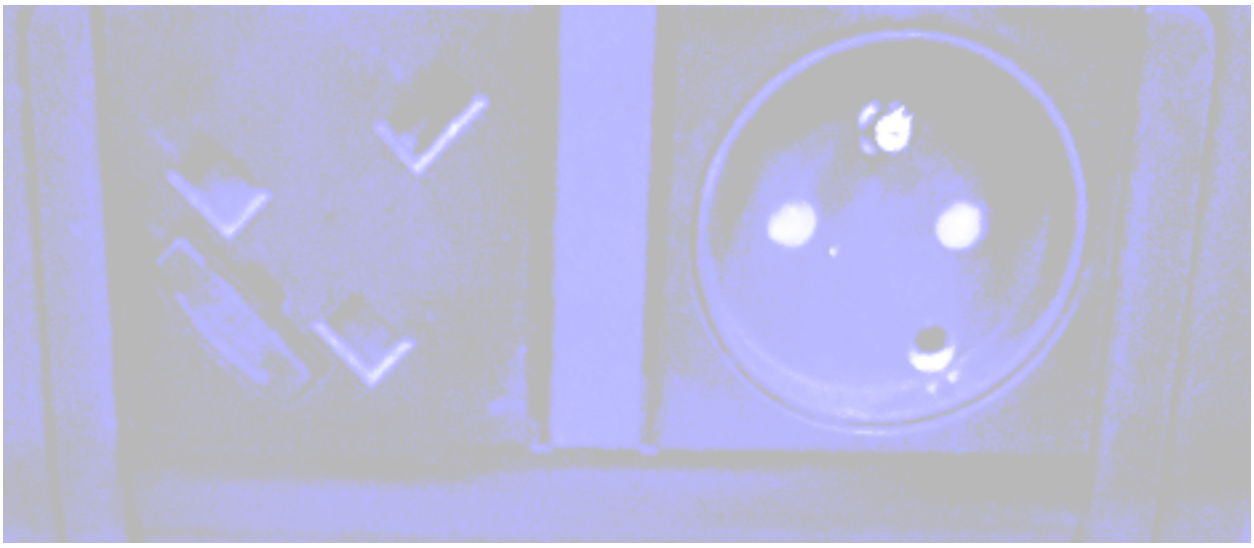
Second international awareness session for international regulators, academia and non-governmental organisations



in London, UK, on March 8th and 9th 2018.

1. Setting The Scene: Introduction to the EU Regulatory Network

We opened with an introduction to the EU Regulatory Network, presented by Riccardo Luigetti, principal international affairs officer.

Ricardo introduced the EEA, EMA's area of operation, including the EU's over 500 million strong population speaking over 24 languages, producing a GDP of ~€13tn and accounting for 27% of global medicines sales. We learned about The Single Market with its 4 fundamental freedoms: the free movement of people, services, goods and capital. The EMA is the focal point of a network of ~50 national regulatory authorities and reports to the European Commision.

EMA's scientific experts, staff and Management Board members must not have any financial or other interest that could affect their impartiality. Assessments are subject to peer reviews and transparent publishing of assessments allow public scrutiny. EMA assesses marketing authorisation applications submitted through the Centralised Procedure (CP), which is mandatory for most innovative medicines and critical therapeutic areas, while optional for new active substances, and for known substances, where significant innovation or interest of patients at community level forms the center of the application. The CP enables one application, one assessment, one market authorisation for the whole of the EU. Martin Harvey, principal international affairs officer, then introduced us to how EMA is structured, between its Management Board, Executive Director, staff and 8 scientific advisory groups (Human Medicinal Products (CHMP), Advanced Therapies(CAT), Orphan Medicinal Products (COMP), Paediatrics (PDCO), Pharmacovigilance Risk Assessment (PRAC), Veterinary MP(CVMP) and Herbal (HMPC) as

well as 28 working parties on a wide range of specific topics, EMA is joined by 4000 European experts in National Competent Authorities (NCAs), the EC and the EP.

