The Regulatory Framework of Drug Development: Regulatory and Pharmacoeconomic Considerations

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Disclaimer

Disclaimer

Information used in this presentation are derived from publicly available documents, regulations as well as published manuscripts where references are provided accordingly.

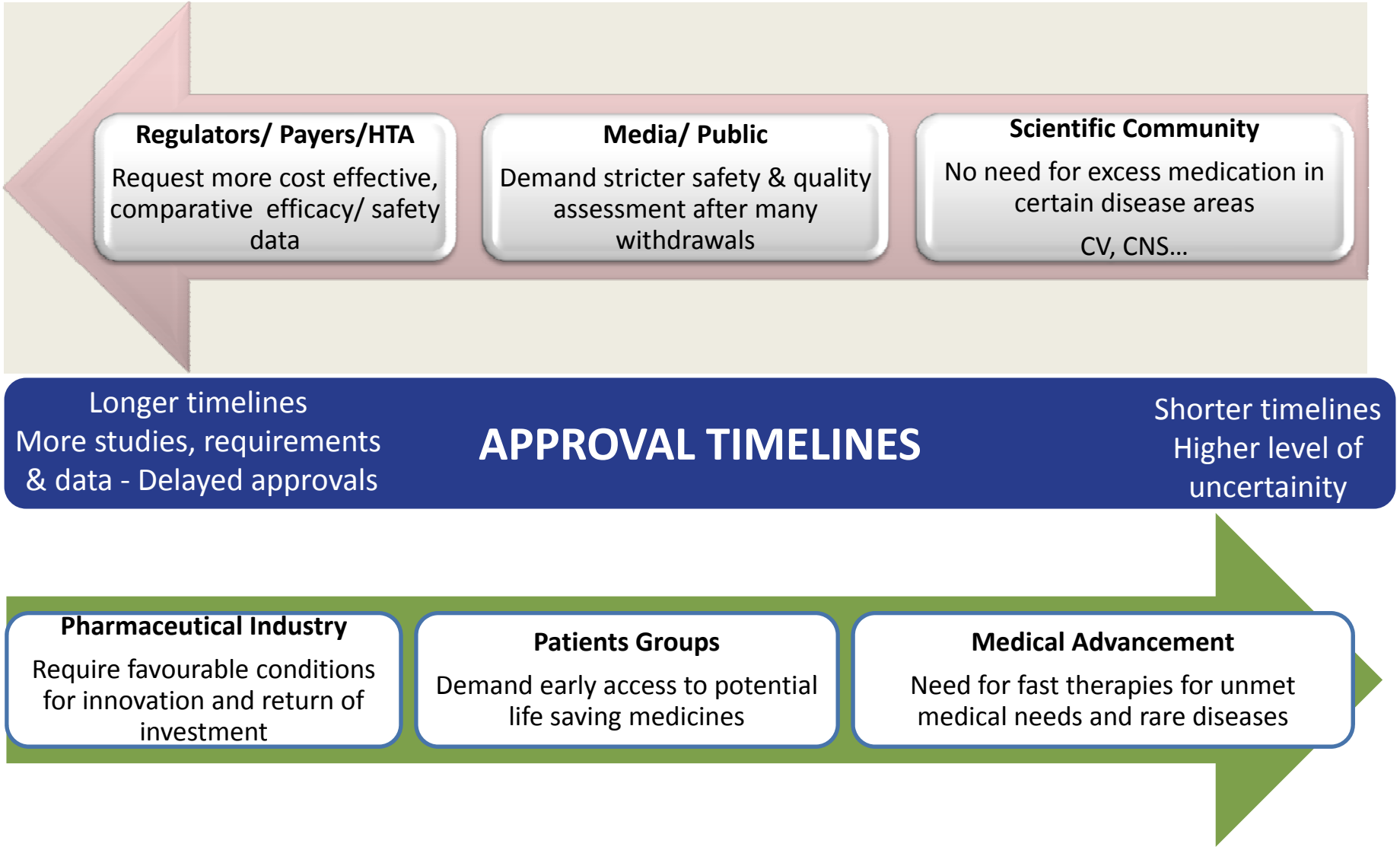
The presentation includes some scientific data related PhD research conducted at the Cardiff University by the presenter in association with the The Centre for Innovation in Regulatory Science (CIRS) .

