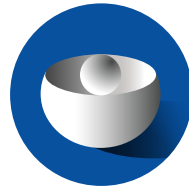




EUROPEAN MEDICINES AGENCY | CELEBRATING 20 YEARS



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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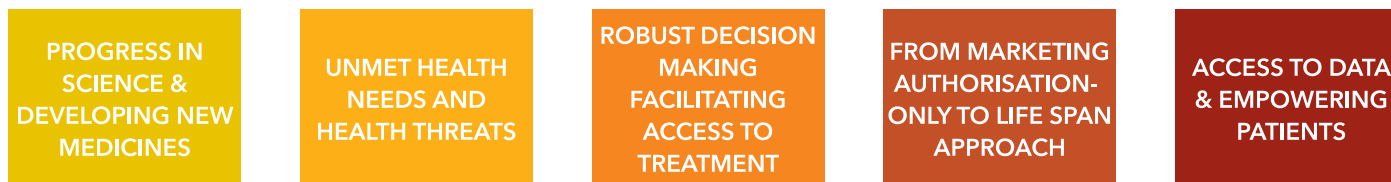
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PREFACE

Twenty years have passed since the establishment of the European Medicines Agency (EMA). Since the creation of the EMA in 1995 the environment in which the Agency operates has undergone major changes, but the primary mission of the EMA, i.e. to promote and protect public and animal health, has always been at the forefront of the Agency's activities. The production of a 20th anniversary book was considered an excellent way to celebrate the achievements of the EMA in fulfilling that mission over the past two decades.

The aim of the book is to capture both the important progress in regulatory science and the societal changes in the field of medicines regulation which have taken place over the past 20 years, and to describe how the Agency has equipped itself to successfully address important public and animal health challenges resulting from these drivers for change.

The book presents a snapshot of major achievements and these have been grouped into five themes:



Within each theme, for each topic, the scientific and societal developments as well as the EMA response have been described.

A total of 41 authors have contributed to these themes and topics, either providing their views on the scientific and societal developments, or highlighting the main EMA initiatives to respond to these drivers for change. These authors have been selected from the wide range of partners and stakeholders involved in the Agency's activities, and they demonstrate - once again - an important feature of the unique and successful European networking model, i.e. working together to improve public and animal health.

We would like to thank everybody who contributed to the book, the authors who provided contributions for the different themes and topics, the Editorial Board for their valuable input, and the EMA staff who supported in an extremely professional way the finalisation of the EMA 20th anniversary book.

The editors,

Sir Kent Woods
Chairman of the EMA Management Board

Pharm. Noël Wathion
EMA Chief Policy Adviser

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It is a pleasure and an honour to be able to contribute to this book marking the 20th anniversary of the creation of the European Medicines Agency - especially since the Agency plays the central role in the protection and promotion of public and animal health, putting the European citizens' interests at the heart of its work.

Since its creation, the Agency has been operating in the ever-changing, challenging environment to become a well-known medicines agency recognised world-wide. Over the years the institution has acquired increasing responsibilities under EU legislation. It has also grown both in terms of its staff and budget. European citizens have been asking for more innovative medicines and more effective generic products, developed in line with new methods in the medical research sector. Addressing these and other issues will remain a challenge and as a result the EMA is bound to play an even more important role in the future.

Medicines are not just business: they are a very specific good; a socially and individually sensitive good. The Commission therefore relies on sound and robust scientific opinions developed by the scientific committees of the EMA. We will work together not only to increase trust and transparency but also to address issues related to the availability and access to medicines and the development of affordable medicines.

EMA must always strive to be the example of an innovative, transparent and fair institution continuing to bring value to the European citizens and contributing to ensuring that the medicines which are authorised in the EU meet high standards of efficacy, quality and safety.

Let us build on the good foundations which have been laid during the past two decades and continue to produce high-quality work for the benefit of public health and, ultimately, patients.



Time flies.

It seems like yesterday, that I travelled from Strasbourg to London to speak on the 10th anniversary of what was then still the EMEA*. Now, looking back on 20 years of EMA: what a success!

The challenge of keeping track with rapidly ongoing scientific research everywhere and its results and impact on the core tasks of the Agency continues to be huge.

At the same time, EMA had to 'absorb' the highest amount of new pharmaceutical and health legislation, adopted by the European Parliament and the Council, with always direct consequences on EMA's organisation and amount of work. It is because the trust of the European Parliament in the EMA and its work was and is so high, that whenever there was a part in a piece of legislation where responsibilities had to be defined, 'EMA' was always the natural and immediate thought and addressee.

Therefore, for example, the respective legislations on Orphan Medicines, Paediatrics, Herbals, Advanced Therapies directly resulted in the creation of new committees. For some of them, EMA was not always immediately enthusiastic, but embraced the topics and the work related to it faithfully and - as expected - in best quality.

*Former abbreviation used by the European Medicines Agency.

And EMA, not sitting in an ivory tower, proved with its policy on conflicts of interests, on transparency, on the right of information for patients and health professionals - for example on clinical trials - with its overall openness and clarity, that it understands the relationship between openness and trust. How valuable, how more and more important such a philosophy is in times of different ways of communication! With all possibilities the internet offers, EMA can play the role of a trusted landmark, a source of information, for the public.

Moreover, with the accompanying role on falsified medicines - a frightening danger - and, just in recent time, with the responsibilities on pharmacovigilance, it becomes more and more obvious that the work and role of EMA goes in the meantime beyond the 'pure' coordination of centralised authorisations; in fact, it fills the place of THE health authority in the EU. And that is good! And there is room for the Member States, their national agencies AND EMA, in its overall, embracing function, for the better of public health. That is why the next years will have to consolidate cooperation and trust between all stakeholders. There is no time for vanity or rivalry. Working for European citizens, protecting health, ensuring patient safety in daily life, but as well in the light of possible health threats tomorrow, still unknown today, cooperation and support with other agencies all over the world creates an immense task.

This needs best expertise, total dedication, loyal belief in the serving role for hundreds of millions of citizens, for the European Union and its Member States: That is what EMA and its team has been over the last 20 years - and, no doubt, will be in future. Keep going and my respect and best wishes to each and everybody in the whole team.




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Twenty years is an important milestone for the European Medicines Agency, and the Agency and its staff can be proud of the achievements made over the past two decades.

When I took up my mandate as Executive Director in 2011, I was excited about building on the many successes and addressing the new challenges for public and animal health ahead.

How can we bring medicines to patients more rapidly and make sure that patients with rare diseases can benefit from treatments? How can we help assure access to medicines in a world of increasing scarcity? How can we better monitor the safety of medicines? And how can we maintain the trust and the credibility of partners and stakeholders who rely on our scientific advice and recommendations?

A few years on, I am pleased to see progress in all these areas, thanks to our close collaboration with the European Commission, the European Parliament, the national competent authorities, patients, healthcare professionals, academia and other stakeholders, and to the hard work and dedication of EMA staff and experts.

There are many highlights, but I see a few key developments, in particular in the areas of transparency, access to medicines and safety, that will continue to play an important role over the coming years.

With the landmark policy on the publication of clinical study reports that entered into force in January 2015, we followed up on our commitment to transparency. The new policy is an important contribution to the ongoing global movement on access to data that will bring more opportunities to benefit from access to the available evidence on the safety and efficacy of medicines.

Due to the Agency's efforts to promote and support innovation and research into new medicinal products, particularly for rare diseases, today, almost all new and innovative medicines are authorised centrally. New initiatives such as adaptive pathways to marketing authorisation will hopefully help to accelerate access to new medicines if no other treatment options are available for patients. We also strengthened our relationships with health technology assessment (HTA) bodies, which is critical to allow new medicines to reach patients in the context of the national health system of their country.

Another important highlight was the creation of the Pharmacovigilance Risk Assessment Committee in 2012. This committee significantly improved the monitoring of medicines and ensures a coordinated response to safety issues.

On a global scale, we continue to play a vital role in the response to the threat of antimicrobial resistance and pandemics such as influenza and Ebola.

The patient has always been at the heart of our work, and it is only through their engagement that we can achieve our ambitious goals. In recent years patients have become more and more involved in all aspects of our work, and I am happy to say that this focus on patient engagement will continue to play a central role in our work at EMA.

In a European Union that has grown from 15 Member States in 1995 to 28 today, our mission continues to be the improvement of public and animal health. In view of the ongoing globalisation, and increasingly stretched budgets, the European Medicines Agency is needed more than ever as a trusted and independent regulator to protect the health of people and animals across the Union.



I had the privilege of leading the EMA for half of its twenty-year history. During this time we saw a massive expansion of the Agency, with the integration of thirteen new Member States, as well as the introduction of several legislative reforms.

Included in these public health reforms were the orphan medicines legislation, with its Committee for Orphan Medicines (COMP); the paediatrics legislation, with the Paediatric Committee (PDCO) and the pharmacovigilance legislation that established the 7th EMA scientific committee, the Pharmacovigilance Risk Assessment Committee (PRAC).

To manage this expansion, we introduced the EMA roadmap, which became an instrumental planning tool in gaining the consensus of our Member States, the European Parliament, the European Commission, as well as the pharmaceutical industry.

The roadmap envisaged how the European regulatory system would support public health. Concepts such as regulatory science were born with the introduction of adaptive pathways, benefit-risk methodology and other initiatives strengthening the scientific aspects of the work of the Agency. We also established a link with the health technology assessment (HTA) bodies to support information sharing, and introduced the parallel scientific advice procedure guiding pharmaceutical companies on their medicines development programmes.

It was not only the internal work within the EU and the Agency that was high on the agenda but also the international collaboration with other regulatory agencies. In 2001, the EMA and the FDA agreed to work together sharing information in close cooperation. This has now developed into a very successful collaboration, and similar agreements have also been extended to many more regulatory agencies in the world, reflecting the globalisation of the pharmaceutical sector.

The EMA is today one of the leading regulatory agencies in the world. This is thanks to the hard-working and dedicated experts from our Member States and the fantastic staff at the EMA.

The Agency and its staff deserve to be congratulated and commended for their achievements and contribution to public and animal health during its twenty-year history.

All the best for the future.



A tradition of excellence at the European Medicines Agency. Over the last twenty years, the EMA has gained a solid reputation for scientific excellence in providing quicker and safer access to innovative treatments for human and veterinary use.

It all started thirty years ago with a plan to achieve legislative harmonisation and coordination of national evaluations for biotech and other high-tech products. A network of national experts worked together, generating trust between all concerned parties, and enabling the adoption in 1993 of the European authorisation system, combining centralised and decentralised procedures. The launch in 1990 of the International Conference on pharmaceutical harmonisation resulted in close cooperation between the European Union, the US Food and Drug Administration, Japan, and many other countries.

From 1995 onwards, the EMA has performed at a high level, comparable to that of the FDA. Initially, a small team dedicated itself to setting up the Agency, whilst national authorities continued to provide their best expertise for our scientific bodies. Patient and healthcare professional organisations were associated with all relevant activities and later included in several committees and in the governance of the Agency. The Agency also provided useful scientific advice, organised product-related hearings and open information days for the pharmaceutical industry.

For the European Commission and the increasing number of EU Member States and European Free Trade Association (EFTA) partners, the EMA has become an indispensable asset for health protection and promotion, scientific evaluation and international harmonisation. The EMA has consistently strived to improve transparency. With the critical support of the European Parliament and non-governmental organisations (NGOs), it will have to regularly review the situation.

I am most grateful for the tremendous support from staff and scientific committee members which I enjoyed during my time at the Agency. I am impressed by the considerable progress made and wish all the best to the EMA, as it has to deal with challenges which lie ahead, such as personalised medicines.



PROGRESS IN SCIENCE & DEVELOPING NEW MEDICINES

The last 20 years have seen both slow but profound changes, and rapid but more visible changes.

Innovative therapeutic options, such as nanomedicines and gene therapy, are no longer science fiction, and pharmacogenetics allow the benefit-risk balance to be refined for specific groups of patients. Personalised medicine is the next step.

Rare-disease models benefit common diseases. Medicines are now assessed on the basis of rigorous evidence, rather than expert statements; methodology and biostatistics have become a determining factor and integral part of the regulatory assessment.

Regulators use more systematic approaches to the collection and analysis of data, for example requiring meta-analyses, and integrating new approaches to assess efficacy, safety and quality.

At the same time, regulators work on making the reasoning in scientific assessments more transparent.

In Europe, regulators are more involved in the steps preceding the tipping point of marketing authorisation to stimulate innovation and increase the chances of success. This is the inaugural phase of transforming the review of data into an earlier, progressive and adaptive process, but firmly evidence-based, with the ultimate goal of making medicines that are safe and effective available to patients sooner.

Simultaneously, the HIV pandemic has demonstrated the reactivity of the medical and pharmaceutical world, which was able over the last 20 years to identify a new disease, its epidemiology and its agent, and invent therapeutic molecules to treat and prevent it, resulting in significantly better understanding of the immune system, with benefits for common and rare diseases.

PROGRESS IN HIV TREATMENT

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

An emerging disease in 1981, the Acquired Immuno-Deficiency Syndrome (AIDS), was to terrify populations worldwide. The response and engagement of healthcare providers and researchers was an exemplary one, in front of an epidemic affecting young people whose life expectancy was dramatically reduced to a few weeks, once infected by pneumocystis. By the end of 1983, a retrovirus was discovered in a lymph node. Serology assays were approved in March 1985 and allowed defining seropositivity. While the pandemic was spreading, at-risk groups were multiplying. In March 1987, without further confirmatory trials, zidovudine was put on the market on the basis of a phase II trial prematurely discontinued when results showed one death in the treated group and 19 in the placebo group. Viral resistance emerged quickly on monotherapy and explained this first therapeutic failure; unfortunately the second antiretroviral was only approved in 1992.

The year 1996 was a landmark: plasma viral load became the validated prognostic factor, and antiproteases were approved for marketing. The ritonavir trial became the last one capable of detecting survival improvement. The EU and the US developed regulatory guidelines to frame antiretroviral development and to promote early access to a maximum of medicines and new classes. From that time on, clinical endpoints were substituted by viral load determinations, cluster of differentiation 4 (CD4) counts and pharmacodynamic results. Safety data from clinical trials and pharmacovigilance were obtained in growing collaboration with patients' organisations to improve therapeutic monitoring and adaptation.

We have now a large number of classes: nucleoside and non-nucleoside reverse transcriptase inhibitors, protease inhibitors, anti-integrase, fusion and C-C chemokine receptor type 5 (CCR5) inhibitors, all of which allow different combinations both to overcome acquired resistance and to prevent them. Combination therapy became all the more relevant as tolerability significantly improved. Once-daily medication is now available and is the gold standard for first-line treatment of adults; there are still unmet needs for children.

Despite strenuous research efforts, vaccines have not succeeded so far; thus in 2014, the World Health Organization proposed to treat more widely seropositive patients to avoid new contaminations. There is an active debate within the community on the benefits of primary prophylaxis with antiretrovirals. Optimally, such use should be regulated.

It can be said that early access to treatment transformed the human immunodeficiency virus (HIV) epidemic, but equally that the HIV epidemic transformed the regulatory approach to patients' empowerment and early access, in particular through compassionate use. Lessons were learned that inspired the recent development on hepatitis C treatments. In addition, developing treatments for AIDS opportunistic infections (cytomegalovirus infections, fungal infections) benefited other patients, e.g. those having received organ transplants. Another milestone to remember was the effective prevention of materno-foetal transmission.

“ IT CAN BE SAID THAT EARLY ACCESS TO TREATMENT TRANSFORMED THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) EPIDEMIC, BUT EQUALLY THAT THE HIV EPIDEMIC TRANSFORMED THE REGULATORY APPROACH TO PATIENTS' EMPOWERMENT AND EARLY ACCESS, IN PARTICULAR THROUGH COMPASSIONATE USE. ”

In 2013, 1.5 million deaths still occurred, mainly in low and middle-income countries. Moreover, the history of infectious diseases tells us that the emergence of resistance to treatment remains a major threat worldwide as long as we have not controlled an epidemic.

In 1996, the first medicines were approved via the centralised procedure under exceptional circumstances (lamivudine, ritonavir and saquinavir), based on results showing significant reduction in the risk of disease progression and mortality in phase 2 studies and/or phase 3 interim results. This regulatory achievement was the response to the significant treatment breakthrough determined by the introduction of highly active antiretroviral therapy (HAART), which consisted of at least three antiretrovirals given in combination.

The first document addressing 'Points to Consider on the Assessment of anti-HIV medicinal products' was adopted by the Committee for Human Medicinal Products (CHMP) in January 1996. Early that year, the European AIDS Treatment Group delegation was invited to the CHMP plenary to share their concerns and reflections regarding unknowns about the value of surrogate markers (cluster of differentiation 4 (CD4) cell count and viral load) as primary endpoints. From that moment, HIV advocates were invited to adhoc expert group meetings on antiretrovirals on a regular basis.

The points to consider were subsequently revised to introduce the work of the Surrogate Markers Collaborative group. Further revisions have included elaboration on the regulatory implications of pharmacokinetics, viral resistance, data requirements in patients failing therapy, and the use of boosted protease inhibitor regimens.

The first fixed-dose combinations of antiretrovirals of the same class were approved between 1998 and 2000.

In 1999, a specific expert group was convened with academia, the FDA, the pharmaceutical industry and patients' representatives with the objective to discuss research strategies on the long-term medical complications related to HAART.