2. Engagement with stakeholders. Juan Garcia Burgos and Marie-Helene Pinheiro, Stakeholders and Communication Division

Opening with the EMA stakeholder relations management frameworks for patients, HCPs, industry and academia. EMA stakeholder engagement ranges from informing, consulting and involving stakeholders to cooperation / participation in EMA regulatory activities. EMA's patient participation reaches back all the way to its creation in the mid-1990s: one year into its existence, in 1996, EMA engaged in a dialogue with HIV patients. A first for any regulatory authority and at a time, when HIV was only starting to overcome its stigmatisation. In 2000 patients joined COMP (orphan medicines) as full members, with the framework of interaction with patients and consumers being put in place in 2005. The same year, patients and HCPs joined the Managing board of EMA. The patients and consumers working party started in 2006. Five years later, in 2011, the new framework for interaction with HCPs came into effect. The current dedicated stakeholder engagement department was created in 2014 and 2017 saw the systematic inclusion of real life experience and clinical practise in EMA work. Currently EMA has piloted the first public hearing with great success. The large number of patients/consumer organisations and learned societies / HCP organisations has recently been joined by a familiar name: EASO and EASO Patient Council.

We further learned about the various activities which patients and HCPs can participate in, such as designation / classification, scientific advice, paediatric plans, market authorisation evaluation and post marketing procedures. The second half concerned EMA's engagement with academia, which while relatively new, already has a dedicated web portal at EMA Academia Portal.

EMA seeks to engage with patients/consumers, HCPs and academia in multi-stakeholder discussions, particularly around topics such as ATMs - exploring solutions to foster development and expand patient access in Europe, identifying opportunities for "big data" in medicines development and regulatory science, an E-health initiative, as well as around shortages and medicines availability.

Industry interaction typically takes place on a trade association level, and does NOT form part of EMA's routine interaction with individual application companies. EMA places a special emphasis on engaging with and supporting SMEs during the marketing authorisation application process in an effort to foster innovation and provide a wider range of treatments to patients across Europe.

Individuals may register their interest in interacting with EMA on their Website.

3. Guidance to R&D programmes: Scientific Advice and the PRIME network - Stiina Aarum, product development scientific support department

Stiina presented EMA's scientific advice and protocol assistance, aimed at speeding up patient access to new medicines through scientific advice, support for SMEs, the priority medicines scheme (PRIME), conditional market authorisations, accelerated assessments and compassionate use programmes. This guidance is prospective, aimed at development strategies, rather than a pre-evaluation of data to support marketing authorisation approval, and takes place pre- and post-MA, the latter for example to extend indications to different age groups and stages of a disease.

Stiina explained the scientific advice network, consisting of the Scientific Advice Working Party (SAWP), the Scientific Secretariat, external experts and clinicians, CHMP and other working parties/committees, as well as patient organisations and HTA bodies.

The programme has grown considerably in recent years, from 67 scientific advice and 7 protocol assistance activities in 2001 to 471 scientific advice and 159 protocol assistance activities last year.

Further on we learned about the eligibility criteria for the PRIME accelerated assessment scheme, aimed at medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation. What stood out in the statistics of granted and denied PRIME eligibility requests, is the low number of academic applications. EMA is looking for increased interaction with the academic community in this area.

Falk Ehmann then presented the Innovation Task Force (ITF) -- a multidisciplinary platform for preparatory dialogue and orientation on innovative methods, technologies and medicines which aims to assist knowledge exchange on innovative strategies involving the regulatory network, support drug development via an early dialogue on scientific, legal and regulatory issues as well as products, methodologies and technologies. The task force is an effort, to address the impact of emerging therapies and technologies on the current regulatory system and a preparation for formal procedures. The nature of ITF users in recent years saw growing involvement of academia and SMEs, which is a trend EMA wants to further nurture.

ITF's multidisciplinary nature allows it to draw from a multitude of resources across EMA and member agencies, within and outside the regulatory network in Europe and globally. Regulators are became gatekeepers and enablers for scientific innovation in the medicines sector. The ITF is EMA's tool for informal early engagement and feedback, facilitating discussion of scientific, regulatory and technical aspects of innovative developments.

