



OUTCOMES OF THE EVALUATION OF THE EUROPEAN MEDICINES AGENCY – THE FUTURE SUSTAINABILITY OF THE SYSTEM

A conference was held at EMA in London at the end of June to discuss the findings of the Ernst and Young evaluation of the Agency and its recommendations for the future. The audience included representatives of the Agency and the consulting company, the Commission, national agencies from across Europe, the European Parliament, industry trade associations, professional representatives (doctors etc) and patient organisations.

Introduction to the Meeting

The meeting was opened by **Nils Behrndt** from the Cabinet of Commissioner Dali, who praised the good foundations, but stressed the need to put patients first and ensure that the future would mean that the benefits of the EU regulatory system would reach ALL patients in the EU – a reference to the issue of access to medicines which is so current.

Thomas Lonngren pointed out the international reputation of the EMA and its unique harmonised system involving 27 member states, noting that the critical success factors were (1) the people involved – staff, experts, agencies - and especially those who made voluntary contributions, (2) the representation of the national agencies on all working groups and (3) the quality that is built into the system by having two rapporteurs and input from all member states at the EU and national level. The support of the Commission and Parliament has been vital, as has the stable financial underpinning.

For the future, the involvement of all stakeholders, particularly patients, and the issue of transparency will be important for continuing success especially against a background of increasing workload and deepening complexity. Scientific developments (personalised therapies, gene therapies) and difficulties in the drug development process require the Agency to respond to industry with competence and be able to offer guidance to help this partnership of regulators and regulated to deliver medicines to EU citizens. So the key question for this meeting was: 'is the current legislation fit for purpose for the next 10-15 years?'

The Report and its Findings

Ernst and Young presented an overview of their findings, which they had gleaned from a research process including observation, interviews with stakeholders, a questionnaire to national agencies (91% responded) and six case studies in a representative sample of

countries. Their focus was the Centralised Procedure and referrals: they did not look at MRP/DCP in any detail.

They concluded that EMA is delivering an increasing number of highly-valued opinions of good quality involving the best experts in Europe. Since 2005, the number of applications has doubled and the EMA system has coped despite political pressures. However, the main committees are 'overwhelmed with work' and consistency between the committees remains a challenge. E&Y suggested the formation of 'pre-committees' for referrals and generics to help decrease the CHMP/CVMP workload.

The EMA Secretariat strongly contributes to the effectiveness of the system but stakeholders are wary of increasing rigidity and bureaucracy. The Secretariat has made efficiency improvements since 2000 and although costs have increased, so has quality.

E&Y noted the disparity in involvement between National Competent Authorities (NCAs), with seven (including Denmark, France, The Netherlands and UK) taking 75% of rapporteurships. It was also noted that the system requires considerable voluntary input especially from academic experts or NCA staff on 'non-fee earning' committees such as COMP, and while this gives flexibility, its sustainability is not ensured. Despite the scientific benefits from participation, the lack of resources at NCA level (and the risk of this becoming even more of an issue in the current economic climate) impacts strongly on their level of involvement in EMA activities and if not addressed, this could jeopardise the sustainability of the system.

The role of committees including COMP, CAT and PDCO was evaluated and issues of co-ordination between these and CHMP or SAWP were raised. The post-marketing activities of EMA (inspections, pharmacovigilance) were generally praised although the complexity of some of the pharmacovigilance tools was raised as an issue.

Communication about the EMA's role to patients and health care professionals was considered to be an area for development and the future provision of better information to HTA bodies was suggested. However, the EMA's efforts towards transparency were thought to be an example to other institutions (although greater transparency on the selection of rapporteurships is to be encouraged). In general, it was felt that the EMA supported the entry of generics and products from SMEs into the EU market, although generic human and veterinary products have been the significant contributors to the increase in workload in recent time.

Although industry felt the fees were generally fair and the system itself relatively affordable (especially when compared to the US FDA), the fee structure is too complex and not well understood, while NCAs feel relatively under-compensated for their input. The fees for Scientific Advice are considered too high, hence the use of national advice by industry and the potential for impact on the consistency of opinions during the regulatory process.

