

MANAGING UNCERTAINTY IN DRUG DEVELOPMENT AND USE INFORMED REGULATION

ENHANCING ADAPTABILITY AND FLEXIBILITY IN PHARMACEUTICALS REGULATION

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The pharmaceuticals sector provides an archetypical example of proactive public sector risk governance. Unlike ordinary consumer products, drugs may not be marketed without advance regulatory approval. Licensing is based on projections of safety, efficacy, and acceptable manufacturing quality, with revisions to the conditions of licenses as safety, efficacy or quality issues arise in use. On 10 October 2014, the OECD and IRGC sponsored a panel on risk governance in pharmaceuticals, with a mandate to describe sources of innovation in pharmaceuticals development and use, to present regulatory, patient and industry perspectives on managing benefits and risks, and discussing current European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approaches to the management of risks and uncertainty over the full life cycle of drugs. The panelists jointly produced this distillation of presentations and summary of discussion themes.

1. Defining the context for pharmaceuticals risk governance: Crises and evolutionary pressures

Kenneth Oye of the MIT Center for Biomedical Innovation and Mark Pearson of the OECD defined the context within which current benefit and risk management reforms are taking place. They described a series of crises that have prompted reforms in drug licensing within the OECD nations. In the late 1950s and early 1960s, birth defects produced by Thalidomide prompted adoption of more stringent standards for demonstration of efficacy and safety in advance of approval and to strengthening of adverse effects reporting systems. In the 1970s and 1980s, the demands of HIV and cancer patients for earlier access to life saving medicines prompted development of accelerated approval and conditional marketing authorization pathways, with deferred validation of biomarkers. In the 2000s, adverse effects caused by Vioxx, Accutane and other drugs prompted improvements in aftermarket surveillance programs and to

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requirements for programs to manage known risks (REMS/RMS). Finally, backlogs in licensing developed, produced by the regulatory challenge of simultaneously improving standards for demonstration of safety and efficacy, providing early access to drugs, managing known risks and strengthening registries and aftermarket surveillance. In the US, the backlog was cleared

as pharmaceutical firms covered the costs of licensing through payment of prescription drug user fees. These crisis-driven reforms have improved detection of severe adverse effects, improved management of identified risks and accelerated patient access to drugs for unmet life threatening medical needs.

Current calls for reform follow less from crises than from sustained evolutionary pressures on regulators, drug developers, patients, providers and payers, see Figure 1.



Figure 1: Evolutionary Pressures for Reform

First, within both the United States and Europe, increasing late stage failures during clinical trials have contributed to rising costs of drug development. In addition, drug companies in the US have added pharmacoeconomic studies to traditional safety and efficacy studies. Marketing requirements, specifically the need to support the addition of new drugs to managed care drug formularies, have contributed to a rise in drug development costs. Globalization of markets has also led to multi-regional clinical trials and additional data collection needs. As Figure 2 suggests, in the United States, R&D efficiency has been declining steadily, with the 2010 cost of bringing a drug to market running at about \$US 1.5 billion. Within Europe, the cost of bringing a complex new drug to market now approaches € 1.7 billion, heavily loaded toward the cost of trials conducted at the back end of the process.

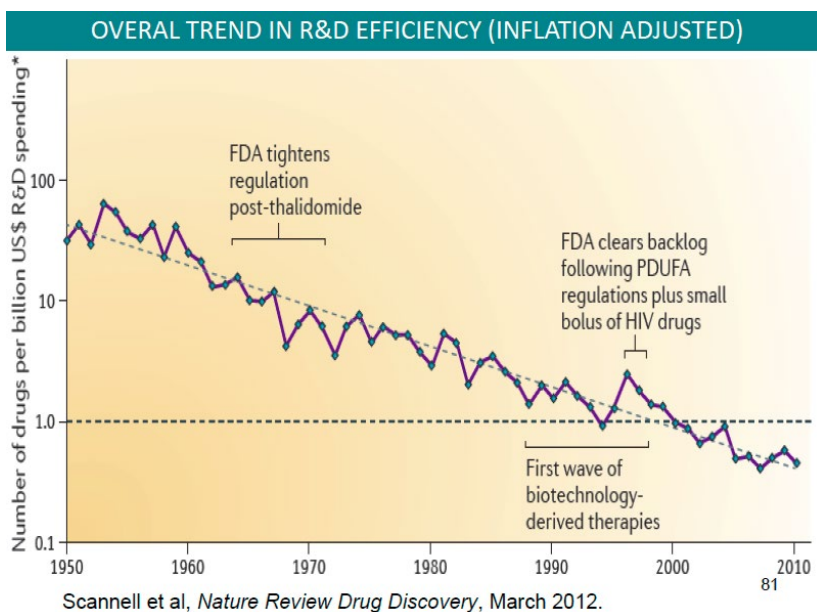


Figure 2: Trends in US R&D Efficiency in Drug Development

Second, as the scientific revolution in genetics reshapes medicine, an increasing number of treatments in development now target smaller genetically defined sub-populations instead of larger heterogeneous populations. This splintering of disease populations and narrowing of labelled indications is improving the effectiveness of medicine. It is also increasing the difficulty of recruiting adequate numbers of confounder cleansed subjects for the clinical trials that provide an evidentiary basis for projecting the safety and efficacy of drugs. As Figure 3 suggests, drugs serving small numbers of patients are priced high. The splintering of

indications has also created smaller market niches that are often filled by only one drug rather than two or more competing drugs, weakening or eliminating market pressures to ease pricing. Smaller market niches affect the size of the base from which sponsors may recover costs, as development and testing expenses are spread across fewer patients. Taken together, these evolutionary changes have simultaneously increased drug development costs and raised drug prices.

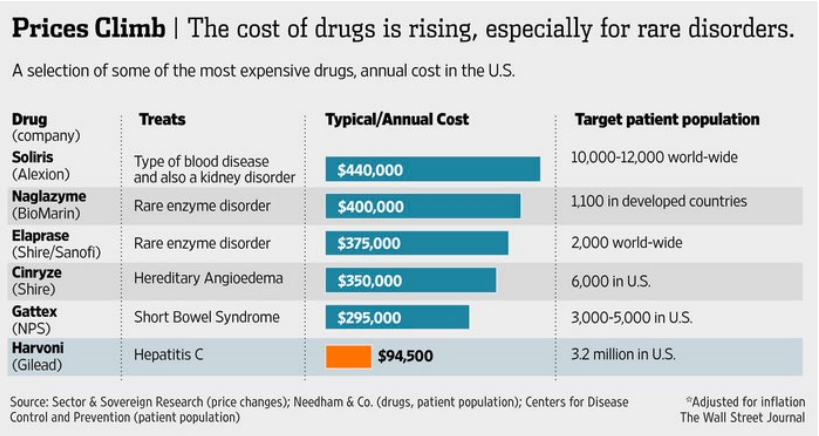


Figure 3: Drug Costs for Selected Rare Disorders

Third, subjects with comorbidities and subjects taking other drugs are excluded from clinical trials to optimize for detection of treatment effects. But because patients often suffer from more than one ailment, take other drugs, and fail to adhere to labels, confounder cleansed subjects taking drugs in trials are imperfect surrogates for patients taking drugs in the real world. **Confounder cleansing of populations of subjects taking drugs in trials increases the ability to detect a drug effect if it is there, but decreases external validity.** Progressive reduction of resulting uncertainties will need to be achieved by way of subsequent studies that could range from clinical trials to the use of data from observational studies. Observational studies should complement, not replace, RCTs. Capabilities within three key domains are important to make observational studies a valuable source of information: data and infrastructure, methodology to address the inherent limitations of non-randomised information, and, lastly, operational enablers including, for example, organisational processes, mind-sets and legal frameworks.

