IMPROVING EFFICIENCY WITHIN THE CURRENT REGULATORY SYSTEM: RESULTS OF THE ESCHER PROJECT

18 September 2014, Brussels, Belgium

INTRODUCTION

Reflections on the workshop discussing the findings of Escher report 'Improving the EU system for marketing authorisation; Learning from regulatory practice' and identifying key messages to take forward.

The reflections presented in this paper are intended to stimulate discussion, and do not represent the views of any single corporate entity or individual named in this document.

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BACKGROUND

Why the project was set up

This paper reflects discussion on the Escher report (released September 2014) entitled "Improving the EU system for the marketing authorisation of medicines – Learning from regulatory practice", which took place at a workshop in Brussels, Belgium.

Escher is the platform for regulatory innovation of TI Pharma, an independent research enabler based in the Netherlands.

The current project was financially supported by two umbrella organisations, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Association of the European Self-Medication Industry (AESGP). EFPIA represents the 33 European national pharmaceutical industry associations as well as 40 major companies. AESGP represents 2000 companies operating in the consumer healthcare sector in Europe, who are affiliated with AESGP directly or indirectly through the national associations. The AESGP constituency includes multinational companies as well as European small and medium sized enterprises (SMEs). Together, these two organisations represent a significant part of the global pharmaceutical industry that is active in Europe. AESGP highlighted that this research was particularly welcome due to the significant changes within the European Parliament in 2014; EFPIA have stated that good data, such as the Escher findings, are required to support proposals for changes in implementation of legislation.

The project described in the Escher report had two objectives: to provide a scientific analysis of topics in a number of key areas in the regulatory system; and to reflect on how the regulatory system can benefit from further research. The intention was not, however, to provide a holistic overview of the regulatory system. Emphasis was placed on what can be done better, rather than on what is already good, as Escher holds the view that the European regulatory system is already effective in performing its key functions. At the same time the project sees an opportunity to build on solid foundations and to make progress within the current system.

In a joint venture TOPRA and DIA brought together delegates and keynote speakers in Brussels (18 September, 2014) to discuss the findings and impact of the Escher report. This TOPRA/DIA workshop aimed to expand upon the report findings by means of these presentations, followed by interactive round-table discussion sessions further assessing the findings and proposals for future actions. The ultimate aim was for delegates to take the discussions, and where possible actions and proposals, back to their colleagues, employers and regulatory networks. This reflection paper also captures the discussions, themes and proposed actions from the workshop.

METHODOLOGY

Survey and Case Studies

The Escher report is built around a number of case studies, the selection of which was based on the experiences of pharmaceutical companies. To facilitate data collection a survey was sent to 47 large internationally operating pharmaceutical companies with a broad product portfolio (23 October 2013). For the design of the survey Escher extracted the areas from the EMA's 'human regulatory' website to compile a comprehensive list of regulatory topics. The resulting list covered 91 areas subdivided into seven categories: the pre-authorisation phase; the authorisation phase; the pharmacovigilance phase; other (non-pharmacovigilance) areas in the post-authorisation phase; types of products; disease areas; and other cross-cutting areas in the regulatory system (e.g. costs/funding, transparency, and harmonisation). To ensure that no important areas were missed, an open comment sections was included to capture 'other areas' thought to be in need of improvement within each of the aforementioned seven categories.

Escher asked respondents to grade each of these 91 areas on a four-point scale according to what they believed to be the need for improvement in that area. Initially, the Escher group summarised the comments made on each of the top ranked 12 areas; subsequently they searched for interconnecting themes amongst these 12 summaries. The survey concluded by asking respondents to submit up to five detailed examples of situations in which they experienced that the system could be improved.