In conclusion E&Y feel the EMA is 'a European Success Story' but the contribution of the NCAs has played a great part in this. The system has reached maximum capacity and will have to adapt to meet significant future challenges.

The Architecture of the European Medicines Agency

Patrick Le Courtois chaired a debate on the Architecture of the EMA. **Eric Abadie (CHMP)** reviewed the historical development of the system and the challenges it currently faces in terms of consistency of opinions, co-ordination between parties, duplication of work, complexity of structure, growth in diversity of tasks performed and resource availability. He suggested that the architecture of the working parties could be improved – at the moment the mandate and composition varies - and so from September the Efficacy working party will disappear and a series of therapeutic circles with a clear mandate will be set up to look at guidelines and scientific advice. Organisation around CHMP weeks will also be improved to try and get issues dealt with outside of these very busy weeks in the EMA calendar, and there will be more focus on new ways of working including e-meetings (which worked well when forced on EMA during the ash cloud crisis earlier this year). A test will take place in September and October 2010. The issues of assessor training and compensation (especially in PDCO and COMP) will also be addressed.

A number of delegates responded to or added to this debate: **Bruno Flamion (SAWP)** noted that the good collaboration of EMA administrators helped coordination between SAWP and PDCO. He felt as that as EMA representatives can't speak for the whole CHMP it would be impossible to make scientific advice binding and so to some extent the question of inconsistency will always be in the system, but the failure of CHMP to comply with SAWP advice is a concern. As the advice is not binding on industry (cf FDA) it is hard to make it binding on CHMP – but good feedback mechanisms would help continuity of the assessment process- and the reward of taking and following scientific advice should be a higher predictability in the regulatory outcome.

Jan Mazg (HMA) spoke from a country not included in the research, but which is so small that he is the Executive Director of the Agency, as well as the HMA and CHMP representative! With this experience in mind he felt the quality of outcome was important but so was the quality of life of the NCA representatives! Improved interactions between committees and a way of making working for the regulators more attractive to outside academic experts was an issue. In a similar vein, **Klaus Cichutek (PEI)** said that extra money to EMA was not enough without proper reimbursement of the NCAs. Their staff are not just 'tools' but experts that need acknowledgement and external experts need to find it attractive to be part of the decision-making process.

On behalf of patient groups, **Christoph Thalheim (EMSP)** thanked those who took the patient and consumer viewpoints seriously. He pleaded for fewer acronyms and a harmonisation of the HTA process (one single outcome would be more welcome than 27 different ones). He noted that patient reporting of pharmacovigilance data has been successful and should be extended. Finally he noted that organisations such as he represented could be key in helping EMA communicate with the public.

On behalf of industry, **Michael Doherty (EFPIA)** was at pains to praise the aspects of the EU system that work well, but asked us to bear in mind that for those outside the EU the history and subtleties of the system can be a barrier. He noted that the system is stretched to the limits now and welcomed attempts to re-engineer committees to help with this. He proposed three critical

areas: (1) Scientific advice – the centralised process needs to be more accessible to reduce the duplication of effort for companies and agencies in using the national procedures (2) Clinical trials – at FDA you only have to go to one place to deal with an urgent safety issue but in the EU it can be many member states and a need to get them to agree to a single risk management plan (in practice, the FDA plan tends to be implemented!) and (3) Paediatrics: a huge workload for PDCO but also a burden for industry so the issue of multiple opinions (PDCO/CHMP/Ethics/National variations) needs addressing. EFPIA also welcomed the greater involvement of patients and expressed concern at the implementation of Eudravigilance.

In the general discussion **Christian Schneider** (PEI) spoke on behalf of CAT, noting that this was not a pre-committee but an expert committee which relied on input from NCAs who had history with these products before the CAT was formed and on experts that keep the academic input into the system and need the motivation of being influential in order to keep them doing so. As an opinion-making committee (eg certification) CAT has to have a structure that allows binding decisions, but a debate on MS representation would be useful.