Regulatory pathways were put in place through Article 58 of Regulation (EC) No 726/2004 to allow the CHMP to give opinions, in cooperation with the World Health Organization, on medicinal products intended exclusively for markets outside the EU. Positive scientific opinions were granted to three antiretrovirals (lopinavir/ritonavir, lamivudine and lamivudine/zidovudine).

In 2005, the Scientific Advisory Group on HIV and Viral Diseases was established to provide an independent recommendation on scientific/technical matters related to medicines under evaluation. This group took an active part in the revision of guidelines, as well as in product-specific discussions.

Paediatric clinical development and the development of age-appropriate formulations have been encouraged. Up to date, several antiretroviral classes are available for the paediatric population, which include nucleoside(tide)analogues, non-nucleoside analogues, protease inhibitors and integrase inhibitors.

Antiretrovirals with improved tolerability and safety, with simple dosing regimens (once daily and small pill size) were needed for lifelong treatment, and in 2013, once-daily fixed-dose combinations (FDC) as single-tablet regimens were approved.

“ANTIRETROVIRALS WITH IMPROVED TOLERABILITY AND SAFETY, WITH SIMPLE DOSING REGIMENS (ONCE DAILY AND SMALL PILL SIZE) WERE NEEDED FOR LIFELONG TREATMENT AND IN 2013 ONCE-DAILY FIXED-DOSE COMBINATIONS (FDC) AS SINGLE-TABLET REGIMENS WERE APPROVED.”

Following the introduction of numerous new and potent HIV medicines in recent years, the development of extensive *de novo* resistance became a rare observation. As a result, placebo-controlled superiority designs are hardly feasible. As a consequence, the guideline is being revised to consider alternative options.

PROGRESS IN CANCER TREATMENT

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Over the past 20 years, vast improvements in cancer medicine development and treatment have been achieved. About 20 years ago, treatment of advanced stages of nearly all cancer types consisted of cytotoxic therapy, and also of hormonal therapy for some forms of cancer. Treatment selection was based on the histological origin of the tumour and a few biomarkers further refined treatment selection. For example, breast cancer was subdivided into lobular and ductal carcinoma, and oestrogen and progesterone receptor expression further guided the choice of therapy and determined the prognosis of the patient. Serendipity and high throughput large tumour cell line systems, in which many thousands of compounds can be tested, characterised the rather inefficient process of cancer medicine discovery. Due to the advancement of science, molecular dissection of the tumours now provides the clinician with a wealth of knowledge about prognostic and predictive markers for treatment selection. Medicine development has benefited spectacularly from increased understanding of the biological makeup of tumours, which has strongly guided the pharmaceutical industry in the selection of 'drug-able' targets.

However, almost exclusively, academia has paved the way for this progress. Basic research has led to the identification of mechanisms of cancer tumour cell growth, division and metastases, as well as mechanisms of unresponsiveness to existing cancer medicine. It also led to the identification of new chemical entities that could interfere with newly established targets.

This has all resulted in a treatment paradigm shift from non-selective toxic chemotherapy to the so-called personalised medicine or targeted therapy. In this thinking, it is mandatory to determine biomarkers for treatment selection in tumour tissue. The current landscape of cancer medicine treatment is roughly determined by four types of new developments, i.e. monoclonal antibodies (mAbs) against transmembrane proteins or ligands to these transmembrane targets, tyrosine-kinase inhibitors (TKIs) against transmembrane or intracellular receptor tyrosine kinases, mAbs and TKIs against neovascularisation of tumours, and mAbs boosting our own immunological response against tumours, the so-called immunotherapy.

Targeted therapy dramatically changed the prognosis of selected patients with cancer. Looking back twenty years, without doubt, the largest impact has been due to the availability of the mAb trastuzumab targeting the transmembrane tyrosine kinase human epidermal growth factor receptor 2 (HER2), which is overexpressed in about 25% of breast cancers, as well as gastric cancers. Its application significantly improved cure rate in the adjuvant setting of HER2 positive breast cancer, and in the setting of advanced disease overall survival. Rituximab targeting B-lymphocyte antigen CD20 in B-cell non-Hodgkin lymphoma, and imatinib targeting breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL) in chronic myelogenous leukemia (CML) and proto-oncogene c-Kit or tyrosine-protein kinase Kit (CD117) in gastrointestinal stromal tumour (GIST) also had a significant impact on patient outcome and served as a template for cancer medicine development. Recent advancements include the availability of vemurafenib against v-Raf murine sarcoma viral oncogene homolog B (BRAF) mutant melanoma and ipilimumab immunotherapy in melanoma. Besides these breakthroughs, new medicines are at the edge of clinical implementation.

Let us not forget the huge improvement due to medicines used in supportive care and prevention and treatment of cancer therapy-induced side effects of nausea and vomiting.

These are all reasons why we may celebrate twenty years of EMA. Further unravelling of the biology of cancer gives us hope that more cancers will become a chronic if not curable disease within twenty years.

TREATMENT

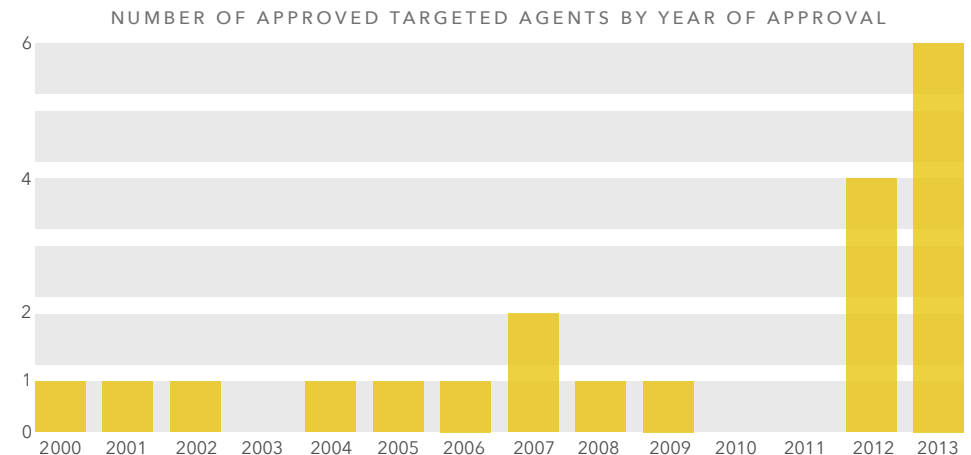
EMA RESPONSE

One of the first medicines approved through EMA's centralised procedure in 1995 was docetaxel to treat breast cancer after failure of prior chemotherapy. The approval was based on a high response rate (tumour shrinkage) in an unselected population. As response rate had traditionally been considered an imperfect predictor for clinical benefit, approval of docetaxel was granted under 'exceptional circumstances'. This required yearly reassessments of the benefit/risk balance as results from additional studies became available. The approval of docetaxel exemplifies the challenge cancer medicine regulators have been confronted with over the past two decades, namely how to balance early evidence of efficacy that might support approval against the need to establish clinical benefit based on conclusive evidence.

While decades ago, cancer medicine development focused on large clinical trials in unselected populations, EMA guidelines have since recommended using predictive biomarkers throughout development. Targeted agents have come with the promise that knowledge about the mechanism of the disease will help identify patients likely to respond, resulting in smaller trials, higher efficacy, less toxicity, and earlier regulatory decisions (see Schellens J.). Since the approvals of rituximab for lymphoma in 1998 and trastuzumab for breast cancer in 2000, a number of targeted therapies have been approved based on early evidence of dramatic activity in conditions with high unmet medical need. Sunitinib was the first medicine to receive a 'conditional approval' based on phase II trials showing a high response rate in patients with renal cancer. This provision allows early access to medicines for serious or orphan conditions provided confirmatory studies are submitted post-approval. It had just been introduced in 2006 and has since been used mainly for cancer medicine approvals with early evidence of benefit. As biological markers have been introduced to separate cancer patients into specific (often rare) subgroups, regulators had to set the level of acceptable uncertainty around benefits and risks at the time of approval, accepting that in some cases the long term clinical benefit would only be confirmed post-approval.

A key factor in ensuring early access to new cancer medicines has been careful consideration of all the available data to make robust decisions and the use of surrogate endpoints likely to predict clinical benefit. Recently, revised EMA guidelines have clarified the role of different endpoints in confirmatory studies. While the clinical relevance of overall survival is undisputed, progression-free survival has increasingly been used as the basis for approval and has been recognised as a clinical benefit endpoint in itself in many indications. The EMA Scientific Advisory Group for Oncology, composed of clinical oncologists, statisticians and cancer patients, has played a key role in guiding the scientific assessment and developing new guidelines. International cooperation among authorities in Australia, Canada, Japan, the US and Europe has also played an important role by promoting communication on the review of new medicines and by enabling congruent standards of cancer medicine regulation.

While we continue to explore ways to optimise approaches to medicine development and regulation (see Hemmings R.), one can only hope that our understanding of the biology of cancer advances as rapidly as '-omics' and computational technologies, and that cancer medicine development continues to shift from large trials that detect small differences in unselected populations to trials that detect larger differences in the right set of patients.



EVOLUTION OF BIOLOGICAL PRODUCTS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Biological medicinal products have had an increasing role in the treatment of many conditions. In particular, biotechnological products have become, in the last 20 years, the treatment option for many chronic conditions such as diabetes, anaemia in patients with renal failure, or hepatitis C. They have also triggered a change in the therapeutic approach to other diseases such as rheumatoid arthritis or cancer. Several widely used vaccines include a recombinant component in their composition (e.g. hepatitis B, papilloma virus or cholera vaccine). These recombinant products have offered enormous advantages over other biologicals extracted from human or animal tissues, such as their unlimited supply, an excellent safety record regarding transmission of viruses and other pathogens, and the possibility to have modified molecules with respect to their native counterpart (e.g. B-domain deleted factor VIII, insulin glargine, darbepoetin) to achieve a different specificity or affinity, pharmacokinetic profile or reduced immunogenicity.

“ BIOTECHNOLOGICAL PRODUCTS HAVE BECOME THE TREATMENT OPTION FOR MANY CHRONIC CONDITIONS SUCH AS DIABETES, ANAEMIA IN PATIENTS WITH RENAL FAILURE, OR HEPATITIS C. THEY HAVE ALSO TRIGGERED A CHANGE IN THE THERAPEUTIC APPROACH TO OTHER DISEASES SUCH AS RHEUMATOID ARTHRITIS OR CANCER. ”

Taking into account the peculiarities and complexity of biotechnological medicines, a centralised marketing authorisation process coordinated by the EMA has been put in place since 1995. The first human medicine approved under this new system was follitropin-alfa. More than 30 biotech medicines had been authorised in Europe earlier, including insulin, factor VIII, erythropoietin, and growth hormone. During the following 5 years, a total of 278 applications for marketing authorisation were received at the EMA; approximately a third were for biotech medicines, including follitropin alfa and beta, insulin lispro, eptacog and nonacog alfa, interferon beta, epoetin beta, and a few monoclonal antibodies. Fusion proteins (e.g. etanercept) and modified molecules (e.g. darbepoetin, PEG-interferon, PEG-filgrastim) also became available. Then polyethylene glycol (PEG)-interferon alpha became the treatment option for hepatitis C in combination with rivabirin, establishing a new standard of care for this indication (currently changing again with the recently approved protease inhibitors). The first two biotech medicines obtained in the milk of transgenic animals (antithrombin alfa and conestat alfa, from goats and rabbits, respectively) are also available.

Monoclonal antibodies have seen a revolution as more than 40 have been authorised by the EMA, some providing an entirely novel approach to the treatment of their respective indications (e.g. rheumatoid arthritis, oncology, macular degeneration or lupus) including rare orphan diseases (e.g. eculizumab for paroxysmal nocturnal haemoglobinuria). In just the last two years, at least 7 more became available, including the first two biosimilars to infliximab. The early concept of conjugating a cytotoxic drug to an antibody has recently become a reality with the approval of brentuximab vedotin and trastuzumab emtansine.

The first two biosimilar medicinal products, approved in 2006, were somatropin products, and more than 20 have now been approved, including epoetin, filgrastim, follitropin alfa, insulin and the first two biosimilar monoclonal antibodies. Europe has certainly established the lead for this new class of products.

Great interest has also developed in advanced therapy medicinal products (e.g. three cell-based and one gene therapy product became available in the last 5 years), paving the way for a promising new category of products. Gene therapy medicinal products under development for haemophilia B or severe combined immunodeficiency (SCID) may even offer a long-term cure.

BIOLOGICAL PRODUCTS

EMA RESPONSE

It is thanks to progressive understanding of the human genome and cell biology, and progress made in technologies for the manufacture/production and in the analytical tools for better characterisation and quality control of macromolecules, that new opportunities (see Ruiz S.) have emerged for realising these new medicinal products. Emergence of these technologies has raised new challenges for the European regulatory system, which was, precisely at that time, in the 80's, undergoing a stepwise construction.

It is noteworthy that the 'biological field' was the catalyst in Europe to put in place better coordination among Member States, engaging them in discussions and sharing of experience to get a harmonised position on these novel topics, which otherwise could have led to unilateral and divergent assessments and decisions. One should remember the creation in 1987 of the 'concertation procedure', a forerunner of the 'centralised procedure'. This procedure was set up for the new medicines (recombinant proteins and products derived from recombinant deoxyribonucleic acid (DNA) technologies). An ad hoc working group on biology pharmacy was set up in Brussels in 1986 to allow discussion, sharing of information and concertation on those products, which became the 'biotechnology working party' - BWP - and moved to the EMA in London in 1995.

The BWP, has since then continued its activities, reviewing new biological applications, developing guidelines and position papers to address, in a consistent and EU-harmonised approach, issues raised in the development and assessment of biological products. In addition, in the context of the now global development of these high technology medicines, the BWP contributed, in the same spirit and objectives of harmonisation, to the International Conference on Harmonisation (ICH), where a set of guidelines dedicated to biologicals, including advanced therapy medicinal products (ATMPs), have been developed.

In the biological field, there is no such thing as 'classical' or 'traditional' approach, nor 'body of evidence', which can be used to assess new products or new findings, or address new threats (e.g. prion disease and biological origin of many medicines, scientific questions raised by ATMPs). Every time a new approach or an adaptation of the previous models, or a new risk-based analysis has to be conducted by regulators, so as to propose the best response, with a constant need for updating the approach (primarily revision of key guidelines).

“ IN THE BIOLOGICAL FIELD, THERE IS NO SUCH THING AS 'CLASSICAL' OR 'TRADITIONAL' APPROACH, NOR 'BODY OF EVIDENCE', WHICH CAN BE USED TO ASSESS NEW PRODUCTS OR NEW FINDINGS, OR ADDRESS NEW THREATS. EVERY TIME, A NEW APPROACH OR AN ADAPTATION OF THE PREVIOUS MODELS, OR A NEW RISK-BASED ANALYSIS HAS TO BE CONDUCTED BY REGULATORS, SO AS TO PROPOSE THE BEST RESPONSE, WITH A CONSTANT NEED FOR UPDATING THE APPROACH. ”

One can mention the most recent change in paradigm with the adoption of the 'risk-based approach', a new regulatory approach foreseen in the EU regulation on ATMPs, to adapt the development plan to the specificities of ATMPs, while respecting the main three technical requirements laid down in the legislation (quality, safety and efficacy).

The constant search for a 'harmonised approach', under the coordination of the EMA and with regulators and experts from the Member States, has been the best way for the EU system to address the new challenges in biotechnology, keeping in mind the safety of the patients who are in need of new innovative and safe approaches.

PROGRESS IN ALZHEIMER'S DISEASE TREATMENT

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

The 'luck' of the therapeutic research in Alzheimer's disease (AD) was that, compared to Parkinson's disease, symptomatic drugs showed only limited efficacy, partly because of widespread neuronal damage in AD. As a consequence, this has promoted a massive engagement of pharmaceutical companies upstream in the disease cascade. Four successive stages can be described in the biological history of the sporadic disease. The starting point of the cascade is still not known, although it certainly implies a complex algorithm combining genetic risk factors that facilitate an intervention of multiple epigenetic environmental agents. Whatever the algorithm, the cascade involves some identified biological pathways (such as amyloid and tau) that are today considered characteristic of the disease mechanisms. The third step is the resulting neural damage leading to a non-specific calcium intra-neuronal influx and apoptosis, which involves a huge number of different cortical and subcortical neuronal networks. The last stage consists in the resulting neurochemical deficits that have been evidenced in the brain of patients.

Given the poor impact on symptoms of the neurochemical replacement and the high number of neuronal systems involved in AD, it was natural to try to intervene at the level of the supposedly specific biological mechanisms of AD, and particularly of amyloidosis, which was promoted by the human autosomal-dominant genetic model of AD.

Interestingly, the treatments developed against amyloidosis do work. This is particularly the case of monoclonal antibodies (mAbs), which act against the brain lesions as demonstrated in animal models (transgenic mice) and also in humans affected by the disease (in post-mortem and neuroimaging studies). However, mAbs work on brain lesions but not on symptoms, the only and ultimate aim. Some of the reasons for these negative results are well known: amyloidosis may have nothing to do with the onset of the disease or of the symptoms; the duration of the trials may have not been long enough to allow a significant reversal of the clinical symptomatology; the patients included in the trials were too advanced or partly misdiagnosed. These arguments are well established: all available data on therapeutic research on AD have been obtained in patients with a massive disorganisation of their brain neuronal network, a severe burden of amyloid lesions and a high rate of false diagnosis. Under these conditions, it may not be surprising that 'disease modifier' trials all turn negative.