The ITF secretariat can be contacted at ITFsecretariat@ema.europa.eu .

The role of the academic experts in scientific advice was then presented by Prof. Dr. Apr. Dieter Deforce. He showed, that aside from being applicants in the regulatory process, they are involved as members of CHMP, SAWP, assessors and in a large number of disease-specific working parties and other groups. All these bodies draw its member base from academic and non-academic experts in different fields, such as biologics/non-biologics quality, clinical/non-clinical and statistics.
The subject was concluded with the encouragement to **Ask Scientific Advice!**

Next on, Patrick Celis presented

4. Advanced therapy medicinal products (ATMP) and ATMP regulation.

ATMPs encompass gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. While these are very different from medicines based on chemical entities or of biological / biotechnological origin, they are subject to the same requirements for testing / controlling each batch. This impacts on cost of manufacture, particularly due to very small batch sizes. ATMPs are authorised in the EU via the centralised procedure, meaning the MA is issued by EMA and automatically carries recognition and authority across the EU/EEA. EMA's committee for advanced therapies (CAT) consists of CHMP/co-opted members, patients, clinicians and experts from national competent authorities (NCAs) and its tasks include, among other things, stakeholder interaction, publications and guidelines, CHMP, COMP (orphan meds), PDCO(paediatric) support and provision of scientific advice.

The advantages of obtaining an ATMP classification include a 60 day procedure (often shorter), no fee, regulatory certainty to ATMP developers (Is the product an ATMP? What guidelines are applicable to the product?) and that the process is aimed at early developments, without expectation of pre-existing clinical or non-clinical development.

Between 2009 and 2017, ~500 CTs using ATMPs in the EU, with about 290 ATMP classifications, 270 scientific advices issued, 19 MAAs reviewed and 10 ATMPs approved. Of the 10 ATMPs, 3 were withdrawn, 1 was suspended, so that 6 are currently licenced ATMPs.

Interesting from my perspective as patient representative, was the mention of patient registries -- organised systems, that use observational methods to collect uniform data on a population defined by a particular disease, condition or exposure and that is followed over time. The key role of patient registries is the monitoring of safety of medicines and long-term efficacy / lack of efficacy. Challenges include coordination between ongoing initiatives at national and international levels, harmonised protocols, scientific methods and data structures, data sharing and transparency as well as sustainability. EMA held a very successful CAR-T Cell therapy registries workshop in February 2018.

Germany's Federal Institute for Drugs and Medical Devices' Karl Broich was next, discussing

5. CT authorisation in the EU: present and future.

Karl opened with an overview, of how Clinical Trials (CT) were authorised in the past, from national rules, different processes and requirements for each EU member state and the delays and complications that ensued, via Directive 2001/20/EC and first steps to harmonisation to Reg (EU) 536/2014 where full harmonisation and combined assessment of multinational trials was achieved. Followed by a comparison between the previous directive and the current regulation, the scope of CT regulation was explained:

Interventional CTs with medicinal products for human use as well as low-intervention CTs, where non-interventional trials (observational studies) and trials without medicinal products (devices, surgery, etc.) are not covered by EMA's CT regulation. The CT authorisation process under the new regulation essentially consists of one submission to all member states concerned via the EU portal, a joint assessment and national assessments by each concerned member state followed by a joint decision and sponsor notification through the EU portal which is the central submission and communication platform at the center of the new regulation. Karl further outlined the challenges faced by National Competent Authorities in integrating the EU Portal into their national IT infrastructure, facilitating the short deadlines

which could lead to tacit approval and withdrawal as well as involving the mostly completely independent Ethics Committees (EC) -- in short: the streamlined process will put pressure on member states to adjust their processes accordingly. The deadlines for sponsors and authorities under the new regulation range from 60 days for CT Authorisations without any issues to up to 106 days for those with validation issues and requests for information during the assessment. Karl closed with showcasing the German pilot project on implementing the new regulation, where with the involvement of 35 out of 50 German ECs, 81 CTAs were jointly assessed and in nearly all cases, the new deadlines were met.

