Viewpoint

Future of the European Union regulatory network in the context of the uptake of new medicines

Joëlle M. Hoebert,¹ Alar Irs,^{2,3} Aukje K. Mantel-Teeuwisse¹ & Hubert G. M. Leufkens^{1,4}

¹Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands, ²Division of Clinical Pharmacology, University of Tartu, Tartu, Estonia, ³Estonian State Agency of Medicines, Tartu, Estonia and ⁴Medicines Evaluation Board, Utrecht, the Netherlands

With the European economy in the midst of the deepest recession since the 1930s and countries struggling to weigh up national and community interests, one may overlook accomplishments made in other areas of the European co-operation. Since the start of the European Union (EU) medicines approval system in 1995, the European regulatory environment has faced many challenges, but also made ample progress. Significant achievements are seen in unifying and improving regulatory practices, streamlining the way of bringing medicinal products to the clinic, thereby improving how new medicines become available to patients in the EU in a harmonized and evidence-based way [1, 2]. With the European Medicines Agency (EMA) co-ordinating a wide array of regulatory procedures, EU member states are contributing in many ways to the regulatory network, e.g. as rapporteur of individual dossiers, by work sharing, guideline development and cross learning. Recently, both the EMA and the Heads of Medicines Agencies (HMA) published their future strategy papers (i.e. European Medicines Agency Road Map to 2015: The Agency's contribution to Science, Medicines, Health and the HMA; A Strategy for the Heads of Medicines Agencies 2011–2015), aiming at strengthening the European regulatory network and its contribution to patients' access to medicinal products, public health and innovation [3, 4].

While the crucial role of the EMA as the engine of the European pharmaceutical regulatory system is evident, the roles of national competent authorities remain equally important. Apart from the EMA, the EU regulatory network consists of around 31 national competent authorities who are responsible for an array of regulatory tasks related to human medicinal products in their national systems [5]. They also provide scientific footing of the system via the membership of the EMA scientific committees, such as the EMA Committee for Medicinal Products for Human Use (CHMP). The CHMP is mainly

composed of the members nominated by the 27 EU member states and the EEA-EFTA states Iceland and Norway, who heavily rely on support from their national agencies with respect to the reviewing and assessment of the claims in the dossiers submitted by industry and the benefit-risk assessment related to a product application [6]. The system of rapporteurs is seen as the backbone of the EU Centralized Procedure, but there are concerns about the large variation among EU member states regarding their individual contributions in terms of the number of (co-)rapporteur roles. Both previously mentioned strategy reports underpin the importance of a re-balance between member states in work-sharing and showing leadership in Centralized Procedures.

Variability in uptake of new medicines and regulatory roles across European member states

We evaluated variation in rapporteur contributions to the EU regulatory network between EU member states in light of the level of availability and market uptake of new medicines in the same EU countries. Previous research has proposed various explanations for this variation ranging from lack of resources and expertise to intentional national policies [7, 8]. We approached this issue from another angle and present data on how new medicinal products approved in 2004 (Table 1) were adopted by national clinical practices as measured through IMS data. IMS collects pharmaceutical consumption data from a mixed sample of wholesalers, hospitals and/or dispensing outlets such as pharmacies and drug stores [9]. In this analysis, the uptake of all new medicines centrally approved in 2004 was followed in the subsequent 5 years (2004–2009). Uptake of each new medicine with a European license granted in 2004 was measured by volume (i.e. standardized units) and

Table 1

Centrally approved medicines in the EU in 2004 ($n = 24$)*

International non-proprietary name	Brand name	Indication	WHO ATC code	Most important usage setting
Abacavir/lamivudine	Kivexa®	HIV infections	J05AR02	Outpatient
Anagrelide	Xagrid®	Essential thrombocythaemia	L01XX35	Outpatient
Aripiprazole	Abilify®	Schizophrenia/bipolar disorder	N05AX12	Outpatient
Atazanavir	Reyataz®	HIV infections	J05AE08	Outpatient
Bivalirudin	Angiox®	Angioplasty, acute coronary syndrome	B01AE06	Inpatient
Bortezomib	Velcade®	Multiple myeloma	L01XX32	Inpatient
Cetuximab	Erbix®	Head and neck and colorectal neoplasms	L01XC06	Inpatient
Cinacalcet	Mimpara®	Hyperparathyroidism, parathyroid neoplasms	H05BX01	Outpatient
Cladribine	Litak®	Leukaemia, hairy cell	L01BB04	Inpatient
Darifenacin hydrobromide	Emselex®	Urinary incontinence	G04BD10	Outpatient
Duloxetine hydrochloride	Cymbalta®, Xeristar®	Diabetic neuropathies, depressive disorder	N06AX21	Outpatient
Fibrinogen/thrombin	TachoSil®	Surgical haemostasis	B02BC30	Inpatient
Fosamprenavir calcium	Telzir®	HIV infections	J05AE07	Outpatient
Fulvestrant	Faslodex®	Breast neoplasms	L02BA03	Outpatient
Ibandronic acid	Bondenza®, Bonviva®	Post-menopausal osteoporosis	M05BA06	Outpatient
Ibritumomab tiuxetan	Zevalin®	Follicular lymphoma	V10XX02	Inpatient
Insulin detemir	Levemir®	Diabetes mellitus	A10AE05	Outpatient
Insulin glulisine	Apidra®	Diabetes mellitus	A10AB06	Outpatient
Mitotane	Lysodren®	Adrenal cortex neoplasms	L01XX23	Outpatient
Octocog alfa	Advate®	Haemophilia A	B02BD02	Inpatient
Oxybutynin	Kentera®	Urge urinary incontinence	G04BD04	Outpatient
Pemetrexed	Alimta®	Non-small cell lung carcinoma	L01BA04	Inpatient
Pregabalin	Lyrica®	Anxiety disorders, epilepsy, neuralgia	N03AX16	Outpatient
Strontium ranelate	Dukoral®	Osteoporosis, post-menopausal	M05BX03	Outpatient