Indeed, we have to consider that things are only starting. The new research criteria recently proposed are changing the rules, as they allow to investigate treatments at an early prodromal stage of the disease with a high diagnostic accuracy. Studies are just starting with such designs. Efficacy on neuronal lesions also validates new approaches in cognitively normal individuals who are carriers of autosomal AD monogenic mutations: these normal subjects can be considered as presymptomatic. mAbs will also be tested in asymptomatic at-risk subjects who are biomarker positive, although we do not know if and when they will convert to a clinical disease; new approaches against other biological agents (anti-tau) have also started.

“ THE NEW RESEARCH CRITERIA RECENTLY PROPOSED ARE CHANGING THE RULES, AS THEY ALLOW TO INVESTIGATE TREATMENTS AT AN EARLY PRODROMAL STAGE OF THE DISEASE WITH A HIGH DIAGNOSTIC ACCURACY, THANKS TO INCORPORATION OF BIOMARKERS. ”

The connection between industrial and academic research has significantly pushed the research in very new directions (prodromal and preclinical stages of the disease). Positive results would have important ethical and public health implications and would force the regulatory authorities to evolve and refine their concept of AD.

ALZHEIMER'S DISEASE TREATMENT

EMA RESPONSE

In spite of the remarkable progress in understanding the molecular underpinnings of Alzheimer's disease, there are still no efficacious treatment options for modification of the natural course of AD or its prevention. Approved therapies, such as cholinesterase inhibitors or the N-Methyl-D-aspartate (NMDA) receptor antagonist memantine, showed statistically significant improvements in cognition and global or functional outcomes. However, effect sizes have been small and their clinical meaningfulness is questionable in many patients. Based on the recent failures of several medicinal products, regulators and academia raise questions regarding: (i) following the right models and theories on the pathogenesis of AD, (ii) including the right patients at the right stage of disease (e.g. prodromal AD versus mild-to-moderate AD) with the right compound (e.g. mechanism of action), (iii) appropriateness of the therapeutic targets and selection of endpoints, and (iv) fostering new study designs (adaptive designs, combination therapy).

The first big change now is the consensus that effective therapies for AD have to start early in the disease process before the full syndrome of dementia is reached. Thus new diagnostic criteria for earlier disease stages have been developed and are now under validation. The second change is that these diagnostic criteria combine early cognitive impairment coupled with specific biomarkers reflecting in vivo evidence of AD pathology. Biomarkers studied include brain amyloid load, e.g. measured by positron emission tomography (PET), and cerebrospinal fluid (CSF) levels of amyloid and tau proteins; however, there is a clear move in academia to update the amyloid hypothesis of AD and to look for biomarkers independent from amyloid approaches.

“EFFECTIVE THERAPIES FOR ALZHEIMER'S HAVE TO START EARLY IN THE DISEASE PROCESS BEFORE THE FULL SYNDROME OF DEMENTIA IS REACHED. THUS NEW DIAGNOSTIC CRITERIA FOR EARLIER DISEASE STAGES HAVE BEEN DEVELOPED AND ARE NOW UNDER VALIDATION. THESE DIAGNOSTIC CRITERIA COMBINE EARLY COGNITIVE IMPAIRMENT COUPLED WITH SPECIFIC BIOMARKERS REFLECTING IN VIVO EVIDENCE OF AD PATHOLOGY.”

The use of biomarkers as endpoints in earlier stages of medicine development is well established for regulators, and there are examples of approval of medicinal products on the basis of their effects on validated surrogate markers, e.g. for antihypertensives. These biomarkers were considered validated surrogate markers because they allow substitution for a clinically relevant end point. In their validation, a link between a treatment-induced change in the biomarker and long-term outcome of the relevant clinical measure was undoubtedly established - this means the regulatory requirements on biomarkers used as endpoints in clinical trials are high. In consequence, EU regulators help applicants in their research and development by issuing opinions on the acceptability of using such biomarkers or a distinct methodology in clinical trials. Since 2011, the Committee for Medicinal Products for Human Use (CHMP) has published several qualification opinions for use in the development of medicines for AD. In these qualification opinions, biomarkers are accepted for identification and selection of patients at the pre-dementia stage, as well as for selection of patients with mild-to-moderate AD. Recently, a qualification opinion for a novel model of disease progression and trial evaluation in mild and moderate AD was adopted. This simulation tool is intended to provide a quantitative rationale for the selection of study design and inclusion criteria for the recruitment of patients. Therefore, the use of this qualification procedure for new approaches and study designs in AD is highly recommended, and allows the EMA to provide regulatory adaptability and innovation in this therapeutic area.

REDUCTION IN ANIMAL TESTING DURING MEDICINE DEVELOPMENT

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Animal tests are commonly used during development of medicines, including vaccines, to demonstrate their safety or lack of toxicity. Furthermore, for biological products that are inherently variable, there is an emphasis on quality control testing of the finished product, often requiring tests in animals to assure their safety and efficacy on a batch-by-batch basis.

In recent years, changing public perceptions in response to vocal animal rights campaigns have led to a re-evaluation of the extent and types of animal tests used, and increased willingness on the part of regulators to consider the use of alternative methods. As a consequence, several alternative in vitro methods have been developed to test the toxicity of new active substances.

“CHANGING PUBLIC PERCEPTIONS HAVE LED TO A RE-EVALUATION OF THE EXTENT AND TYPES OF ANIMAL TESTS USED & SEVERAL ALTERNATIVE IN VITRO METHODS HAVE BEEN DEVELOPED TO TEST THE TOXICITY OF NEW ACTIVE SUBSTANCES.”

In the case of veterinary vaccines there is even more scope to reduce the use of animals for quality control tests which are carried out for every batch manufactured. Animals have particularly been used to test for potency of inactivated vaccines, freedom from extraneous agent contamination of live vaccines and freedom from toxicity of vaccines against diseases mediated by potent toxins. Furthermore, safety tests used to be carried out on each batch of vaccine in animals of the target species.

One aspect that has facilitated the reduction of animal testing for quality control purposes is the requirement that all medicinal products produced for the European market must be manufactured in accordance with good manufacturing practice (GMP), which, together with extensive controls carried out during manufacture, means that batches can be manufactured to a consistent quality standard. As a result, it has been possible to scale back the amount of testing carried out on the finished product and to adopt confirmatory tests instead of tests to demonstrate the efficacy of vaccines in animals. One particular outcome for veterinary vaccines has been the recognition that a target animal batch safety test is no longer necessary and its consequential deletion from the European Pharmacopeia.

Replacement of animal-based potency tests has proved more difficult, because of the need for product-specific validation. Animal-based tests are often easier, faster and cheaper to develop and implement than in vitro alternatives and there is little incentive for manufacturers to undertake development work to validate alternative methods for vaccines that are already authorised. However, in vitro methods have been developed for some leptospira vaccines. Furthermore, when animal tests are still required, progress has been made by adopting less severe methods, e.g. the implementation of humane endpoints and serological potency test methods instead of virulent challenge whenever possible. Guidance on 3Rs (replacement, reduction, refinement) testing approaches has also been developed, describing scientific and technical criteria for validation of 3Rs testing approaches and pathways for regulatory acceptance.

It is likely that some tests in animals will continue to be needed for the foreseeable future, particularly where the effects of a medicine in living animals cannot be predicted from in vitro methods. However, pharmaceutical manufacturers and regulators should ensure that alternative methods are developed and used wherever possible. If in vivo tests are unavoidable, then these should use the lowest number of animals and have the least adverse effects on the animals commensurate with the objectives.

TESTING

EMA RESPONSE

Animal studies may be carried out to support first administration of a new medicinal product to either humans or the target animal species, or before performing clinical trials in even larger populations, or before marketing authorisation, or to control quality during production. Ethical and animal welfare considerations require that animal use is limited as much as possible. Directive 2010/63/EU on the protection of animals used for scientific purposes unambiguously fosters the application of the principle of the 3Rs when considering the choice of methods to be used.

In this respect, the EMA committed to apply the 3Rs to regulatory testing of human and veterinary medicinal products. As such, today, the 3Rs are embedded in the relevant regulatory guidance both at the European and (Veterinary) International Conference on Harmonization ((V)ICH) levels.

“THE EMA COMMITTED TO APPLY THE 3RS TO REGULATORY TESTING OF HUMAN AND VETERINARY MEDICINAL PRODUCTS. AS SUCH, TODAY, THE 3RS ARE EMBEDDED IN THE RELEVANT REGULATORY GUIDANCE BOTH AT THE EUROPEAN AND (VETERINARY) INTERNATIONAL CONFERENCE ON HARMONIZATION ((V)ICH) LEVELS.”

With respect to non-clinical testing requirements for human medicinal products, reduction and replacement of animal testing has been achieved by the regulatory acceptance of new in vitro methods, either as pivotal, supportive or exploratory mechanistic studies. Whilst replacement of animal studies remains the ultimate goal, approaches aimed at reducing or refining animal studies have also been routinely implemented in regulatory guidelines, where applicable (e.g. ICH M3(R2), ICH S6 (R1), ICH S9, ICH S2(R1) and ICH S10). Moreover, data analysis following the publication of the concept paper on the need for revision of the guideline on single-dose toxicity led to the complete removal of this guideline and its requirements, and thus a significant reduction in animal use. Recently, a paradigm shift in regulatory thinking on the non-clinical development of biosimilars has emerged in Europe whereby in vivo testing should follow a step-wise approach rather than being performed by default.

In October 2010, the EMA established a Joint ad hoc Expert Group (JEG 3Rs) with the mandate to improve and foster the application of 3Rs principles to the regulatory testing of medicinal products throughout their lifecycle. This group also provides advice and recommendations to the EMA scientific committees on all matters related to the use of animals in regulatory testing of medicinal products. The JEG 3Rs is composed of experts from the EMA scientific committees and the working parties to which animal testing is relevant. The JEG 3Rs can be complemented by specific experts. It works in close cooperation with the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM). In addition, JEG 3Rs coordinates responses to requests from EURL-ECVAM for preliminary analysis of regulatory relevance of new alternative methods.

The JEG 3Rs' mandate was recently renewed. This group is now recognised at international level and cited as an example of how regulatory agencies should commit to tackle the 3Rs issues whilst providing a clear entry point for questions in this area, for which Europe is clearly a global frontrunner.



UNMET HEALTH NEEDS & HEALTH THREATS

The focus of regulators has evolved over the last two decades, and unmet needs have become drivers for regulatory actions.

The success of the approach for orphan medicines, based on a response to market forces and an innovative, successful collaboration with patients has modelled the response to the unmet needs of children. Similarly, regulatory incentives for minor uses and minor species (MUMS) have facilitated the development of much-needed medicines.

The global threat of antimicrobial resistance, on the other hand, has been calling for complex measures and actions involving the EMA and the European regulatory network, and an effective international collaboration.

MEETING THE NEEDS OF RARE DISEASES

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Since its creation, the Committee for Orphan Medicinal Products (COMP) has dealt with innovation in several forms, including cutting-edge therapies long before they were labelled as 'advanced', and for many years acted as the 'gate-opener' at the EMA for innovative and medically plausible research. Rare diseases have often led the way for medical advances in neglected or even more common diseases. Although the market exclusivity granted for an orphan product lasts for 10 years (with a 2 years extension based on paediatric development), the knowledge gained during the development process is eternal.

Research in specific rare diseases has often led to the discovery of molecular pathways in non-rare conditions, thus providing new targets for medicines' development. An example of the advancement of science through research in rare diseases is the discovery of the two forms of severe combined immunodeficiency (SCID), namely X-linked SCID and adenosine deaminase deficiency. This enabled further testing of insertion vectors lacking the oncogenic component in children with X-linked SCID and another immune deficiency, called Wiskott-Aldrich Syndrome. Following these results, researchers tested the technique in other immune disorders

such as β -thalassaemia and X-linked adrenoleukodystrophy, as well as to treat conditions such as leukaemia and Leber's congenital amaurosis.

Also, research in rare diseases allowed the development of non-clinical models, including inter alia the GAA-knockout mouse model for Pompe's disease, the Sgca-null mouse model for α -sarcoglycanopathy and the RPE65 deficient Briard dog model for Leber's congenital amaurosis. To face the growing challenges resulting from the advancements in science, strengthened interactions between the COMP, the Committee for Human Medicinal Products (CHMP), and more recently the Paediatric Committee (PDCO), were necessary, providing innovative approaches to the development of orphan medicines, thereby bringing science into regulation and regulation into science. The COMP is also pursuing a publication strategy to share transparent and updated scientific information allowing fragmented information to be compiled and analysed. This includes the review of animal models relevant for establishing medical plausibility in some rare diseases and the use of biomarkers in the context of the EU Orphan Regulation. This has translated into an increased number of orphan products undergoing assessment by the CHMP. In 2014 one can only assume this is the result of the successful implementation of the Orphan Regulation.

The numerous orphan designations and various mechanisms behind the incentives provided by the Regulation have allowed companies to reach the market. A significant benefit for patients has been identified for most of the approved therapies, and relates to a clinically relevant advantage and/or to a major contribution to patient care. This undeniably demonstrates the commitment of all stakeholders to providing further scientific innovation and more treatment options for patients affected by rare diseases. In order to translate more research into treatment, a structured, responsive capacity to the continuous evolution occurring in the interface of science and regulation is expected, aligned with the aim of having more, better, efficacious and safer orphan medicines in the years to come.

“THE NUMEROUS ORPHAN DESIGNATIONS AND VARIOUS MECHANISMS BEHIND THE INCENTIVES PROVIDED BY THE REGULATION HAVE ALLOWED COMPANIES TO REACH THE MARKET. A SIGNIFICANT BENEFIT FOR PATIENTS HAS BEEN IDENTIFIED FOR MOST OF THE APPROVED THERAPIES, & RELATES TO A CLINICALLY RELEVANT ADVANTAGE AND/OR TO A MAJOR CONTRIBUTION TO PATIENT CARE.”

OF RARE DISEASES

EMA RESPONSE

The EU orphan medicines policy is a success: tangible health outputs delivered to patients, and high attraction of international investments in uncharted scientific and medical areas triggering innovation in life sciences, highly qualified jobs, and sustainable growth.

Beyond the 140 rare disease therapies (orphan or not) with a marketing authorisation to date, approximately 1400 orphan designations granted to promising research provide reasonable hope to 30 million families challenged by unmet medical needs in Europe. The underlying promise of rapidly growing scientific knowledge with potential translation into therapies was the rationale behind adopting an orphan medicines regulation in the 1980s in the USA and in the 1990s in the EU. In turn, the EU orphan medicine policy drives clinical research, across a wide range of rare diseases, into patient registration and data collection, natural history studies, new animal models, genotype-phenotype, and physiopathology studies, as well as the establishment of best reference practices of care.

The key success factor for the implementation of the EU Regulation on Orphan Medicinal Products adopted in December 1999 was the EMA's preparedness and leadership. The EMA successfully anticipated the adoption of the new regulation with corollaries, e.g. a second committee for medicinal products in humans, rules and procedures for this committee, and guidelines for applicants that the COMP started as early as April 2000! The European Commission was a diligent regulator all along.

“THE KEY SUCCESS FACTOR FOR THE IMPLEMENTATION OF THE EU REGULATION ON ORPHAN MEDICINAL PRODUCTS ADOPTED IN DECEMBER 1999 WAS THE EMA'S PREPAREDNESS AND LEADERSHIP.”

The COMP was the first regulatory committee in the world to have patient representatives as permanent full members (three) alongside representatives from Member State regulatory authorities. The COMP has also established a tradition of a patient representative being Vice Chair. Patients have been appointed as experts for COMP hearings and invited as experts in the scientific advice and protocol assistance procedures. This has set a precedent and established a recognised track record, opening the door to patients' participation in several other EMA scientific committees, either as permanent members, observers, or experts. In 2013 alone, 551 patients' representatives were directly involved in the EMA work! Over the years, the EMA has engaged in active patient involvement, listening to their proposals to optimise this engagement, e.g. setting up criteria to identify and select patient representations and organising training at the EMA.

Patients' participation in the COMP coupled with EMA readiness has opened new ways of working at the EMA. Two examples: The COMP was the first committee to adopt a work programme and to prepare an end-mandate report to reflect on its technical regulatory work as much as on its public health mission, international collaborations and points for improvements. The COMP also pioneered dialogue with all stakeholders by creating the COMP Working Party of Interested Parties; a mini-revolution with industry representatives as members of an EMA group for the first time, alongside academic or patient representatives.

In coming years, the EMA readiness to address current challenges will mean better interfacing at three levels. Firstly, within the EMA, between all relevant scientific committees and procedures, with a rolling-on assistance to the development of life assets. Secondly, between the EMA and the FDA leading to more converging guidance in support of global clinical development. Finally, better interfacing between science, society and the EMA where early dialogue becomes a routine, reaching out more to SMEs, and proactively calling for the development of orphan medicines in areas of unmet medical needs.