Information presented in this presentation consists only of data, outcome views and research results of studies of the presenter personal interest and interpretations and thus do not represent the views of any of the institutions the presenter is affiliated with professionally or academically

Agenda

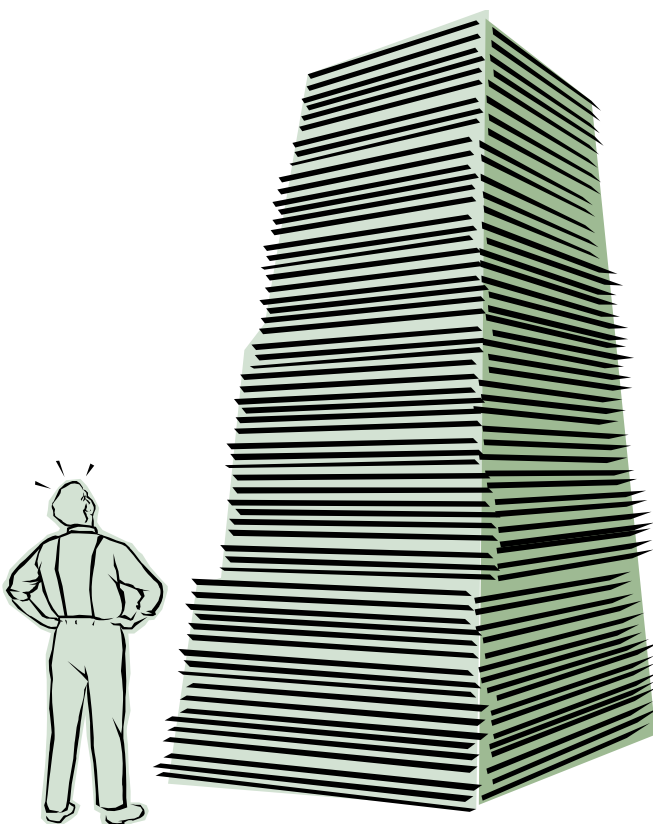
- The Regulatory Dilemma
- Drug Development Regulatory Frameworks
- Key concepts of Pharmacoeconomy
- Key Messages

The Regulatory Dilemma: Drug Development vs. Access



«Eichler et al., «Balancing early market access to new drugs with the need for benefit/ risk data: a mounting dilemma», Drug Discovery, vol.7, Oct. 2008

Drug Development is a Complex Process:
It takes 12-14 years & costs 1-2 Bn$



"Looks like you've got all the data – what's the holdup?"

It looks like you have all the data for safety, efficacy & quality so what is the hold up to patient access?

The regulatory dilemma: Benefit versus risks

PRODUCTS WITHDRAWN FROM THE MARKET

DRUG NAME					COUNT OF CASE REPORTS
sibutramine					blood pressure eart rate
sitaxent					titis failure
ximelag					a from mized clinical
rosiglitazone					**0834** cardiovascular disorders
clobutinol	cough			prolongation	**14** cardiac arrhythmias

Regulatory approval is based on limited data during development but subsequently the Benefit-Risk Balance often changes during post marketing phase.