Transparency on Clinical Data.

EMA's Karen Quigley opened with an interesting list of ways to access clinical data at EMA:

Type / legal basis	URL
1. European public assessment reports (EPAR) Article 13(3) of Regulation (EC) No 726/2004	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
2. Access to documents (ATD) Regulation (EC) No. 1049/2001	http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001R1049&from=EN
3. Clinical Data Publication (CDP) website (Policy 0070)	http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf
4. Clinical Trial Regulation (CTR) (EC) No. 536/2014	http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

While EPARs are widely known, available online and used by various stakeholders, ATD applies to any documents held by EMA provided to the requester upon request. CDP and CTR are proactively published, CDP on the web and CTR in an EU database. EMA performs anonymisation and provides an anonymisation report where commercially confidential information needs to be redacted. Such redaction is not accepted by EMA, if the information in question is available in public domain, does not bear any innovative features, reflects common knowledge within the scientific community, justification provided is irrelevant to the text in question, or commercial harm of releasing the information is not or insufficiently explained. Anonymisation aims to turn data into a form which does not identify individuals, or which makes identification unlikely; it ensures a low risk of re-identification and the anonymisation report explains the process, the methodology used and the impact of anonymisation on data utility.

Within one year, EMA has published 54 procedures, with a total of 3279 documents or 1,308,244 pages.

This talk was followed by Marisa Papaluca - Co-Chair of the EU Innovation Network - introducing us to

6. EMA Support to Innovation: Operation of the EU Innovation Network.

Among the early development services at EU level which come with a fee reduction for academics, are the SME Office, the Innovation Taskforce, qualification of novel methodologies and Scientific Advice. Another range of free services include at the ATMP classification, the Paediatric investigation plan, the Orphan Medicine designation, the PRIME scheme and the EU Innovation

Network.
The EU IN was established through strengthened cooperation between EU national competent authorities in order to support medicine innovation and early development of new medicines in the EU. Both EMA and HMAs across the EU adopted the mandate of the EU IN in October 2016.
On the national level, NCAs are responsible for key tasks, such as:
Authorisation- and GMPs, CT authorisation, AMTPs hospital exemptions, compassionate use, NCA's scientific advice, NCA's innovation offices.
National innovation offices join the EU IN on a voluntary basis, their services are directed at hospitals, academic groups, SMEs, research foundations and consortia. Some innovation offices have expressed interest in hearing from patient interest groups and funding/networking organisations.

A list of national innovation office contacts can be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228157.pdf

EMA Regulatory Science Observatory and Horizon Scanning.

Presented by Tony Humphreys. In the light of new development paradigms progressing with unprecedented speed, products that are increasingly complex and challenging to develop, manufacture, evaluate and make available to patients, a new approach to innovation is required. Particularly the shift from treatment to potentially curative medicines requires a new perspective on assessment, payment and financing.

With constraints driving strategic allocation of resources, regulators want to see themselves as more than a gateway between science and national healthcare systems; the want to become a catalyst and enabler for science to be translated into patient centered healthcare, that is fit for the current reality in healthcare systems. In order to achieve this, EMA and its fellow regulators want to scan the horizon, identify the main gaps and bridge them, by connecting various stakeholders together.

Kristina Dunder, Swedish member of the Committee on Human Medicine Products(CHMP) introduced us to the

7. Benefit-Risk Assessment for Initial Marketing Authorisations and Standard of Evidence

next. This task is performed by the CHMP, which consists of one member and one alternate member per member state, one member from Iceland and Norway each and 5 to 6 co-opted members. The purpose of this B-R-Assessment, is to identify the condition, population(s) and conditions for use, for which it is established, that benefits outweigh the risks. It serves as a final reflection/conclusion of CHMP's assessment of the data submitted. Preferred primary and secondary endpoints are defined in scientific guidelines, objective, subjective and surrogate endpoints are considered. Challenges are posed in the areas of deciding the value of a certain benefit or risk, the choice of qualitative or quantitative analysis to weigh benefits against risks and the choice of performing absolute or relative B-R-Assessments, ie. should the CHMP compare the new product to already available alternatives.