SPECIAL POPULATIONS

SPECIAL POPULATIONS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

It has long been considered unethical and impossible to involve children in clinical trials on new medicines. As a consequence, many medicines used by children are insufficiently documented with regard to dosing, efficacy and safety, and off-label use has been extensive in the paediatric population (1). It is well known that pharmacokinetic and pharmacodynamic responses to a medicine can differ substantially in children compared to adults, and change with growth and maturation. Suitable doses for children have often been derived by scaling down from adult dosage. This does not give good enough estimates to predict efficacy and safety, particularly not across all age ranges. There is also a lack of medicines suitable for children with regard to formulation and taste, forcing carers to dilute, crush and mix medicines, which may lead to safety concerns.

Despite the unmet need for well researched medicines for children, medicine therapy is widely used in childhood. The most commonly prescribed medicines are antibiotics for systemic use, medicines for the respiratory system and analgesics (1). In a national registry study, almost three quarters of the entire paediatric population aged below 2 years were reported to have received at least one prescribed medicine in a given year (2). Studies estimating medicine use in hospital care suggest that at least half of all hospital prescriptions for children are medicines not labelled for children. In particular, among the most vulnerable, critically ill neonates and infants, almost all prescribed medicines are used off label. Common medicine categories where there is an apparent unmet need in hospital care include analgesics, antibiotics and cardiovascular drugs (1).

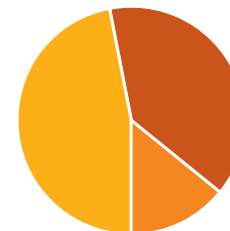
Medicine exposure may also occur during foetal life. Recent studies suggest that more than half of women have used a prescribed medicinal product during their pregnancy (3). Even after a long time on the market, our knowledge is limited with regard to potential effects of many medicines on the foetus. New medicines are generally not tested in pregnant women, and warnings and contraindications rest on animal data, although such data are inconclusive.

In the past, studies focused on early pregnancy exposure and risk of malformation. During recent years, epidemiological studies, often based on national registries, have provided valuable information on foetal effects of a number of important medicines (antibiotics, antiepileptics, analgesics, antidepressants, etc.). Such studies have included exposure during organogenesis but also studied possible effects of exposure throughout pregnancy on neonatal adaptation and on later growth and development. Studies that have collected exposure information prospectively and controlled reasonably well for confounding can be valuable, whereas long-term follow-up studies of medicine exposure during pregnancy may be severely confounded and difficult to interpret.

During the last decades, there has been a paradigm shift in the attitude towards clinical medicine testing in previously neglected populations. Beside a change in legislation, new approaches for clinical trials in small populations, improved methodology, growing acceptance of placebo controlled trials including children, use of modelling and simulation, increasing use of registries for pregnancy and long-term follow-up studies have resulted in a general change in attitude. Today it is considered unethical not to obtain robust data on new medicines, including performing clinical trials in children.

- (1) Kimland E, Odling V. Off-Label Drug Use in Pediatric Patients. *Clin Pharmacol Ther* 2012; 91 (5):796-801
- (2) Olsson J, Kimland E, Pettersson S, Odling V. Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care--a nationwide study. *Acta Paediatr* 100, 1272-5 (2011)
- (3) Stephansson O, Granath F, Svensson T, Haglund B, et al. Drug use during pregnancy in Sweden - assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol* 3: 43-50 (2011).

PAEDIATRIC USE OF DESIGNATED ORPHAN MEDICINES



- 47% Children and adults
- 39% Adults only
- 14% Children only

N=1219 designations, 2013

For decades it was common consent that medical research in special populations like children and adolescents and pregnant women was a no-go area due to ethical aspects.

Therefore, many medicines authorised in Europe were not studied adequately or authorised in children and pregnant women. This caused difficulties for prescribers treating these patients.

This had to be taken into account to balance the risks between conducting clinical trials in a vulnerable population against treating these patients, depending on the mode of action of the medicinal product based on an insufficient benefit-risk evaluation, with unproven dosages and/or inappropriate formulations.

Since the early 1990s some aspects in this handling by regulators, pharmaceutical industry and healthcare professionals were scrutinised by patients, care givers and physicians.

First steps to change this were taken in 1997 at a round table of experts organised by the European Commission and the EMA to discuss the lack of paediatric medicines, with the conclusion that there was a need to strengthen the legislation.

This had to be seen in conjunction with the Directive 2001/20/EC on Good Clinical Practice for Clinical Trials, adopted in April 2001. The directive laying down the rules concerning the development of medicinal products for human use, in order to meet the specific needs of the specific population without subjecting these patients to unnecessary clinical trials, came fully into force in May 2004.

In addition, an international discussion on the performance of clinical trials in vulnerable populations resulted in International Conference on Harmonization (ICH) guidelines on developing medicinal products for children and adolescents and for pregnant women to harmonise the standards to facilitate medicinal products development, and to provide an outline of critical issues in the development and approaches to the safe, effective and ethical study of medicinal products.

After several years of discussion and consultation, in January 2007 the Regulation (EC) No 1901/2006 on the development of medicinal products for the paediatric population came into force.

A Paediatric Working Group had been set up in 2001 and was replaced by the Paediatric Committee (PDCO), which was established in July 2007 in accordance with the aforementioned Paediatric Regulation, to be involved in relation to the development of medicinal products for children (e.g. paediatric investigation plans) including age-appropriate formulations. Opinions on paediatric development of medicinal products are given at a point in time but have to evolve in parallel with advances in the scientific environment. In addition, the Paediatric Committee is concerned by long-term safety and can advise on monitoring of medicines' use after marketing authorisation in collaboration with the Pharmacovigilance Risk Assessment Committee (PRAC).

One of the major steps to implement the new understanding of clinical trials in children has been the establishment of the European Network of Paediatric Research at the EMA (Enpr-EMA) - a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children. It aims to foster high-quality ethical research on quality, safety and efficacy of medicines to be used in children. It has set up quality criteria for paediatric research and currently includes 30 networks with different competences and scope.

In a broader perspective of addressing the needs of neglected populations, the EMA has also published a strategy on medicines for elderly populations and for pregnant women.

MUMS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Is it reasonable in a developed society to expect treatments for the common diseases in most species are available? This is not the case in many EU countries or in respect of products for minor use or minor species (MUMS).

Ever since the original Directive on veterinary medicines was transposed into national Member State laws in the mid 1980s, and more particularly since the introduction of legislation governing medicine residues in foodstuffs in 1990, the availability of an adequate range of veterinary medicines to treat the wide variety of animal species in the EU has become a challenge. Despite repeated efforts by stakeholders, including the European Commission, national competent authorities, the EMA, and others, the (non) availability of authorised medicines to treat rare diseases or uncommon species continues to vex those concerned about animal health and welfare.

The reasons for this are multi-factorial but may be summed as follows:

- Increasing economic pressures on the purveyors of veterinary medicines who invest to make a profit;
- Unremitting developments in regulatory science, perhaps exacerbated by technological and analytical developments;
- Sequential and uncoordinated reviews of products by different national competent authorities over different periods;
- The expansion of society's perception of risks, extending the scope of regulatory reviews;
- Further requirements for medicine monitoring and reporting;
- Requirements for improved transparency and corporate governance in the regulatory processes, with their associated administrative burden.

The primary objective for marketing authorisation holders of veterinary medicines is to have a sustainable and profitable business; the smaller the market and the more demanding the requirements, the greater this challenge. In most Member States, the development of MUMS products is not supported by government. For many potential MUMS products, the development costs required to generate robust scientific data which would meet the required regulatory standards far exceed the potential market returns.

Although the regulatory standards have been reduced over those required for veterinary medicines in major species over the years, for many innovators the study costs required are still considered uneconomical.

More recent societal concerns in the areas of environmental risk, antimicrobial resistance and medicine residues in food products have all led to calls for further legislative restrictions. Time will tell whether the legislative response which ordinarily follows such interest addresses the issues adequately, or in fact may lead to new risks being created due to well-intentioned but over-zealous legislation that further restricts treatment options. Regulators charged with implementing scientific policies to safeguard public and animal health that are benchmarked against specified legal requirements which do not differentiate between different levels of product use face a struggle to safeguard societal concerns. By contrast, in this information age, many animal owners may feel that it is an unacceptable consequence if, as a result of the legislative and regulatory policies being followed, animal health has to be compromised and niche farm production made more difficult when medicines could be developed and authorised to meet their needs.

In the late 1990s it became clear that a consequence of the new Maximum Residue Levels (MRL) regulation would be the loss of hundreds of veterinary products and indications, in particular for animal species where the market was limited. This severely increased the longstanding problem of lack of approved veterinary medicines for many diseases. Animal health and welfare is central in farmed and companion animals, and a real crisis was emerging. The EMA and its veterinary scientific committee, the Committee for Medicinal Products for Veterinary Use (CVMP), voiced concern and put a lot of effort into solving the availability problem over the next decades, together with the EU regulatory network and legislators. The unmet treatment needs relate to several factors, e.g. the many different animal species with their individual diseases and production systems, geographical diversity in disease distribution across the EU, assurance of food safety and environmental safety, and the cost of studies, authorisation and surveillance relative to the expected return on investment for industry.

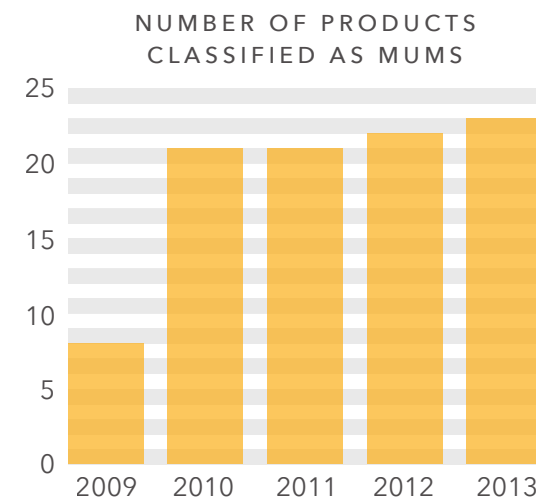
The EMA acted on many levels. An analysis was made of the possibility to extend MRL values to other species or classes of animals, and several successful free rounds of extension improved the situation to some extent. Data requirements for MRLs for minor food-producing species were tailored to the risk for the consumer of animal products. In recent years, each new MRL assessment comprises a structured evaluation for the potential extrapolation to more species and foodstuffs.

For the product authorisation, the CVMP and its working parties developed guidance allowing reduced data packages for MUMS products, e.g. accepting the omission of a large, expensive field study. Specifically for immunological products, a pan-European survey investigated the gaps in vaccines availability across the Member States, i.e. the animal species and diseases for which vaccines were particularly needed, and a list was published. This gap-list and the reduced data requirements have been highly appreciated by applicants, and several new products have come to the market as a result.

The EMA recognised that applicants would need regulatory and scientific support to increase the predictability of their investments for MUMS products, and introduced a scheme for scientific advice with reduced or waived fee.

This initiative was particularly helpful for the very small applicants interested in e.g. medicines for bees, aquaculture, birds and horses. Later, the Agency adopted a MUMS policy where the CVMP can designate an intended MUMS product eligible for reduced data requirements and potentially for financial incentives, e.g. reduced application and maintenance fee, and within the first 3 years of operation, this resulted in over 70 classifications. The financial incentives are now tailored to products for food-producing species where the need for authorised products for minor species like ducks, rabbits, goats, etc. is most severe.

The availability problem is not yet solved for the animals in Europe, and much work remains to be done, but these and other successful initiatives contributed to the increase in treatment options for diseased animals of all species.



ANTIMICROBIAL RESISTANCE

ANTIMICROBIAL RESISTANCE

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

The EMA has become an essential part of the alliance of parties, both at EU and global level, involved in the management of the rapidly evolving issue of antimicrobial resistance (AMR), which developed into a serious threat to global public health over the last decades.

The resistance issues occurring both in the human health area, in particular multidrug resistant tuberculosis, resistance in gonococcal infections, resistance in the nosocomial and community acquired infections, and in animal health, in particular resistance in zoonotic bacteria having the potential to cause diseases in humans and resistance in important veterinary pathogens, have been addressed by the EMA as part of the EU 'One Health' approach.

Within its responsibilities, the EMA actively contributed to all prioritised areas to contain AMR, through responsible use of antimicrobials, recommendations on infection control/biosecurity and support in development and authorisation of new medicinal products, which became a field of special focus in the human medicines area.

The EMA contributed to the AMR issue proactively from the late 1990s by means of risk assessment, identification of scientific data gaps, presentation of recommendations for further actions/risk management measures and adoption of strategies which directed the priorities and regulatory perspective - not only for the EMA and its scientific committees - but across the EU. Furthermore, the EMA actively engaged in the development of regulatory guidance documents in the areas of quality, safety and efficacy for medicinal products for human and veterinary use which significantly improved the level and consistency of assessment of antimicrobial medicines across the EU.

Besides (re)assessment of new and existing medicinal products on the EU market, the Agency assisted pharmaceutical industry in regulatory requirements for new products development, introduction of innovative products and alternatives to the use of antimicrobial drugs, in particular by providing scientific advice to the industry.

Taking this holistic approach, the EMA matched with the objectives of the European Commission Action Plan against the rising threats from AMR and it effectively contributed to the implementation of this plan and to decision making to manage the AMR risks by providing the policy makers with scientific evidence and scientific opinions.

“TAKING THIS HOLISTIC APPROACH, THE EMA MATCHED WITH THE OBJECTIVES OF THE EUROPEAN COMMISSION ACTION PLAN AGAINST THE RISING THREATS FROM AMR AND CONTRIBUTED TO THE IMPLEMENTATION OF THIS PLAN BY PROVIDING THE POLICY MAKERS WITH SCIENTIFIC EVIDENCE AND SCIENTIFIC OPINIONS.”

In pursuing its tasks and responsibilities, the EMA relied heavily on the collaboration with its partners in the EU regulatory network and its scientific resources and infrastructure, and on collaboration with other bodies and organisations in the EU and at international level, in order to ensure that the scientific assessment reflects an up-to-date level of scientific evidence and that the proposed risk management measures and policy options are based on the widest feasible consensus view and interdisciplinary approach.

The work accomplished by the EMA and its scientific committees so far, and the time-proven effective model of collaboration with different partners in the EU and worldwide, gives a good basis for the EMA to cope with the upcoming challenges in the area of AMR, like, for example, availability of effective and safe antimicrobial treatment for current and emerging pathogens in the human and veterinary field, environmental concerns related to AMR and food safety.

In 2009, the EMA and the European Centre for Disease Prevention and Control (ECDC) jointly issued the report 'The bacterial challenge: time to react'. This report for the first time brought together relevant and updated information on the burden of disease, both in human and economic terms, associated to AMR. At the same time, the report highlighted that the increase in antimicrobial resistance was paralleled by a significant decrease in the number of new antibacterial agents under development, with a worrisome gap in new medicines to treat multidrug resistant gram negative infections, nowadays a major public health issue in Europe and globally.

The EMA subsequently started a program of revision of its guidance documents on the regulatory requirements for clinical development of new antibacterial agents for human use in order to clarify the European position on several aspects that were particularly contentious and were perceived as posing difficulties to developers. Among the major achievements, a new streamlined regulatory approach for approval of new antibacterial agents addressing unmet medical needs related to AMR has been developed. This approach would possibly allow more rapid authorisation of new antibacterial agents in restricted pathogen specific indications based on limited clinical data. Extremely beneficial in the definition of these new approaches has been the discussion with the FDA, a relationship that has been consolidating over the years with a closer collaboration. The EMA has also been eager to contribute to international initiatives related to AMR, in recognition of the global scale of the problem, such as those initiated under the auspices of the World Health Organization.

“ AMONG THE MAJOR ACHIEVEMENTS, A NEW STREAMLINED REGULATORY APPROACH FOR APPROVAL OF NEW ANTIBACTERIAL AGENTS ADDRESSING UNMET MEDICAL NEEDS RELATED TO AMR HAS BEEN DEVELOPED. ”

With respect to already available antibacterial products, the EMA has conducted several referral procedures for medicines for human use aimed at harmonising the product information of relevant antibiotics such as meropenem and ciprofloxacin across Europe. This activity is very important in order to make sure that consistent and appropriate indications for use are included in the product information of these products, as this will have a positive impact on steering appropriate use of antibacterial agents in the EU.

In order to foster research and development in this area, the European Commission has allocated considerable funds to initiatives such as the Innovative Medicines Initiative (IMI) and the 7th Framework Programme. In particular, IMI has started a series of projects under the overarching framework programme called 'New Drugs for Bad Bugs' with inclusion of clinical development activities for specific new investigational anti-bacterial agents. The EMA has been keen to contribute in the context of external advisory boards as liaison on regulatory aspects.

For veterinary medicines, the Committee for Veterinary Medicinal Products (CVMP) reflected on the risks related to the use of various classes of antimicrobials (e.g. fluoroquinolones, 3rd/4th generation cephalosporins, macrolides, lincosamides, polymyxins and pleuromutilins) and risks related to selected resistant microorganisms, namely methicillin resistant Staphylococci, and proposed risk management measures to contain AMR as part of its assessment.

The EMA took a leading role in the European Surveillance of Veterinary Antimicrobials Consumption, a system which succeeded to collect and report data on consumption of veterinary antimicrobials from nearly all EU Member States and which became an essential source of evidence for risk assessors, risk managers and policy makers at all levels in the EU, for industry stakeholders, and a source of information for research areas.