*A total of 29 medicines obtained approval through the Centralized Procedure. Medicines were excluded if approval in 2004 concerned extension of the indication or a new orphan designation ($n = 2$), if the medicine had been on the European market for many years and the current utilization of the medicine had been influenced by many other factors ($n = 1$) or because their usage was so low that they could not be divided into quartiles ($n = 2$).

expressed per 1000 inhabitants per year. Population statistics were obtained from the website of the United Nations, Department of Economic and Social Affairs for the years 2006 and 2009 [10].

In Figure 1, the actual availability in 2005 and 2009 of these medicines is shown for each individual EU member state. This figure demonstrates the variation in actual availability of these medicines between the individual EU countries, a strong factor behind variation in the uptake of these new medicines. In some countries like Portugal and the Baltic States over 40% of the studied products were not available at all, even 5 years after the moment of a formal EU market authorization.

As a next step, for each product the volumes consumed in 2009 across all countries were divided into four equal parts (quartiles). Each EU member state was ranked according to their consumption into a quartile. A member state was ranked in quartile one when the market uptake of the new medicine was within the lowest 25% of the data, member states were ranked in quartile two when the market uptake of the new medicine was above the cut off lowest 25% of data, but beneath the median (second quartile), in quartile three if market uptake of the new medicine was above the median but below the cut off

highest 25% of data and in quartile four when the market uptake of the new medicine was above this point. Finally, the average ranking of quartiles per EU member state for all medicinal products was calculated and crossed against the number taking the lead in a Centralized Procedure as a (co-)rapporteur between 2004 and 2009 (Figure 2).

Figure 2 shows the wide variability between EU member states in contributions to the Centralized Procedure as rapporteur vs. the level of uptake of new medicines. Countries in the upper right quadrant ($n = 4$) show a high uptake of medicines and frequent contributions as rapporteur for products following the Centralized Procedure. The contribution as rapporteur of Denmark, Spain and France is below those member states that contribute most, but they show the highest uptake of new medicines in Europe. In the upper left quadrant extending almost to the middle, there are countries in which the uptake of new medicines appears quite high despite a low or moderate contribution as rapporteur. The lower left quadrant includes countries, predominately newer EU member states, with a relatively low uptake of new medicines and small numbers of contributions as rapporteur compared with other EU member states. Finally, Portugal is a

Figure 1

Availability (in %) of all centrally approved medicines (2004) in 2005 and 2009. Countries are ordered (increasing order) on the x axis according to their number of rapporteur roles between 2004 and 2009. Data used for this study were obtained for all 25 EU member states (per 01/05/2004), except for the Mediterranean islands of Malta and Cyprus for which IMS had no data. Within countries, IMS uses the same method but the methodology used varies between countries and depends on the nature of the pharmaceutical supply systems. IMS collects data in over a hundred countries world-wide. Volume data were expressed in standard units (SU). This is a measure used by IMS derived from the number of doses. It is measured differently depending on the formulation of the medicine. Usually one SU equals one capsule, one tablet, one prefilled syringe, one dose of inhaled medicine or 5 ml of an oral suspension etc. If IMS does not collect data from all suppliers in a country they project the sample of a particular distribution channel to the national level. A medicine was defined as available if consumption in that year was ≥ 100 SU. The years 2005 and 2009 were chosen to see the differences between fast and slow uptakers. Countries are ordered along the x axis according to their contribution to the EU regulatory system with countries on the left hand side contributing to a lesser extent than countries on the right hand side. *For certain countries only retail data and no hospital data were available from IMS. These are marked with an asterisk. In these countries availability was determined for medicines used in the outpatient setting only (see Table 1). □, 2005; ■, 2009