For the herbal community, **Konstantin Keller** (HMPC) regretted the narrow focus of the report on the EMA as a 'factory' issuing Marketing Authorisations, whereas the development of scientific (not product specific) standards is important and currently no fees are involved for tasks such as these. He suggested that a new regulatory model be considered such as herbals have done in recent time: such innovative approaches are needed when resources are low, and he was disappointed in the deficiency of radical ideas in the report.

Nikos Dedes (EATG) also criticised the report for being 'conservative and superficial' especially in its failure to capture the dynamic of the value of patient input. He felt that patients' opinions should be proactively sought in the development of new legislation and systems. The IAPO representative (**Albert van der Zeijen**) echoed the sentiment, saying that the three patient organisations interviewed by E&Y, from a potential of over 90, was a mere 'drop in the ocean'.

Dagmar Roth-Behrendt (European Parliament) was vocal in her non-agreement with the E&Y report: she urged a consideration of leaner management, fewer committees, independence for PDCO and less domination of CHMP, and in particular clear attention to the issue of conflict of interest in appointing experts.

Martin Terberger (EU Commission) confirmed their commitment to deal with patient groups (who seem more enthusiastic about liaising with him since the move to DG SANCO!), but with only 35 staff it can be difficult to make as many meetings as they would like.

Patrick O'Mahoney (EMA Management Board) pointed out that the main point was that EMA was not complacent and has a culture of continuous improvement. Cross border working, even with the most magnificent structure, can only be effective if it delivers extra resource and not using the same resource. He added to the debate on conflict of interests of the 'very professional' experts used by EMA: a clear and transparent system needs to be in place so that any potential conflict is in the open and understood by all stakeholders.

The European Medicines Network

The second discussion session was chaired by **Aginus Kalis** (HMA). **Jean Marimbert** (HMA) set the scene by emphasising that the network was a key part of the EMA system bringing collective expertise of the agencies supplemented by external experts. This structure was a pragmatic solution that has worked well in delivering consistency, managing the move to generics while supporting innovation, and coping with challenges. It delivers a robust assessment capacity and sustained commitment from NCA. But the increment from 15 to 27 countries has been hard as had the number of recent legislative changes (paeds and herbals have been introduced with no new resources), and there are constraints on national agencies due to public workforce policies, particularly now. Volunteer rapporteurships will be more difficult to secure going forward. Pragmatic solutions will include the avoidance of unnecessary work duplication, work-sharing, planned resource management and prioritisation on the basis of relative risk and public health benefit. Marimbert suggested three possible ideas for discussion: developing joint assessment teams for rapporteurships, virtual meetings and voluntary co-operative arrangements between NCAs so that any NCA retains the right to be a member of a committee but one NCA represents another one or two and shares information.

Peter Arlett (EMA) clarified the role of the EMA Secretariat as laid down in Article 56 and 57, highlighting the many positive things that E&Y mentioned in their report (quality, learning, improvement driven etc). He demonstrated the breadth of activities that it is involved in (including admin, IT, fees, data management, communications, scientific processes and networks, public health initiatives, and international interfaces). The guiding principles going forward are to protect and promote public health, strive for excellence, work as a team with EMA Committees and NCAs, embrace frontiers in science, regulation and society and identify research needs and if appropriate conduct that research. One key area will be the reduction of the administrative burden for scientific assessors: this is already being done and will be developed further and more support for those NCAs that need it (not all). The Secretariat will also need to develop ways to monitor EMA consistency of output, and more co-ordination of IT related projects so that there is a genuine European IT architecture: Arlett acknowledged that there are some frustrations in this area! A key role will be the continuing of quality assurance procedures.

In the following panel discussion, **Martina Cvelbar** (Slovenia and HMA) called for balance at the EU and national level and the need to avoid duplicating competencies. She reminded the audience that the EMA was developed for innovative medicines but the increase in workload has come from generics and biosimilars. E&Y had suggested a new committee but she noted that the CMDh already existed!

The EGA representative (**Beata Stepniewska**) agreed that generics are a major fee contributor to the system and in that case the system should be balanced and predictable, with better coordination of inspections, single DMF assessment, and more use of the existing synergies that the network can offer. The E&Y report did not make the mandate for the suggested generics sub-committee clear, or how it would relate to CHMP. In principle, EGA supports anything that would make the system more efficient but consistency of outcome and not adding burden to CHMP are two important caveats.