ROBUST DECISION-MAKING FACILITATING ACCESS TREATMENT



The scientific assessment of medicines has evolved over the last two decades, going from the evaluation of efficacy and safety in isolation towards assessment of the benefit-risk balance.

In addition, the focus has been increasingly on the evaluation of clinical outcomes instead of intermediate end-points. In addition to these approaches, the impact of globalisation in regulatory cooperation resulted in numerous harmonisation achievements in the quality area, such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on good manufacturing practice (GMP) risk management.

New challenges such as biosimilars on the one hand and advanced therapies on the other have been drivers for regulatory and scientific improvement and adaptation of the European evaluation system. The exchanges with other medicines agencies and experts outside the European Union have also contributed to the robustness of the decision-making.

The recent collaboration with health technology assessment (HTA) bodies at an early stage of the development of new medicines will certainly bring added value and provide more timely patient access to new medicines and avoid multiplication of clinical trials.

PROGRESS IN QUALITY

PROGRESS IN QUALITY

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

In the last 25 years, the model for manufacturing medicines and delivering high quality products has changed drastically. Globalisation and the regulatory environment are two significant elements contributing to this evolution.

Globalisation leads to a highly fragmented supply chain associated with a concentration of manufacturing sites. Reliable and complete traceability of the real source of raw material (active pharmaceutical ingredient (API) and excipients) and getting quality oversight is a real challenge, particularly when the succession of subcontractors and suppliers is complex and when the primary source originates from a country not regulated by a stringent authority.

In parallel, a natural scientific evolution provides new technologies, such as operating 'In- control process' and adjusting, in real time, the manufacturing process using process analytical technology (PAT) with/or without a valid modelisation, testing material online with better and faster micro-testing methods and obtaining easier monitoring of manufacturing and analytical processes. The need to align the regulatory environment to the advancing technology comes to light.

The quality by design (QbD) approach initiated by Europe was taken to the global level through International Conference for Harmonization (ICH) initiatives. QbD, also called new quality paradigm, is aimed at regulating a life cycle approach from development to discontinuation, including post approval management process (PAP), which is decisive in facilitating change management led by continuous improvement, learning and integration of new technologies.

During the implementation process of this new paradigm, the pure compliance approach was evolving towards a more scientific assessment and, by consequence, led to multiple interpretations from the industry and regulators. Initiatives were taken to narrow and align the implementation process.

The EMA and other key agencies such as FDA lead the way towards a better regulatory convergence, avoiding confusion and multiplication among quality standards. The efforts of the EMA need to be complemented by increased global efforts to align standards on an international level, particularly outside of ICH regions.

The quality challenge originating from the globalisation and the complexity of the supply chain led the industry and the regulators to specifically focus on quality oversight of API. The recent 'FMD' EU directive 2011/62/EU sets the milestone for a long-term approach to regulate other key stakeholders of the supply chain by engaging with regulators from the non ICH region in order to align API good manufacturing practice (GMP) standards worldwide.

The increasing role of the emerging countries is not limited to API suppliers and sub-contractors but they are also influencing the future as emerging regulatory bodies and key economical players.

The main hurdle to overcome remains the convergence of global quality standards and their implementation, as this is not yet achieved. European inspectors initiated the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (jointly referred to as PIC/S) which now has expanded largely beyond Europe. PIC/S is highly valuable to disseminate European GMP and provide ad hoc training related to GMP standards. It is expected that the EMA will continue to lead the efforts in this area.

Progress in quality in the last two decades has been huge and ambitious; however, the journey is not over yet. Focusing on consistent implementation and seeking an efficient regulatory environment to facilitate continuous improvement is critical.

Pharmaceutical quality has undergone significant changes in the last two decades, since the start of the work of the EMA. The EU has always required robust pharmaceutical development and quality of medicinal products; however, in early times, this relied more on end-product testing. Nowadays, more and more manufacturers apply advanced analytical procedures and statistical tools to monitor and better control their processes, with less reliance on product testing. This enhanced knowledge results in better management of risks, leading to greater assurance of the quality of medicines available for the patient.

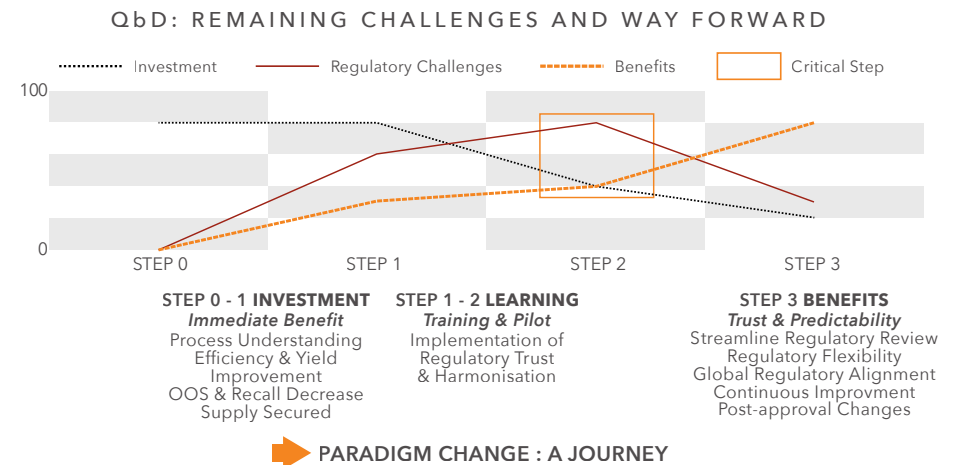
The technical advancement in industry over recent years has put challenges to regulators and it is without doubt essential to highlight discussions which took place at the ICH. This has led to what is nowadays commonly called a new paradigm in pharmaceutical quality (QbD): the combination of science, risk management and quality systems over the life-cycle of a product, which facilitates continual improvement, process robustness and ultimately avoids supply problems. In a globalised world, this harmonisation process is essential in order to ensure global acceptance of standards. In the veterinary area, similar progress can also be seen.

To further facilitate a harmonised implementation of the new paradigm, a parallel assessment has been established between the EMA and the FDA, not only for new applications but also for scientific advice given during development. This has enabled a better understanding of divergent points of view between European and US regulators, leading to a more consistent approach in assessment. Experience from this process has also resulted in the publication of questions and answers to provide clarity to stakeholders.

At the EU level, it is important not to neglect the progress in regulatory science resulting from the interaction and discussion between national and EMA experts through the forum of the EMA's different working parties, which provide the extensive scientific expertise available to the EU.

Another important contributor in the pharmaceutical area is the European Directorate for the Quality of Medicines (EDQM) with the European Pharmacopoeia (Ph. Eur.) and processes such as the certification procedure. Thanks to the provisions in the EU pharmaceutical legislation and the excellent collaboration with the competent authorities, Ph. Eur. has managed to adapt its monographs according to progress of science and technology. EDQM is one of the bases for establishing harmonised quality standards throughout Europe for regulatory authorities with activities complementary to those of the EMA. During the transmissible spongiform encephalopathy (TSE, commonly known as 'mad cow disease') crisis, EDQM with its certification procedure made an enormous and speedy contribution to guarantee safe pharmaceutical raw materials.

Of course, the story never ends. Science is regularly progressing and regulators will have to address new challenges, for instance in the area of advanced therapies, nanotechnology and new devices, among others. The challenge will be how to enable best implementation of the new paradigm concepts in order to better manage manufacturing changes in a more flexible way. Again, the EMA will be actively involved via ICH to facilitate these discussions.



The availability of applicable clinical information for the health technology assessment (HTA) of newly marketed medicines has been debated for a long time. Quite often, crucial information on the relevant comparators, clinical endpoints and quality of life was insufficiently available in the submission files that were prepared by pharmaceutical companies for reimbursement. Based on these experiences, which seriously impacted the availability of sometimes promising new medicines, HTA agencies realised that scientific advice or early dialogue, more or less in collaboration with the regulators, before the start of pivotal clinical trials might help to initiate clinical trials that would collect relevant information for regulators and HTA agencies. Although in some countries independent HTA scientific advice or even combined scientific advice with regulators existed, joint or 'parallel' European scientific advice with regulators did not exist. Starting in 2010, Zorginstituut Nederland (ZIN) participated in a number of European initiatives piloting early dialogue/scientific advice between HTA agencies and with regulators and other stakeholders, such as the Tapestry supported initiative, the early dialogues in the European Network for HTA (EUnetHTA), Shaping European Early Dialogues (SEED) and the joint scientific advices with regulators initiated by the EMA.

Among regulatory authorities and HTA agencies alike, a need to develop joint/parallel scientific advice procedures is felt. However, there remain some critical issues that need considerable attention in the further development of this process. It is essential that the effect of the early dialogues on the reimbursement decisions a number of years after the early dialogues is measured. Although there are some results that indicate that scientific advice by regulators will increase the chance to receive marketing authorisation, these data are not available for the scientific advices in which HTA agencies participate.

“AMONG REGULATORY AUTHORITIES AND HTA AGENCIES ALIKE, A NEED TO DEVELOP JOINT/PARALLEL SCIENTIFIC ADVICE PROCEDURES IS FELT.”

Secondly, alignment in the requirements that are essential to submissions for marketing authorisation and reimbursement would make these efforts more efficient. For instance, the national use of EUnetHTA joint assessments on relative effectiveness may lead to more alignment between HTA agencies across Europe. Alignment of requirements between HTA agencies and regulators is more problematic because of the different remits of these stakeholders. However, despite these challenges, we feel that there is added value in working towards reaching more common ground on issues like endpoints and the choices for comparators.

These efforts may help to decrease the complexity of clinical trials that need to fulfil the needs of both regulators and HTA agencies.

Finally, this European process must increase the efficiency of the national processes, particularly in middle-sized and small countries in Europe. Building on the trust that has been developed in EUnetHTA, it may be possible to divide these activities between European HTA agencies. This may support the structural continuation of scientific advice/early dialogues in the future without absorbing an unrealistic part of the resources of the national HTA agencies.

In conclusion, I believe that current developments in European parallel scientific advice between HTA agencies and regulators are worthwhile, and I expect that these activities will finally lead to a permanent activity in which regulators and HTA agencies provide scientific advice on a voluntary basis to developers of new technologies.

As the first step to market access, a new medicine requires a marketing authorisation from a medicines regulatory agency. The second step is the assessment of its usefulness to the healthcare system that rests with a payer or healthcare guidance and HTA bodies who advise them. It is recognised that some new medicines authorised by the EMA fail to be reimbursed and/or used as expected. One reason for this is that sponsors are not often aware of the needs of payers and healthcare guidance/HTA bodies because they did not have the possibility of early dialogue. There is a need, therefore, to initiate dialogue between medicine developers, the EMA and HTA bodies to discuss and align, when possible, standards for clinical development programmes to support the different requirements early in the medicine development phase.

In this context, the EMA's Committee for Medicinal Products for Human Use (CHMP), through its Scientific Advice Working Party (SAWP), together with HTA bodies are in a position to help identify methodologies in medicine development that enable assessment of both benefit/risk profile and added therapeutic value, to continue to address unmet medical needs. Such a dialogue can be opened up in the framework of early parallel scientific advice which focuses on the clinical development program and could benefit from joint discussion from the perspectives of benefit-risk for

licencing by the regulators and demonstration of added value to fulfil HTA requirements.

This parallel procedure was launched in July 2010 as a pilot project and since then 35 procedures have been finalised or are ongoing.

A wide spectrum of indications were covered, such as diabetes, heart failure, lung cancer, breast cancer, pancreatic cancer, melanoma, mesothelioma, asthma, rheumatoid arthritis, multi-resistant infections, food allergies, diabetic gastroparesis, Alzheimer's, depression, osteoporosis, migraine, myasthenia gravis and an ophthalmological condition.

Questions can be addressed both to regulatory authorities and HTAs if they are of common interest for the clinical trial design, i.e. the comparator, the duration, the primary and secondary endpoints. Questions on added value and pharmacoeconomics can be addressed to the HTA bodies only within the same procedure. The experience showed that on several occasions the participants could find a way forward for a single protocol which could answer the questions from the different stakeholders.

In November 2013, the EMA hosted a landmark workshop to look at the need for, and the current use of, parallel scientific advice from regulatory authorities and HTA bodies during the medicines development process. The objective of the workshop was to discuss lessons learned and ways to optimise the process of parallel scientific advice. The workshop brought together over 280 representatives from, among others, the European Commission, European regulators, HTA bodies, EUnetHTA, the industry, payers, patients and healthcare professionals.

“ IN NOVEMBER 2013, THE EMA HOSTED A LANDMARK WORKSHOP TO LOOK AT THE NEED FOR, AND THE CURRENT USE OF, PARALLEL SCIENTIFIC ADVICE FROM REGULATORY AUTHORITIES AND HTA BODIES DURING THE MEDICINES DEVELOPMENT PROCESS. ”

The current pilot follows the EMA scientific advice procedure. Guidance for handling of parallel scientific advice procedures and on the interface between EMA and HTA bodies independently or through the EUnetHTA network was developed by a task force consisting of regulators and HTA colleagues, and published.

The overall objective of the exercise is to mitigate the risk that separate and sequential studies are needed for different decision makers, introducing delays to patient access that could be avoided through collaborative discussion.

POOLING OF EXPERTISE

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

The EU network model in medicines regulation is a unique tool in many ways - it is building trust and consensus between the EU national authorities, it is also speeding up the decisions addressing both the putting on the market of new products as well as the emerging safety issues.

The main strength of the network however lies in its incredibly wide basis of scientific resource which even the largest national competent authorities struggle to achieve in a single agency.

The centralised marketing authorisation procedure has its roots in the era where biological products gained wider importance in medicine and along came the necessity to have expertise for the evaluation of these - which many of the then regulatory bodies lacked. EU-wide collaboration allowed smooth assessment of the new products and at the same time building up a larger expert workforce.

The network has been moving from its traditional territories of marketing authorisation of mass-manufactured medicinal products to the areas of early advice to the developers, including a possibility to combine the advice on authorisation requirements with the expectations of the health technology assessment, and to the product categories which tended to be of academic rather than of practical interest for many years - the gene, cell and tissue therapies.

These developments are exciting and have a potential to greatly impact the access to treatment in areas of desperate medical need, but have also created a new need of expertise in fields like modelling and simulation, adaptive trial designs, clinical study methods for small populations and novel, often individualised therapies, as well as the quality assessment of the advanced therapy products.

The EMA has been proud of its expert base of unrivalled scientific coverage, at the same time it is fair to say there have been practical impediments in identifying and mobilising the right experts in a timely manner to address the issues in front of the EMA.

In the last few years the EU regulatory network and the EMA have been successful in finding ways to better utilise the expert resource from the Member States. The coordination by the EMA secretariat allows from one hand the scientific issues in the assessment of the marketing authorisation applications or in the provision of scientific advice to be addressed by the best European experts and, on the other hand, it also enables the experts to find the issues they are best qualified to address.

“ IN THE LAST FEW YEARS THE EU REGULATORY NETWORK AND THE EMA HAVE BEEN SUCCESSFUL IN FINDING WAYS TO BETTER UTILISE THE EXPERT RESOURCE FROM THE MEMBER STATES. ”

The inter-agency cooperation in compiling the multi-agency assessment teams for the regulatory procedures, initially seen as a topic for smaller agencies, is also gaining attention of the bigger agencies by 2015. The initial experience has been promising and has enabled the national agencies to provide specialised expert input also in cases where their resources would not allow taking up the whole rapporteurship role.

After a pilot phase championed by the national agencies of the Baltic Sea region, the Committee for Medicinal Products for Human Use (CHMP) has formalised a procedure for the use of inter-agency Rapporteur/Co-rapporteur teams. The arrangement which benefits from the logistic support of the EMA may fuse interest for similar collaboration schemes in other EMA scientific committees.

One of the primary design objectives of the EMA is to provide the European regulatory network with the very highest quality scientific opinion on any question concerning the development, authorisation and supervision of medicinal products. In order to deliver such high quality opinions it was envisaged to have a system capable to mobilise the very best expertise that may be found across the EU from all Member States as needed. Recognising the pace of progress in pharmaceutical development, together with the more fundamental understanding of the cellular mechanisms driving many disease conditions and their treatments, the need for the very broadest range of expertise and its constant renewal was clear. There is an undoubted strength and synergy to be gained by bringing together multidisciplinary teams of experts to tackle the regulatory challenges inherent in novel therapies ranging from gene therapy to tissue engineering as well as applying the very latest genetic understanding in the major disease conditions such as cancer, infections, diabetes/obesity and degenerative diseases such as Alzheimer's and Parkinson's.

