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Expert Review of Pharmacoeconomics & Outcomes Research

ISSN: 1473-7167 (Print) 1744-8379 (Online) Journal homepage: informahealthcare.com/journals/ierp20

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To cite this article: Brian Godman, Ken Paterson, Rickard E Malmström, Gisbert Selke, Jean-Paul Fagot & Jana Mrak (2012) Improving the managed entry of new medicines: sharing experiences across Europe, Expert Review of Pharmacoeconomics & Outcomes Research, 12:4, 439-441, DOI: 10.1586/erp.12.44

To link to this article: https://doi.org/10.1586/erp.12.44

Published online: 09 Jan 2014.

EXPERT REVIEWS

Improving the managed entry of new medicines: sharing experiences across Europe

Expert Rev. Pharmacoecon. Outcomes Res. 12(4), 439–441 (2012)

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The Managed Introduction of New Medicines
Ljubljana, Slovenia, 19–21 March 2012

The 3-day course on the managed entry of new medicines was run by the Piperska group, which is a pan-European group striving to enhance the health of the public as a whole and the individual patient through exchanging ideas and research around the rational use of drugs. Participants included health authority and health insurance personnel, academics and those from commercial organizations. The principal aim of the conference was to bring together people to discuss ways to improve the managed entry of new drugs.

Keywords: demand-side measures • horizon scanning • HTA • indicators • managed entry • pharmaceuticals

Pharmaceutical expenditure is a concern with increases driven by factors including ageing populations, rising patient expectations and new, expensive drugs [1,2]. Among these, new expensive products are the greatest challenge to equitable and comprehensive healthcare [2]. Scrutiny over the value of new drugs has enhanced – for example prices of US$25,000 per month for new drugs for cystic fibrosis patients [3], with only approximately 10% of new drugs seen as truly innovative [4,5].

This has resulted in new models. The three pillars include prelaunch activities incorporating horizon scanning and budget forecasting, critical drug evaluation perilaunch (including risk-sharing), and postlaunch activities, including patient registries and monitoring of prescribing practices against agreed guidance [4]. These pillars formed the basis of the 3-day course.

Course proceedings (key highlights)

Speakers came from across Europe, the WHO and the European Federation of Pharmaceutical Industries and Associations. The course was opened by Samo Fakin (director of the Health Insurance Institute of Slovenia, Ljubljana, Slovenia), followed by presentations on clinical pharmacology and pharmacoepidemiology. Nina Sautenkova (program manager of Health Technologies and Pharmaceuticals, WHO Regional Office for Europe) subsequently discussed the need for the rational use of medicines, emphasizing that the main principles have stayed unchanged since the 1985 WHO conference held in Nairobi (Kenya), confirmed by the International Conference for Improving Use of Medicines in 2011. These include considerations regarding rational prescribing, dispensing and the compliant use of medicines, which have to be effective and of acceptable quality and safety. Multiple interventions are typically needed to enhance the rational use of medicines, which are not limited to rational prescribing. It is very important that measures include education of health professionals and the public, regulation of the promotion of medicines in line with WHO ethical criteria and the monitoring of all measures introduced.

Gisbert Selke (Wissenschaftliches Institut der AOK, Berlin, Germany) endorsed the need to assess the true value of new drugs with escalating costs. This has resulted in early assessments of their additional benefit in Germany against current standards. Assessments are now divided into five groups: substantial additional benefit; considerable additional benefit; small additional benefit; unquantifiable additional benefit and no additional benefit (similar to the classification in France [6]); there is also a sixth group: less benefit than current therapy. If there is a

 10.1586/ERP.12.44 ISSN 1473-7167

perceived lack of additional benefit with the new drug, it is rapidly assigned to a pre-existing reference group for pricing purposes. Otherwise, price negotiations take place between the individual Sickness Funds and the manufacturer. The intention is to base these negotiations on current prices paid among 15 European countries for the new drug, including any current discounts.