Michael Wilks (CPME, doctors and other healthcare professionals) said that healthcare professionals want rapid evaluation but also safety and reliable and accessible information. EMA is a trusted source of centrally – coordinated information, (less confusing than when done nationally), but he noted that HCPs put info into the system (eg PV) but don't get much feedback as to what will happen as a result.

Kent Woods (MHRA, HMA) raised the issue of resource and in particular the booking of slots for the DCP. Use of the system has risen sharply, but 50% of slots booked are not used and notice is not given soon enough to allow re-allocation of the resource. If this could be resolved in some way, the DCP could be used for more applications and the Centralised Procedure 'protected' for truly innovative products that need full scientific resource - he noted that only 37% of the products using the CP were compelled to go this route.

Dagmar Roth-Behrndt commented that anticipating the numbers of applications is a problem and can vary up or down. The 'main funding' for EMA is through public funding, but the network is reliant on fees. She raised the question of why there are so few innovative products and applications for the CP and suggested that this meant we are not meeting patient needs.

Lise Murphy (EURODIS – patient association for rare disorders) asked how patients could be introduced in to the work of the network. A representative from the Polish agency asked for less striving for excellence in IT and more focus on 'fit for purpose'.

In summing up this session, **Martin Terberger** noted the inequalities that had been highlighted and suggested that agencies should be paid for the work they do. No fees are payable for PIPs and monographs and few agencies can do these without pay (it was suggested that as these are for public health reasons perhaps the fees should be from public funds). The EMA has doubled in people and procedures in the past 5 years and committees have grown from one to five. It is possible to celebrate the positives, but there is a long list of 'wants'. EMA need the time to do all the tasks expected of them as well as take on the newly agreed PV proposals.

Topics Specific to Veterinary Medicinal Products

David Mackay (EMA) chaired this session which centred on a proposal document that had been tabled by IFAH.

This is a different industry, with 'private' clients (not governmental) and complexities including the range of species and environmental issues. There is no re-imburement issue and the industry is small and fragmented. There are concerns about the availability of vet products in the EU as many applications are national and referrals are common. The current system is complex with divergent competencies both at national and EU level, too many layers in decision making and parallel assessment by national agencies is a waste of resource. E&Y had cautioned that for these reasons the vet system must not be a mirror of the human medicines but needs its own specific organisation and regulation.

Brigitte Boenisch (IFAH-Europe) presented the proposal and started by introducing the concept of the Euro-schnitzel... a schnitzel made in Austria can be eaten in ANY member state, but the vet products that may be used in the animal are variably regulated. This makes

nonsense of the existing system and IFAH are calling for a 1-1-1 Concept for ALL products: 1 single EU dossier, 1 single scientific assessment by the best available competence and 1 decision issued by a central co-ordinating body (CCB). NCAs would continue to be the 'backbone' of resourcing and delivering a more harmonised implementation of the legislation and the suggestion is that the experts used should be selected on the basis of their expertise and not nationality and assess the dossier on behalf of all member states.

In response, **Kornelia Grein** (EMA) noted that the CVMP would not exist under these proposals. In her view, improvement of the existing system would be preferable to changing the system completely. However support for the 1-1-1 concept came from **Jan Vaarten** (FVE) on behalf of veterinarians: the proposal allowed the use of specialist experts in response to a specific need (eg bee-keepers, equine specialists, experts able to respond to new diseases coming from Africa). He called for one true market and not too much pharmacovigilance. For the generics industry **Inge Sandberg** (EGGVP) also supported the 1-1-1 proposal, noting that the vet system must not be a copy of the human one but much more simple. As an example she gave the costs of translations for all member states as far too high for small specialist products and generics. The 1-1-1 was also supported by representatives of farmers.