“THERE IS AN UNDOUBTED STRENGTH AND SYNERGY TO BE GAINED BY BRINGING TOGETHER MULTIDISCIPLINARY TEAMS OF EXPERTS TO TACKLE THE REGULATORY CHALLENGES INHERENT IN NOVEL THERAPIES AS WELL AS APPLYING THE VERY LATEST GENETIC UNDERSTANDING IN THE MAJOR DISEASE CONDITIONS AND DEGENERATIVE DISEASES”

The primary organisational model for such expertise is in the form of the principal scientific committees of the EMA, e.g. CHMP, the Committee for Medicinal Products for Veterinary Use (CVMP) and the Pharmacovigilance Risk Assessment Committee (PRAC), as well as their associated working parties, involved with providing advice to developers as well as issuing technical guidelines to pharmaceutical industry. Historically, such scientific committees and working parties have been composed of experts emanating from the national medicine regulatory authorities, but there has been a conscious enrichment of their membership by representatives from patient and healthcare professional organisations whose expertise brings a vital perspective to the scientific discussions. In order to further enrich expertise within the system, a concerted effort has been made to constitute various specialised scientific committees, e.g. the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT) with experts working directly in the clinical field in e.g. university hospitals and research institutions. A similar approach has been followed with the advent of scientific advisory groups composed of highly expert and active clinicians in the major therapeutic areas, e.g. cancer, diabetes, central nervous system and anti-infectives. All of these various pools of expertise are coordinated by the EMA in a very flexible manner to support the work of the primary committees in their pursuit of high quality scientific opinions.

Such opinions are evidence-based, and a further feature and key strength of the network system is its ability to rapidly pool data resources from a multiplicity of sources to address emerging questions concerning the evaluation and supervision of medicines within the EU. The EMA plays an increasing role in providing a coordinating platform to structure and harmonise such data resources, as exemplified by the various best-evidence research networks in paediatrics (European network of paediatric research at the EMA (Enpr-EMA)) and pharmacoepidemiology (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCEPP)). It is expected that the interplay between these data resources and the continued mobilisation of the very best expertise from across the network will underpin robust decision making in the complex scientific environment of the future.

BIOSIMILARS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Twenty years ago I was working as resident in a paediatric university hospital. The first biotechnological products had arrived in the routine care of patients but were still considered 'cutting edge'. As a practising paediatrician the awareness of the processes that regulate development and eventually lead to the approval of these medicines was rather low if not absent. But this may have also reflected an inherent trust in the approval process that was more prevalent at that time, in particular with regard to the evaluation and control of pharmaceutical quality. There were no discussions on such topics, new products were generally regarded as a contribution to the therapy armamentarium.

Working in specialised paediatric departments increased the chances of gaining experiences with biomedicines. Epoetin and somatropin were administered in the paediatric nephrology clinic and many discussions arose around optimising the therapy using these medicines. It was also clear that these new therapies promised unprecedented benefit to the children with various degrees of kidney damage. Epoetin made transfusions unnecessary and also decreased the risk of infections transmitted by transfusion. Unfortunately for some children, the availability of affordable and safe somatropin came too late to provide for a normal adult height. However, after somatropin was introduced as a standard of care many patients benefited. The situation was also difficult for patients with autoimmune diseases where there were no satisfactory treatments available and patients had only limited treatment success.

Many new biological medicinal products have been authorised since then and the treatment algorithms have undergone profound changes in many diseases. In addition to the abovementioned examples - especially in the product class of monoclonal antibodies - unprecedented therapeutic successes have been achieved. Remarkable advances have been made in production technologies, resulting in highly consistent manufacturing of batches, in the biochemical and physical characterisation of biological molecules and in the understanding of the structural basis for functional characteristics. These technical advances have provided a very high degree of assurance on the consistency and control of these complex biotechnology products.

Access and cost played no prominent role 20 years ago when the first biotechnological products reached the paediatric clinic. Although rarely discussed, it is likely that this was because of the small population size. The expanding range of products and, more importantly, the achievable therapeutic successes in an increasing number of indications led to a significant number of patients receiving biological medicinal products, with ensuing strains on health-care systems. Therefore, society and regulatory systems had and still have to address these challenges. The pathway for the authorisation of biosimilar medicinal products as developed could be an important component in ensuring continued access to biological medicines. An important issue is therefore the acceptance of the biosimilar concept in general and biosimilar medicinal products specifically by the prescribers. As outlined above, physicians commonly have only a very limited knowledge about regulatory processes. Especially for ensuring functioning of pharmacovigilance, it would be important to further disseminate this knowledge.

“ THE PATHWAY FOR THE AUTHORISATION OF BIOSIMILAR MEDICINAL PRODUCTS AS DEVELOPED COULD BE AN IMPORTANT COMPONENT IN ENSURING CONTINUED ACCESS TO BIOLOGICAL MEDICINES. ”

Medical biotechnology, i.e. the production of highly specific and potent medicines in living organisms like cell cultures, has undoubtedly revolutionised modern medicine. However, their development costs have been quite large, also due to their complex manufacturing process. This already early in the beginning of the 2000s raised discussions in the regulatory world if 'generic' versions, once data protection and patents would have run out for the original medicines, would be possible. The first medicine developed as a 'copy' version could, legally spoken, not readily be authorised, because it became clear that the generic framework would not be fit for purpose due to the structural complexity of biotechnology-derived medicinal products and the technical limitations for producing an 'identical' molecule to the reference biological medicine. Technically seen, even several batches of biological medicines are never 'identical' to each other, since they are produced from living organisms, and therefore have to be tightly regulated with a set of 'specifications' that ensure consistent quality. Therefore, a 'copy' version of such medicine would rather have to establish that it is as similar as possible (and not identical) in its quality, safety and efficacy, notwithstanding minor and clinically irrelevant differences. Therefore, the term 'similar biological medicinal product' or 'biosimilar' was generated.

The EMA already at that time had good experience with the scientific principles that in fact could be applicable to establish 'biosimilarity', namely those from changes in manufacturing processes for biotechnology-derived medicines where manufacturers have to establish that the postchange product is comparable to the pre-change product. A working group was therefore founded that already had experience - maybe an early example of efficient use of resources that also, at the same time, would introduce consistency in scientific concepts. The group, evolving towards a Biosimilar Medicinal Products Working Party (BMWP), came up with a first set of general and also product-specific scientific guidelines that were introduced to the scientific community in a public consultation process, and discussed in a large conference in Paris in 2005. Here, the Agency already exercised processes that have become more common these days, but which were milestones also procedurally seen: to discuss with stakeholders their key regulatory documents in order to ensure that all voices are heard. The discussion of the guidelines at that conference was very controversial between the companies developing the original products and those who wished to develop copy versions. By listening to both stakeholders' needs, the EMA finally was in a position to develop a set of scientifically sound guidelines that strike the delicate balance between regulatory demands and feasibility. These guidelines have pioneered the concept of biosimilars, a concept that has ever since spread throughout the world with similar concepts, to the benefit of many thousands, if not millions of patients who can benefit from cheaper yet high-quality medicines - and from competition where originator companies continuously evolve their portfolio with next generation cutting-edge medicines that can then outcompete their predecessors.

“THESE GUIDELINES HAVE PIONEERED THE CONCEPT OF BIOSIMILARS, A CONCEPT THAT HAS EVER SINCE SPREAD THROUGHOUT THE WORLD WITH SIMILAR CONCEPTS, TO THE BENEFIT OF MANY THOUSANDS, IF NOT MILLIONS OF PATIENTS WHO CAN BENEFIT FROM CHEAPER YET HIGH-QUALITY MEDICINES”

The EMA has ever since mastered this balance between fostering innovation on one hand, and enabling for greater competition on the other.



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FROM MARKETING AUTHORISATION-ONLY LIFE SPAN APPROACH



Over the past 20 years, the EMA has created various mechanisms for engaging in early dialogue with sponsors. Depending on the profile of the medicinal product, as well as its stage in development, sponsors can seek scientific advice or protocol assistance.

Early and prospective dialogue between sponsors and the EMA on regulatory and scientific issues during product development has been shown to facilitate regulatory predictability and earlier availability of medicines. New initiatives have started to provide more timely patient access to medicines, such as the adaptive pathways project.

But no effective medicine is without risk, and the benefits of a medicinal product always need to be weighed up against its risks. The challenge has been to find the right balance between timely availability of new medicines and the fact that knowledge on the safety profile is limited at the time of marketing authorisation. For this reason, once placed on the market, medicines continue to be monitored to ensure that any aspect which could impact on their safety profile is detected and assessed, and that necessary measures are taken. This monitoring is called pharmacovigilance.

The 2010 legislation strengthened and rationalised the system for monitoring the safety of medicines for human use on the European market. It improves patient safety and public health through better prevention, detection and assessment of adverse reactions to medicines. It has shifted medicines monitoring from 'passive' monitoring to active surveillance.

EARLY INTERACTIONS WITH REGULATORS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

There are large companies, medium-sized companies and small companies. There are also large medicines agencies and very small agencies. For a small company the regulatory world is a jungle, but large multinational companies also need guidance. After having worked in this system for approximately 10 years on both sides of the table I am slowly getting the whole picture. Meeting with the single-person company with great beliefs and enthusiasm on the one hand and the more formal delegations of multinational 'Big Pharma' on the other, gives an interesting perspective of the spectrum. The goal is the same but the guidance very different. The EMA system has addressed these differences in several ways and in my mind made it possible from a regulatory standpoint for small projects to advance. Fee reductions or waivers, pre-submission meetings and involvement of the Innovation Task Force (ITF), scientific advice and general regulatory guidance are all good examples. The steady increase in advice requests are hopefully not reflecting an increased complexity of the regulatory system, but rather the perceived benefit for all parties. The scope of scientific advices is rapidly evolving as more innovative methods are being implemented in medicine development. The era of personalised medicine with very specific biomarkers is already here. New methods are expensive and advice is increasingly given in collaboration with health technology assessment (HTA) bodies. Qualifications of new methodologies are on the rise for the same reasons, again led by the scientific advice procedure. Involving patients in the advice and development phase is a challenging initiative but of special importance in rare disorders where the individual perspective is crucial. Medicine hardly gets more personalised than this.

“THE SCOPE OF SCIENTIFIC ADVICES IS RAPIDLY EVOLVING AS MORE INNOVATIVE METHODS ARE BEING IMPLEMENTED IN MEDICINE DEVELOPMENT AND ADVICE IS INCREASINGLY GIVEN IN COLLABORATION WITH HEALTH TECHNOLOGY ASSESSMENT BODIES.”

Smaller agencies with a few dozen employees have naturally been less involved in centralised procedures than the large ones with hundreds of employees. A recent pilot project introducing multinational assessment teams as an alternative to the more traditional national agency teams is proving to be a great success. Initially the thought was to enable smaller agencies with partial teams and few experts to be involved in full assessments of medicine applications. Often the missing link is only one or two experts in a particular field. The trial was very well received by staff of the agencies and supported by the Committee for Medicinal Products for Human Use (CHMP), and the first procedures are being finalised. The pilot opened the eyes of the whole CHMP to the fact that larger agencies often lack a certain expertise, and this can perhaps be found in smaller ones. As a result, a database of available expertise is being developed across all national authorities. Such collaboration between countries is exactly in line with the European spirit, but was inadvertently inhibited by tradition rather than rules. The sustainability of the European regulatory system for medicinal products will come through these types of collaborations and initiatives. Having local regulatory expertise in each Member State will in itself encourage innovation.

Stimulation of the development of medicines for areas of unmet medical need, facilitation of new approaches to medicine development and addressing the high failure rate of the medicine development process are strategic goals of the EMA. Early interactions between regulators and developers of new medicinal products are essential for achieving these goals.

The scientific committees of the EMA, in particular the CHMP, have created a wide selection of scientific guidelines for development and assessment of medicinal products. Scientific advice (SA) provided by the Scientific Advice Working Party (SAWP) of the CHMP, gives individual applicants the regulatory view on issues that cannot be solved by the existing guidelines. In addition, 'pre-competitive' SA can be given for qualification of a method or a biomarker. It is also possible to request parallel SA with the FDA or with experts on HTA. Protocol assistance is special scientific advice that is given to applicants developing orphan medicinal products and is also provided by the SAWP.

EMA SA is associated with a favourable outcome of the subsequent marketing authorisation process. However, SA is mainly requested by large, established pharmaceutical companies at the late stages of medicine development, whereas small companies and other enterprises that are struggling with early development seem not to reach for SA.

The EMA has addressed this problem in two ways; by establishing the ITF and the office for small and medium-sized enterprises (SME office). The goal of the ITF is to establish a discussion platform for early dialogue with applicants, in particular SMEs. These discussions can proactively identify scientific, legal and regulatory issues of emerging therapies and technologies. Briefing meetings are held with applicants covering regulatory, technical and scientific issues, such as nanotechnology, synthetic biology, biomaterials, modelling and simulation. The ITF also gives input to the eligibility of products for the scientific services of the EMA ('classification'), especially for the 'borderline' products, such as medicine-device combinations.

The ITF is not only a service to developers but also a useful tool for the EMA to monitor emerging therapies and technologies. The ITF may signal the need for legislative change, new guidance or expertise.

The SME office provides information and assistance to SMEs. The EMA keeps a register of such enterprises and provides the SME user guide, workshops on relevant topics of medicine development and regulation, as well as a dedicated newsletter.

However, it is obvious that the scientific services of the EMA do not yet involve many of the smallest local enterprises involved in innovative medicine development. Fortunately, some national agencies have established local ITF-type 'innovation offices'. The EMA is planning a formalised cooperation between the ITF and local innovation offices in order to establish an 'EU-innovation network'. This network may create more early contacts to regulators and channel SMEs further to the EMA ITF and to national or EMA SA.

“ IT IS OBVIOUS THAT THE SCIENTIFIC SERVICES OF THE EMA DO NOT YET INVOLVE MANY OF THE SMALLEST LOCAL ENTERPRISES INVOLVED IN INNOVATIVE MEDICINE DEVELOPMENT. THE EMA IS PLANNING A FORMALISED COOPERATION BETWEEN THE ITF AND LOCAL INNOVATION OFFICES IN ORDER TO ESTABLISH AN 'EU-INNOVATION NETWORK'. ”

The remaining challenge is to develop a single interface and database for the pre-submission processes of the EU regulatory network, and to integrate regulatory processes and other related processes that are necessary for the access to new medicines, such as HTA.

FROM PASSIVE MONITORING TO ACTIVE SURVEILLANCE

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

At the time of grant of a medicine's marketing authorisation, knowledge of its benefit-risk balance is incomplete. Yet the public's aspiration for more therapeutic options demands that no unnecessary hurdle should delay prompt access to new medicines. Even so, unforeseen aspects of a medicine's risk profile can seriously compromise its use unless effectively investigated and managed.

This key challenge for medicines regulation has been tackled in Europe by a far-reaching revision and strengthening of regulatory systems. A new proactive, planned approach has replaced the former reactive activity, resulting in continuous life-span benefit-risk monitoring of medicines. What were the societal drivers and regulatory scientific developments which enabled the network of member states and the EMA to lead this change?

“ THIS KEY CHALLENGE FOR MEDICINES REGULATION HAS BEEN TACKLED IN EUROPE BY A FAR-REACHING REVISION AND STRENGTHENING OF REGULATORY SYSTEMS. A NEW PROACTIVE, PLANNED APPROACH HAS REPLACED THE FORMER REACTIVE ACTIVITY, RESULTING IN CONTINUOUS LIFE-SPAN BENEFIT/RISK MONITORING OF MEDICINES. ”

The public's attitude to risk has both influenced and been profoundly influenced by medicines safety concerns. A series of safety issues – antidepressants and suicidal behaviour; vaccines and childhood autism; the withdrawals of a statin and an anti-inflammatory medicine – occurred in a context of unease about the effectiveness and transparency of regulatory systems ranging from food safety to the environment.

A scientific examination of the medicines safety systems by the European Commission confirmed that collecting reports of suspected adverse reactions was the general approach. Many Member States held large volumes of adverse reaction data, and a major scientific development came with the application of validated statistical approaches to such large datasets to enable rapid identification of trends or signals.

Yet the limitations of spontaneous reporting – the biases and lack of a denominator of medicine exposure – could not be solved by such technical advances, and though appropriate for the identification of signals of hazard, the weak evidential value of such data was an inherent drawback. The relevance of the growing discipline of pharmacoepidemiology, the study of medicines in populations, became apparent to regulators. Across the EU, centres of pharmacoepidemiological expertise were established, with scientists and academics motivated by public health protection coming together to better understand the safety of medicines in real world use.

Innovative conceptual thinking, driven by a concern about sudden medicine withdrawals, focused on the key question: why not define the knowledge gaps before a medicine is authorised and then systematically put in place studies and methodologies to address these gaps? Why not use this approach to continuously identify, quantify, and manage a medicine's risks? In 2001 the European Risk Management Strategy was born, based on sound principles and collaboration between the EMA and Member States and guided by an implementation plan endorsed by the Heads of Medicines Agencies. The areas in which the European legislation needed to be clarified and strengthened became apparent.

The journey is not over. The landscape of medicines continually evolves, with the move to biological products and personalised medicines for long-term use, bringing new patterns of adverse reactions. Regulatory science moves forward, and offers new tools including pharmacogenomics. What has not changed in two decades is the public expectation for robust systems for health protection. This means constant vigilance, enhanced by proactive integrated systems, scientific leadership and readiness to test and try new methodologies, in the context of open communication. With all this in place, European regulators are optimally placed to protect the health of EU citizens.

MONITORING TO ACTIVE

EMA RESPONSE

The 20th EMA anniversary arrives at the time of consolidation of the pharmacovigilance legislation in effect since July 2012. The synergistic efforts of the network of national regulatory agencies of the EU, with the key role of the European Risk Management Strategy group, and under the coordination of the EMA, have been crystallised in a unique system of trust and collaboration aimed at protecting public health.