Considerations upfront include the applicant's proposal for indication, the aims of the therapy and key efficacy endpoints. An awareness of the main available treatment options and unmet needs is required. Furthermore, randomisation, blinding, control, dosing and study size of the main clinical studies

are taken into account upfront. When considering the clinical relevance of the benefits, the magnitude of the effect is examined, as well as the type of knowledge this judgement is based on.

If surrogate endpoints have been used, the expected outcome on the clinical endpoint is reviewed.

The importance of risks for the patients is examined in respect to severity, reversibility and treatment withdrawal, and how those relate to the severity of the disease.

The impact of uncertainties and limitations associated with the risks and benefits can lead to warnings, restricted indications and mandatory follow up studies. The potentially different favourable and unfavourable effects on subgroups of the proposed target population are also reviewed.

Tradeoffs between benefits and risks are considered based on knowledge from assessors, CHMP, experts and patients. The assessment may also result in a broader or more restricted population for which the B-R balance is positive, than the population defined in the applicant study. In such a case, it is important to consider how such a conclusion was arrived at.

Communication of the B-R-Assessments finds its way into Summary of Product Characteristics (SmPCs), European Public Assessments Reports (EPARs) and press releases on EMA and NCAs' websites. Different stakeholders (prescribers, patients, HTAs) do have different preferences concerning the description / assessment of benefit/risk balances.

Andrea Taft went on to describe how

Pre-Submission Guidelines and Use of Experts ensure Scientific and Regulatory Quality

EMA's committees pool their expertise in this process, where particularly the CHMP delivers scientific opinions to the European Commission and WHO, determines compliance with quality, safety and efficacy requirements and a positive B-R balance of products. CHMP also prepares EU guidelines and policies, gives scientific advice and protocol assistance to applicants, establishes and works with working parties and scientific advisory groups and interacts with international regulators. Standing working parties exist for patients, consumers, HCPs etc, while temporary working parties/drafting groups focus on disease areas with scientific advisory groups taking responsibility for specific diseases such as diabetes or neurology.

A list of European Experts is available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/experts.jsp&mid=WC0b01ac058043244a

A wide variety of expertise in the CVs listed there, shows many experts worked for long periods in the industry or as HCPs before joining their country's respective regulators, with the majority of experts being postgraduates or PhDs.

The guidelines formulated by these experts are "soft law", meaning they have no legal force. But they do represent a harmonised EU position on how to interpret and apply requirements to demonstrate quality, safety and efficacy as set out in the directives. It is required, that guidelines be followed to facilitate development, assessment, approval and control of medicinal products in the EU and alternative approaches must be duly justified in the dossier at the time of the market authorisation application submission. EMA scientific guidelines exist in the fields of quality, biologicals, non-clinicals, clinical pharmacology and pharmacokinetics, clinical safety and efficacy, multidisciplinaires, herbal medicinal products and ICH.

There is also a guideline for writing guidelines:

Procedure for EU guidelines and related documents within the pharmaceutical legislative framework, March 2009 (EMEA/P/24143/2004 Rev. 1 corr)

This process too is designed to provide the maximum amount of transparency with comments from stakeholders and EMA's response / outcome all publicly documented online, for example at:

http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2016/07/WC500209945.pdf

any member of the public can review and retrace the process of how requests for comments were either accepted and incorporated into a guideline or rejected and why. In this specific case for the **Guideline on clinical evaluation of medicinal products used in weight control' (EMA/CHMP/311805/2014)**

Once a final guideline is agreed by the working party, it is adopted by the committee, published to the EMA website and implemented 6 months after publication. EMA provides training and workshops for assessors/experts, considers revisions on an annual basis and communicates "what's new" on the EMA website. Typically a guideline takes 2-3 years to pass through all the stages towards publication. Where urgency for public health is identified, the process can be sped up.

