisations that previously had oversight for regulatory affairs for drugs and medical devices. The goal of this independent agency was to reduce submission timelines and improve the quality of submission applications in order to bring safer and more efficacious medicinal products to the market in a more timely manner.

For a new drug registration in Japan, full Japanese bridging clinical development (Phase I–III) is required as per ICH E5. PMDA will accept Asian data provided that includes a “significant number” of Japanese patients.

The different clinical development/regulatory strategies that can currently be considered options in Japan include:

- Japan-only (single-country) development
- Bridging strategy to extrapolated data generated outside of Japan
- Fully integrated global development including confirmatory global clinical trials involving Japan.

When Japan is part of a global development, a decision needs to be made to include Japan is a full global development study or programme that also incorporates the US and/or the EU, or devise an East Asia development strategy that covers some or all of the countries of Japan, China and South Korea (and potentially the different regulatory requirements of Taiwan and Hong Kong).

These are important decisions, at a critical stage of development (decisions should be made before Phase II, or in early Phase II at the latest) and will necessitate an analysis of the target product profile (TPP), the clinical trial protocol(s), timing and costs of the clinical development, subsequent timing of drug registration and the ultimate value of the product to the market and the sponsor.

Collaboration between China, South Korea and Japan

Considering the globalisation of new drug development, investigating East Asian data may be the key in confirming appropriate doses for the Asian population and to establishing a good foundation for global studies including these populations.

The proposed collaboration is based on ethnic similarities among Chinese, Korean and Japanese people (including genetic and cultural similarities), with the aim to improve the clinical trial environment and to meet the requirements for emerging drug markets in this region. These three countries concluded that regulatory collaboration is important in order to develop better drugs through collecting clinical data efficiently in East Asia.

From 2008 to 2011, there were several meetings between the respective regulatory authorities of these three countries, represented by Director-General Meetings and meetings of Working Groups on Pharmaceutical Affairs.

At the outset, the China-Japan-Korea Director-General Meeting on Pharmaceutical Affairs (“DG meeting”) established a working group (WG) to perform substantive works regarding the following two projects:

1. **Research on ethnic factors in drug clinical trial data from the three countries.** The aim of this research is to evaluate ethnic factors in clinical trial data from the three countries, primarily in terms of PK and PD. Any observed ethnic differences will be subject to deeper analysis and, according to the results, consideration will be given to full sharing of clinical data generated from these three countries. An implementation project is being coordinated by Japan. The work-plan and implementation of the project will be reported by the WG to the DG meeting, and will be initiated once there is consensus between the three countries. A principal researcher is designated by each of the three countries and is allocated to the WG. These researchers will collaborate to review data from each of the three countries. Progress will be reported to the WG which can then establish a subsidiary group – a Research Group. The Research Group is a scientific discussion group (not decision-making) where experts will develop proposals to the WG.

2. **Information exchange and cooperation on drug clinical trials.** The objective here is to exchange information on drug clinical trials both regularly and on an ad hoc basis. Korea is coordinating this project. The regulatory authorities of the three countries will, according to the agreement on the scope of information, exchange information on drug clinical trials. This does not prevent any of the three participants from providing any kind of information to other regulatory authorities on any basis. When information is exchanged between authorities, this will be shared with the relevant sponsor.

Following the fourth DG/WG meeting, held in Tokyo in October 2011, the PMDA website published a summarised discussion of outcomes, covering the undertaking of three key projects:

1. **Research on ethnic factors.** This project will be coordinated by Japan. To assess ethnic differences in PK, it is recommended that a single protocol controlling extrinsic factors should be used and applied uniformly to the study populations. From existing data, it can be seen that for some drugs, ethnic differences in PK were found to be non-existent under controlled conditions. As polymorphisms of the relevant genes affects the PK of a drug, genotypes of study subjects should be identified and taken into consideration before evaluating the clinical data. It was agreed to continue further research on ethnic factors from the viewpoint of PK and PD analysis.

2. **Information sharing.** This project will be coordinated by Korea. It was acknowledged that this project is critical to ensuring and increasing mutual understanding of the regulatory frameworks for clinical trials in the three countries. It was agreed that the WG continues to progress this project and ensure information exchange on clinical trials between the three countries.

3. **Guidelines on regional clinical trials.** This project was proposed by China. It was recognised that this project is of practical
importance in order to strengthen the cooperation between Korea, China and Japan. The DG agreed that China will coordinate the WG’s work to create guidelines on regional clinical trials in conjunction with Korea and Japan. China will prepare a concept paper on a future guideline for regional clinical trials, with the cooperation of Korea and Japan.

The fifth China-Japan-Korea Director-General Meeting was held in Qingdao, China, on 19 November 2015. At this meeting there were presentations of regulatory updates from each country and discussions were held on associated topics such as multi-regional clinical trials (MRCT). Further details regarding the outcome of this fifth meeting are still pending. The next China-Japan-Korea Director-General Meeting will be held in the second half of 2016.

This initiative has the potential to bring beneficial results for East Asia collaboration in the following ways:

- Based on genetically similarity, pathogenesis and prevalence of diseases similarity, dietary habit/social factor similarity, indications of diseases that are prevalent and relevant in the region can be jointly investigated and developed.
- Shorter timelines for new drug approvals as the benefit of clinical data sharing among the three countries is realised.
- May result in more common clinical data requirements and lead to more efficient development of products.

Regulatory considerations for global trials in East Asia

There are several factors to be taken into consideration relating to global clinical trials being conducted in Asia, including:

- Commercial priority: For what purpose are the data required? Is it for market approval in an East Asian country or countries, and/or for US or EU approval? Or is it worth considering a separate East Asia clinical trial for drug registration in this area? Will sufficient patients be allocated to meet regulatory requirements and expectations? Each country has its own new drug registration and bridging data requirements which need to be taken into consideration. A detailed discussion with regulatory experts is crucial to develop a regulatory strategy for this area.

- Epidemiology/disease prevalence/perceived seriousness of disease in East Asia, comparing to that of the US and EU: For diseases with high morbidity in East Asia (eg. gastric cancer, hepatitis) of which the conduct of confirmatory studies in one country alone is difficult, proactive planning of a global clinical trial in East Asia may contribute to the improvement of the efficiency and quality of clinical development of a drug.

- Ethnosensitivity: What is the clinical relevance of observed differences between East Asia and other populations? It is essential to ensure PK/PD inter-ethnic dose-finding studies early in drug development, as clarity on any ethnosensitivity is critical. Global clinical trials conducted in East Asia need to be designed and conducted based on prior sufficient evaluation of the effect of ethnic difference on the efficacy and safety of the drug. Where a sponsor is able to provide relevant evidence, from good quality scientific and technical reviews, of likely ethnosensitivity (or lack of ethnosensitivity) there is a reasonable opportunity to successfully manage the scope of the clinical trial(s) required to an appropriate level, reducing the costs and time of development. This also requires high-quality, regular communication and information-sharing with the scientific decision-makers at the regulatory authorities. Over time, such evidence will promote deeper understanding of drug-related ethnic factors and drive further rationalisation in requirements and process.

- Consider the regulatory timelines in East Asian countries compared with the schedule of a global programme. For example, China CFDA approval for global trial IND usually takes up to 12 months, excluding around three to four months of dossier package translation/preparation, and around another six months for site EC approval and start-up, as CFDA and site EC approval are not in parallel. For Japan, a company will need to consider whether a pre-IND consultation meeting with PMDA is necessary, especially for first protocol submission of new drugs in Japan; usually it will take around four to five months to plan and execute this PMDA consultation meeting.

- Comparator drug approval: It is important to establish whether the drug used as a comparator in the protocol has been approved in each country. For example for China, if the comparator drug and its indication have not been approved in China, the protocol cannot be approved by CFDA.