Figure 2

Average uptake in the year 2009 of all centrally approved medicines in 2004 and the number of rapporteur roles in 2004–2009 of each member state. *For certain countries only retail data and no hospital data were available from IMS. These are marked with an asterisk. Filled in markers ($n = 8$) refer to countries that joined the EU per 1 May 2004, the open markers ($n = 15$) refer to older EU member states

significant outlier with a contribution that can be ranked as moderate but with a limited uptake of new medicines; most likely due to the limited availability of medicines (see Figure 1). A similar result was found when analyzing data for 2006 instead of 2009, when assessing medicines used in the in- or out-patient setting only, but also when limiting to or excluding the expensive (oncology) medicines.

Understanding such variability between EU member states and its implications

This study shows that innovative medicines are not equally available for all citizens in the EU in a timely and equitable manner. The discrepancy in the uptake of medicines between EU member states seems to reflect to a certain degree the economic situation and resource possibilities of these countries. Our analysis confirms a correlation between the market uptake of new medicines and key macroeconomic variables such as gross domestic product and government expenditures, as also demonstrated by others studies [11–13]. Although barriers to market authorization of medicinal products have virtually diminished across Europe, regulatory practices affecting actual prescribing and usage (i.e. reimbursement and pricing, formulary policies, promotion regulation) show large variation, significantly influencing the availability and uptake of new medicines into clinical practice. This is also an area where the pharmaceutical industry which benefits significantly from a centralized and harmonized regulatory system, but who is not always willing to market an approved EU product in a low-resourced market, should show more and sustained responsibility.

As stated by the EMA itself, a critical factor for the Agency's success has been the provision of high quality scientific resources for the evaluation and supervision of medicinal products by individual EU member states. Pivotal for achieving this is the strengthening of the co-operation of all individual member states. Our analysis stresses that the required input of high quality specialist expertise provided by the member states to the EU regulatory system is not proportionally shared. There may be many factors contributing to this variability, ranging from constraints of resources, limited (scientific) expertise and/or experience at the national competent authorities that is needed to be appointed as rapporteur or the lack of interest in contributing to the assessment of medicinal products that at the end of the day are not used anyhow by the citizens of the concerned individual member state. The variability in rapporteurships does not seem to relate to the size of the country or the size of the national competent authority. Sweden or the Netherlands do not appear as extremely big countries or national competent authori-

ties but contribute in a sustained fashion. Another explanation could be that it is more difficult to participate actively in the CHMP for newer EU member states as the older EU member states are more settled, resulting in more rapporteurships based on previous experiences or involvement during the clinical development phase (e.g. scientific advice) or because they have the best available expertise in the EU on the relevant scientific area (as requested in the 'CHMP rules of procedure') [14]. In terms of solutions it is important to build further in the European regulatory network on sustainable resources, expertise and regulatory science, but also the political will of member states to invest in contributing to the assessment of new products remains a critical factor.

It should be kept in mind, however, that this analysis only includes the contribution of EU member states to the centralized system in terms of (co-)rapporteurships. There are various other possibilities for countries to be actively involved in the EU regulatory system, such as acting as reference member states in the Mutual Recognition Procedures or the Decentralized Procedures or being involved in paediatric deferrals. Contributions to these EU procedures might be, for some countries like Estonia or Slovakia, more interesting as much of these procedures relate to generic products with high consumption rates in these countries. Statistics of the HMA and EMA show a prominent role of these countries in these EU procedures. Estonia, for example, is often involved in the evaluation of the paediatric investigation plans.

Furthermore, it should be noted that the peer review process and work sharing projects also contribute to the learning process, a process that is even more established through the twinning programme of the EMA [15]. New Member States will achieve a progressive gain of experience and confidence and will be keen on being more involved. Even if Member States do not directly take (co-)rapporteurship their contribution to the discussions is considered as important and useful [16].

Every sustainable system of collaboration between countries depends heavily on a certain level of proportionality, whether it is economics or the regulation of medicinal products. Bringing new medicinal products to the European market in terms of licensing has been harmonized over the last decades in a significant way. However, actual availability and uptake of these products in EU member states still varies strongly. This is not a new finding and is inherent to the fact that EU member states remain responsible for the way they build and fund their national health care systems [7, 8, 13]. However, when variability in contributions to the pharmaceutical regulatory system goes hand in hand with variability of actual prescribing and usage, as reflected by the countries (the predominantly newer EU member states) located in the lower left quadrant of Figure 2, there is ample reason for concern about sustainability of the regulatory network that depends heavily on European partnership and community respon-

sibility. Such responsibility is likely to blossom better in an environment where work sharing in bringing new pharmaceutical products to the market pays off in also safeguarding patients' interest on a national level. Obviously, this is not the case.