These developments define a complex setting for benefit-risk management in pharmaceuticals. Risk management in medicine now entails engaging with risks associated with medical and other health products, risks to public budgets from the adoption and coverage of new therapeutics, and risks to patient privacy from novel uses of medical data. The European Union and the United States have been converging in their approaches to drug licensing, with substantial areas of commonality and some differences remaining. With reference to speed, the US FDA approves cancer drugs more quickly than the EU EMA. With reference to process, the US FDA is more demanding than the EMA for biosimilars. The EU offers generalized handling of PROMS while the US retains a symptom specific approach. With reference to outcomes in licensing of oncology drugs, 50 percent of drugs are treated identically, 30 percent of drugs have some differences in labelling and in 20 percent of cases a drug is accepted by one and rejected by the other. Contrary to conventional wisdom, there do not appear to be differences in attitude to risk on population level, with some differences in regulation on a case by case basis. Future trends suggest continuing convergence, with greater patient involvement in defining willingness to accept risks, with life cycle approaches to the management of risks of product and with integrated assessments of benefits as well as risks.

As will be discussed by Hans-Georg Eichler, Theresa Mullin, and Anton Hoos, OECD nations face four challenges.

First, market entry regulation will be under sustained pressure for reform. New therapeutic technologies will continue to focus on smaller populations, uncertainty over the efficacy, safety and effectiveness of these emerging technologies will continue to rise, and novel products will strain market entry regulations. For example, therapeutics that are half medicine and half medical devices, regenerative medicines and other living therapeutics simply do not fit easily within existing licensing frames.

Second, clinical trials need to be harmonized and streamlined. In 2013, the OECD issued recommendations on the governance of clinical trials. These recommendations aimed at improving consistency in the interpretation of national regulations, introduced a proportionate regulatory approach, and enhanced protection of trial participants. Both the US and European Union have launched initiatives to simplify and improve regulation of clinical trials.

Third, regulatory science needs to be modernized. This will entail encouraging dialog between innovators and regulators, to improve understandings of scientific developments while maintaining sensitivity to risks of regulatory capture. This also entails increasing transparency in decision-making processes with open acknowledgement of ethical concerns, open recognition of local values and open engagement with patients and providers as well as payers and sponsors.

Finally, the traditional focus on benefit-risk in the context of evidence generation on safety and efficacy for licensing must now be broadened to include a second focus on benefit in the context of evidence generation on the effectiveness for treatment and reimbursement. Faced with rising costs for pharmaceuticals and increasing political pressure to contain costs, patients, physicians and payers are demanding better information on the effectiveness of drugs. Although beyond the purview of traditional pharmaceutical regulatory agencies such as the EMA and FDA, the acquisition, analysis and interpretation of evidence on effectiveness of drugs in use will be an increasingly significant element of health care policy.

2. Developments in Europe: Managing uncertainty over the life-span of drug development and use

Hans-Georg Eichler, Senior Medical Officer of the European Medicines Agency, described recent EMA developments including pharmacovigilance legislation, greater trials data access, the EMA/EUnetHTA Post Market Data Plan, and the EMA adaptive licensing pilots. Regulators have to manage competing objectives. Under traditional approaches to drug licensing, drug companies rely on models, in vitro studies and animal studies and randomized clinical trials using confounder cleansed subjects to demonstrate the safety and superior efficacy of a drug. Former FDA Deputy Commissioner Murray Lumpkin speaks of the “magic moment” when a drug is either approved or

rejected. Carefully monitored subjects become lightly observed patients, experimental therapeutics become accepted treatments, drugs are transformed from unproven to safe and effective.

This traditional binary model of drug approval, described by the upper diagram in Figure 4, is now changing rapidly toward explicitly adaptive approaches to licensing with patient experience contributing to evidence development. The bottom diagram describes an adaptive approach to licensing. At the front end, approval would come earlier, would be limited to patients with the most favorable priors benefit/risk and would be conditional. At the back end, observations of patient experience would be strengthened through greater reliance on registry and electronic health records, with systematic analysis of that experience to evaluate safety and effectiveness, and with modification of labels and the terms and conditions of licensing based on patient experience. Conditions now favor implementation of adaptive approaches to risk governance, with both demands for more adaptive approaches to licensing and factors enabling implementation of adaptive approaches. The arguments below are developed more fully in Eichler *et al.* "From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients", in *Clinical Pharmacology & Therapeutics*, Volume 97, Issue 3, pages 234–246, March 2015.

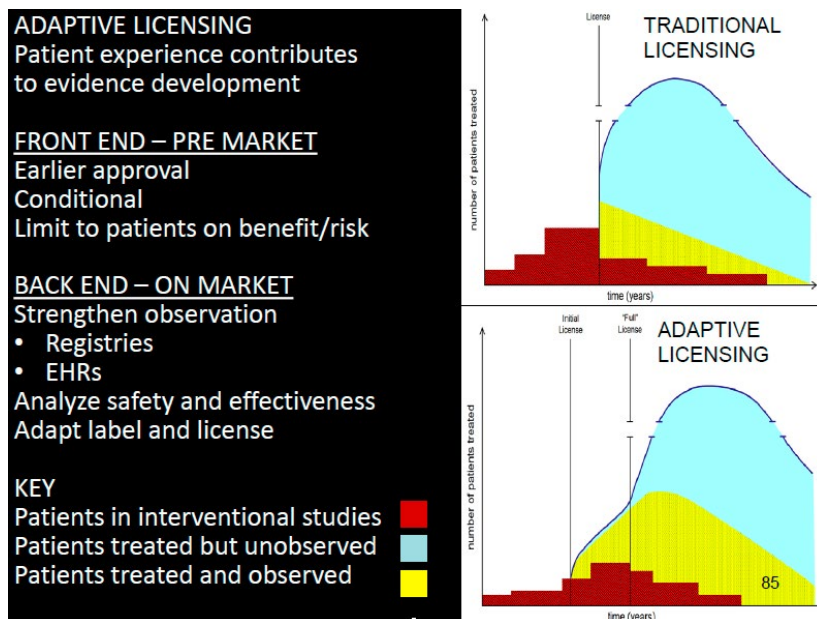


Figure 4: Traditional and Adaptive Licensing

2.1

The demand side: Conditions creating support for adaptive licensing

Four environmental changes described below have converged to heighten interest in the use of adaptive pathways for the development of new drug products.