Conclusions

Considering the global nature of clinical development (and subsequent registration and launch onto East Asian markets), there will continue to be an increased focus on the inclusion of a large number of patients in China, Japan and South Korea. This is illustrated by the steady increase in clinical trial activity in Asia Pacific overall, with pockets of growth observed in various East Asian countries.

However, as each country has developed its own set of regulations on new drug registration and bridging data requirements, the current challenge is how to develop the most cost-effective and time-saving strategies for clinical plans. In order to launch new products, an in-depth understanding of the local regulatory environments is required, with an overall consideration of the similarities and differences between each country.

Although there is currently no regulatory harmonisation between China, Korea and Japan, clinical trial data with subjects from these countries could provide relevant data and offer strong support for local IND or NDA evaluation based on the ethnic similarities of the populations. Since 2008, the heads of the health authorities from these countries have held annual meetings to discuss regulatory collaboration, including research on ethnic factors through PK and PD analysis, promoting mutual understanding and sharing clinical trial information with a view to developing harmonised new clinical trial guidelines for the region. This regional regulatory collaboration will add great value to new drug research, the benefits of which will not only be seen in East Asia but also globally.

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Maintaining a global clinical advantage: A year in Australian regulatory affairs

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**Keywords**
Australia; New Zealand; Therapeutic Goods Administration (TGA); Clinical Trial Notification; R&D Cashback; Biosimilars; Orphan drugs.

**Abstract**
The Australian regulatory environment offers pharmaceutical developers the opportunity to reach the clinic faster and at lower cost than in other Western countries, with additional significant tax incentives. The Therapeutic Goods Administration (TGA) is a full-cost recovery regulatory agency, tasked with effective and timely regulation of therapeutic goods in the country. Over the past year, domestic and international affairs have led to a number of reviews of TGA working policy and utility, seeking to maintain Australia’s regulatory advantage and high standards, while looking to future need. In this article, we review some of the key recent news events affecting the Australian advantage – and potential new future advantages.

**Domestic affairs**
In December 2003, an agreement was reached between the Governments of Australia and New Zealand to establish a joint agency for therapeutic product regulation,1 borne from awareness of geographic proximity, longstanding friendship, a historical, political and economic relationship and a shared commitment to safeguarding public health and safety. The intended fusion of the Australian Therapeutic Goods Administration (TGA) and New Zealand’s Medsafe to form the Australia New Zealand Therapeutic Products Agency (ANZTPA) was initially targeted for establishment on 1 July 2005. This was eventually pushed back to mid-2016 with three stages of implementation:

- Commencement of a programme of business-to-business (B2B) projects and work-sharing, to consolidate national regulatory systems and resources and to streamline and improve regulatory practices
- Establishment of a single entry point for industry and agreeing a common trans-Tasman regulatory framework
- Integration of business operations.

By the final stage, implementing legislation would mandate that the TGA and Medsafe be absorbed into the ANZTPA. However, delays followed, and in November 2014, in a joint statement between the Ministers of Health of both Australia and New Zealand, the two countries agreed to terminate the ANZTPA project, justified by the findings of a comprehensive review of progress and assessment of the costs and benefits to each country of proceeding. Both countries stated intentions to pursue further harmonisation programmes, including a new information-sharing agreement and mutual recognition of good manufacturing practice (GMP) audits. Subsequently, the New Zealand Government has announced intentions to develop a new therapeutic product regulatory regime, with a Bill to be introduced to Parliament in 2016. Such a regime will cover medicinal products, medical devices and advanced therapy medicinal products (ATMPs) which are currently not fully regulated in New Zealand.2 The Guideline on the Regulation of Therapeutic Products in New Zealand (GRTPNZ), which will replace the existing New Zealand Regulatory Guidelines for Medicines (NZRGM), is under construction, having been delayed by prior uncertainty over the fate of the ANZTPA.

Both separate to and as a result of the termination of the ANZTPA project, the TGA has been pursuing active review of its regulatory procedures and programmes, key performance indicators and transparency. In October 2014, the Australian Government announced a review of the country’s regulatory framework for medicines and medical devices, seeking to identify unnecessary, ineffective and duplicative regulation eligible for modification or removal, and to identify opportunities to enhance the framework such that Australia remains on top of global trends in marketing, manufacturing and regulation. Recommendations followed in June 20151 that focus on expansion of marketing approval pathways, including:

- Expedited assessments in defined circumstances and the capacity to use assessment reports from comparable overseas regulators
- Identification of comparable overseas regulatory authorities using transparent criteria
- Enhanced but streamlined post-marketing monitoring requirements
- Improved transparency
- Streamlined access to medicines unapproved in Australia
- Infrastructure rearrangements to support the above.

A second review, focusing on complementary medicines and advertising of therapeutic goods, followed in July 2015. The review of medicines and medical device regulation represents a substantial portion of progress by the Australian Government and TGA in implementing the contents of a 2011 Blueprint for TGA reforms, published in response to major reviews of TGA transparency, regulation of medicine advertising, health technology assessment (HTA) and the existing complementary medicine and medical device regulations.3 In addition, in May 2015, the TGA released a discussion paper regarding the utility of the Orphan Drugs Program;4 established in 1997, the programme waived fees for evaluation and registration of drugs for rare diseases, with some jurisdictions providing additional tax benefits, increased periods of market exclusivity and grant programmes, to provide incentives to sponsors to bring medicines for a small population to market. The 2015 review sought to ascertain whether the programme was still fulfilling its intended purpose.
For example, by virtue of definitions specified in the Therapeutic Goods Act 1989 (as amended) and the Biologicals Regulatory Framework 2011, products made from, or containing, human cells or human tissues used to treat, prevent or diagnose disease, injury or susceptibility to injury or that modify physiological processes of a patient do not qualify for orphan designation in Australia — thus suggesting a therapeutic product class with potential utility in treatment of rare disorders may be excluded by outdated legislation.

Finally, in January 2015, the TGA released a discussion paper on the appropriateness of current Australian regulations relating to autologous stem cells, which, under certain conditions, bypass the Therapeutic Goods Act 1989. This has raised concerns, particularly with autologous mesenchymal stem cells, for which it has been suggested that greater regulation may be appropriate. The TGA has not, to date, published the outcomes of the orphan drug and stem cell consultations.

**TGA on the global stage**

Australia has committed to multiple international collaborative and harmonisation programmes, placing it at the leading edge of regulatory developments. Furthermore, Australia offers a fast and pragmatic regulatory pathway for Phase I–II studies, providing an attractive place for biotech companies to conduct initial clinical trials. The Clinical Trials Notification (CTN) scheme means that sponsors can pass a review cycle of four to eight weeks based on a protocol, investigator brochure and, if required, an independent toxicology report. Australia therefore represents a much faster timeline into the clinic compared with other countries. Nonetheless, the Australian National Health and Medical Research Council (NHMRC) continues to further streamline its research governance process. A “Good Practice Process for Site Assessment and Authorisation Phases of Clinical Trial Research Governance” document was published in July 2015.8

Australia is a member of the International Generic Drug Regulators Programme (IGDRP), which in 2014 launched an information-sharing pilot using the EU decentralised procedure (DCP) as a model for the sharing of information during the scientific assessment phases of the DCP, effectively making Australia a pseudo EU member state. From January 2015, this was extended to the EU centralised procedure, with the European Medicines Agency (EMA) committing to sharing its assessments of applications for generic medicines in real time with the TGA and other IGDRP non-EU agencies, including those of Canada, Chinese Taipei and Switzerland. Acceptance of European starting materials for non-recombinant biologics and designations for as of November 2014, Australian medical device manufacturers can use conformity assessment certification from European notified bodies when making applications to the TGA.