SUMMARY OF RESULTS

Outlined in the Escher Report

Almost 70% of the companies that were invited to participate in the survey responded. This response generated a prioritised list of regulatory areas perceived to be in need of improvement:

1. Paediatric medicines
2. Variations (eg, type IA/IB/II/unforeseen [article 5]) variations
3. Other areas in the pharmacovigilance phase (this is a residual category)
4. Costs/funding of the system (including fees)
5. Article 46 paediatric studies
6. Transparency and accountability (e.g. confidentiality, transparency measures, release of trial data, data exclusivity)
7. Harmonisation (e.g. between Member States, between EU and other regions)
8. New regulatory pathways (e.g. adaptive licensing)
9. Conditional marketing authorisation
10. Accelerated assessment
11. Risk-management plans
12. Mutual recognition procedures

Respondents also mentioned the following general, but often interconnecting, problem areas:

Flexibility and (un)certainty

Responses called for balance between flexibility and certainty in how legislation is implemented. In some areas, respondents stressed the need for a more flexible application of legislation and requirements: for example requirements for paediatric studies; the way variations can be grouped; the use of the conditional marketing authorisation pathway; and timelines in the accelerated assessment procedure. However, in other areas respondents desired less flexibility and more predictability on the outcome, for instance by asking for more detailed guidance and more specific requirements. Calls for further guidance included the classification of variations, and risk-management plans. Furthermore, respondents thought that more specificity could be beneficial in the following areas: a better differentiation between fees for innovative products, well-established products and orphan products; and for when deciding when and how to disclose patient data.

Under-utilisation

Furthermore, respondents believed that some regulatory instruments are being underused, both by regulatory authorities and companies. For example the conditional marketing authorisation pathway and the accelerated assessment procedure, could both be used more often according to respondents' experiences.

Timelines
Respondents called for timelines to be improved: Assessment reports are not always provided in due time by the authorities (for example in the MRP, the accelerated approval procedure, and with respect to risk-management plans and variations); or conversely the requested timelines are considered inappropriate, e.g. with respect to the early submission of paediatric investigation plans.

Harmonisation
Harmonisation – or lack of it – was perceived to underlie much of the regulatory complexity and burden. Respondents believed that better alignment with the US is needed for paediatric investigation plans; the publication of clinical trial data; good manufacturing practice; and the introduction of 'adaptive' pathways. Respondents also assumed that harmonisation could be improved between Member State agencies, for example with regard to the classification and timelines of variations, the timelines of the MRP/DCP, the legal status of medicines and also dossier requirements.

Linkage with health technology assessment
Improvements were called for in the linkage between marketing authorisation and HTA/ reimbursement. Better alignment was particularly requested between approval and market access procedures in order for the conditional marketing authorisation procedure to become a success. This also has an impact on future adaptive licensing developments.

Interaction between companies and authorities
Respondents also believed that the interaction with agencies could be improved. They mentioned the need for more open discussions regarding requests for conditional marketing authorisation; more support during accelerated assessment procedures; and a dialogue with payers early in development. Some respondents also believed that the European Commission consultation process could be strengthened in order to involve companies in a more constructive way.

Five case studies were deemed to merit further analysis, both in the Escher report and at the subsequent TOPRA/DIA workshop:

- Experiences with the mutual recognition and decentralised procedures;
- Use of the conditional marketing authorisation pathway for oncology medicines;
- Timing of submission, development status, and outcomes of paediatric investigation plans;
- Pharmaceutical industry resources required for compliance with European pharmacovigilance requirements;
- The cost-effectiveness of post-authorisation safety studies for new active substances in Europe.

THE WORKSHOP AND CASE STUDY FINDINGS

PIP should be viewed as a development concept initially focused on the strategy of key elements, then expanding to cover scientific content

The TOPRA/DIA workshop investigated each of the five key areas by means of an Escher presentation of the data, followed by industry then regulator reflection. The day aimed to expand upon the report findings by means of these presentations, followed by interactive round-table discussion sessions further assessing the findings and proposals for future actions. The ultimate aim was for delegates to take the discussions, and where possible actions and proposals, back to their colleagues, employers and regulatory networks.