Demand from patients for timely access to address unmet medical needs: A key driver for adaptive pathways is growing pressure for timely access by patients and their advocates. In the words of a patient representative, "I do not benefit from a drug that is approved on the day of my funeral. The safest drug that one cannot afford or that arrives too late is of no benefit to a patient." Calls for rapid access to new treatments originally came from advocates for patients with HIV, cancer and orphan conditions. Patients with chronic, slow irreversibly progressing diseases with unsatisfactory treatment options are now making the same plea for urgent access as do those with fast progressing conditions. From a patient's perspective, duration of the disease course should not be the key input variable when making the access

versus evidence trade-off. Adaptive pathways recast this ethical dilemma to achieve an appropriate trade-off between ‘unmet need’ and ‘less certainty.’

First, under an adaptive licensing approach, patient-access to treatment should be driven by the likelihood that the treatment will succeed in addressing an unmet need. Decisions on whether to accept a new treatment on a smaller evidence base can be guided by response rates on surrogate endpoints in small patient cohorts or by considerations laid out in FDA criteria for breakthrough therapy designation.

Second, adaptive licensing is not about changing benefit-risk trade-offs. Under any licensing or coverage paradigm, expected benefits should outweigh expected risks for a defined patient population. Anything else is unethical. The issue is whether uncertainties around benefit and risk estimates must be resolved at the time of initial licensing and coverage decisions or whether positive decisions may be based on the balance of probabilities with continuous monitoring.

Third, any acceptance of ‘less certainty’ about a product can only be temporary, even in the face of high unmet need. Adaptive licensing is designed to foster the progressive reduction of uncertainty by way of pre-agreed evidence generation plans and timeframes, with tight utilization management, monitoring in the marketplace, and an ability and political willingness to restrict or withdraw a product if benefit-risk or value for money is less than expected. Together, these precautions should reduce realized risks for patients relative to current approaches.

Demand for regulations appropriate to stratified treatment populations: Improved understandings of pathologies have led to a growing number of defined treatment subpopulations, with disease stratifications based on genotypic biomarkers and dedicated companion diagnostics.

First, screening-out those likely to develop serious toxicity may allow others to continue to benefit from a drug. In the past, without the ability to identify those patients likely to experience serious adverse events, many patients were denied potential benefits of treatments. Over the next decade, increasingly sophisticated sub-stratification will pose challenges for decision-making on licensing and coverage. Heterogeneity and complexity will result in a large number of narrowly defined patient subgroups. For example, some mutations are more common than others and conventional RCTs will be feasible for some subgroups and not for others. As a consequence, obtainable levels of evidence at the time of licensing decisions will vary across mutation groups. For less common mutations, benefit-risk information may be based on real-world data accrued late in a product’s lifespan.

Second, the trend is from subgroup specific medicines toward ‘custom-made’ medicines. For example, patients receive individualized treatments in gene therapies based on modified patient-derived cells, antisense oligonucleotides and other types of advanced therapies. Treatment-eligible populations are now approaching an ‘n of 1’. Basket licensing of a family of products with individual variations may be the only viable route to market, but even minor changes in the molecular structure of a drug could result in significant

changes in toxicity profiles. An adaptive development and licensing approach with modification of initial basket licensing decisions grounded on rigorous observation of patients may be needed.

Finally, ethical questions on trade-offs between the interests of future versus current patients will likely have different answers for each individual sub population. Acceptable uncertainty will be dependent on patient subgroup disease burdens, potential for benefit, and declared preferences on trade-offs across uncertainty and access to new therapies.

Demands from payers for evidence-based reimbursement: Only a small and shrinking fraction of expensive new drug treatments are paid out-of-pocket by patients. Decisions by third party payers on whether and how to reimburse are gaining increasing importance to both patients and marketing authorization holders. Regulatory approval is a necessary but not sufficient pre-condition for effective patient access. There is growing awareness among many payers that they, like the regulators, cannot escape the acrimonious debate over access versus evidence. Payers recognize that the distinction between experimental versus medically necessary is based on a simplified view of evidence and uncertainty, with explicit recognition of the evolving strength of evidence. Many payers are shifting from seeing decisions on reimbursement as a one time binary decision, to seeing reimbursement decisions as on-going processes aiming at providing greater certainty about value for money as evidence accumulates. Once a coverage decision has been made, payers have an interest in limiting initial use to subpopulations with the best benefit-risk ratios, in improving patient adherence, in monitoring treatment outcomes and in modifying conditions of reimbursement in light of evidence on effectiveness.

Demand from pharma/investors for sustainable drug development: The low productivity of bio-pharmaceutical R&D is the result of factors largely beyond the scope of this paper. However, part of the problem rests on factors that may be partially addressed through **harmonized** adoption of adaptive approaches to drug development, licensing and reimbursement. Industry is moving from blockbuster to niche buster business models, even as payers increase evidence requirements for reimbursement and regulators seek to revise licensing terms in light of evolving evidence from use. While regulators have achieved some degree of inter-regional harmonization of evidence standards, payers are at an earlier point in that dialog. The lack of alignment results in differences in standards for drug development. How will adaptive pathways help? Because adaptive licensing requires early engagement with all stakeholders, an adaptive approach to licensing should catalyze consensus building among payers both within and across regions. In fact, the European Federation of Pharmaceutical Industries and Associations (EFPIA) is now working to create a framework for implementation of 'Medicines Adaptive Pathways for Patients' (MAPPs).

2.2

The supply side: Conditions enabling adaptive licensing

Even as the factors discussed above have increased demand for adaptive licensing, other developments have improved the prospects for implementation of adaptive pathways.

Better understanding of disease: The revolution in genetics noted above and the use of epidemiological data in reanalysis of past clinical trials may improve the efficiency of RCTs and improve validation of surrogate endpoints. This may reduce the need for concurrent control groups in rare diseases and provide better reference points against which post-licensing evidence generation may be assessed.

Innovative clinical trial designs: Adaptive trial designs offer an opportunity to use accumulating results to focus on patient subgroups that respond better to a therapy and to evaluate populations of patients similar to targeted patient groups. Adaptive trials provide a method for improving operational continuity from pre to post-authorization phases. Adaptive trial designs can also improve the terms of trade-offs between robust evidence generation and patient access to promising therapies in trials by minimizing placebo exposure of patients through interim adjustments.