In late 2014, Australia committed to the International Coalition of Medicines Regulatory Authorities (ICMRA), driven by the globalisation of medicinal products distribution, supply chain and use; growing complexity of medicinal products and associated risks; and the range and diversity of existing international initiatives. Collaboration was seen as essential to ensure the ability of a regulator to assure the safety, quality and efficacy of a medicinal product domestically. Over seven working groups, the ICMRA will facilitate improved integration of international regulatory initiatives; prompt and coordinated multi-country response to emerging issues; efficient use of existing networks; better informed risk-based allocation of regulatory authorities’ resources; increasing coordination of regulatory technical expertise and infrastructure; and awareness of the imperative of strong regulatory systems.

After public consultation, Australia has, over the past year, adopted and conformed to European guidelines on the following:
- Quality risk management
- Active substance master file (ASMF) procedures
- Nonclinical and clinical issues pertaining to biosimilars
- Pharmacokinetic evaluation of modified release dosage forms
- Quality of oral modified release products
- Mutagenic and elemental impurities
- Starting materials for non-recombinant biologics
- Pharmacovigilance
- A reflection paper on clinical aspects related to tissue engineered products
- Indication-specific clinical guidance.

**TGA and biosimilars**

Australia was the first country to approve a biosimilar medicinal product, approving Sandoz’ Omnitrope in 2004, and the past year has seen the country making further waves in terms of biological medicinal products, and specifically biosimilars, regulation. First, the TGA began reviews of its biologics and biosimilar guidance: in January, with the prior publication of World Health Organisation (WHO) policy on biologicals naming, the TGA abandoned its own biologicals naming programme that combined the WHO international nonproprietary name (INN) system with Australian Biological Names (ABNs) and instigated a review of the policy; and in April, the TGA began a review of its guideline “Evaluation of Biosimilars”.9 Next, the TGA extended support for fees and charges associated with implementing the Biologicals Regulatory Framework to the Australian eye and tissue sector until March 2016.

Most significantly, however, has been Australia’s advances in biosimilars regulation, biosimilar interchangeability and substitution, whereby in the former a biosimilar may be prescribed in the place of its originator product with same expectations of efficacy and safety, and in the latter a biological and its interchangeable biosimilar may be exchanged at the pharmacist level. Alongside advances towards substitution in Europe, Australia has also looked favourably on substitution.10 In March 2015, the Australian Pharmaceutical Benefits Advisory Committee (PBAC), which decides on products covered by the Pharmaceutical Benefits Scheme (PBS), tabled eligibility criteria for product labelling that would pave the way for biosimilar substitution; and in June 2015, the Australian government proposed a new PBS package that provides for substitution of products approved as “interchangeable”, part of a Bill later approved by the Australian Senate. However, industry pressure led to a public consultation on the issue, effectively pausing the possibility of substitution in Australia for now. Finally, in October 2015, Australia was central to negotiations in the Trans-Pacific Partnership (TPP), delaying talks over disagreements regarding data protection for biological medicinal products, eventually successfully arguing for five years’ data protection on biological medicinal products, rather than 12 years as tabled by the US.11 The agreement ensures no significant impact on biosimilar timelines to market access in at least 11 of the 12 TPP signatories.12

**Summary**

The past year has seen the potential for dramatic upheaval in the Australian regulatory environment, with the planned establishment of the ANZTPA, replaced by the beginnings of a potentially significant internal overhaul. Meanwhile, Australia has maintained a major position on the global stage, with involvement in global pilots and
programmes for generic medicines and harmonisation, and the spokesman for biologics protection, thereby maintaining present biosimilar timelines to market access in the Pacific region. Thus, Australia (and the TGA) is a major world player in regulatory affairs, but one facing imminent changes.

References

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Meet the regulators – interview

Actively engaged

FDA Assistant Commissioner Heidi Marchand describes the bedrock of her work – stakeholder engagement with patient and healthcare professional advocacy groups. Interview conducted by Monique Garrett, CEO, PrismWorks, US

Introduction
Heidi C Marchand, Assistant Commissioner, Office of Health and Constituent Affairs, Office of External Affairs, US FDA, was interviewed about her role and the FDA’s activities at the Office of Health and Constituent Affairs. Working with external stakeholder organisations such as health professional organisations, patient advocacy groups and consumer advocacy organisations is all part of the agency’s efforts to address the issues associated with protecting and promoting the public health.

Q: Could you tell our readers a bit about your background, what attracted you to the regulatory arena and how you came to join the FDA?
A: I trained as a clinical pharmacist and practitioner in a community hospital, and I learned early on in my career that introducing new therapies to patients was a primary focus of pharmacy operations. Evaluating, comparing and ultimately recommending or deferring pharmaceutical products from introduction to our hospital fell squarely on my shoulders. Through the hospital’s Pharmacy and Therapeutics Committee, I presented new products for consideration. The Committee members had lively and robust discussions and often pharmaceutical companies’ representatives were key sources of ongoing interactions about new products.

I joined the FDA during the early 1990s; it was an exciting place to work and as a reviewer in the Division of Drug Marketing, Advertising and Communications (DDMAC), I became familiar with many of the pharma companies and their marketed products. That first FDA role launched a “full” career as a regulatory professional. I have been very fortunate to work in many different, multi-faceted regulatory roles.

Q: What does your current role involve, and what are your favourite aspects of this role?
A: My current position as Assistant Commissioner of Health and Constituent Affairs is perhaps one of the most challenging jobs that I’ve had at the FDA. Stakeholder engagement – building trusted relationships with the FDA’s diversity of stakeholders on public health issues of mutual concern – is also one of the most creative jobs that I’ve held since coming to the agency.

The Office of Health and Constituent Affairs (OHCA) supports the FDA mission by helping stakeholder organisations access accurate, science-based information about human medicinal products and the health and safety issues associated with these products.

Let me focus on patients and their families as examples of my office’s work. OHCA is familiar with the concerns confronting patients and families dealing with difficult and often severe health problems. These problems are intimate and personal to the family. OHCA understands that for patients and even health professionals, the FDA can be overwhelming; knowing where to begin can be challenging. Our office is a place for patients, and all of our stakeholders, to begin. We guide stakeholders in navigating the agency. We provide information about the FDA’s regulatory processes, clinical trials, administrative process for making decisions, and facilitate stakeholders in linking with agency experts and managers.

Another important part of my office’s work involves MedWatch – a programme which collects and reviews reports from health professionals and consumers about possible problems with drugs, medical devices and other products regulated by the FDA.

Reports of potential problems with FDA-regulated products provide information we need to protect consumers. In the 1950s, the FDA was alerted to the fatal blood disorders associated with the antibiotic chloramphenicol as a result of a lone physician’s report. This dramatic illustration of the importance of voluntary reporting prompted our initial efforts to encourage physicians to systematically report potential adverse medical product reactions.

MedWatch was launched in 1993 and during the past 20 years or so, MedWatch has prevented serious illnesses and even deaths by alerting the FDA to problems. Actions range from removing products from the market to adding warnings of risks on product labels. MedWatch expanded to:

- Make it easier for providers to report serious events
- Make it clear to physicians and others what types of reports the FDA wants to receive
- More widely disseminate information on the FDA’s actions that have resulted from adverse event and potential product problem reporting
- Increase physician understanding and awareness of drug- and device-induced disease.

To continue that tradition, the FDA’s MedWatch launched a new, consumer-friendly reporting form with less technical language. Additionally, MedWatch worked with consumer groups to encourage more participation.

The FDA also launched MedWatchLearn, a web-based learning tool
designed to educate students, health professionals and consumers on reporting in a way that provides the best information for the FDA’s reviewers to further investigate a potential problem. Stakeholder engagement in MedWatch is invaluable, and enables us to continue to help ensure that the medical products we regulate are safe and effective.