Paediatric Case Study Findings and Discussion

The Escher paediatric case study, presented by Jacoline Bouvy, a postdoctoral researcher at Utrecht University, concluded that there is redundancy in the current system with significant downstream modifications and termination of adult development (21%). Proposals to counter this redundancy included: a reduction in the level of detail in initial PIPs; differential Article 7 and Article 8 PIP requirements; and staggered approaches to PIP submissions. These changes were welcomed by industry, echoing the Escher view that although paediatric considerations have become integral to development, the PIP submissions are too early and based on limited data and discussions. Angelika Joos (Executive Director, Global Regulatory Policy, MSD, Europe) also highlighted that there is no mechanism in place to withdraw a PIP, even on termination of the adult development. It was proposed that the PIP should be viewed as a development concept, initially focused on the strategy of key elements, to be expanded to cover scientific content in conjunction with the current adult regulatory framework of development. The deadline for PIP submission following "completion of human pharmacokinetics studies in adults" was considered to be an inadequate criterion, as although human PK studies are typically conducted during Phase I, many such studies are now conducted at each of the other three stages of product development. Furthermore it was suggested to remove the "partial compliance check" in favour of a more administrative adult MAA validation step. Jordi Llinares Garcia (Head of Product development scientific support, EMA) stated that the EMA supported initiatives to evaluate implementation of the paediatric legislation and prompted significant audience muttering by reiterated the flexibility of the EMA with regards to current processes. Applicants were encouraged to engage in dialogue with PDCO and to provide justification to support later PIP submission dates. Delegates welcomed similar PIP analysis by Escher however with more recent cohorts and a better definition of "redundancy".

In the paediatric breakout group the focus was on how can we best balance the timing and content of PIP submissions (and discussions) while satisfying the mutual goal of complying with legal obligations and better fitting into the drug development process? The scope of the discussion looked only at improvements which do not require change to legislation:

1. Changes to the timing of initial PIP submissions (current flexibility in the legislation for PIP submission later than end of Phase I and current practices of companies)
2. Changes to the content of initial PIP submissions (level of detail; mandated content; optional content)
3. Desirability and design of a staggered approach (timing; mandated content & optional content)

CMAs are under-used: either not granted or requested enough or not used in the way that it was expected or intended to be.

Conditional Marketing Authorisation (CMA) Case Study Findings and Discussion

The Escher CMA case study concluded that the procedure is under-used: either not granted or requested enough; or not used in the way that it was expected or intended to be. Escher determined that of 11 oncology CMAs which were granted since 2006, only 2 proactive CMA requests were made, with the others viewed more as a rescue-option following issues with standard MAA procedures. In all granted CMAs the timelines for assessment were longer than conventional MAAs, largely due to additional oral explanations and SAG-O meetings. Sue Forda (Eli Lilly and Company) reflected on this and asked delegates if collectively we had met the spirit of "responsibility". She also shared an informal, but insightful analysis of the global mechanisms available to accelerated development and regulatory reviews which indicates that the USA was consistently quicker via all assessment methods. Of 21 conditional or accelerated EU MAs (2010–2013), 19 of these received US NDA/BLA approval; however, conversely of 77 products approved via "alternative" regulatory routes such as fast-track, breakthrough, priority and accelerated, only 57 of these were approved in the EU under any route. A call was made from industry for more frequent and focused dialogue with greater compatibility to use various and multiple alternative regulatory mechanisms. The European Commission CMAs data expanded on the Escher findings: 7 of the 11 oncology approved CMA products had fulfilled all specific obligations (SO) and hence converted to a full MA (on average taking 3 years); however, SOs generally were subject to a 10-month delay in completion compared to agreed timelines. Perhaps controversially, Olga Solomon asked if the delays in approvals were due to longer assessment times, or through time lost due to the wrong application type being chosen.

MRP/DCP – priority for improvement is the National Phase

The conditional MA discussion looked initially to the current challenges and perceived issues within current regulatory framework and identified. It was felt to be difficult to convince senior management to follow CMA, particularly with an increasing number of post-approval measures often with a mismatch between the EU versus US, coupled with too little experience and/or poor experiences. Furthermore Specific Obligations (SO) were often the limiting factor, with uncertainty over how the additional data for confirmation can be obtained, particularly in niche populations and to confirm benefit-risk in the same. CHMP preference and recommendation is for the SO study to start ahead of the CMA application with more integration into the product development plan, however, there remain challenges due to recruitment and ethical study conduct reasons. Non-integration with the HTA and regulatory bodies was recognised as an inherent challenge and the CMA brings additional pricing and reimbursement hurdles. Additionally, the lack of proactive and frequent dialogue and underlying communication mechanisms were a common discussion point. Comparisons were made to the FDA and in particular breakthrough designation which offers continued proactive dialogue with a dedicated senior scientific FDA team who will be assessing the product.