Other supportive documents issued by EMA include: public statements (important immediate information, e.g. withdrawal of a product), reflection paper (current status of scientific discussion, invitation to comment/discuss in areas where scientific knowledge is limited), Q&A (additional clarity on particular aspects, guidelines, products), Addendum to guidelines (usually specific topics, e.g. paediatrics), recommendations/procedural advice (technical and regulatory documents).

Malgorzata Zienowicz then talked about various

Types of Approvals and Commitments

in the regulatory process for granting marketing authorisations. She pointed out, that EMA provides opinions to the European Commission while the EC makes the official decisions, a process that typically takes two months. Various factors can lead to MAs being either not granted or granted with specific requirements (non-standard MA). It is uncommon that the EC grants an MA against EMA's recommendations, whereas the EC might impose further restrictions out of political, economical or other necessities.

Uncertainties in the approval decision may be addressed by commitments in a risk management plan (RMP), studies as part of a pharmacovigilance plan and risk minimisation measures. Marketing Authorisations can be tied to conditions, such as post-authorisation efficacy and safety studies.

While normal MAs usually require a 100% comprehensive data package for approval to take place, conditional MAs may receive approval at a much earlier stage with conditions attached that will see a complete or beyond comprehensive data package being required in the future. Exceptional MAs may receive approval at an earlier stage with no obligation to reach a fully comprehensive data package, which could be due to a number of factors, such as rare indications, scientific limitations or ethical barriers.

Carlos Aicardo Muñoz continued in this area, presenting the topic of

B-R-Assessment throughout the medicinal product lifecycle.

Typical B-R-management activities post-approval include periodic evaluations of the B-R balance(annual renewals, periodic safety update reports - PSURs/PSURA, Annual Reassessment, post authorisation measures - PAMs, Renewals), development and maintenance of the product (ie. new

solutions for patients / variations) and Ad-hoc evaluations of a product's B-R-balance in light of concerns on the safety, efficacy and quality of medicinal products(Urgent Safety Restrictions, Referrals).

Sources of evidence include randomised CTs, uncontrolled CTs, spontaneous adverse event reports, registries, observational studies, expert committee reports, opinions of respected authorities/experts, publications.

The next topic was

8. Dealing with specific populations and types of products,

where Enrica Alteri opened on

paediatrics and orphan medicines.

Paediatrics regulation in the EU is legally anchored in regulation (EC) No 1901/2006 of the EP and Council of 12 Dec. 2006. The EU guideline 2014/C 338/01 also applies. Its objectives are the increase of high quality, ethical research into the medicines for children, increase availability of authorised medicines for children and increase information on medicines, all without unnecessary studies in children and without delaying authorisation for adults. The core of this aim is the paediatric investigation plan (PIP), which is required for new MAs, and existing MA if new indications arise, new administration routes become available or new formulations get released. Cases where the PIP is not required, include a new product belonging to herbal medicines, homeopathic products, generics, hybrids or biosimilars.

PIPs should be requested at the end of phase 1, with amendments usually made during phases 2 and 3. The Paediatric medicine designation is awarded to completed PIPs, where the product's development is compliant with its agreed PIP, the results of relevant studies are included in SmPC and patient leaflets, and the product is authorised in all member states (except for PUMA).

Non-orphan products receive a 6 months extension on their patent protection. OMPs gain an additional 2 years of market exclusivity and PUMA products receive 8+2 years of data and market protection. Product or class specific waivers don't trigger the above rewards and neither do inconclusive studies. The results of these efforts can be seen in the 267 new medicines for use in children and 42 new pharm. forms appropriate for children authorised in the EU between 2007 and 2016, as well as the increase quality and quantity of information for prescribers and patients, with ~140 to product information published by end of 2015.

Better paediatric R&D can be observed as well as increased regulatory support for paediatric matters. Paediatrics are now an integral part of medicine development.