Q: How do you interact with patient and health professional advocacy groups and other stakeholders?

A: Stakeholder engagement, including our relationships and interactions with patient and health professional advocacy groups, is the bedrock of my office. Our “constituency” is as broad as it is diverse. Let me take a moment to discuss our liaison efforts with patient and health professional advocacy groups. We have various ways that we interact and engage with patient and health professional groups; and we are regularly thinking of new ways to reach our stakeholders.

The internet is one of our key approaches for sustaining an ongoing communication with our patient and health professional communities. OHCA’s two primary webpages are structured as newsletters for each of these particular stakeholder groups: “For Patients” (www.fda.gov/ForPatients/default.htm) and “For Health Professionals” (www.fda.gov/ForHealthProfessionals/default.html). Both of these webpages are uniquely tailored to connect the FDA’s activities with the interests, concerns, and issues of importance to these two stakeholder constituencies – patients and health professionals. Both of these webpages can be accessed on the FDA’s homepage (www.fda.gov).

Through these webpages, OHCA loops our stakeholders into information from across the agency that is relevant to their interests, in this case, of interest to patients or health professionals’ organisations. These bi-weekly online newsletters reach more than 70,000 subscribers with a current review of the FDA’s actions from the preceding two weeks. They feature FDA guidance documents and direct links to FDA dockets open for public comments. This particular link to our open dockets enables our stakeholders to easily access the docket and submit their comments on a proposed regulation, a link to our open dockets enables our stakeholders to easily access the docket and submit their comments on a proposed regulation, a draft guidance document or register to participate in a public meeting, workshop, or advisory committee meeting. This is one way that we take administrative procedures and transform them into a more user-friendly fashion for our stakeholders.

Q: What changes have you introduced or seen at the agency since you took on the role, and what are your aims for future changes within the organisation?

A: Since I assumed my role, I have put significant effort into developing systematic communications with the FDA’s stakeholders. By doing so, I have been gratified to see a steady increase in the number of subscribers to OHCA’s newsletters, visitors to OHCA’s webpages and an increasing number of patient representatives serving as special government employees. I have reorganised to include expertise for consumer advocacy stakeholders and co-sponsorship agreements/memorandum of understanding with external entities from nearly every sector. Building on OHCA’s contacts with health professional groups, OHCA has moved forward to introduce regular roundtable discussions, establish FDA placement in health professional newsletters and journals while continuing to promote and encourage use of the FDA’s MedWatch safety reporting system. All of these efforts have been built on an established foundation of OHCA’s early work with HIV/AIDS and cancer patient engagement, and has grown over the years into a robust, broad, dynamic Office of Health and Constituents Affairs. As an external affairs office, we actively look outside of the agency to understand the issues of our stakeholders, while not forgetting the importance of maintaining strong networks within FDA’s corridors.

Q: What current legislation, initiatives or trends have the most impact on your job?

A: In July 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA). The section of FDASIA that has an impact on my office is Section 1137. FDASIA Section 1137 requires the agency to develop and execute strategies to solicit the views of patients during the medical product development process and to consider the perspectives of patients during regulatory discussions.

Section 1137 permits, patient representatives, as Special Government Employees (SGEs), to participate in appropriate agency meetings with medical product sponsors and investigators.

OHCA currently manages and evaluates the FDA’s recruitment, training, and retention of nearly 200 patient representatives who participate on as many as 47 FDA advisory committees. These patient representatives advise the agency decision-making associated with medical products for more than 300 different diseases or conditions. We have obtained substantive comments from the public on activities the FDA can take to enhance stakeholder engagement. We are preparing a summary report of those comments and expect to publish the report before the end of this year.

Q: What do you hope to achieve in your role at the agency in the next five years?

A: OHCA communicates with many different stakeholder organisations, including health professional organisations, patient organisations, and individual patients as well as consumer advocacy organisations on behalf of the FDA. We are always considering ways to provide ongoing updates and serve as a source of information about regulatory processes, new products and initiatives. As new regulatory processes and initiatives are implemented we seek new ways for communicating about the FDA’s work and decisions that impact public health. Another important focus has been to explore new approaches to engage with our stakeholders on issues of importance to them and ensure their voices are heard by the agency and their concerns addressed. Building on this is an important aspect of our work for the next five years and beyond.

We continue to learn about ways we can engage patients and other stakeholders. For example, last December we were fortunate to have an exchange of ideas from our European Medicines Agency colleagues while hosting Ms Nathalie Bere at the FDA. Building on some of these identified opportunities has given us encouragement for further discussions. (For more information go to: http://blogs.fda.gov/fdavoice/index.php/2015/02/european-medicines-agencyfda-patient-engagement-fellowship-a-time-to-learn-and-share).

Q: On a professional level, who has influenced you most, and why?

A: As members of the global regulatory professional community, I think it is fair to say that Dr Frances Oldham Kelsey stands as an example of the qualities that we all try to bring to the everyday decisions, problems, and hard work we encounter in safeguarding the public health. Dr Kelsey is recognised as one of our most notable and respected pioneers in consumer protection. She remains a role model in her dedication, courage, and integrity to public health, despite adversity, criticism, undue pressures, and hostility.

Dr Kelsey died on 7 August 2015 at the age of 101. Her reflections serve as an inspiring testimony to her steadfast commitment to
It is very difficult to single out an individual who has most impacted my career – building my career has been a convergence of many mentors, influences, successes and failures, in trying to integrate personal and professional obligations.

Early on, the FDA decided that its stakeholder engagement programmes had to be located at the highest levels of the agency organisation and report directly to executive-level officials, if stakeholder views, concerns, and issues were to influence the agency’s thinking, focus and decisions. Within the context of this longstanding commitment to the value of stakeholder engagement, OHCA is positioned within the Office of the Commissioner and primarily focuses on the more complex, confounding, and controversial public health problems associated with the FDA’s consumer protection mission.

I am fortunate to have a job that brings me together with some of the most remarkable thought leaders and public health experts, both within and outside of the agency. Every project we undertake to reach and engage leading stakeholder organisations in the FDA’s activities brings with it an opportunity to experience new dimensions of problem-solving, leadership, innovation, networking and leveraging, creativity, and genuine regard for the talents and resources that each individual employee brings to the table.

My position enables me to have the rare opportunity to personally work with truly brilliant leaders and gain an invaluable glimpse into the tangible, and most importantly, intangible qualities of executive excellence. Whether it’s crafting productive stakeholder roundtable discussions with former FDA Commissioner Margaret Hamburg, MD, or bringing young Hispanic scientists sponsored by the National Alliance for Hispanic Health together with the FDA’s Acting Commissioner Stephen Ostroff, MD, and the FDA’s medical product safety experts to explore the opportunities and pathways for working in public health – every stakeholder engagement has an influence and teaches an enduring lesson about leadership, commitment, energy, and passion for the job.

Q: And finally, on a more personal note, what was the last book you read?

A: I am an avid reader. While I did recently read George Friedman’s “The Next 100 Years: A Forecast for the 21st Century,” my last read was actually a “re-read.” I just finished re-reading the “Biologics Price Competition and Innovation Act of 2009 (BPCI)”. Reading (much less re-reading) legislation may not be everyone’s cup of tea, but for me, this legislation has particular importance for our stakeholders, especially patients, their families, and patient advocacy groups.

Very briefly, the BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product, called the “reference product.” One of the FDA’s priorities is to engage its stakeholders as the agency continues to move forward to address the issues associated with biosimilars and ensure they are informed and their voices are heard.