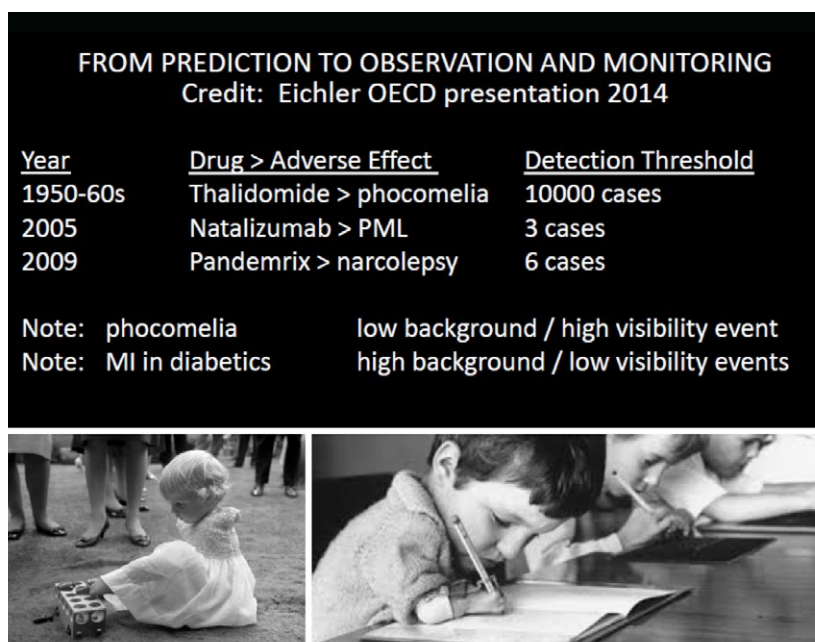
Rapid learning systems in the healthcare environment: While imperfect, electronic data in health records or dedicated registries are increasingly standardized, reliable and complete. Data on patient reported outcomes, treatment adherence data, morbidity, and daily activities are likely to become more available as e-health records expand and data compatibility is increased. At the same time, methodologies have been developed to address, to the extent possible, confounding and selection biases in observational studies. Finally, data owners are now developing common data models, protocols to query data sets, and governance models. These developments have resulted in significant improvements in the detection of safety signals and evaluation of effectiveness in the real world, including the US FDA Mini-Sentinel Initiative, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the US Patient-Centered Outcomes Research Network called 'PCORnet'.

Bringing patients to the table: Patients' views should be paramount when judging the acceptability of levels of clinical uncertainty for a given treatment scenario. Obtaining representative views from patients is an on-going mutual learning process for both patient representatives and decision-makers. Regulators and HTA bodies now invite patients to declare their preferences on clinical trial endpoints and benefit-risk-uncertainty trade-offs, with promising results to date. Most fundamentally, actively engaging patients in decision-making about their own care enhances transparency, earns trust and enlists patient support for the secondary use of health data to enable evidence generation through the post-licensing phase.

From prediction to monitoring: A common adage among regulators used to be that once a drug ‘is out the door’ their powers to monitor and steer use and to detect or mitigate risks was limited. In recent years, progress has been made on two fronts that may enable regulators to move from a prediction to a monitoring paradigm.

First, regulators can now impose and enforce on marketing authorisation holders an array of post-licensing requirements to improve information on benefits and risks. Although the imposition of post-licensing information gathering requirements is less common in the US than in the EU, the legal authority to impose additional post-licensing requirements exists in both jurisdictions.

Second, post-licensing identification of adverse drug effects has improved dramatically, see Figure 5. In the 1950s and 1960s, thalidomide use in pregnancy caused phocomelia, a highly visible adverse effect with a low background incidence. It took around 10,000 cases before healthcare professionals made the connection between thalidomide use and phocomelia. Contrast this tragically slow learning with recent rapid detection of adverse effects. Adverse effects of tysabri natalizumab were detected after only three cases of PML were reported. Adverse effects of H1N1 pandemic flu vaccine Pandemrix were investigated after the Swedish Medicines Agency received only six reports of narcolepsy following vaccination. Yet our ability to detect adverse drug reactions with small risk ratios on high-background events is limited.



Targeted prescribing: When a drug is initially intended for use by a well defined subset of patients, wide-spread use by patients outside of the target group might open the door to negative patient outcomes. Regulators have some limited tools to steer drug utilization by way of controlled access programs, prescriber restrictions, educational requirements, and clinical reminder systems. In practice, payers, healthcare systems providers and professional societies, rather than regulators, are the stewards of appropriate prescribing. As new premium priced drugs enter the market, payer interests in effectiveness and cost-containment are leading to increasingly regimented use through pre-authorization requirements, prescribing audits, prescriber restrictions, tiered co-payments and mandatory treatment protocols. Regulator and payer actions in cooperation with the bodies that produce clinical practice guidelines are likely to improve prescription controls, particularly for diseases that are treated in specialist centers.

Figure 5: From Prediction to Observation and Monitoring

2.3 Conclusion

This presentation treats environmental changes that have increased demand for adaptive approaches to benefit-risk management and that enable the transition from traditional to adaptive approaches. However, significant challenges remain if the potential benefits of adaptive approaches to licensing are to be realized.

Some potential problems are technocratic and legal. Adaptive approaches to risk governance require the integration of lessons from post-marketing observational data and data from experimental trials in a manner that compensates for the weaknesses of each. Observational data including payer records and electronic health records are subject to selection biases, misrepresentations of indications, simple errors and noise, presenting problems in terms of internal validity of inferences. The development of methods of data standardization and curation and methods of causal inference suited to data with biases and selection effects present technical challenges. Clinical trials of limited duration, with high patient adherence in populations cleansed of comorbidities and use of other drugs present problems in terms of external validity – generalization from trials to ordinary treatment populations. The integration of observational and trial-based information, including working back from hypotheses generated from post-market observational data to limited trials to confirmatory targeted trials, presents legal as well as technical challenges. To make adaptive licensing function effectively will require work on terms of access to data, including analysis of intellectual property rights, human subjects protocols and privacy rules.

Some potential problems are political and economic. First, experience has shown that it is politically challenging to remove a drug from the market or to restrict payment should the initial benefit-risk balance not be confirmed post approval. Once patients have access to a drug, resistance to withdrawal can be intense. These issues will require substantial discussion before rather than after conditional approval of drugs, with inclusion of patient groups as critical stakeholders. Second, once early access is obtained, not all developers will be interested in making good on controls, observation and potential narrowing of terms of access that constitute the ‘back end’ of adaptive licensing. Care must be taken to ensure that this post-marketing ‘back end’ of adaptive licensing is fully implemented. Controls on initial prescriptions, systematic post-marketing observation of safety and effectiveness of drugs-as-used, and modification of the terms of licensing and reimbursement based on real world experience are critical to effective management of uncertainty over the life cycle of drugs. In practice, this will depend on engagement with payers – with a clear interest in evaluating effectiveness - as well as sponsors.