Fees

Session 4 of the conference looked at the thorny issue of fees. The Chair, **Andrzej Rys** (Commission) reminded the audience that the fees were in Council Regulation of 1995 and a taskforce was in place to report to the Commission by 24 November 2010 as there is a legal requirement for a review by this date laid down in the Regulation. The EMA is not a boutique from which to buy individual services: it is part of a regulatory system and costs have to be covered. The push to become fairer has led to increased complexity of the fee structure and he suggested that a better approach might be one (like the UK Royal Mail), where a 'cluster' of services can be bought for a single set fee.

In the presentation, **Ulrike Nagl** (EMA) said the EMA Secretariat considers that the current complex system, involving 131 different fee types, cannot be maintained as the administrative burden is high for both EMA and applicants. EMA is vulnerable in that 80% of its activity is funded by fees. Stakeholders do feel that the fee level is fair especially when compared to other major agencies such as FDA. They also acknowledge that some groups (SME, Vet products) are deserving of special attention, but some activities are non-fee attracting and this puts the sustainability of some activities supplied by NCAs in doubt. Between the revision of the Fees Regulation in 2005 and the present day, SME regulations, conditional MAs, Paediatrics, Advanced Therapies, Variations regulations to name but a few have all been introduced and the number of MS has risen to 25+2. The combination of fee incentives and more evaluation has led to a 'more work-less fee' situation that affects both EMA and the network.

The fee structure must be 'future fit' to cope with anticipated changes in the legislative environment as envisaged in the pharma package. It must give compensation to NCAs for all services while still maintaining incentives for certain types of applications. The proposal is to abandon the current model and develop a new model with 'bands' of fees for pre-authorisation, post-authorisation, referrals and 'other services'. It is not possible to have a 'one size fits all'

approach in the EU, as in FDA which only has five fee types, but the proposals under consideration would have the potential for a three-fold reduction in the total number of fee types so being administratively easier, and as a by-product, more transparent.

Andreas Pott (EMA) asked the audience to remember that the fees are paying for the regulatory system and not for the EMA (which is a non-profit body). **Pat O'Mahoney** (EMA Management Board) said that the fees paid to the NCAs are a Management Board responsibility but they will not offer an opinion until the proposal is put to the Commission. **Christa Wirthumer-Hoche** (Austria) was happy to hear that all services would be reimbursed in a new system as many MS are self-financing and not funded from their health Ministries (and where the Ministry is contributing, this is going down all the time!). A simple, fair and transparent system would benefit everyone. **Edwin Ruighaver** for EFPIA stressed that industry wanted the excellent standards of service to continue and the research-based industry is prepared to pay fees that allow that to be so, but a simpler system that is easier to administer would be welcomed and the fee should reflect the level of effort required. Imbalances exist in the current system, and for group variations, there can be big budget implications not predicted. He also noted that Scientific Advice has a high costs and this was leading to national advice being taken instead.

Emmanuel Chantelot (EBE) spoke from the SME point of view. She called for a 'fees for service' concept where the fee charged was fair and commensurate for the service and a minimising of admin burden for SMEs, with no overall increase in costs to SMEs (as in her view they were already high even with incentives in place). While praising the support offered by the SME office, she also asked for clarity in the incentives offered (eg for type of company, type of product, type of procedure) and noted that the financial criteria used at present for SMEs were not useful due to the high funding they had to attract for research which could distort their financial position. She also suggested that the Commission should fund the aspects of the system that reflected 'public health responsibilities'.

On the veterinary side **Neil Craven** (IFAH) noted that animal health fees were 3% of the market, paid 5% of the fees but consumed 10% of the resources. The admin burdens carried by vet products tend to be for public health issues, so he felt that public funding should contribute to a lowering of fees in this sector and that perhaps veterinary products should be treated as 'orphans'. Fees should be proportionate to the service given and not a barrier to innovation. IFAH has no concerns about complexity of vet fees and in fact the worry about banding fees together is a loss of visibility on how proportionate the fees might be relative to the activity.

AESGP, for the non-prescription industry, feels that the fees for well established substances should be less.