Authors' contributions

JH was responsible for the conduct of the study including cleaning and analyzing the data and for the drafting and revising of the article (she is the guarantor). AMT supervised study conduct, data analysis and drafting of the manuscript. HL and AI had the idea for the article and were responsible for the regulatory perspective and important intellectual content. All authors were responsible for critically reviewing earlier versions of the manuscript and providing final approval for submission.

Competing Interests

There are no competing interests to declare.

The department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, has received unrestricted research funding from the Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (<http://www.tipharma.nl>, includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board, the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer, and others). AI is Lecturer in clinical pharmacology, Deputy Director General of the Estonian State Agency and a member of the CHMP of the EMA. HL is Professor in Pharmaceutical Sciences, Chair of Dutch Medicines Evaluation Board (MEB) and co-opted member of the CHMP of the EMA. Disclaimer: the views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or any other regulatory agency, or one of its committees or working parties.

Pharmaceutical sales data used in this paper were kindly provided by Peter Stephens (IMS Health).

REFERENCES

- 1 Healy EM, Kaitin KI. The European Agency for the evaluation of medicinal products' centralized procedure for product approval: current status. *Drug Inf J* 1999; 33: 969–78.
- 2 European Medicines Agency. What we do. 1995–2010. 2012. Available at <http://www.ema.europa.eu/ema/>
- 3 European Medicines Agency. The European Medicines Agency Road Map to 2015. London: The Agency's Contribution to Science, Medicines, Health, 2010.
- 4 Heads of Medicines Agencies. A strategy for the heads of medicines agencies, 2011–15; 2010.
- 5 Heads of Medicines Agencies. Contact points for HMA and HMA-WGs: list of contacts. 2008. Available at http://www.hma.eu/fileadmin/dateien/HMA_joint/Contact_HMA_and_HMA_WGs.pdf (last accessed 24 March 2011).
- 6 European Medicines Agency. CHMP: overview. 1995–2010. 2012. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&murl=menus/about_us/about_us.jsp&mid=WCOB01ac0580028c7a (last accessed 30 October 2012).
- 7 Nolte E, Newbould J, Conklin A. International variation in the usage of medicines. A review of the literature. RAND Corporation 2010.
- 8 Richards M. Extent and causes of international variations in drug usage. Secretary State of Health; 2010.
- 9 Buysse IM. Impact of the Economic Recession on the Pharmaceutical Sector. Utrecht: Utrecht University, WHO CC for Pharmacoepidemiology & Pharmaceutical Policy Analysis, 2010.
- 10 United Nations, Department of Economic and Social Affairs. World population prospects: the 2008 revision population database. 11 Mar 2009. Available at http://esa.un.org/unpd/wpp/unpp/panel_population.htm (last accessed 19 November 2010).
- 11 Cohen J, Faden L, Predaris S, Young B. Patient access to pharmaceuticals: an international comparison. *Eur J Health Econ* 2007; 8: 253–66.
- 12 McCabe C, Bergmann L, Bosanquet N, Ellis M, Enzmann H, von Euler M, Jönsson B, Kallen KJ, Newling D, Nüssler V, Paschen B, de Wilde R, Wilking N, Teale C, Zwierzina H. Market and patient access to new oncology products in Europe: a current, multidisciplinary perspective. *Ann Oncol* 2009; 20: 403–12.
- 13 Miltenburger C, Günther OH, Justo N, Karampampa K, Texier-Richard B, Schweikert B. A Survey of Barriers to Treatment Access in Rheumatoid Arthritis in France, Germany, Italy, Spain and the UK. October 2009. Available at http://www.comparatorreports.se/RA%20Barrier%20Report_FINAL_050110.pdf (last accessed 20 September 2010).
- 14 European Medicines Agency. CHMP rules of procedure. 2007. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004628.pdf (last accessed 24 March 2011).
- 15 European Medicines Agency. Strategy for regulatory and scientific training within the EU regulatory network. 2012. Available at http://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/Office_Training/2011_05_OTSG_Strategy.pdf (last accessed 14 August 2012).

16 European Commission. Evaluation of the European Medicines Agency. Final Report. 2012. Available at http://ec.europa.eu/health/files/pharmacos/news/emea_final_report_vfrev2.pdf (last accessed 14 August 2012)

CORRESPONDENCE

Mrs Aukje K. Mantel-Teeuwisse PharmD PhD, Utrecht Institute for Pharmaceutical Sciences (UIPS) Division of Pharmacoepidemiology and Clinical Pharmacology P.O. Box 80082 3508 TB Utrecht, the Netherlands.
Tel.: +31 30 253 7324
Fax: +31 30 253 9166
Email: a.k.mantel@uu.nl

RECEIVED

9 April 2012

ACCEPTED

23 September 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

8 October 2012