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The 10th annual review of the activities of the European Medicines Agency (EMA) and the national agencies that work within the European regulatory system, and a look at the challenges ahead for the EMA, national regulators, industry and other stakeholders.

Delegates were first welcomed by Thomas Kühler, TOPRA President, and Andreas Pott, Deputy Executive Director, EMA. The first session, chaired by Carolyn Hynes, Senior Director, GSK, was devoted to the development of new medicines and focused on the regulatory role in supporting and fostering innovation. The first presentation was given by Corinne de Vries, Head of Science and Innovation Support Office, EMA. This is a relatively new Office within the EMA, having been established in March 2015. Dr de Vries noted the general challenges facing both the industry, such as increasing costs of R&D, and society as a whole, such as the ageing population and the resultant increased healthcare associated costs. She also highlighted that the number of clinical trials conducted in the EU continues to decline, which may be partly explained by the diverse healthcare systems and different EC and R&D committees across the EU.

Efforts are being made by both the EMA and the wider EU Regulatory Network to facilitate medicines development and innovation. These include the Committee for Medicinal Products for Human Use (CHMP) scientific advice/protocol assistance which continues to grow (553 requests in 2014) and EMA-HTA parallel scientific advice (62 procedures to date with involvement of around 12 national health technology assessment (HTA) bodies). The role of the EMA’s SME Office also includes various incentives and assistance available to small and medium-sized enterprises (SMEs).

The role of the Innovation Task Force was described, including its role in addressing the impact of emerging therapies and technologies on the regulatory system and training needs across the EU. Current topics under discussion include borderline products, “bedside manufacturing”, eHealth and personalised medicine.

The next two presentations focused on business pipeline planning from both the EMA’s and industry’s perspectives. Enrico Tognana, Business Pipeline Coordinator, EMA, addressed the agency’s activities on business pipeline planning and horizon scanning. Historically, a drop in the number of marketing authorisation applications (MAAs) in 2000 came as a surprise and highlighted the need for better planning to help both the EMA and the scientific
committees manage workload fluctuations. The agency gathers information from both internal (eg, letters of intent (LoI) and scientific advice requests) and external sources (eg, publications, company press announcements) and provides forecast and planning analyses to relevant stakeholders.

The agency also holds business pipeline meetings with companies. These are not product-specific meetings but have a broader, pipeline focus and can be initiated either by the EMA or the sponsor. The meetings are free of charge and currently the EMA holds around 25 per year. The sponsor and agency agree on the scope of topics and issues to be discussed. Examples of recent topics include adaptive pathways, paediatric medicines, animal models, compassionate use and development strategies. Such meetings are mutually beneficial. From the industry perspective they can provide an opportunity for early dialogue with the EMA, highlight new development approaches to regulators and may help identify issues impacting pipeline progress. From the EMA’s side they can help with workload planning (number and types of applications), identifying expertise needed and help to identify areas where new approaches may need to be considered in regulatory guidance.

Dr Mairead Noone, Global Regulatory Affairs, GSK, then presented a case study describing the preparations and conduct of a recent EMA business pipeline meeting, which focused on GSK’s immuno-inflammation portfolio. The entire process from acceptance of invitation to agreed minutes took around 11 months. Dr Noone emphasised the importance of: identifying the discussion topics carefully and having potential questions in mind; avoiding narrow scope questions that may be better addressed through scientific advice; obtaining senior stakeholder engagement from the outset and assigning an overall coordinator to work across the identified topics.

Although not required, preparing a briefing document was useful in shaping the company’s position on the topics and facilitated the preparation of slides for the meeting. The meeting itself was attended by senior clinical and regulatory personnel from the franchise, as well as development team and regulatory project leads. In terms of meeting structure, this followed a typical format of an introduction and overview of the therapy area followed by discussion on each of the identified topics. In terms of benefits to the company, the meeting provided an opportunity to help shape future regulatory pathways, assisted with planning for future scientific advice and provided insight into the EMA’s thinking on innovative paradigms not addressed in existing guidelines.

**SESSION 2: Optimising your regulatory strategy by using accelerated regulatory pathways**

*Reported by Fiona Bright, Regulatory Manager, DLRC Regulatory Consultancy, UK.*

This session was chaired by Angelika Joos, Executive Director Global Regulatory Policy MSD (Europe) Inc, Belgium. She set the scene for the session by talking about the new and exciting procedures that are being developed to facilitate quicker access for patients with a high unmet medical need.

Jordi Llinares, Head of Product Development Scientific Support, EMA, gave the first presentation, which provided a summary of the PRIME [Priority Medicines Scheme] initiative. This new initiative aims to enable accelerated assessment for products with a high unmet medical need. PRIME will use the existing regulatory framework and will encourage prospective planning, earlier interactions with stakeholders and the generation of robust data. Currently, confirmation that an application will be reviewed according to an accelerated timetable is only possible just prior to filing. Under the PRIME initiative, new medicines fulfilling the accelerated review criteria can be identified much earlier in development and once identified, enhanced regulatory support will be on offer. Eligibility for the PRIME initiative must be based on data that demonstrate a potential major public health interest. Entry to the scheme for SMEs could be as early in development as proof of concept or prior to Phase II. For larger companies, entry to the scheme is envisaged at proof of concept or prior to Phase III studies. The rationale for the different entry points is that one key aim of PRIME is to help SMEs in the very early stages of product development, where products may be lost due to lack of funding or lack of understanding of the development process and requirements.

Key benefits of the PRIME initiative were explained, and included

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**Acronyms and abbreviations**

- ATD – Access to Documents
- CCI – Commercially Confidential Information
- CMA – Conditional Marketing Authorisation
- CHMP – Committee for Medicinal Products for Human Use
- CSR – Clinical Study Report
- CTA – Clinical Trial Application
- CTR – Clinical Trial Regulation
- EFPIA – European Federation of Pharmaceutical Industries and Associations
- EMA – European Medicines Agency
- GCP – Good Clinical Practice
- GVP – Good Pharmacovigilance Practice
- HCP – Healthcare Professional
- HTA – Health Technology Assessment
- IMPD – Investigational Medicinal Product Dossier
- IPD – Individual Patient Data
- LoI – Letter of Intent
- MAA – Marketing Authorisation Application
- MAH – Marketing Authorisation Holder
- NME – New Molecular Entity
- PASS – Post Authorisation Safety Study
- PAES – Post-Authorisation Efficacy Study
- PRAC – Pharmacovigilance Risk Assessment Committee
- PRIME – Priority Medicines Scheme
- PROTECT – Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
- PSMF – Pharmacovigilance System Master File
- PSUR – Periodic Safety Update Report
- PSUSA – PSUR Single Assessment
- QPPV – Qualified Person for Pharmacovigilance
- RMP – Risk Management Plan
- SAG – Scientific Advisory Group
- SMEs – Small and Medium-Sized Enterprises
- SmPC – Summary of Product Characteristics
- SOP – Standard Operating Procedure
- STAMP – Safe and Timely Access to Medicines for Patients
early identification of eligibility and stakeholder involvement, rapporteur appointment at proof of concept stage, kick-off meeting with the rapporteur and relevant committees, scientific advice at key development milestones, collaboration with national incentive schemes and fee incentives for SMEs on scientific advice requests.

The PRIME initiative was greeted with much enthusiasm from the delegates with numerous questions for example around the stage of entry, the restriction to new molecular entities (NMEs) and the eligibility criteria. An overview of PRIME, as well as other early access tools, is given in Figure 1.

Olga Solomon, Deputy Head of Unit Medicinal products – authorisations, European Medicines Agency, DG SANTE, European Commission, gave the next presentation, which provided information about the commission group of experts known as STAMP, or Safe and Timely Access to Medicines for Patients. The adaptive pathways pilot project was launched in March 2014, and questions were raised around whether the existing legislation would be fit for purpose. STAMP was created to address these questions and to further improve safe and timely access to medicines for patients. In 2015, STAMP discussed experiences from national early patient access schemes and the optimisation of three existing tools: conditional marketing authorisations (CMAs), accelerated assessment including PRIME, and the adaptive pathways pilot project.