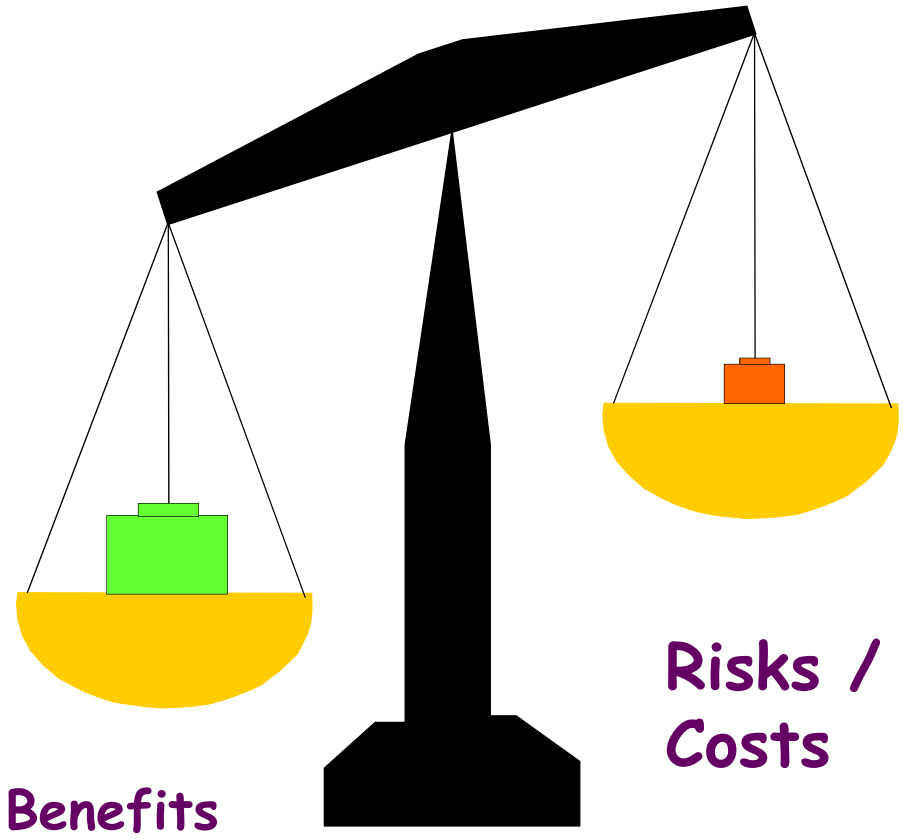
Products withdrawn from the EU market between 2002 and 2011 | McNaughton R, Huet G, Shakir S. BMJ Open 2014.

indicates that the decision was made by EMA

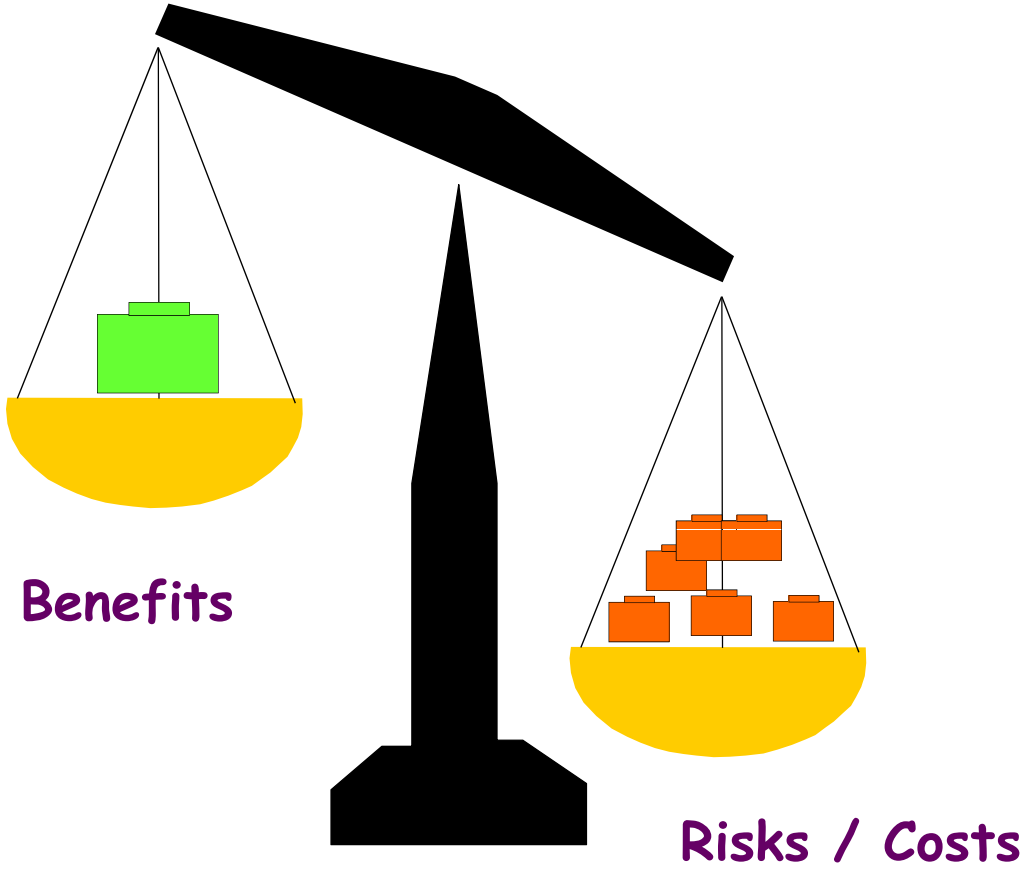
Therefore A Framework for Regulatory & Pharmacoenomic Decision-Making is Critical!