Finally, implementation of adaptive pathways will be more difficult in the US than the EU. For example, limiting access to an approved drug to a subset of the population will be more difficult in the US, where the practice of medicine allows for off-label use, than in the EU. While sponsors, regulators, HTA bodies and payers are now collaborating in the EU, other jurisdictions, notably the US, do not have national healthcare systems with centralized management on access and payment. Conditions within the EU have allowed the EMA

to conduct pilot projects to assess the feasibility of adaptive pathways to licensing. At the end of the day, the characteristics of adaptive approaches to licensing will be shaped by differences in national and regional conditions and by observation, analysis and feedback from regulatory experience.

3. Developments in the United States: Managing risk and uncertainty through the drug life cycle

Dr. Theresa Mullin, Director of the Office of Strategic Programs of the US Food and Drug Administration Center for Drug Evaluation and Research, described recent US developments, including patient-focused drug development, FDA Breakthrough Product Designation, formalized benefit-risk assessment, and use of pharmaceutical quality metrics. A benefit-risk approach frames all FDA risk management decisions across the life cycle of a drug, with emphasis on transparency and continuous learning. FDA initiatives include Patient Focused Drug Development and FDA Breakthrough Product Designation early in the drug life cycle, the use of pharmaceutical quality metrics in manufacturing of generics late in the drug life cycle to cover off-patent drugs 80 percent of which are generic, and the use of benefit-risk analysis throughout the life cycle.

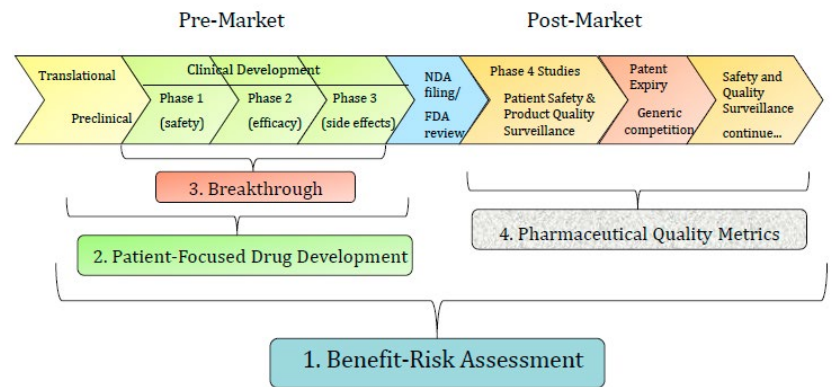


Figure 6: Initiatives in Context of Drug Life Cycle. Source: US Food and Drug Administration, www.fda.gov

The FDA uses a **Formalized Benefit-Risk Assessment** approach to structure and manage the technical complexity of new drug assessment, see Figure 6. This assessment is informed by science, medicine, policy, and judgment. The law and regulations concerning the drug review process generally provide broad principles and are not case-specific, so FDA works to develop consistent policy in taking action within its legal and regulatory authority, to make decisions in a way that is fair, not arbitrary or capricious. FDA communicates this policy through guidance. However, in a given case it may determine that a generally applicable guidance is inappropriate, and in such cases retains the flexibility to take a different approach. Since each decision either is made in the context of established policy or establishes new policy, this serves FDA as a sort of ‘case law’. Although the quantity of information to be evaluated and considered by FDA is substantial, there are residual uncertainties resulting, for example, from the gaps in the data or current scientific understanding, and human judgment and values must come into play. The framework for benefit-risk decision-making summarizes the relevant facts, uncertainties, and key areas of judgment, and clearly explains how these factors influence a regulatory decision. This helps inform and clarify the regulatory discussion. It also serves to communicate the basis for FDA’s regulatory decision to the public, while documenting the decision for reference as FDA considers similar benefit-risk assessments in the future.

As shown in Figures 7 and 8, the FDA framework for benefit-risk assessment is structured in terms of the following five major considerations (corresponding to the rows): the analysis of severity of the disease condition being targeted by the drug; a review of current treatment options to determine the degree of unmet medical need; benefits observed in clinical trials; risks reflected by the safety findings from clinical trials; and consideration of whether the identified risks can be managed to ensure benefits would exceed risks. Each of these five considerations is further structured into two areas to identify (a) the facts that are known versus residual uncertainties for each consideration, and (b) the conclusions and reasons of the reviewers' assessment of the evidence and uncertainties.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>For each decision factor...</p> <p>What is the key information/data that supports your conclusions:</p> <ul style="list-style-type: none"> • What you know (facts) • What you don't know (uncertainties and underlying assumptions) 	<p>For each decision factor...</p> <p>What are your overall conclusions about:</p> <ul style="list-style-type: none"> • The strength of the evidence • The clinical relevance and significance of the evidence • Any implications on the regulatory decision
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary and Assessment		

The FDA uses a qualitative approach that is grounded in quantification of data elements at the time of marketing approval. Benefits are grounded in data on efficacy endpoints from controlled clinical trials. Risks are grounded in data on harms reported in clinical trials and from spontaneous adverse effect reports. The evaluation of benefits and risks is dynamic, with understandings of both benefits and risks evolving over the product life cycle. This is not a mechanistic process.

Figure 7: FDA Benefit-Risk Framework (Columns). Source: US Food and Drug Administration, www.fda.gov

FDA developed the **Patient Focused Drug Development program (PFDD)** in recognition that patients are uniquely qualified to inform clinical context for FDA's benefit-risk assessment: in particular the impact of disease on

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>Sets the context for the weighing of benefits and risks:</p> <ul style="list-style-type: none"> • How serious is this indicated condition, and why? • How well is the patient population's medical need being met by currently available therapies? 	
Current Treatment Options		
Benefit	<p>Characterize and assess the evidence of benefit:</p> <ul style="list-style-type: none"> • How compelling is the expected benefit in the post-market setting? • How clinically meaningful is the benefit, and for whom? 	
Risk	<p>Characterize and assess the safety concerns:</p> <ul style="list-style-type: none"> • How serious are the safety signals identified in the submitted data? • What potential risks could emerge in the post-market setting? 	
Risk Management	<p>Assess what risk management (e.g., labeling, REMS) may be necessary to address the identified safety concerns</p>	
Benefit-Risk Summary and Assessment		

patients, i.e., the analysis of condition, and the effectiveness of currently available therapies in treating the disease impacts that matter most to patients. The traditional patient representative program only enabled participation of individual patients who received conflict of interest screening and some regulatory process training, and those patient representatives have had burden of speaking for all those with a disease. Yet one size does not fit all who are afflicted with a given disease. The FDA needed more diversity. In a pilot exercise, FDA is setting up 20 different public webcast

Figure 8: FDA Benefit-Risk Framework (Rows). Source: US Food and Drug Administration, www.fda.gov

meetings in 20 different disease areas. Only patients are allowed to speak. The patient input in the meetings held since the start of this initiative in 2013 have been well-attended by patients and have provided powerful insights for FDA reviewers and also for industry sponsors who have attended the meetings. Public stakeholders and industry have identified this initiative as a priority for further expansion in the coming years, see Figures 9 and 10.