Rickard Malmström and Björn Wettermark (Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden and Stockholm County Council, Stockholm, Sweden, respectively) discussed the current model in Stockholm (Sweden) [4,7], which incorporates horizon scanning and forecasting activities up to 2 years with critical drug evaluation 3–6 months before launch. This includes clear guidelines on criteria for use, information and education campaigns, registries to determine whether drug use is according to guidelines, and monitoring of relevant effects and adverse events. New oral anticoagulants are an example, as they show promise in stroke prevention and atrial fibrillation [8,9]. However, concerns exist in older adults, particularly those with poor renal function [8,9], since there is no known antidote and consequently there is the potential for excessive bleeding that is difficult to handle [9,10]. There are also concerns with adherence, as currently there is no way of measuring this [8]. In addition, no standard method to evaluate the coagulation status of patients, coupled with no antidote to excessive bleeding, also suggests potential problems with surgical interventions, particularly emergency surgery. These concerns led to a comprehensive campaign in Stockholm to make physicians aware of the issues. These are being explored further by Piperska members to provide future direction.

Roberta Joppi (Institute for Pharmacological Research 'Mario Negri,' Milan, Italy, and Pharmaceutical Drug Department, Azienda Sanitaria Locale of Verona, Verona, Italy) discussed the experiences in Italy [4,11]. Activities include producing periodical lists of emerging drugs 12–36 months before authorization, evaluating their potential clinical impact and cost–effectiveness, giving well-timed information to improve regulatory decisions and identifying further research fields. Reports approximately 12 months before marketing authorization include clinical need and burden of disease data, a summary of efficacy/safety data from available clinical trials, clinical critical assessment, social/economic impact and ongoing trial(s) for the same or other indication(s).

Silvio Garattini (director of the Institute for Pharmacological Research 'Mario Negri', Milan, Italy) started day 2 reviewing the bias in clinical trials, including the excessive use of placebo as a comparator. There are also concerns with noninferiority trials, particularly if the rationale is to extend choice; for example, superiority should be tested in subsets not responding to current therapies. There is also concern with using surrogate end points and translating these into beneficial outcomes, particularly when premium prices are requested. Modeling may help; however, this may be difficult if the relationship between surrogates and outcomes is unproven. Finally, there can be a bias in articles published as demonstrated by the selective serotonin reuptake inhibitors [12]. Payers must be aware of this when reviewing submissions.

Ken Paterson (Scottish Medicines Consortium, Glasgow, UK) reviewed the top ten issues of pharmaceutical companies, which need to be taken into account when submitting health economic (HE) evaluations to the Scottish Medicines Consortium in Scotland. These include the choice of comparator where a single comparator is better than no comparator. Scotland takes a pragmatic view in recognition of the fact that it is not the largest market. Consequently, the methodology for indirect comparators must be robust. Alongside this, the dose of the comparator is important. Doubtful use of the clinical data in the HE submission, including poor correlation between HE and clinical data sets, concerns with the results of any extrapolation if not fully supported, overoptimistic modeling assumptions, failure to use cost/quality-adjusted life years unless justified, inadequate sensitivity analysis as well as undue complexity/lack of clarity in the submission are concerns. Linked to this, the length of the submission, use of questionable utility values and how these were derived (particularly if unjustifiably magnifying the benefits of new medicines), poor cost–effectiveness in the submission, and questionable generalizability of the data to Scotland are also concerns.

Key factors for instigating successful risk-sharing arrangements include: the objectives and scope of the schemes need to be explicit; translational science suggests good effectiveness; health gain can be determined within a relatively short timeframe; schemes have appreciably lower costs, having factored in all administration costs; and patient compliance is not a major issue [13].