Cost Effectiveness

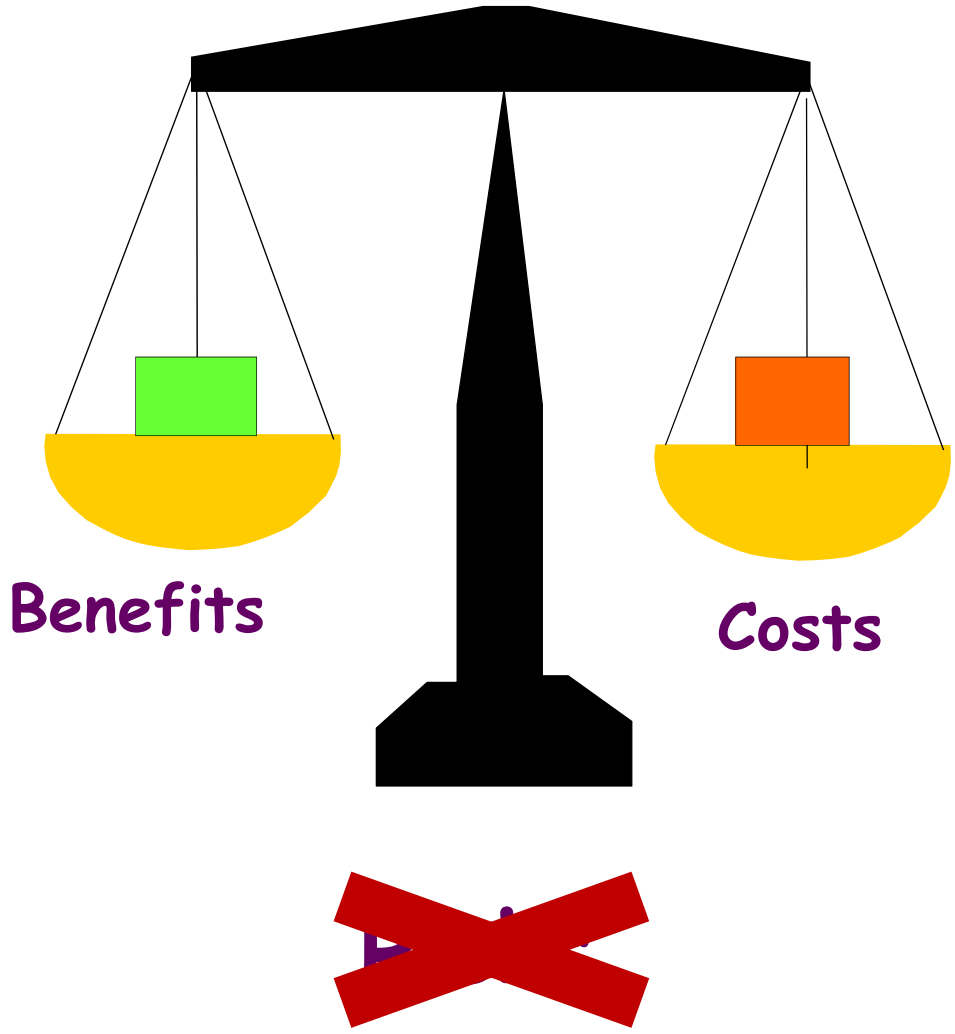
How to Balance Benefits, Risks & Costs: A Pharmaceutical Company Perspective?



How to Balance Benefits, Risks & Costs: Regulatory Agency Different Perspective?



How to Balance Benefits, Risks & Costs: A Patient's Different perspectives?