STAMP discussed a number of ways to optimise CMAs, including encouraging the prospective planning of a CMA rather than viewing it as a rescue solution, and considering the availability of CMAs for new indications.

STAMP also discussed the PRIME proposal and had various ideas to ensure the success of the scheme. Examples included early HTA involvement and the definition of clear eligibility criteria. Discussions around the adaptive pathways pilot included the involvement of HTA bodies and how to deal with real-world data and registries.

Overall, a holistic approach utilising all of the currently available tools to support and facilitate early access for patients was advocated (see Figure 2) and was well received by the delegates.

Session 3 was chaired by Clare Lavery, Policy Director, Chief Medical Office, AstraZeneca, UK. 2016 is an important year for the industry on several topics including clinical data sharing and information disclosure. This year will see the first documents set to be published in accordance with the EMA’s policy on publication and access of clinical reports (Policy 70). As Policy 70 co-exists alongside the agency’s access to documents policy (Policy 43), insights into current working practices and the all-important lessons learned are key for stakeholders.

The opening address of this session which focused on the latest news and guidance from the EMA on Policy 70, was delivered by Noël Wathion, Chief Policy Adviser, Head of Stakeholders and Communication Division (ad interim), EMA. Mr Wathion reminded the audience of the EMA’s commitment to continuously extend its approach to transparency on scientific data. Policy 70 (in force since 1 January 2015) is intended to enable public scrutiny, establish/maintain trust in the regulatory systems, avoid duplication of clinical trials – thus limiting unnecessary patient exposure – and enable increased knowledge in future scientific and clinical research. This policy implementation follows a long consultative period and interaction with stakeholders over the past three years. The scope of the policy is applicable to clinical data such as clinical reports (ie, clinical overviews (Module 2.5), clinical summaries (Module 2.7) and...
clinical study reports – CSRs (Module 5), together with appendices 16.1.1, 16.1.2 and 16.1.9) and individual patient data (IPD) submitted under the centralised procedure. There are plans for a phased introduction where the first phase is intended to offer publication of clinical reports only, with the second phase covering review of various aspects in relation to IPD. The policy applies from 1 January 2015 to any new MAA and Article 58 applications submitted as of that date; 1 July 2015 was the implementation date for extensions of indication/line extension applications for centrally authorised products submitted as of that date. Other post-authorisation procedures have yet to have a confirmed effective date. This is a completely new activity for the EMA, requiring several new arrangements to be put in place in a cost-efficient way. Communication with stakeholders continues to be of crucial importance as new guidance documents are put in place. All published guidance documents will be “living” documents, with intended updates downstream post-experience. Companies are encouraged to refer to the EMA website for continued updates and more detailed information on the process for submission of clinical reports for which guidance is being finalised.

The second presentation was given by Ann-Sophie Henry-Eude, Head of Access to Documents, Stakeholder and Communication Division, EMA. Ms Henry-Eude presented updates regarding the EMA status report on access to documents policy (Policy 43). The EMA access to documents (ATD) policy was created in August 2013 with the number of requests for access growing year on year. By the end of 2015, the EMA anticipated receiving more than 600 requests for documents with more than 2,500 documents released. The EMA website contains detailed information on this complex process and a guide on access to unpublished documents is available (EMA/304162/2014). Clinical data (Modules 2, 5 and CSR) represent approximately 35% of the documents being requested. The EMA has strict redaction principles and criteria around commercially confidential information (CCI), thus this aspect remains an extremely complex area for all concerned parties. There are plans in place for the ATD policy to be revised. The estimated timeframe for completion of this revision is Q4/2016 – Q1/2017. The industry can expect to see a public consultation, including stakeholder meetings, on the draft revised policy and output tables. The revision will be based on ATD experience over the past five years, and it will also aim to reflect the introduction of new EMA committees/documents introduced in recent years.

The third and final presentation of this session offered experiences from an industry perspective and was delivered by Rachel Adams, Senior Director and Regulatory Therapy Area Lead, EMEA, Janssen Pharma R&D. Ms Adams discussed the practicalities of implementing data disclosure policies within her organisation. The audience were, once again, reminded of the main purpose of transparency of clinical trial data. Ms Adams revealed that most of Janssen’s centralised MAAs resulted in ATD requests, the majority being clinical summaries and clinical study reports. These requests are unscheduled and, not surprisingly, labour-intensive for the company. There is therefore a need to understand what is expected and to understand the implications of such data disclosure policies in place. Some examples of accepted and rejected redactions by the EMA were highlighted. Accepted redactions examples included: some details of manufacture; partner companies; manufacturers; details about internal audit process; attachments to pharmacovigilance system; contact details for Qualified Person for Pharmacovigilance (QPPV). Rejected redaction examples included entire questions or blocks of text, manufacturer details, response to major clinical objection and names of the quality/nonclinical/clinical experts.

Ms Adams concluded by informing delegates that six submissions made by Janssen in 2015 fell under Policy 70. Some recommendations were made as to how sponsors could handle this anticipated workload. This includes proactive preparation of documents and staying up

Figure 2: A holistic approach to early access with currently available tools.
to date through continual engagement and communication with stakeholders, which includes provision of comments/feedback on released guidance through European Federation of Pharmaceutical Industries and Associations (EFPIA) and EMA webinars.

The panel discussion which concluded Session 3 reinforced the aspects presented by all three speakers and highlighted some further examples as to how this topic will be a key area for stakeholders in the pharmaceutical industry through 2016 and beyond.

SESSION 4: Regulator roundtable

Reported by Patricia Hurley, Associate Director, Development Solutions, Regulatory Affairs, PPD, UK.

This vibrant and lively open roundtable session was chaired by Dr Tomas Salmonson, CHMP Chair and Medical Products Agency (MPA), Sweden. The theme of this session focused on the EU Medicines Network Strategy to 2020 (see Figure 3).

A number of discussions on the overall advancements and plans within the regulatory environment were discussed. For example, the planned restructuring of the ICH to have a more global perspective rather than just a tripartite agreement between the US, EU and Japan. There were a number of interesting questions from the audience and sharing of experiences with different procedures at the agency. Overall, experiences and agency interactions were positive, as expected, with several stakeholders commenting on the excellent collaborative elements between the committees within the agency and indeed, with sponsors. The concepts of having early engagement with the EMA were reinforced as a common theme, with the general viewpoint that the typical 90-minute timeframe usually granted for discussions on topics such as on design concepts is often perceived as feeling “a little rushed” for stakeholders. However, it was also understood and appreciated by all parties in the discussion that the allocated time is a balance of workload versus available time.

Experiences with the adaptive pathways to date were discussed. The industry is eagerly awaiting future reports which are planned for release by the EMA in 2016. The reports should be expected when enough data have been formally processed through the Committees to contribute to content. In addition, as expected, the new Clinical Trial Regulation was a hot topic of discussion during this dynamic and engaging session. The highlights and latest information on the Clinical Trial Regulation are addressed in the focused session summary on this specific topic as presented in Session 8 of this meeting report, and not reiterated in this session summary.

SESSION 5: Involvement of patients and HCPs in the work of the EMA and its committees

Reported by Justine Revell, Director, Global Regulatory Consulting, INC Research, UK.