The FDA established **Breakthrough Therapy Designation** to foster more rapid development of drugs that offer the potential of substantial improvement in patient outcome. The FDA Safety and Innovation Act (FDASIA) of 2012 Section 902 provided for a new Breakthrough Therapy Designation. A breakthrough therapy is a drug which: (a) is intended alone or in combina-

tion with one or more other drugs to treat a serious or life threatening disease or condition and; (b) preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Breakthrough designation is based on preliminary clinical evidence of potential improvement on a clinically significant endpoint relative to available therapies. By contrast, Fast Track designation is based on nonclinical or clinical evidence of the potential to address unmet medical needs. Both Breakthrough and Fast Track programs are intended to expedite the development and review of drugs for serious or life threatening conditions.

- Establishing the therapeutic context is an important aspect of B-R assessment
 - Patients are uniquely positioned to inform understanding of this context
 - Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review
- PFDD offers a more systematic way of gathering patient perspective on their condition and treatment options
 - FDA will convene at least 20 meetings on specific disease areas over the next five years
 - Meetings can help advance a systematic approach to gathering input

Figure 9: Patient-Focused Drug Development. Source: US Food and Drug Administration, www.fda.gov

If a drug is designated as a Breakthrough Therapy, FDA will expedite development and review of the drug. The program is establishing a rolling review process with additional engagement between FDA staff and applicants. Prequalification based on the criteria outlined in Section 902 is required. Requests for breakthrough designation may be submitted with the Investigation of New Drug (IND) application with at least one phase I trial complete. Breakthrough designation has substantial benefits to the sponsor, with almost unlimited meetings to discuss study designs and development processes to avoid delays and mistakes. These measures have reduced clinical development time by half, down from an average of 7 to 10 years, with clear benefits for sponsors seeking to reduce development costs and patients seeking earlier access. As of October 2014, 190 applications for breakthrough designation had been submitted and 57 applications had been accepted, see Figure 11.

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| <p>FY 2013 (Conducted)</p> <ul style="list-style-type: none"> • Chronic fatigue syndrome/myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy <p>FY 2014 (Conducted)</p> <ul style="list-style-type: none"> • Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis | <p>FY 2014 – 2015 (to be announced)</p> <ul style="list-style-type: none"> • Alpha-1 antitrypsin deficiency • Breast cancer • Chronic Chagas disease • Female sexual dysfunction • Functional gastrointestinal disorders • Parkinson's disease and Huntington's disease <p><small>*FDA will initiate another process to determine the disease areas for FY2016-17.</small></p> |
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Figure 10: PFDD Meetings FY 13-15. Source: US Food and Drug Administration, www.fda.gov

The FDA **Pharmaceutical Quality Metrics Program** addresses risk management challenges in global regulatory oversight of drug manufacturing, which is relevant to both pre-market evaluation of facilities and subsequent monitoring of the state of manufacturing quality control for marketed drugs later in their life cycle. With increasingly global supply chains, active ingredients, excipients, and finished dosage forms are typically produced overseas in different facilities in different countries some of which have limited regulatory capacity and less developed infrastructure. Because consumers and health care payers (i.e., the market) often cannot discern differences in quality there has been less of a market incentive for manufacturers to invest in quality. As shown in Figure 12, failures to invest in manufacturing quality, presumably in order to remain cost competitive, have

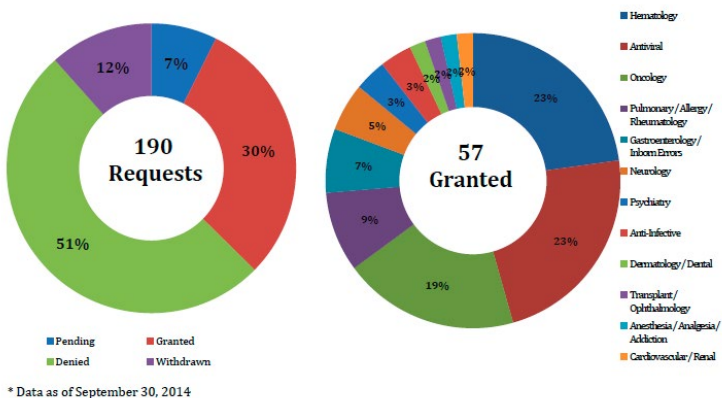
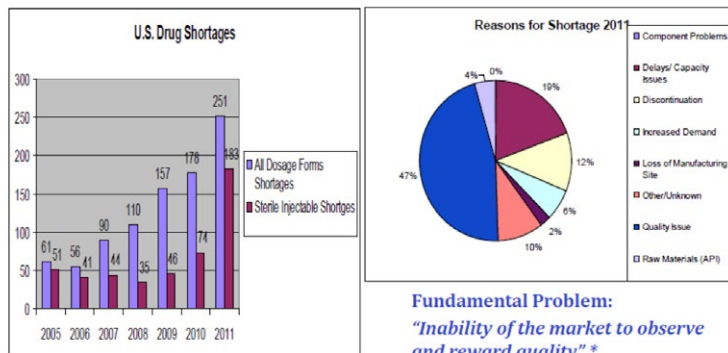


Figure 11: Breakthrough Therapy Designations. Source: US Food and Drug Administration, www.fda.gov



*J. Woodcock and M. Wozinska, Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages. *Clinical Pharmacology and Therapeutics*. 23 January 2013

Figure 12: Drug Shortages and Quality Problems. Source: US Food and Drug Administration, www.fda.gov

Fundamental Problem:
*"Inability of the market to observe and reward quality" **

FDA surveillance of the state of the firms' quality systems and product and process capability, with less frequent inspections for better performing sites. The program should also support the aim of achieving enhanced product quality without the need for extensive regulatory oversight and ultimately may help to drive a reduction in quality-related shortages and recalls.

been identified as a leading factor in recent and widely publicized drug shortages. FDA's new program to explore the use of manufacturing quality data that is already required by statute to be provided to FDA investigators upon inspection of a facility, could help inform this important dimension of value.

The intention of the program is to induce industry to improve manufacturing and oversight of manufacturing and to facilitate a more risk-based inspection schedule, via improving

4. A call for adaptability and flexibility from a patient and industry view

Anton Hoos, Principal of M4P (Medicines4Patients) Consulting at the time of the conference and currently Vice President of Amgen, examined EMA and US initiatives from the perspectives of industry and patients. He examined sponsor interests in how regulatory reforms mesh with product development realities and patient interests in access to safe and efficacious medicines. All stakeholders in the health area must serve the needs of patients and society, but the collective and individual needs of patients vary widely. The range of expectations of the benefit associated with a particular medication and the potential risk a patient / caregiver is willing to accept depends on the condition to treat or to prevent. For vaccination of healthy individuals, acceptance of potential adverse effects is typically low. For life threatening conditions that may lead to death within a very short period of time, acceptance of potential adverse effects is typically substantial, see Figure 13.