Dagmar Roth-Behrndt agreed with the concept but said that only a fully tailor-made fee structure would ever be totally fair. Any generalisation would introduce some unfairness, but she did feel that EMA should not get fees for very well-established substances. In the current climate this discussion was also about how to save money and she suggested that there are too many subcommittees (35) and more virtual meetings should be conducted. A representative of the Finnish agency observed that parallel development of IT systems in individual member

states was a waste of money. **Thomas Lonngren** observed that 2011/12 would be difficult financially and savings would HAVE to be made, as any new fees would not come in until 2013/14.

The EMA Road Map

The final session of the day was chaired by **Thomas Lonngren** and was an overview of the outcome of the public consultation on the Road map. **Noel Wathion** (EMA) reviewed the objectives and priorities in the Roadmap for the next 5 years and summarised the 71 responses from the consultation. Overall the feedback had been very positive, with overall support for the objectives and priorities. There were comments that it should be clear that the 'public health' remit was in the context of medicines regulation. There were some comments on the EMA's independence from industry and isolated comments on conflict of interest and funding. Some respondents requested a broadening of the remit to cover devices and clinical trials. 'Transparency' should be a specific objective and a priority.

From an operational point of view there were comments on how the architecture of the system could be developed in the light of the E&Y report. Specific veterinary issues were raised – an emphasis on the 'one world, one health' concept and divergent views on the separation of the legal framework between human and veterinary medicines. There were suggestions that the EMA core business should include non-prescription, biosimilars and generics, herbals, alternative medicines and contrast agents and that EMA should focus on this core business which should not be affected by other proposed activities.

There was a desire for EMA to be a more active facilitator of interaction with partners and stakeholders of all kinds, but the comments on interaction with HTA bodies were more varied with a plea for this not to become a 4th hurdle in licensing.

In terms of the scientific review process there were divergent views on conditional MAs, a need for clarification of 'staggered' approval, and support for a focus on efficacy post-licensing (not just risks) as long as this does not mean requests for more data. Scientific advice was agreed to be important but the process needs to be improved, and ongoing dialogue is good but should be optional.

The needs of special populations including the elderly, women etc were highlighted and in particular high-quality pharmacoepidemiology with more emphasis on the prevention of medication errors. EMA needs to be an authoritative source of information and so should reinforce communication strategies and consider e-communications.

Dagmar Roth-Behrndt commented that her goal was to meet the needs of all EU patients – not just special patient groups, and the question of availability of treatment is fundamental. Innovative drugs are lower in number and so the whole research policy needs guidance and incentives. While EMA cannot play a real role in that or influence research policy, it can perhaps highlight the need for a new drug (an unmet medical need) and be more active in this regard in the long-term. In her view EMA has enough to do already without adding non-medicated devices and clinical trials to their remit! Her main concern is the conflict of interest between EMA

experts and industry. She accepted that experts are highly professional and she was not casting aspersions in that direction, but the *perception* is very important. If the public perceives a conflict it harms the agency. **Thomas Lonngren** stressed in reply to this that no scientific committee at EMA is chaired by anyone who has any relationship to the pharmaceutical industry.

Kent Woods (MHRA) gave support to the 'direction of travel' but warned of the importance of the use of terminology in regard to 'HTA'. This is used in ways that can lead to confusion. HTA is a scientific analysis using methods to assess cost effectiveness. However, decisions made on the *basis* of HTA (eg NICE) are very local and cannot be run at a supranational level. It needs to be clear that the common ground is measuring effectiveness but EMA looks at risk-benefit and HTA bodies at cost-effectiveness. EMA can make sure that irrelevant clinical studies are not done but must not tangle with decisions regarding costs and relative efficacy – attempts to measure the latter are fraught with difficulty.

Hubertus Cranz (AESGP) sees his sector as 'special' as evidenced by consumer demand for non-prescription drugs. The Risk element of risk/benefit should not be over-emphasised.

Wills Hughes Wilson (EUROPABIO) noted it was pleasing that the Road map considered Biotech as E&Y did not consult with any of their representative bodies. Such collaboration and inclusive thinking by EMA is to be welcomed and should continue to extend to patient organisations. The meeting ended with a reminder of the worry when EMA was first established and yet here we are celebrating its success!