The first session of the second day was chaired by Christine Meyer Nicolai, Head of Global Regulatory and Scientific Policy, Merck. The aim of this session was to provide a deeper understanding of how patients and healthcare professionals (HCPs) currently provide input into various topics, such as risk minimisation and focusing on possible areas for improvement of processes and methods. This session was held as a panel discussion which aimed to look to the future and see what needs to be done based on the current situation and the knowledge of what is working within the current framework. The panel participants were Tomas Salmonson, CHMP Chair & MPA, Isabelle Moulon, Head of Patients and Healthcare Professionals Department,
Stakeholders and Communication Division, EMA, Rosa Giuliani, EMA HCP Working Party, David Haerry – European Aids Treatment Group (EATG), Co-chair of Patients’ and Consumers’ Working Party, Lode Dewulf, Chief Patient Affairs Officer, Vice-President UCB. The EMA has an increasing number of activities which involve patients and HCPs.

Patient representatives and experts have been involved as participants of scientific advisory groups (SAGs) and oral explanations during the assessment of MAAs. One example is the review of the MAA for Clinuvel’s proprietary first-in-class photoprotective drug, Scenesse. At the SAG set-up during the review, the patients were able to help by providing the context for life with disease, and they also advised of the difficulty of performing the studies for the individuals concerned. The product was approved under exceptional circumstances. However, only a limited number of patient representatives can be invited to these committees, and they must be able to converse in English, which means the patient pool may not be fully represented. The revised pharmacovigilance legislation has delivered the potential opportunity of public hearings for referrals which may be initiated for the Pharmacovigilance Risk Assessment Committee (PRAC) meetings but may be opened up to cover other aspects of the approval process.

Patients and HCPs are increasingly involved in the policies that are being implemented, but there is no one methodology that fits all. The EMA is trying to identify a pool of patients but it is struggling with the conflicts of interest and pharmaceutical company influence. There is a divergent view on whether it is good to involve patients, who maybe under the influence of pharmaceutical companies with their bias towards drug approval, either for themselves or other family members. It has been shown that after interaction with the regulators they understand there is another aspect which should be considered. For HCPs, clinical practice needs to be considered. The EMA often deals with innovator products which are administered by specialists but when patients are discharged and problems occur they are usually seen by general practitioners, who may not be aware of all the risks associated with the products and so need to have a better understanding.

It is important to educate the patients on the need to be professional and not emotional when invited to participate in discussions involving regulators. Dialogue needs to be open so that patients hear the complete picture from both the regulators and pharmaceutical companies. There needs to be transparency and consistency with the involvement of patients and HCPs to get the best out of the current and future systems.

The focus is changing for a requirement to gain real-world data but there is difficulty in collection and consistency. Less than 1% of the population is involved in the development of clinical trials, which is not really representative of the true patient population. Databases for identical diseases often have no standardisation, and there are no quality control systems in place. It is believed that there needs to be more collaboration between companies and databases to facilitate collection of real-world data.

There are still opportunities for further involvement by both patients and HCPs in the development and licensing of pharmaceuticals.

SESSION 6: Reflections on 2015 – Review of evaluation highlights, surveys and progress in the area of telematics

Reported by Vera Franzén, Regulatory Affairs Consultant, Vera Franzén Consulting AB, Sweden.

This session was chaired by Fiona Reekie, Director of Regulatory Policy, Europe and Global Emerging Markets, Biogen Idec Ltd UK.

Michael Berntgen, Head of Scientific & Regulatory Management Department, Human Medicines Evaluation Division, EMA, gave the

Figure 4: Therapeutic areas covered by positive opinions for initial marketing authorisations.
In all, there have been 74 positive opinions on new medicines and 45 on variation extensions, two negative opinions and five withdrawals (see Figure 4 for a breakdown of positive opinions by therapeutic area). A large number of new medicines are within the areas of oncology and psychiatry, although in the case of psychiatric indications all but one of the 13 MAAs were for generic applications.

With regard to new active substances, 33 received a positive opinion, and of the generics applications 70% were for three active substances. Among the highlights mentioned were:

- New treatment options to control high levels of cholesterol using monoclonal antibodies
- Innovative cancer treatment activating the immune system for advanced melanoma and advanced lung cancer
- A new mechanism of action for the treatment of heart failure which has shown a clear reduction in deaths.

Negative outcomes and withdrawals were also discussed and for these applications, the main deficiencies were in the areas of quality and efficacy, including good clinical practice (GCP) issues.

Oncology was the leading therapeutic area for extension applications to indication. In eight cases the new indication resulted in an additional year of market exclusivity.

Statistics were also presented for referrals depending on divergent views (see Figure 5). Referrals are a substantial body of work reflecting new and emerging data and often lead to label changes.

The next part of the presentation was on “contributors”, and there seems to have been little change in the pattern of distribution of rapporteur- and co-rapporteurships. It was noted that 96% of all positive opinions were adopted by consensus. A new feature was the appointment of multinational assessment teams. SAGs are often involved in evaluation activities and in 13 out of 15 SAG meetings, patient and healthcare representatives had taken part.

On “Use of early access tools”, the focus is on what can be done within the legal framework to make early access of important new medicines possible. Accelerated assessment, for which requests and acceptance have increased over the past number of years, and conditional approvals which are still at a low level, are two areas under discussion. Revised guidelines are out for consultation and expected to be finalised early next year. It should be noted that:

- Around a third of procedures granted accelerated assessment were reverted to standard timelines
- Conditional approvals should be converted to full marketing authorisations and on average it has taken around four years to switch.

As a post-meeting note, the data given here have since been updated by the EMA, and can be found under “Human Medicines Highlights 2015” on the EMA website (www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199664.pdf).

The final part of the presentation discussed scientific guidelines and workshops. As new knowledge is gained, guidelines need to be updated, and examples were given of scientific guidance documents and workshops held at the EMA. Scientific guidelines published in 2015 included:

- A reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases
- A guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products.

Alberto Ganan-Jimenez, Head of Evaluation Procedures Service D, Procedure Management Dept, EMA, then presented a post-authorisation survey carried out between 1 April and 30 September 2015.

The survey comprised type IB and type II variations and periodic safety update reports (PSURs) for centrally approved (human) products, and the questions had been agreed with EFPIA and also shared with other industry organisations. Questions were to be
answer after each procedure and were for SMEs and big pharma and orphan drug developers as well as non-orphan. The target response rate of 10% was not quite reached, especially not for PSURs. Responses from industry indicated that:

- Guidance for the procedures was not used by all but was considered generally clear by 90% of those who did use it
- Although there is an option for pre-submission queries, most companies did not use it – but those who did were happy with it
- Validation was generally considered to be timely
- During the evaluation phase, there was a high level of satisfaction with interactions with the EMA, but slightly less so for PSURs
- The quality of the evaluation report was rated high.

Responses from the EMA were as follows:

- A request for supplementary information during validation was issued in 44% of type I B and 48% of type II procedures
- There was a high level of satisfaction in the quality of submissions of PSURs
- Overall satisfaction on the timeliness and the level of communication with marketing authorisation holders (MAHs) varied, and was greatest for PSURs.

In conclusion, the outcome of the survey was positive. It also gave a good basis for identifying areas of improvement, where one aim is to decrease the need for requests for supplementary information.

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### SESSION 7: Post-approval activities

*Reported by Roz Sutton, Regulatory Manager, DLRC Regulatory Consultancy, UK.*

Georgy Genov, Head of Signal Management Service, EMA, began the session with a presentation titled: “Simplifications and process efficiencies in pharmacovigilance activities”. He looked back at the implementation of the new pharmacovigilance legislation between 2011 and 2014. We now have three years’ worth of experience to draw on from joint CHMP/PRAC assessment of risk management plans (RMPs). Version 2.0 of the RMP is now required with a refocus on what is important and on lifecycle management (likely to be available in Spring 2016).