All the processes of pharmacovigilance have been strengthened and given legal support, from risk identification to the evaluation of the impact of the risk minimisation measures taken in a harmonised way throughout the EU. The overall impact has been to drive forward the shift from reliance on passive monitoring of adverse reactions, to active surveillance of medicines in clinical use.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA plays a key role, with experts from national agencies of all Member States and external experts nominated by the European Commission, including healthcare professionals and patient representatives. The legal mandate of this Committee is to deal with all aspects of the risk management of the use of medicinal products, including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

At the time of medicines authorisation, a risk management plan is now in place to further characterise the most relevant identified and potential risks, fill in the gaps in knowledge of effects in specific sub-populations, and establish the adequate measures for risk minimisation. This planning is continuously updated once the medicine is authorised, taking into account all the new evidence being gathered. This is systematically assessed by the network, and decisions therefore take into consideration how medicines are used by healthcare professionals and patients across Europe.

Protocols for post-authorisation safety studies which are considered relevant for the benefit-risk assessment of the medicines are agreed, so that the same protocol is in place in all centres where the study is to be performed throughout the EU.

Ways for facilitating reporting of suspected adverse drug reactions by healthcare professionals and citizens are being introduced, emphasising the importance of reporting for newly authorised medicines and those with an imposed post-authorisation safety study. A standardised procedure for detecting and evaluating signals in the EU has been established, focused on the European database of suspected adverse reactions, EudraVigilance, a key tool for this purpose.

“ A STANDARDISED PROCEDURE FOR DETECTING AND EVALUATING SIGNALS IN THE EU HAS BEEN ESTABLISHED, FOCUSED ON THE EUROPEAN DATABASE OF SUSPECTED ADVERSE REACTIONS, EUDRAVIGILANCE, A KEY TOOL FOR THIS PURPOSE. ”

Efforts have also been made in order to improve communication of emerging risks of medicines to healthcare professionals and citizens, both in frequency and content, and on providing useful information on how to prevent or manage risks, with specific materials where appropriate. Whether communications have achieved their purpose is also subject to study and reflection in a continuous learning process.

ADAPTIVE PATHWAYS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Adaptive licensing (also known as adaptive pathways) has been discussed in one form or another for almost ten years. However, there was little progress in advancing beyond conceptual discussions. Historically, regulatory innovations have largely been mobilised in response to public health crises. In the absence of such a crisis, change is more challenging, and particularly with adaptive licensing where implementation requires coordination with other stakeholders. In this case, a number of compelling pressures and opportunities have converged to reach a tipping point, thus, moving the healthcare system to consider adaptive licensing. Key among these change drivers/enablers are the following:

- Medical science has advanced to a point where 'precision medicine' is becoming a reality. While much progress is still needed, there is an increasing ability to stratify patient populations based on their likely response to a given therapeutic. Leveraging the public health value of this emerging capability requires that we move beyond the traditional binary go/no go decision model informed solely by randomised controlled trials.
- Knowledge-generation tools, methods and infrastructure are advancing in important ways that increase our potential to effectively implement life span-based management of benefit, harm, and uncertainty. Enhancements in electronic medical records and patient registries, observational study methods and big data analytics, and access to pooled data sources through pre-competitive and federated governance models are all contributing to our armamentarium.
- Economic pressures for sponsors threaten the sustainability of pharmaceutical innovation as we know it. The growing demand from health technology assessment (HTA) bodies/payers for quantifiable measures of relative clinical value has become as unpredictable a hurdle for access as is regulatory approval. For sponsors, the increasing cost and complexity of clinical development, the growing use of generics, and uncertainties associated with coverage and pricing are critical concerns. For investors, the increasing risk and uncertainty of pharmaceutical innovation represent substantial disincentives to investment.
- The engagement of patients throughout the innovation lifecycle has emerged as a powerful force of change. In the age of nearly unlimited and instantaneous information from the internet and social media, patients have become empowered and, rightly so, are demanding to have a voice so that their needs and preferences are addressed. Their ability to effectively organise and drive new models of funding, participation in key decision-making processes, and clinical trial recruitment are innovation game-changers.

It is the convergence of these external pressures that I believe have helped set the stage for stakeholders to move adaptive pathways beyond its conceptual phase. Just as the change drivers involve all key stakeholders in the healthcare system, a fundamental principle of the Massachusetts Institute of Technology (MIT) New Drug Development Paradigms (NEWDIGS) systems approach is that all stakeholders need to be part of the solution. In 2010, MIT NEWDIGS created its collaborative 'safe haven' environment, and a structured methodology for confidential prospective case-based adaptive pathways 'scenario design' discussions with broad stakeholder participation. A coalition of the willing reached beyond their comfort zone to contribute to advancing this important evolution in pharmaceutical innovation. The EMA contributed to the advancement of adaptive pathways in bold and progressive ways, by establishing its formal collaboration with MIT NEWDIGS in 2010, as well as announcing the world's first pilot program in March of 2014, thus creating the opportunity for the healthcare community to move one step closer to making this paradigm a practical reality.

Adaptive licensing, also referred to as medicines adaptive pathways to patients, combines optimal use of available tools and flexibilities with multi-stakeholder dialogue to promote medicine development programmes that are efficient in collecting data to inform licensing, reimbursement and prescribing decisions.

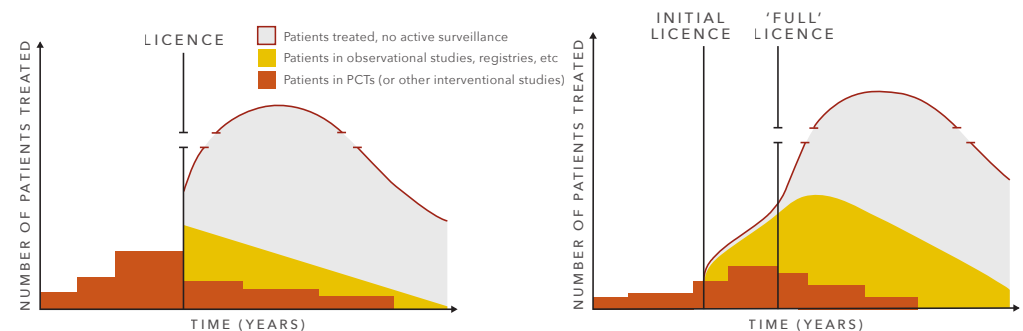
From a regulatory perspective, tools and flexibilities have been introduced through legislation over a period of years. These include (i) early access possibilities such as compassionate-use opinions from the Committee for Medicinal Products for Human Use (CHMP), (ii) licensing flexibilities such as conditional marketing authorisation and marketing authorisation under exceptional circumstances, (iii) capacity for post-licensing data collection, including prospective post-authorisation studies, for license iterations and the progressive reduction of uncertainty related to initial decisions, and (iv) opportunities for early dialogue that includes not only developers and regulators, but also HTA bodies, prescribers and patients.

This last point is critical in supporting an efficient pathway from bench to bedside. That different stakeholders have different responsibilities, different questions to address, is not at stake. However, it is concerning if a lack of dialogue means that clinical data to address the needs of each stakeholder are generated in a disjointed and inefficient manner, leading to delays in patient access. Adaptive pathways will not seek to change the mandate of each stakeholder, but through better understanding each other's needs and preferences, will lead to a more efficient generation of evidence. Since 2010 the EMA has been in dialogue with EUnetHTA and has engaged in joint scientific advice with HTA bodies at the request of medicines developers. Over 30 such meetings have been conducted and it can be expected, as familiarity grows in respect of scientific standards, expectations and preferences, that synergies can be identified more and more commonly.

The risk that the adaptive pathways concept remained a mere thought experiment was addressed in 2014 with the launch of the EMA adaptive pathways pilot project. This project created a safe-harbour environment, outside formal regulatory interactions such as scientific advice, in which medicine developers could engage in dialogue with regulators and other stakeholders. This dialogue, with all parties entering with open minds, is used to plan the most efficient pathway not only to the initial regulatory approval, but to downstream decisions from other stakeholders and to using post-licensing data, including real world data, to iterate and revise those initial decisions.

There is a 'chicken-and-egg' question here. Instead of thinking of adaptive pathways as a new regulatory tool or route to marketing authorisation, it may be argued that the tools and flexibilities developed over multiple iterations of European medicines legislation, including multi-stakeholder dialogue, have been such that an adaptive pathways approach is now possible. Nevertheless, the pilot will serve to identify any gaps in the current regulatory toolbox and will, hopefully, be one important source of experience for other decision-making stakeholders to conduct a similar introspection.

There is no argument that medicines with favourable benefit-risk should be brought to patients as efficiently as possible, in particular when a high unmet need exists. This will require all stakeholders to have appropriate tools and flexibilities brought together through multi-stakeholder dialogue. The work of the European regulatory network will continue to be important in achieving this common goal.



BUILDING THE INFRASTRUCTURE IN A LEARNING HEALTHCARE SYSTEM

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

The poor efficiency of pharmaceutical research and development (R&D) at delivering truly innovative medicines, despite escalating costs, has been in focus for some years. There are many healthcare challenges to be addressed along the entire pathway of translating therapeutic innovation into standards of care. A paradigm shift in the way medicines are developed, authorised, and reimbursed is paramount to ensure that innovation reaches and benefits patients rapidly. To achieve this, the engagement of all stakeholders, from industry to academia, patient organisations and regulators, in an unprecedented collaborative effort, is essential. This is the mission of the Innovative Medicines Initiatives, IMI, a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA) which aims to speed up the development of safer and more effective medicines for patients and boost the competitiveness of Europe's pharmaceutical sector. Set up in 2008, IMI is the largest public-private partnership for healthcare worldwide that fosters collaborative research. As of today over 50 collaborative projects are up and running or about to start. With the recent launch of its second phase to run until 2020, IMI will have committed more than €5 billion to create multi-stakeholder, trans-disciplinary and cross-sectorial consortia.

“ A PARADIGM SHIFT IN THE WAY MEDICINES ARE DEVELOPED, AUTHORISED, AND REIMBURSED IS PARAMOUNT TO ENSURE THAT INNOVATION REACHES AND BENEFITS PATIENTS RAPIDLY. TO ACHIEVE THIS, THE ENGAGEMENT OF ALL STAKEHOLDERS IS ESSENTIAL. THIS IS THE MISSION OF THE INNOVATIVE MEDICINES INITIATIVES. ”

IMI consortia are developing solutions that will help to accelerate the development of innovative therapies in areas of major public health importance such as the development of methods and tools for patient stratification, patient-level data standards, patient registries, target validation, biomarkers for disease activity or medicine safety, monitoring the safety of medicines, benefit-risk assessment of new therapies, novel clinical trial designs, and new schemes to ensure timely patient access to medicines.

In its role of regulating the EU's medicines and in view of its experience and expertise in areas related to medicine development and medicine safety, the EMA has clearly a place in this partnership. With the EMA growing support for research and innovation, collaboration between IMI and the EMA has strengthened over the years.

Several levels of engagement exist under the neutral umbrella of IMI:

- consultation on the definition of IMI priorities and contribution to the assessment of projects' outputs, particularly through EMA membership in the IMI scientific committee;
- engagement in the activities of several consortia either as full partner, including in a leading role as illustrated in the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project, or as member of their advisory boards;
- scientific and regulatory support through the qualification advice/opinion procedure of novel tools and methodologies for medicine development;
- regular interactions between IMI, the EMA and the FDA on strategic topics of common interest.

IMI is now playing an important role in generating science-based evidence that drives regulatory science - most IMI projects deliver concrete results of regulatory relevance and new projects under IMI 2 will focus more on patient access to innovative therapies and technologies. IMI is therefore looking forward to continuing its fruitful collaboration with the EMA.

INFRASTRUCTURE

EMA RESPONSE

'Improving and strengthening the monitoring of the benefit/risk of medicines marketed in Europe': this was the title of an ambitious call for expressions of interest published by the IMI in April 2008. Ambitious but visionary, and an important step in the building of a collaborative approach to monitor medicinal products in Europe. Its origin? The realisation that a thorough post-marketing surveillance of authorised medicines is essential to facilitate access of novel treatments to patients. In choosing to create a consortium and apply to the call, the EMA took the unprecedented step to lead a research programme closely linked to its mission: to foster scientific excellence in the evaluation and supervision of medicines. Five years later, PROTECT integrated 35 participants from regulatory agencies, academic institutions, small and medium-sized enterprises, pharmaceutical companies and the World Health Organization to develop and test methodologies in pharmacovigilance, pharmacoepidemiology and the post-authorisation benefit-risk evaluation of medicines. PROTECT sought to answer key questions such as: how to best communicate information on benefits and risks of medicines to patients? How to measure patients' preferences? How to involve patients in the choice of different treatment options? Through PROTECT, the EMA and its partners added an important piece of knowledge to the complex jigsaw of how to measure and represent a benefit-risk profile and how to convey a change in that profile over time when new data arise.

“ IN CHOOSING TO CREATE A CONSORTIUM AND APPLY TO THE CALL, THE EMA TOOK THE UNPRECEDENTED STEP TO LEAD A RESEARCH PROGRAMME CLOSELY LINKED TO ITS MISSION: TO FOSTER SCIENTIFIC EXCELLENCE IN THE EVALUATION AND SUPERVISION OF MEDICINES. ”

ADVANCE is another research project where the EMA contributes to scientific excellence. Lessons learnt from the A/H1N1 epidemic highlighted the imperative need to develop methods to quickly assess vaccine safety and effectiveness during immunisation campaigns. They led IMI to launch a project aiming to build an integrated and sustainable framework for continuous vaccine benefit-risk monitoring in Europe. This initiative responded to an urgent public health need and the EMA considered it should support it with the development of a good practice guidance and code of conduct for vaccine studies that can be agreed by regulators, public health bodies, academics and industry, and consolidate a complex and fragile infrastructure.

Improvement of standard processes is a task continuously pursued by the EMA and other regulators. The example of patient registries illustrates this approach. Registries may be requested in the context of risk management plans or the authorisation of certain medicinal products, but the current approach to registries is sometimes suboptimal in scientific and resource terms. In collaboration with its scientific committees, the EMA therefore launched an initiative to improve the quality and added value of patient registries through an early dialogue between involved parties, appropriate use of data sources that already exist in many countries, and use of standard methodologies and governance principles.

"Art is made to disturb. Science reassures." said the French painter Georges Braque. Over the last decade, the EMA contributed to scientific excellence in benefit-risk evaluation and process improvements. These activities should reassure the public, patients and healthcare professionals about the robustness of the European regulatory system, the authorisation process for medicines and the monitoring and management of their potential risks.



ACCESS TO DATA & EMPOWERING PATIENTS

For any public body dealing with medicines, transparency and openness are essential to maintain the trust of its stakeholders.

Information is either provided in a reactive way or through proactive publication. Over the years, there have been increasing requests for information and openness on the various activities of the EMA, facilitated by the regulation on access to documents.

Efforts have been made over the last decade to increase the proactive publication of information on medicines, building on the European public assessment report (EPAR), a novel concept introduced with the EMA founding regulation. The most recent trend sees a shift from providing only information on the outcome of the assessment towards publication of the data underpinning the scientific review. This trend goes hand in hand with increased interaction with civil society, from involvement towards engagement, thereby empowering patients.

The involvement of patient representatives and healthcare professionals in the regulatory processes has proved extremely beneficial, providing a 'real life' perspective in the scientific discussions.

FROM INVOLVEMENT TO ENGAGEMENT OF PATIENTS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

Allow me to start with a true story: I recently participated in a high level advisory board as an experienced 'chief lobbyist' of more than 600,000 people with multiple sclerosis in Europe. The group consisted of key opinion leaders (KOLs) in neurology and myself. I was the only person representing patients' voices in this group and the only one without a medical/academic title.

I suggested to invite a senior nurse as an additional expert because the subject of the meeting was a reference document that would focus on every aspect of patient care. Every one of the KOLs pretended not to have heard me, ignoring what I said, and discussed the potential involvement of even more neurologists. I repeated my proposal twice - with no acknowledgement at all. To tell you the truth: at this moment I felt I was being used as a 'fig leaf' of patient involvement; I realised (again) how distant daily practice is from true patient participation. I mention this example to show how some continue to ignore and disrespect the presence of patient experts, while others have moved towards true patient participation.

In contrary to this recent disappointing experience, the EMA has, since its establishment, developed more and more opportunities for meaningful patient involvement and empowerment. I note the Patients' and Consumers' Working Party, the benefit-risk assessment within scientific advisory groups, transatlantic workshops and training sessions, patient representation on all scientific committees, consultation on clinical trial guidelines through to patient participation in EMA's Management Board. The EMA is excelling while others are retreating behind walls of partisanship.

The input of patients and consumers, in the form of constructive criticism, has influenced the EMA policies on access to data and other areas. Not only has the input of patients been listened to, it has been respected and often used to implement small, but continuous steps of improvement. Being taken seriously and considered an expert in one's disease is vital and will enable a better use of the resources available in our society in healthcare. We can no longer afford to listen to scientists and industry alone - future sustainable healthcare can function only with an educated, health-literate and fully involved patient community, with individuals accepted and respected in their roles as experts in their field by all other stake holders.