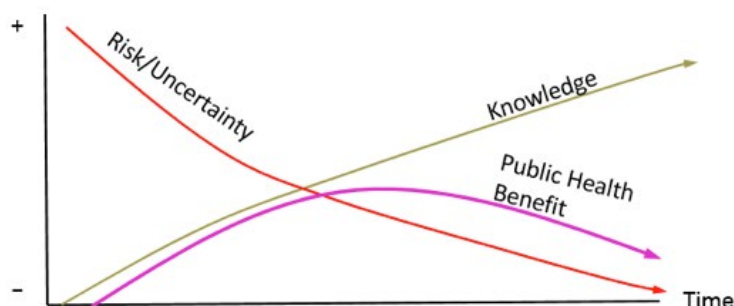


Figure 13: Risk/Uncertainty Reduction vs. Public Health Benefit

involved in the health system have requested more data to optimize their individual data set without coordination with other parties. This is true of regulators, HTA agencies and payers, both within and across each of these silos. This has led to an enormous increase of cost for the pharmaceutical sector and it may lead to a net disadvantage in terms of public health benefit.

In this context it is important to reach an understanding across all stakeholders about the benefit and risk of a therapeutic or prophylactic intervention and the degree of uncertainty associated with the available data at any point in time. The more data that is requested for a particular therapy or intervention the more time or cost will be required to make a therapy available. Historically all gatekeepers

Compared to any other sector, R&D expenditure in pharmaceutical industry are enormous:

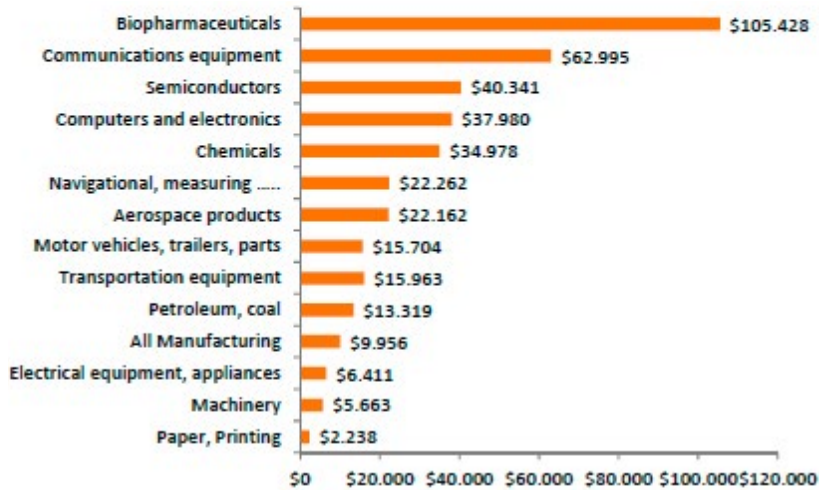


Figure 14: R&D Expenditure per Employee 2000-2007

While all stakeholders are making an effort to work with patients, their voice has not been heard sufficiently. A recent study by the UK Genetic Alliance reported that patients find the current regulatory process slow, bureaucratic, paternalistic and opaque. A European insight derived from the UK Genetic Alliance study reveals that some 50 percent of patients would like to see joint decision-making from setting the research agenda via designing clinical trials to regulatory decisions:

Q12-15 How much do you think patients should be involved in...	Setting the research agenda	Designing clinical trials	Marketing authorisation decisions	Post-marketing authorisation decisions
	%	%	%	%
Patient decides	10.1	7.8	10.1	10.3
Joint decision making	57.8	48.8	48.6	55.1
Involvement	18.9	27.2	23.0	19.8
Consult before deciding	13.2	14.3	18.3	14.8
Total	100	100	100	100

Figure 15: Patients' View on Decision-making

Interestingly many patients would be open to accept higher risk and uncertainty when offered access to new medicines. As Figure 16 suggests, patients believe that regulators should allow patients to secure access to medicines even if earlier access means that tests would rely on smaller numbers of subjects in trials and that approvals would be granted with more uncertainty over efficacy and safety. However, patients expressed reluctance to accept serious side effects and significant risk of death as the price of early access.

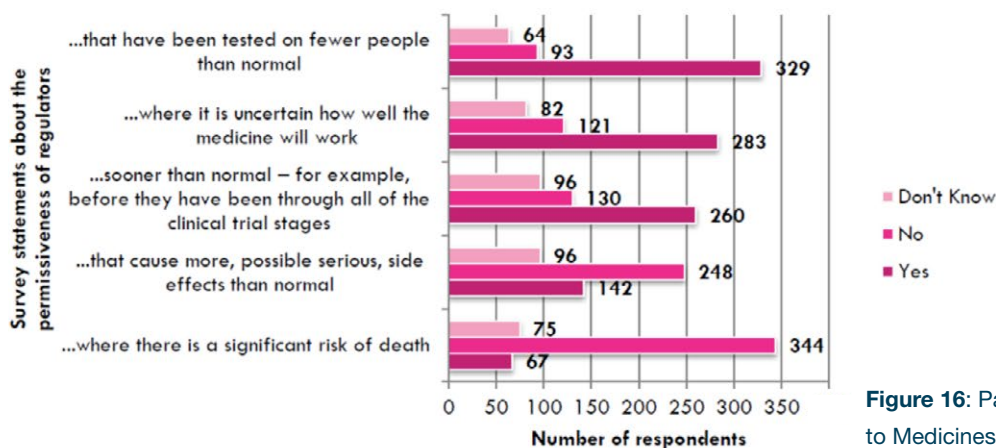


Figure 16: Patients' View on Access to Medicines

Patients are increasingly engaging in the drug development, approval and reimbursement process with the goal to secure timely access to medicines that they need. The US National Health Council published their view about patient involvement in the regulatory process as follows:

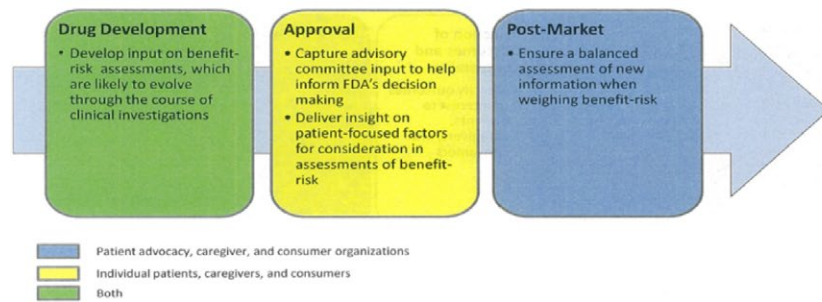


Figure 17: Patients' View on Engagement

The mandate of all regulators is to license safe and efficacious medicines. Given that all stakeholders, first and foremost patients, seem to be willing to accept a higher degree of uncertainty in return for earlier access to much needed medicines, adaptive approaches to drug licensing and reimbursement are needed. Key aspects will include joint prospective planning, agreement on the acceptable degree of uncertainty and risk as well as continuous evaluation of benefit and risk during a gradual broadening of access to patients. In March 2014 the EMA started its pilot program for adaptive licensing to determine whether and how these principles might be translated into practice.