Positives so far include RMP submission only when there is an impact on the safety specifications, pharmacovigilance or risk minimisation plans plus empowering of MAHs to consider prospectively the planning needs following submission of new data. With greater flexibility, the burden for both MAHs and assessors has been reduced with fewer unnecessary RMP submissions. Post-authorization safety studies are now deemed to be better planned and scrutinised with pilots ongoing for valproate (joint studies) and PRAC involvement with the Scientific Advice Working Party. With the introduction of PRAC, safety signals are seen to be detected more quickly, and then managed appropriately, particularly with the translation step being managed by the EMA (see Figure 6). Outputs from PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) demonstrate investment in regulatory science and provide an evidence basis for process improvements.

The generics arena has also seen recent improvements. From 2015, PRAC recommendations leading to changes in product information requiring variations by originator and generics companies are now performed in parallel rather than subsequent to each other. This should lead to faster implementation of labelling changes in generic summaries of product characteristics (SmPCs). The PSUR single assessment (PSUSA) process is under review, with changes in generic summaries of product characteristics (SmPCs).

Another area of simplification is through efficient systems

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### Figure 6: Safety signals – Faster detection and management of new and changing safety issues.

![Number of signals discussions at PRAC](image.png)

<table>
<thead>
<tr>
<th>Month</th>
<th>Referral evaluation</th>
<th>Routine pharmacovigilance</th>
<th>Update of product information</th>
<th>Update of RMP</th>
<th>PASS</th>
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A key next step regarding the Article 57 database which has subsequently been given the green light by the EMA is that MAHs now no longer need to submit type IA variations for changes in QPPV contact details or location of their pharmacovigilance system master file (PSMF). Delegates were reminded that from 16 June 2016 the use of the PSUR repository will be mandatory; however, this means MAHs will no longer be obliged to submit PSURs to national competent authorities.

Emma Du Four, Senior Director Regulatory Policy & Intelligence, Abbvie, then gave an industry viewpoint on expectations for post-approval efficacy and safety studies. She highlighted how real-world data is increasingly contributing to benefit-risk lifecycle management by supporting confirmation of the initial assessment and/or prospectively planned extension of the product’s label. Studies may be interventional or non-interventional and may have both safety and efficacy endpoints.

Good pharmacovigilance practice (GVP) Module VIII, post-authorisation safety studies (PASS), is under revision. The PRAC is responsible for assessing protocols for PASS studies as well as their results. It was noted that the EMA PASS Q&A can be used for non-imposed PASS protocols. The conditions for mandatory post-approval efficacy studies (PAES) were also explained (in operation since April 2014) and include use of the medicinal product under real-life conditions and potential lack of efficacy in the longer term. Much of the data are still expected to come from real-world studies rather than mandated PAES. Useful guidance was provided on whether a study is an interventional clinical trial or an observational/non-interventional study, as this is an area of disarray among regulators. A study remains observational when the physician remains responsible for the decision on treatment option rather than being driven by the protocol and when recognised treatment guidelines are followed. The EMA draft PAES Scientific Guideline (under consultation since 6 November 2015) highlights the need for such studies to be feasible, ethically acceptable and of a design that will deliver results targeting the scientific uncertainty to be addressed.

The Q&A session covered a range of topics including changes in consumer behaviour (use of smart phones and tablets) and the Falsified Medicines Directive. We live and work in a complex environment but – as was concluded at the end of this session – we have no other choice but to simplify medicines, so process efficiencies should and will continue.

**SESSION 8: The new EU Clinical Trial Regulation**

Reported by Dianne Lee, Director of DLRC Regulatory Consultancy, UK.

The first presentation of this session, given by Anabela Marcal, Head of Compliance and Inspections Department, EMA, focused on the transparency aspects of applications under the Clinical Trial Regulation (CTR) and how a balanced approach is required to allow members of the public the access to information about clinical trials.
to which they are entitled, while respecting the needs of developers and researchers to protect their investment.

In order to operate a workable system, automatic rules are necessary to manage the multiple processes per trial in the database. These rules will be designed to give a consistent and predictable outcome concerning what will be made public, and when. A manual over-ride will be available in exceptional circumstances to correct errors or when public interest prevails. There will be few exceptions to the data and documents made publicly available. No personal data of trial subjects will be recorded in the database. However, details of sponsor staff that are legal representatives, principal investigators and names of signatories on clinical study reports will be available.

All trial results will be made available within one year of completion. However, deferrals can be requested for Phase I, Phase “0”, bioequivalence, similarity for biosimilars and other equivalence trials, up to the time of the marketing authorisation that uses the trial or seven years after the end of trial – whichever is earlier. For Phase II and III studies, deferrals can be requested for the protocol, investigator’s brochure, investigational medicinal product dossier (IMPD), and assessment reports for up to five years or the time of the marketing authorisation using the trial. Timelines for deferrals have been determined from stakeholder comments. All data will be available within 30 days of conclusion of a marketing authorisation procedure irrespective of the outcome. Certain documents will not be made public at any stage, eg, the IMPD quality section, personal data about the applicant, sponsor staff, sponsors, agreements between the sponsor and investigator sites and the annual safety reports.

In conclusion, increased transparency supports public confidence, participation and critique and enables innovation.

Dr Ana Rodriguez, Head of Clinical and Non-Clinical Compliance Service, EMA, gave a highly informative presentation on development of the EU portal and database. The new CTR specifies that the EMA must deliver, maintain and update the IT platforms for implementation, and a data warehouse will be part of these projects to facilitate the reporting and link clinical trial related information within and between the systems. The CTR will mean there is a single submission within EU member states to cover both ethics and health authorities with a joint assessment for Part I facilitated by collaboration tools and a single decision.

An overview of the system showed workspaces for sponsors, member states and the public/EMA. The sponsor’s workspace will include search facilities for ongoing studies, current state of trials and the ability to initiate, amend and notify end of trials. Sponsors will be able to cross-refer to other trials for common data, eg, IMPDs, and view formal and informal requests for information from member states, as well as viewing deadlines for requests and alerts and notices for trials. In addition to being able to access trial submissions from sponsors, the member states will have task-specific forms relating to activities, be able to upload documents for the sponsor for other member states to see, for national purposes and to the EU database for public viewing when appropriate. There will also be a facility to upload inspection reports.

Implementation timelines have changed and the draft plan is to go live in Q4-2017, six months after publication of a successful audit of the system by the Commission. (A draft high-level timeline as of late November 2015 is shown in Figure 7.) Training for users of the portal and database will be available online, face-to-face and with ongoing support through webinars and query management by the EMA.

Fabien Peuvrelle, Director, Knowledge Management, Regulatory Intelligence & Policy, EMEA Regulatory Affairs, Celgene R&D, Switzerland, gave an industry viewpoint on behalf of the EFPIA Clinical Trials and Transparency Working Group. The system is being designed to give the needed flexibility for multiple users, eg, where a contract research organisation (CRO) needs to have access. There is no limit on the number of personnel with access, and tasks can be assigned to specific individuals. Sponsors will receive alerts periodically as a reminder of when summary results are due, incorporating the various timelines in an automated fashion. The workspace and application builder are user-friendly and easy to navigate. User and organisation management issues are mostly resolved, eg, mass transfer of clinical trials following a merger/acquisition. However, there are still some issues to solve, such as redundancy in the application forms and safety reporting and many open questions in the results module. More information is needed on how to build a clinical trial application (CTA) outside the workspace, and more discussion will take place on the system design and eCTD version 4 compatibility.

To be prepared, companies should evaluate standard operating procedures (SOPs) that will need to be updated, prepare their organisations for the changes with new systems or upgrades, align with CROs, conduct internal training and define a transition plan for all ongoing trials. There will be a three-year transition period from the date of implementation.

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