After more than fifteen years working as a European patient advocate I believe that I have a certain credibility when I consider EMA's practice of patient and consumer involvement in its work as exemplary. My only wish is that this good practice of the EMA would influence the actions of other healthcare experts, policy makers, industry representatives and other vital parts of society much faster than it actually does. I hope the actions of these groups would be more like the brain's neural pathways and synapses - with an extraordinary ability to grow and adapt to a changing environment - rather than the previous limiting theories on the human ability and resilience

NT TO ENGAGEMENT

EMA RESPONSE

I would particularly like to highlight two areas of patient involvement in the EMA's work.

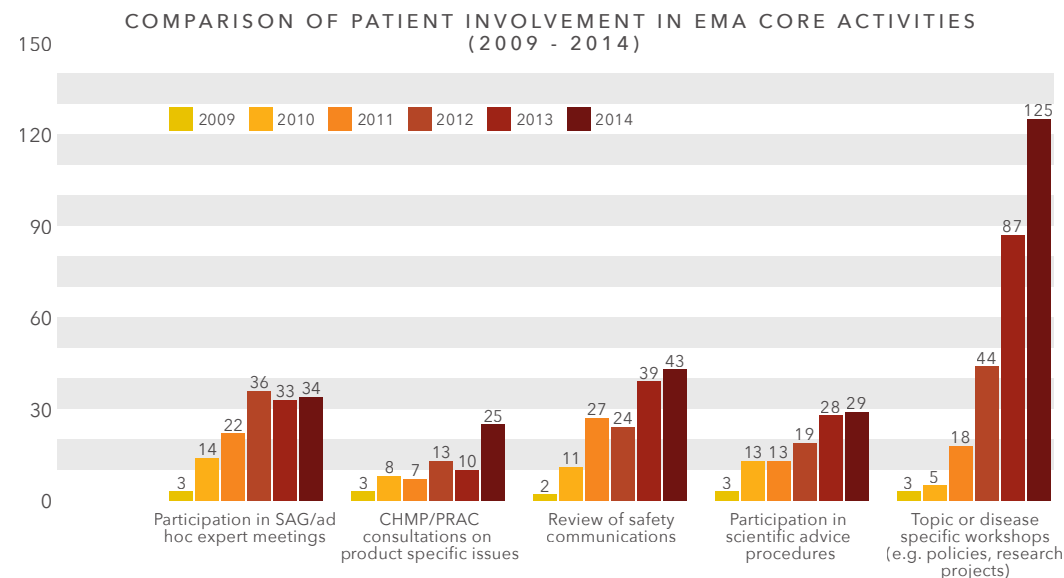
Involving patients in the critical area of benefit-risk evaluation has not been without surprises. We quickly realised the value and unique perspectives gained from living with the disease in meetings convened by the Committee for Medicinal Products for Human Use (CHMP) or the Pharmacovigilance Risk Assessment Committee (PRAC). Their opinions and judgments were often different from what has been assumed by the assessors. What regulatory professionals may consider as a minor effect can be perceived as a game changer by somebody living with a debilitating disease - when a small effect allows patients to eat and drink on their own, this is perceived as significant and important to them.

Experience in the PRAC has shown that patients play an important role in contributing to decisions on wording and timing of risk communication which play a fundamental role in ensuring medicines safety. Functioning communication channels between the scientific committees and patients' organisations play an invaluable part in explaining the concepts of benefit-risk evaluations.

If such interaction happens on a rather high level of exchange today, we need to remind ourselves that this has been a long journey involving many dedicated actors at patient and consumer organisations and at the EMA itself. What started with involving a patient for the first time in a safety crisis situation in 2007 has led to formally involving them in the PRAC itself. Patient presence in the PRAC needs to be strengthened still; one person is not enough. Further progress is required in the area of benefit-risk evaluation, communication and visualisation.

Set up in 2007 with the paediatric legislation, the Paediatric Committee (PDCO) also has a responsibility to consult views and opinions of children and young people. A concept paper was compiled in 2012 and a public consultation held in the same year. Its objective was to develop a framework of interaction for the involvement of children and young people in the PDCO's work, particularly a) when and to what extent, b) how their views can be sought, and c) the manner in which their views can be applied. Benefits, challenges and interested parties were identified. The comments led to a first draft of a reflection paper.

On this basis, the 6th annual workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA) was held at the EMA in June 2014. A main discussion topic focused on the involvement of children in clinical research. During the discussion, the importance of engaging children at every feasible stage of the research activities as ambassadors for young people in research was highlighted. The outcome of the workshop is currently being further reflected upon.



WORKING WITH HCPs, ACADEMIA & RESEARCH ORGANISATIONS

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

The perspective of a European pharmacoepidemiology researcher: the evaluation of the use and effects of medicines following their approval through observational epidemiological studies is critical to the safe use of medicines by European patients and worldwide. This type of research requires either direct involvement of patients and their health care practitioners or access to their health records in paper or electronic format, named or anonymised. Methods and data collection options have been developed over the years and currently pharmacovigilance and risk management guidance across Europe, North America and the Asian Pacific regions encourages implementation of pharmacoepidemiology studies, which have become essential by providing evidence from patient experience in a real-life healthcare setting.

The EMA has been instrumental in fostering collaborative post-approval observational (epidemiologic) research in Europe through the development and support of the European Network of Pharmacoepidemiology and Pharmacovigilance Centres (ENCePP). At a time when it was becoming clear that individual academic and research centres working in isolation were unlikely to address the needs in the field, the EMA dedicated resources to the identification of academic and research centres in Europe and bringing them together in this network. More than 100 research centres and data providers participate nowadays. By working together, and with the contribution of EMA experts and support staff, ENCePP researchers developed standards and guidance on observational research specific for the field, a code of conduct encouraging independence and transparency, and a registry of studies (currently also used as EU post approval study registry) to promote transparency and learning. A key impact of this work has been to foster and accelerate the collaboration between centers in the conduct of multi-center studies evaluating the use and effects of medicines, and to increase the visibility of centers to funders, both public and private. A second instrumental contribution of the EMA was to facilitate independent research on the safety of medicines by identifying medicine safety research priorities for European patients through its Pharmacovigilance Working Party/Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP), and liaising with the European Commission to agree funding opportunities through the EU Seventh Framework Programme for Research. This has expanded the funding bodies for medicine safety research beyond national public funding or that of pharmaceutical companies. Results of all these studies have and increasingly continue to assist all stakeholders to take decisions around the risks of medicines and the effectiveness of measures to mitigate their risk to patients.

“ AT A TIME WHEN IT WAS BECOMING CLEAR THAT INDIVIDUAL ACADEMIC AND RESEARCH CENTRES WORKING IN ISOLATION WERE UNLIKELY TO ADDRESS THE NEEDS IN THE FIELD, THE EMA DEDICATED RESOURCES TO THE IDENTIFICATION OF ACADEMIC AND RESEARCH CENTRES IN EUROPE AND BRINGING THEM TOGETHER IN THIS NETWORK. ”

What will the future hold? Certainly challenges remain: studies still take a long time, often because of administrative aspects; access to available health data can be delayed, at times hindered because of misperceptions about patient data protection concerns. However, as we continue to work together, we are increasingly better prepared to address challenges, and design and conduct studies through collaborations that will only improve over time.

ACADEMIA & RESEARCH

EMA RESPONSE

For all Member States, the EMA represented a major advance in regulatory practice in the EU. It became clear that the new agency aimed to improve standards, consistency and the science associated with approval of medicines, and this has been very definitely the case.

One important aspect of that improvement was liaison with health care professionals and with the scientific community in general.

As national authorities, we have formal and informal contact with physicians and pharmacists, but such contact at European level involved many new and different considerations. In addition, awareness of the new agency in the clinical or scientific community was limited.

To improve the standard and content of medicine authorisations, it was essential that we consider medicines in the context of current medical practice. Development of relevant, up-to-date scientific guidelines could not be done in regulatory isolation, but required the participation of relevant experts from the medical and scientific community.

Members of the CHMP are appointed on the basis of their expertise, but as the limited membership cannot cover all therapeutic areas, the EMA recognised the need for participation of those with expertise in scientific fields not adequately represented, and additional expertise was included.

With the increasing complexity of applications, it became apparent that the involvement of specialist clinical experts in the assessment was both desirable and necessary in order to answer the increasingly complex and specific questions.

“ WITH THE INCREASING COMPLEXITY OF APPLICATIONS, IT BECAME APPARENT THAT THE INVOLVEMENT OF SPECIALIST CLINICAL EXPERTS IN THE ASSESSMENT WAS BOTH DESIRABLE AND NECESSARY IN ORDER TO ANSWER THE INCREASINGLY COMPLEX & SPECIFIC QUESTIONS. ”

The CHMP identified that needs for advice in particular clinical areas was more frequent, and specific scientific advisory groups (SAGs) were created, with expertise as the main requirement for membership. These SAGs provide the CHMP/EMA with access to world-class advice on any issue. In addition, as issues can arise in any scientific field or in relation to any medicine, ad hoc expert groups can also be convened.

Following from this positive experience of clinician input, legislation concerning the regulation of advanced therapy medicinal products, paediatric medicines and pharmacovigilance included specific references to the inclusion of clinicians and specific areas of expertise, such as surgery and ethics, on the respective committees. These clinicians are appointed to allow direct input to the assessment process for these products.

Health care professionals are important participants in provision and supervision of medicines, and the need for regular dialogue with all of these professionals, including nurses, pharmacists and physicians who are so involved in patient care, is clear. As the users of the summary of product characteristics (SmPC), the ultimate deliverable of the regulatory process, their input and opinions are essential if we are to improve both the content and quality of the SmPC. The Working Party with Healthcare Professionals Organisations (HCPWP) facilitates contact and dialogue which was previously lacking, and through its membership promotes interaction with a wide variety of European professional groups and academia. This working party allows interaction with all relevant experts involved in the assessment, use and supervision of medicines.

Over the last 20 years, the EMA has realised the importance of involvement of previously insufficiently recognised partners in medicine development and assessment, and has progressively increased involvement of health care professionals and academia.

REGULATORY TRANSPARENCY

REGULATORY TRANSPARENCY

SCIENTIFIC AND SOCIETAL DEVELOPMENTS

To understand the need for regulatory transparency, we refer to a definition of regulatory transparency formulated by the Organisation for Economic Cooperation and Development (OECD) in its 2001 report as “the capacity of regulated entities to express views on, identify, and understand their obligations under the rule of law”. In recent years a notable increase of emphasis on medicine regulatory transparency has been observed in the EU, which has led to the introduction of relevant legal provisions, and the development of proactive disclosure practices by the EMA and the national competent authorities. The inspiration for this trend has come from the need to improve regulatory quality and to enhance public trust in regulatory decisions, particularly in view of some crisis situations with medicines, which negatively impacted on the public perception of medicine regulators. Therefore it has become essential to demonstrate that medicine approvals are not arbitrary or biased decisions but are taken in standardised and clear procedures based solely on scientific merits and adequately proven positive risk-benefit balance. An important tool to explain to the public the scientific rationale to authorise the product is the European public assessment report (EPAR) at the EMA and public reports at national level. EPARs are based on the assessments made by the relevant EMA scientific committees, so it is only logical that their activities are open and transparent and their opinions, agendas and minutes are public. Each authorised medicinal product throughout its life span may pose newly detected safety or efficacy problems and require changes of the marketing authorisation. The EMA scientific opinions are made public and provide explanations for regulatory decisions. It should be noted that because centrally authorised medicinal products are usually highly sophisticated and may provide innovative therapies, it is particularly important to clarify and communicate to the healthcare professionals and the public the scientific aspects of the regulatory decision making process.

“ IN RECENT YEARS A NOTABLE INCREASE OF EMPHASIS ON MEDICINE REGULATORY TRANSPARENCY HAS BEEN OBSERVED IN THE EU, WHICH HAS LED TO THE INTRODUCTION OF RELEVANT LEGAL PROVISIONS, AND THE DEVELOPMENT OF PROACTIVE DISCLOSURE PRACTICES BY THE EMA AND THE NATIONAL COMPETENT AUTHORITIES. ”

Another aspect relates to transparency of scientific data on which regulatory decisions are made, through reactive and proactive disclosure of industry data in support of their applications. The EMA is bound by the provisions of Regulation 1049/2001 regarding public access to documents, which sets the framework for disclosure, making only few exceptions, one being commercial interests of a natural or legal person, including intellectual property; however even this exemption may be overridden by public interest in disclosure. There is no legal definition of ‘commercial interest’ and the topic has been discussed extensively in the EU regulatory network, resulting in the adoption of a common guideline on which parts of a dossier of a medicinal product may be regarded commercially confidential. Apart from the aforementioned Regulation 1049/2001, the EMA recently adopted a policy to proactively make clinical reports available once a decision has been taken.

A very important aspect of transparency is its anticorruption effect. Publicly available declarations of interests of experts and regulators involved in assessments of medicinal products serve to ensure that the scientific and regulatory opinions and decisions are not influenced by any external factors. A notable achievement of the EMA has been to develop a process for the handling of declarations of interests, which has become a model adopted by several national competent authorities.

EMA’s accomplishments in the area of transparency have set high standards for the whole network of EU medicine regulators.

Look at the website of the EMA - it is full of valuable information! Regulatory transparency is really something which increased tremendously during the past 20 years. I personally was able to follow this development and I would say that about 30 years ago at national level we had no transparency at all about the scientific decision making process.

Since 1995 the EMA started to be as open as possible about how it works and how it comes to its decisions. Publishing the EPAR for a centrally authorised medicinal product (MP) was a novelty at that time. This unique document describes the basis for opinions on how medicines should be used. This document is updated over the whole life span of a medicine, explaining the scientific changes to the marketing authorisation and the procedural steps taken.

One of the most important outputs of the scientific review of a medicine is the product information which has to be published in all EU national languages within a database. The goal to publish in such an EU database all in the EU authorised MPs, together with the product information, has not yet been reached, but will hopefully be realised soon.

Publication of agendas and minutes for meetings of the various EMA (scientific) fora started in 2009 with the EMA Management Board, followed by the EMA scientific committees in 2012/2013, and the amount of information released is still increasing. Other transparency measures in this area relate to summarising highlights shortly after the meeting, meeting reports, presentations and sometimes even video recordings (these can be found on the Agency's You Tube channel) after workshops - some of which are open for the public.

Transparency in the area of pharmacovigilance steadily increased over time. A first major achievement was the access to aggregated data on adverse reactions contained in the EudraVigilance database. A further 'explosion' on transparency took place through new pharmacovigilance legislation at the end of 2010, and we still have not yet implemented all the provisions on transparency, such as the procedures for having public hearings for discussing safety issues of MPs.

Starting with regulatory transparency on the outcome of scientific assessment 20 years ago, there is a big shift now in transparency. Patients have the right to know on which data and grounds a medicine is prescribed to them, and physicians and pharmacists should have the ability to know on which basis a medicine is granted access to the

market. Therefore we are now broadening transparency on scientific data on which regulatory decisions are based. In any case, personal data and commercially confidential information has to be protected and will never be released. The EU regulatory network worked together on a common understanding for transparency issues between agencies in response to requests for information on new applications for medicinal products before and after an opinion/decision.

“ PATIENTS HAVE THE RIGHT TO KNOW ON WHICH DATA AND GROUNDS A MEDICINE IS PRESCRIBED TO THEM, AND PHYSICIANS AND PHARMACISTS SHOULD HAVE THE ABILITY TO KNOW ON WHICH BASIS A MEDICINE IS GRANTED ACCESS TO THE MARKET. THEREFORE WE ARE NOW BROADENING TRANSPARENCY ON SCIENTIFIC DATA ON WHICH REGULATORY DECISIONS ARE BASED. ”

Information about clinical trials is available in the EU Clinical Trials Register and the EMA in October 2014 committed to publish data sets from clinical trials.

In the European system, we are working within a network - experts from the EMA and national competent authorities from 28 Member States within a unique system. Scientific competence is guaranteed by the nominating authority, independence and integrity assured through public declarations of interests in order to ensure impartiality.



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A FEW FINAL WORDS...

Dear Reader,

The foregoing has shown you the horizons of the EMA's activities, from where we come and what our aspirations are for the future.

Our success is based on the cooperation within the European medicines regulatory network, our scientific committees, the engines of the regulatory system in Europe, the partnership with the European Commission and the medicines regulatory authorities in the EU and the EEA. The strength of this network is the sum of all the daily interactions between EMA staff, delegates and experts. This close collaboration is the cornerstone of our 20-year track record of ensuring quality, efficacy and safety of medicines for patients across Europe.

Back in January 1995, the Agency had just 16 members of staff, several of whom are still working here today, two scientific committees and two and a half floors of office space. These days, we have grown considerably, working over ten floors, in a new building, and supporting the work of seven committees, around 30 working parties and we hold over 800 meetings each year. Today, almost all new and innovative medicines in Europe are authorised centrally. This is a remarkable achievement.

None of this could have happened without the help of all the partners in the network and our colleagues in house.

Every day, we are impressed by the hard work and dedication shown by all of them, without which we would simply not be able to fulfil the challenging workload that we face as an EU agency with rapidly growing tasks and responsibilities. We are also struck that against some trends, potentially over-emphasised by certain media, the European spirit at the Agency and among partners, the dedication to work together in this union of states, and to add value to public and animal health by pulling all forces together, is undiminished and forms a forceful glue to our partnership. This has been essential for the continued success of the Agency.

Mr Andreas Pott
Deputy Executive Director

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