Another area which is actively supported by regulators and EMA, is that of Orphan Medicines, a designation, which is awarded free of charge for human use medicinal products and can be requested at any stage of development by sponsors such as companies or individuals that are established in the EU/EEA. This 90 day procedure involves a COMP (Committee on Orphan Medicinal Products) assessment and its incentives are based on a European Commission decision.

The designation criteria include rarity (prevalence) and the prospective lack of return on investment (condition affecting not more than 5 in 10000 in the EU/EEA to the extent where without incentives, the necessary investment might not be economically viable), seriousness (life threatening or chronically debilitating disease), significant benefit (if satisfactory method exists, sponsor should

establish the benefit). Significant benefit in the framework of the EU orphan regulation requires a clinically relevant advantage and a major contribution to patient care. Showing this benefit may also facilitate the work of the HTAs and reimbursement bodies.

Incentives include fee reductions/exemptions and extended incentives for SMEs, 10 year market exclusivity (+2 if paediatric), product development support, a community authorisation and further national incentives.

Some of the aspects CHMP assesses when determining similarity to other orphan medicines for the same designated condition, include molecular features, mechanism of action and therapeutic indication. The EU orphan regulation has achieved 1805 orphan designations between 2000 and 2016, of which 128 have resulted in authorised medicinal products.

Information on EMA Orphan Medicines regulation can be found here:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41

The next module concerned itself with good

9 Good Practice and Inspections.

It was moderated by Anabela Marçal - head of committees and inspections at EMA.
Good Practice supervision at EMA is mainly performed in three fields: GMP (good **manufacturing** practice), GCP/GLP (good **clinical/laboratory** practice) and GVP (good **vigilance** practice).

Manufacturers who supply to the EU no matter where they're based or who are are located in the EU no matter where they supply to, both need to adhere to EU GMP. Operators in the supply chain are subject to authorisation/registration and are inspected to ensure compliance with legal requirements (GMP, requirements in MA or CTA). EU law is providing for formal mutual recognition of inspections across EU member states.

EMA's role in GMP inspections

includes ensuring a common interpretations of EU GMP requirements, developing EU-wide procedures, facilitating cooperation between member states, developing and maintaining EudraGMDP.

The GMP status of manufacturing sites can be verified online at:

http://eudragmdp.ema.europa.eu

EMA has mutual recognition agreements with other global regulators to ensure inspections carried out by authorities with harmonised procedure won't have to carried out again and to eradicate the need for re-control upon import. An EU-US MRA is currently in the process of being implemented and full reach full scope by 2022.

On GCP and GLP

Sophia Mylona provided us with interesting insights. Analogue to EudraGMDP, good clinical and laboratory practice is documented the in EudraCT database. All clinical trials that are part of a marketing application dossier can be subject to a GCP inspection, while not all applications necessarily give rise to an inspection. Inspections can be triggered by concerns regarding deviations from GCP or routine. Inspection findings can range from critical to major and minor. The latter are conditions, practises or processes that would not be expected to adversely affect the rights, safety or well-being of subjects and/or the quality and integrity of the data. The top 10 critical findings of GCP inspections include deficiencies

in essential documents, source documentation, monitoring, reporting in CRF/diary, data management, SOPs, qualification/training, supply/storage/retrieving/destruction, organisation/personnel and protocol compliance. Consequences can range from none (data accepted, no consequence), over further inspections of new sites / trials, rejection of data from selected sites, correction of data to the rejection of an entire trial and thus possible delay or rejection of the application.

10. Patient Safety and Pharmacovigilance

Good Vigilance Practice (GVP) is also a responsibility of EMA and the outcome of inspections can be escalated to PRAC - the pharmacovigilance risk assessment committee. Information on the outcomes of inspections is shared within the EU network on pharmacovigilance inspections.