5. Discussion

Theresa Mullin and Hans-Georg Eichler emphasized similarities in the US and European approaches to risk management. Mullin spoke of flexibility and discrimination within the US process, with degrees of acceleration, strength of controls on initial use, and reliance on adaptive elements tuned to patient interests in safety, efficacy and early access to address unmet needs. Eichler spoke of how the US and EU share common goals, with similar upstream pre-licensing processes, similar policies addressing quality problems in licit, counterfeit and illegal drugs, and emerging differences in post-licensing downstream risk management.

Those downstream differences are a product, not of philosophical differences, but of sharp differences in the structure of reimbursement. The EU has public payers while the US has a plethora of public and private payers. Within Europe, payer policies on reimbursement may control off-label use and limit inappropriate utilization and prescription. Within the US, the FDA may indirectly affect utilization and prescription by altering labels and issuing warnings, thereby reshaping liability exposure and altering payer and provider behavior. Mark Pearson noted that European public payers had a theoretical option to "dereimburse" drugs if warranted by emerging evidence on safety or effectiveness. Although not widely used, a payer-based approach to adherence could be used to encourage physicians and patients to practice evidence-based medicine, with practices updated on the basis of emerging information. Anton Hoos reinforced Pearson's observation on controls of inappropriate drug

use, noting that industry as well as payers could exercise some controls on distribution and use by physicians. Theresa Mullin picked up on the theme of improving physician risk-benefit governance, stressing the need to set up accessible information systems and risk management protocols.

Hans-Georg Eichler offered some cautionary words, noting that many of the proposed remedies are self-limiting. Risk management by limiting the right to prescribe to trained physicians can work well, as it has done with the re-introduction of thalidomide. But this approach can only work for a small number of therapeutics and physicians. Similarly, relying on physicians and payers to analyze dossiers to establish patient eligibility with complex screening criteria can work well, but is personnel intensive. Decision support tools will be needed if that strategy is to be used more broadly. Finally, drug prices will affect the viability of complex benefit-risk management strategies. As a drug becomes cheaper, industry interest in addressing risks to market the drug will decline.

6. Questions from the floor

Question: Double blind randomized placebo controlled clinical trials are commonly viewed as the gold standard. How prepared are regulators to deal with non-randomized data? For basing decisions on information other than RCTs?

Response: Hans-Georg Eichler noted that RCTs are the best tool that we have to avoid bias and selection effects. But regulators commonly authorize drugs on the basis of information from sources other than large RCTs. Many drugs today never see this randomization. Regulators expect to see smaller targeted RCTs, more case studies, and observational studies with real life data. Regulators will need to learn to use all of these data sources and are moving on this trajectory. Theresa Mullin agreed. She noted that Bayesian methods needed to be used in analysis of evidence from RCTs and in extrapolating from that evidence base to post-licensing observation of drug benefits and risks. She added that the expanded use of clinical trial data from multiple regions with heterogeneous patient populations could improve the quality of those inferences by increasing variation within study populations, but that international variations in standards governing the conduct of trials posed challenges. Agencies from the US, EU, Japan and others are now actively conferring on harmonization of regulatory standards for multi-regional clinical trials data. Finally, Kenneth Oye noted that the traditional sequence of RCTs first and observational data second might have to be altered. As hypotheses on safety, efficacy and effectiveness emerged from studies based on observational data, targeted RCTs to confirm or disconfirm hypotheses emerging from observational studies and to probe causal inferences will come to be used more frequently.

Question: How will these developments affect developing countries?

Response: Theresa Mullin suggested that generalizations across the extremely diverse set of non-OECD countries may be ill advised. RCTs are now

conducted on a global basis. For example, most US companies have sites for conducting trials in other continents and secure marketing authorization in many countries. While differences in the terms of licensing are common, there is significant work sharing. Developing countries typically look at licensing decisions by advanced industrial countries and may reference approval elsewhere. The New Pharmaceutical Regulators Forum came together to discuss operational issues and to leverage the experience and knowledge of others.

Question: Will adaptive licensing be useful for approval of biosimilars? What are the potential challenges for international harmonization on biosimilars?

Response: Hans Georg Eichler suggested that regulators seek to make new technologies available as soon as is justified by need and risk profile. By that definition, a biosimilar is not an innovation. Biosimilars have a place at the table because they break monopolies, not to provide access to a new therapy. It is not clear why levels of certainty should be reduced if patients already have an option. Kenneth Oye noted that as indications splintered and target treatment populations grew smaller, more and more monopolies could be expected. He suggested that breaking monopolies should be viewed as a legitimate factor in drug licensing. Mark Pearson noted that the ultimate objective of regulatory policy is not just to license drugs, but rather to deliver better health care to populations. Pearson urged regulators to consider licensing drugs to break monopolies and increase access, but also noted that such decisions had to be mindful of preserving incentives to innovate.

Question: What are the prospects for drawing on innovations in information technology to improving monitoring for efficacy and adverse effects? These innovations include digital prescribing with better records, individual bracelets that track exercise, sleep, and vital signs, and drug delivery systems that report on use to central locations.

Response: Anton Hoos described an extensive set of initiatives that make good use of new technologies for monitoring use with apothecaries, hospitals, and doctors. The FDA Sentinel project, Optum Laboratories data analysis systems, and Myownmed.com are among many initiatives that capture data and make data bases talk. Industry is definitely coming to this big time. Hans-Georg Eichler and Theresa Mullin agreed. Without improvements in technologies for monitoring, we would be back in the Thalidomide age. The technologies are developing and it would be foolish not to use them. Risk Evaluation and mitigation strategies can work better with these new tools. Mark Pearson, Theresa Mullin and Kenneth Oye offered some notes of caution. New online data sources are useful only if they are used. Only four OECD countries are linking primary care data to hospitals in a manner that allows evaluation of the effects of care. Finally, technical issues matter. Data standards, fundamental infrastructure, linkages across data bases and tools to extract information from unstructured data are needed. To whom is data provided, at each phase in the life cycle of drug development and use? How could utilization of data affect the size of markets and rates of reimbursement? Private owners of data often lack incentives to place that information into the public domain.