Postlaunch activities (day 3) included demand-side measures, registries and indicators. Examples of education included the Stockholm Wise List with approximately 200 drugs for routine use in both primary and hospital outpatient care [14]. High adherence rates are achieved through multiple factors, including trust in the physicians compiling the list, strict selection criteria, regular monitoring of adherence and financial incentives [14]. The driving force is a strong drugs and therapeutics committee. However, high adherence takes time to achieve and requires a comprehensive communication strategy to healthcare professionals and patients [14].

Jean-Paul Fagot (Département des études sur les pathologies et les patients, Direction de la Stratégie, des Etudes et des Statistiques, Caisse Nationale d'Assurance Maladie des Travailleurs Salariés, Paris, France) reviewed available administrative databases in France: Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIRAM) with linkage to Programme de Médicalisation des Systèmes d'Information (PMSI), the national hospital discharge database. SNIRAM contains data on the whole French population from 2006 including physicians/professionals involved in care, reimbursed medicines, procedures, biological tests and medical devices. There is also a prospective database of 1 in 100 random sample of individuals with follow-up from January 2003, allowing multiple crossanalyses with linkage to ambulatory-hospital data. These databases were used to review benfluorex and the risk of valvular cardiopathy, as well as the risk of bladder cancer with pioglitazone.

Any developed indicators must have content validity, face validity (relevance, credibility and acceptability), concurrent validity (compared with gold standard), construct validity (theoretical construct of quality), and predictive value to be of use. They are

increasingly used to improve the quality of prescribing including targets and 'pay-for-performance'/'pay-for-results' (P4P) schemes. Examples include the voluntary P4P scheme in France. Quality targets include those for vaccinations and chronic diseases. Efficiency targets to increase prescribing of generics include generic versus all antibiotics (target = 90%), generic versus all proton pump inhibitors (target = 85%), generic versus all statins (target = 70%), generic versus all antidepressants (target = 80%) and generic versus all antihypertensives (target = 65%). There is a potential total bonus of €9100/general practitioner, with a maximum of €2800 for efficient prescribing. Early analysis of the pilot P4P program (Contrat d'Amélioration des Pratiques Individuelles) indicated a positive influence on physician behavior. Consequently, this has now been extended to all general practitioners in France.

Indicators in Germany include the Quality Indicator System for Ambulatory Care indicators developed by the Institute for Applied Quality Improvement and Research in Health Care GmbH and the Allgemeine Ortskrankenkassen Sickness Fund [101]. Efficiency indicators include a percentage of scripts as generics, a percentage included in reference price classes and a percentage of me-too scripts, particularly those with high-potential savings. Quality indicators include a percentage of scripts in negotiated regional formularies, the number of patients with concomitant use of drugs prone to undesired interactions, the share of patients with high use (>30 defined daily dose/quarter) of anxiolytics, sedatives and hypnotics, the share of patients with high use (>75 defined daily dose/quarter) of NSAIDs, the share of older patients (≥65 years) with polypharmacy (>5 different agents per quarter), and the share of older patients receiving potentially inadequate medication – derived using the Delphi method (government funded) and including 83 drugs from 18 areas (mainly psychoactive substances, NSAIDs/analgesics and those for the heart/circulation).

Slovenia has just started introducing quality indicators. The first one is aimed at improving prescribing in ambulatory care and is titled "Quality prescribing in general practice". These include polypharmacy: patients prescribed ten or more substances (Anatomical Therapeutic Chemical level 4), or between 5–10 substances over a 3-month period per general practitioner. The Health Insurance Institute feedback the findings quarterly to physicians to instigate discussions on rational prescribing.

Overall, the course was well received. Over 90% of delegates found the presentations either good or excellent, and reacted similarly to the 3-day course as a whole. Over 90% were fully or mostly satisfied that they had an opportunity to learn about the different initiatives and approaches across Europe. As a result, the Piperska group will be holding another course within 3 years. Further details of the Piperska group can be found on their website [102].

Financial & competing interests disclosure

G Selke, J-P Fagot and J Mrak are employed by health insurance agencies. RE Malmström undertakes critical assessments of products for Stockholm County Council. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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