Recommendations from the CMA breakout session were for Escher to expand project scope to study additional CMA therapeutic areas (outside oncology) and also an analysis of the pricing and reimbursement implications following CMA product approval. Parties agreed that within the current regulatory framework CMA could move to be an instrument in adaptive licensing (perceived to be more flexible), when coupled with enhanced preplanning within product development plans. Delegates also requested a mechanism for enhanced, frequent dialogue with senior regulators at key product milestones, looking to the impact of the USA breakthrough status to provide some best-practice. However, it was recognised that these additional activities and interactions would likely increase resources and fees for all involved.

Experiences with MRP/DCP Case Study Findings and Discussion

Hans Ebbers summarised the Escher findings looking at the 2822 Mutual Recognition Procedures (MRP) and 7563 Decentralised Procedures (DCP). No significant differences in the relative frequency of referrals were observed for: biologicals vs. small molecules; pharmaceutical form; and anatomic therapeutic class main group. However despite the limited number of referrals, MRPs were four times more likely to reach referral compared to DCPs. Potential serious risks to public health (PSRPH) objections were predominantly related to the design and outcomes of the clinical studies rather than to quality related matters and procedural discussions on authorised indications, rarely lead to overall negative opinions. The survey identified considerable differences between Member States regarding the implementation of European decisions at national level and this requires further investigation. Peter Bachmann (CMDh Chair) eloquently stated the fundamental difference - the Centralised Procedure is a process; whereas the MRP/DCP is a process and a strategy which involves history, lack of harmonisation and company commercial input. It was hoped that the Process Improvement Working Party would bring further insight and enhancement to the MRP/DCP assessments. From an Industry perspective the main issue was deemed to be the lack of "mutual" actions within the mutual recognition and decentralised procedures, with many Member States questioning the findings of the Reference Member State. Christine Eising (Novartis Consumer Health SA) presented key performance indicators and findings from an AESGP coordinated study which concluded that significant delays in the national phase were experienced for both MRP & DCPs (MRP data range 60–280d and up to >1yr with DCPs of 70–180d, up to >1yr). The reasons were postulated as: final national artwork submission (mock-ups); Trade names, e.g. list of trade names not available for PIL text, which caused significant delays; and reimbursement/pricing approvals. The CMDh Task Force on Self-medication Project aimed to explore making the MRP/DCP more attractive and the resultant Best Practice Guide is deemed to be a good foundation which can be further improved.

Following interactive cross-party discussion the MRP/DCP session concluded that the priority for improvement is the National Phase, including translations. Increased transparency is required to identify causes and provide evidence for decision makers. To enable this, the possibility of a "CESP-like" electronic system was raised, for both information submission and importantly recording of timelines.

Pharmacovigilance (PV) Case Study Findings an Discussion

One year after implementation of the new PV legislation, 95% of participating companies reported an increase in total workload, particularly relating to the Pharmacovigilance System Master File (PSMF), the New PBRER format and Risk Management Plans (RMPs). Escher recommended careful future monitoring of company activities and the impact on workload of the new legislation. The second element of the Escher PV case study assessed the cost-effectiveness of post-authorisation safety studies (PASSs) that were requested at market entry for centrally approved new active substances in 2007: 22 of 47 NAS MAs had at least one PASS requested; 52% of the requested PASSs resulted in change to the product's SmPC. Escher concluded that PASSs should not be the main source of post-marketing safety information, and there are substantial costs involved (€6.5 million to €18.0 million per additional safety-related SmPC change). They recommended that methods to increase the efficiency of PASSs, as well as the societal value of PV activities should be explored.

The PV Case Study seemed to have more of a united consensus from Industry (David Jefferys; Eisai Europe) and Regulators (Fergus Sweeney; EMA PV Division) with recognition of the historical PASS issues and increasing resource burden, but both parties keen to work together to enhance dialogue and implement further improvements towards enhanced public health. It was also noted that there are now appropriate PV templates and tools, but further improvements will be implemented over the next 24 months. The key to gaining momentum was felt to be a different perspective of the current legislation by both industry and agencies, and to view PV as a continuum from product development into the MA lifecycle activities. Fergus Sweeney stressed that it is not necessarily the safety of the product which needs to be investigated and improved, but rather the improved or consistent use of the product as the burden of adverse events on society remains high. However, the PASS may no longer be the most suitable tool for this and there were calls for Escher to repeat the study looking at more recent implemented post-approval measures.