The EU Pharmacovigilance System

was explained to us next. Its goals are anchored between health promotion (fulfill unmet needs, plan evidence generation throughout life cycle, plan for optional risk management at authorisation and support of authorisation decisions through a robust PhV system) and health protection (robust monitoring for safety issues, rapid decision making, effective action to minimise risk and demonstration of positive impact). The monitoring of medicines safety is based on a number of potential data inputs that may lead to safety concerns, such as clinical studies, medical literature, **safety reports from patients and HCPs**, **patient registries** and regulatory bodies outside the EU. They're then subjected to an assessment by EMA's PRAC (pharmacovigilance and risk assessment committee), which results in a PRAC recommendation, that could take the form of: maintaining, changing, suspending or revoking a medicine's market authorisation. This recommendation is then communicated to the network and leads to a final decision by the member states or the European Commission.

Among the stakeholders in pharmacovigilance, patients and HCPs take a special role, due to their hands-on experience with the disease and its treatments. Patients bring a 'real-life' experience as well as specific knowledge and expertise to regulatory decisions, while HCPs have specific knowledge and expertise to offer, as prescribers and handlers of the medicines.

EMA has extensive information on the subject available on its website.

Claire Espinasse proceeded with outlining the

EU Risk Management Plan (RMP)

and how at the time of authorisation, while a wealth of information is available, some data is not available by nature of lack of feedback from using a medicinal product in the field. Such as effectiveness of the product in normal clinical practice (compliance, resistance, populations are not included in trials), lack of a full safety profile including adverse drug reactions (rare, delayed, long-term exposure, medication errors, off-label use, abuse/misuse, populations not yet studied in the trials. A risk management plan is then a detailed description of a risk management system.

The key documents in a RMP are the GVP module V rev2 and the RMP template rev2 both available on the EMA website. An important part of risk management is risk minimisation. This can can take the form of routine measures, such as legal status of medicine (restricted access etc), pack size, SmPC, package leaflet, labelling. Additional risk minimisation measures can include HCP education, patient education, prescribing algorithms/checklists, controlled access programmes and others. The

effectiveness of risk minimisation needs to be measured, as the legislation requires active monitoring of its outcome, which is an additional pV activity in the RMP. GVP Module XVI provides further guidance.

An important source of information on suspected **adverse drug reactions (ADR)**, is **EudraVigilance (EV)**, a single access point pharmacovigilance database. It contains suspected ADRs from both pre- and post- authorisation phases, transmitted securely by NCAs, MA-holders and sponsors of CTs, these three groups are the exclusive data submitters to EV, however they can nominate / register third parties to act on their behalf by providing services related to EV. It also contains medicinal product information in the EV Medicinal Product Dictionary (xEVMPD).

Academia, HCPs, patients and the general public can however access EV data for their own analysis by either contacting EMA or using the public interface at

http://www.adrreports.eu

Both EMA and NCAs perform **EV Signal detection and validation** for their respective areas of competency (centrally authorised products / nationally authorised products). MA-holders also monitor EV for new signals and may engage with EMA/NCAs pro-actively.

Gaelle Bec next talked to us about

Periodic Safety Update Reports (PSURs)

PSURs are reports prepared by the MA-Holder describing the worldwide safety experience with a medicine at a defined time after its authorisation. It forms part of the life cycle benefit-risk management of a medicine. Their legal requirements are established in Regulation (EC) No 726/2004 and Directive 2001/83/EC. The PSUR contents are described in GVP Module VII.

While the first post-authorisation PSUR is due after 6 months from the date of authorisation, subsequent PSURs submission frequencies are set in the list of Union reference dates (EURD) and can range from 6 months to up to 3 years.) Findings are published in for example as European Public Assessment Reports (EPARs) (“Find medicine” on http://www.ema.europa.eu).

The final module of the 2nd International Awareness Session concerned itself with

11. EMA and international regulatory cooperation.

It was presented by Riccardo Luigetti and Martin Harvey Allchurch, EMA International Affairs department. EMA cooperates internationally on a daily basis with other regulators such as FDA, PMDA, Health Canada, TGA, SwissMedic and WHO. New emerging players in medicinal products regulation are China, India, Brazil, Africa, Mexico and Russia.