During the breakout session the group discussed how to quantify public health impact. It was felt that consensus was needed on the methodology before initiating evaluation. In terms of the Drug Utilisation Study (DUS), the question was posed on how to obtain pan-EU data and who should be obtaining it? There was also a question over the data which was already available in companies and how should Marketing Authorisation Holders monitor risk minimisation measures? Delegates also saw the merits in considering EMA audit of actions taken by companies, in terms of what worked and what did not. The general theme was of the, increasingly demanding, public needing to trust the data with this trust coming via intermediaries such as GPs, social media, etc. However, where do the public fit in on determination of acceptable safety? Future developments were proposed to consider the pharmacovigilance implications of personalised medicine, adaptive licensing and potentially more PASSs.

THEMES IDENTIFIED

Removing unnecessary burdens

Emergent as the themes for the day and shared by both industry and agencies were:

- dialogue and discussion
- transparency
- cooperation

One recurrent theme within the survey comments was that the system results in an unnecessary burden on companies, in light of a perceived limited contribution to public health. Moreover, respondents noted that this burden is increasing. In many instances, respondents specified this general concern and highlighted two effects: costs for companies, and the effects on public health. These themes were echoed during the TOPRA/DIA workshops

Each case-study repeated the need for on-going cross-functional discussions, looking not only within the existing regulatory frameworks, but also considering the wider R&D needs, the commercial focus and the financial implications within an increasingly global pharmaceutical climate. Delegates were encouraged to think positively on the current EU regulatory framework and to recognise its strengths; by doing so it is therefore possible to work within the framework to improve particular elements, rather than generating new legislation.

CONCLUSION

Bridging the gap

Escher identified several cases where a gap seems to exist between initial objectives and real-world effects of regulatory instruments.

The conditional marketing authorisation route is meant to provide early access to medicines, provided that benefits to public health outweigh the risks inherent in the requirement for additional data. However, the case study on conditional marketing authorisation (CMA) found that, in practice, the use of CMA for oncology medicines is often perceived as a 'rescue' option by regulators and companies, rather than as a pathway to grant early authorisation to medicines that show promising effects. Furthermore, total time needed for the CMA was longer than for standard market authorisation and applicants voiced concerns about subsequent HTA procedures and reimbursement decisions.

The annual number of periodic safety update reports (PSURs) submitted to regulatory authorities has decreased, as was intended, after the introduction of the new pharmacovigilance legislation. However the impact of the periodic benefit-risk evaluation report (PBRER) was not taken into consideration. The survey of pharmaceutical companies indicated that the number of hours spent by companies on preparing and submitting one report (ie, a PSUR in 2011 and a PBRER in 2013) has increased by about 60% on average, offsetting the foreseen change to simplified requirements. Although these are self-reported data from companies, and the legislation is relatively recent, these data indicate that a gap between the original impact assessment and actual practice might exist.

For the medicines included in the study on the cost-effectiveness of newly requested post-authorisation safety studies (PASSs), 52% of all requested PASSs resulted in a change to the SmPC. This accounts for 9.5% of all post-marketing safety variations for these medicines and led to an incremental cost-effectiveness ratio of €6.5 million to €18.0 million per additional SmPC change. Whether or not this substantial investment was expected by the legislator, or effectively converted into societal value, is unclear at the moment.

RECOMMENDATIONS & KEY POINTS

Three main messages

The Escher report highlighted three main messages and high-level recommendations namely:

1. Discrepancies between the initial objectives of legislation and the effects of regulatory instruments in actual practice should be addressed;
2. Learning during implementation of legislation can make regulatory instruments more effective;
3. Regulatory science studies can help to assess real-world outcomes of the system and to identify opportunities for improvement.

The subsequent TOPRA/DIA workshop identified that both industry and agencies recognised a benefit from enhanced dialogue and discussion, coupled with more transparency and cooperation. There was also a call for further Escher analysis, particularly allowing more current data cohorts to be gathered and the impact of recent legislative changes to be analysed.

Presentations from the interactive workshop are also available from the DIA website. Further information and a copy of the full Escher Report can be found online: http://escher.tipharma.com