Is a Structured Approach for Regulatory Decisions the Way Forward: 'WHO Golden Rules'

- ***Weak or inefficient regulatory systems do not serve the interests of consumers, patients, industry or the health care system***

- ***All regulatory systems should be science based, respect international standards and best practices***

- ***Regulatory framework and cost effectiveness analysis should be adopted at early stage of development to access***

- ***Collaboration should lead to mutual benefit and measurable public health gains***

The methods of science rely on core questions:

AND…

a new regulatory framework is emerging based on:

- Pricing
- payment decisions,
- outcomes/pharmacoeconomic studies,
- evidence-based quality of care,

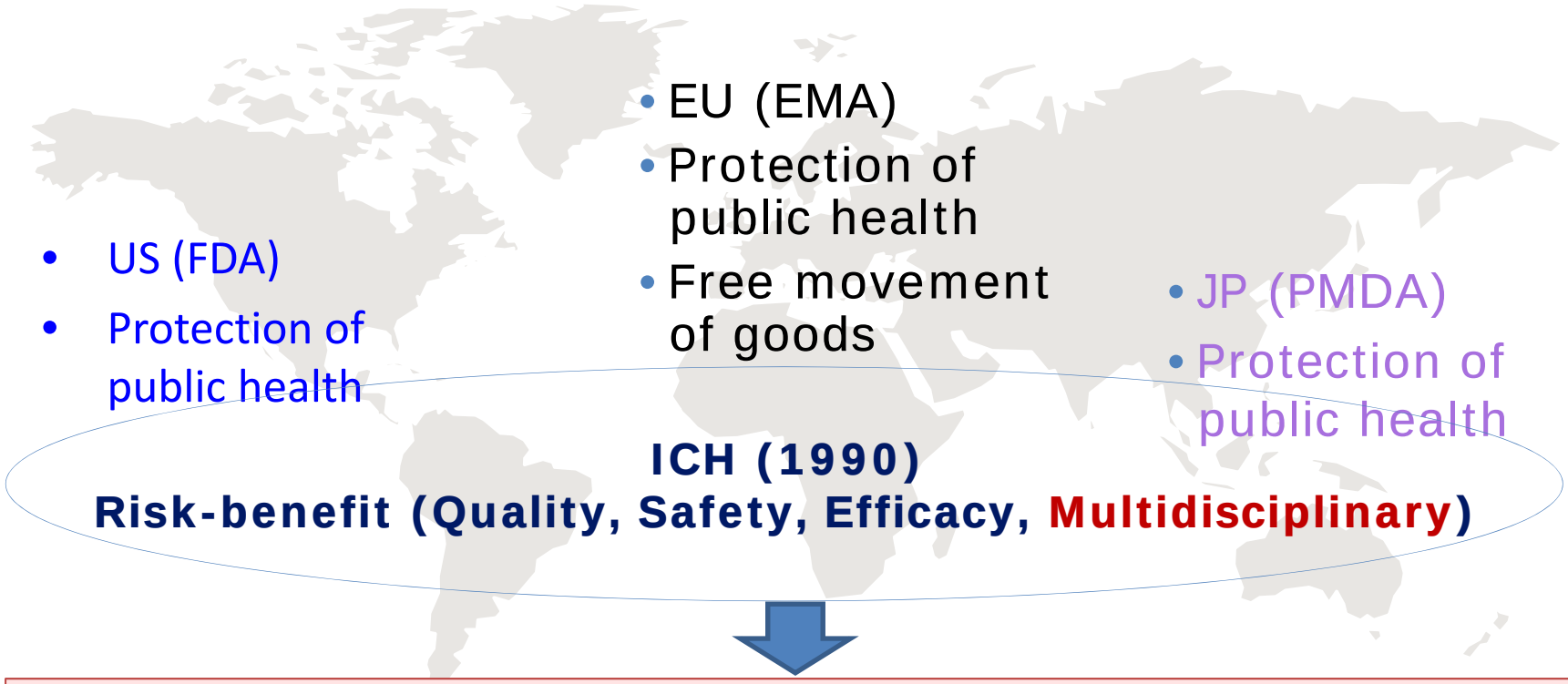
Rational use of a medicine in the overall context of cost-effective and evidence-based health care delivery

Increasing scope & complexity in Drug Development & Regulations

…National Regulatory Focus….

Global Regulatory Focus

"Protection of public health" is the legislative basis for approval of a new product

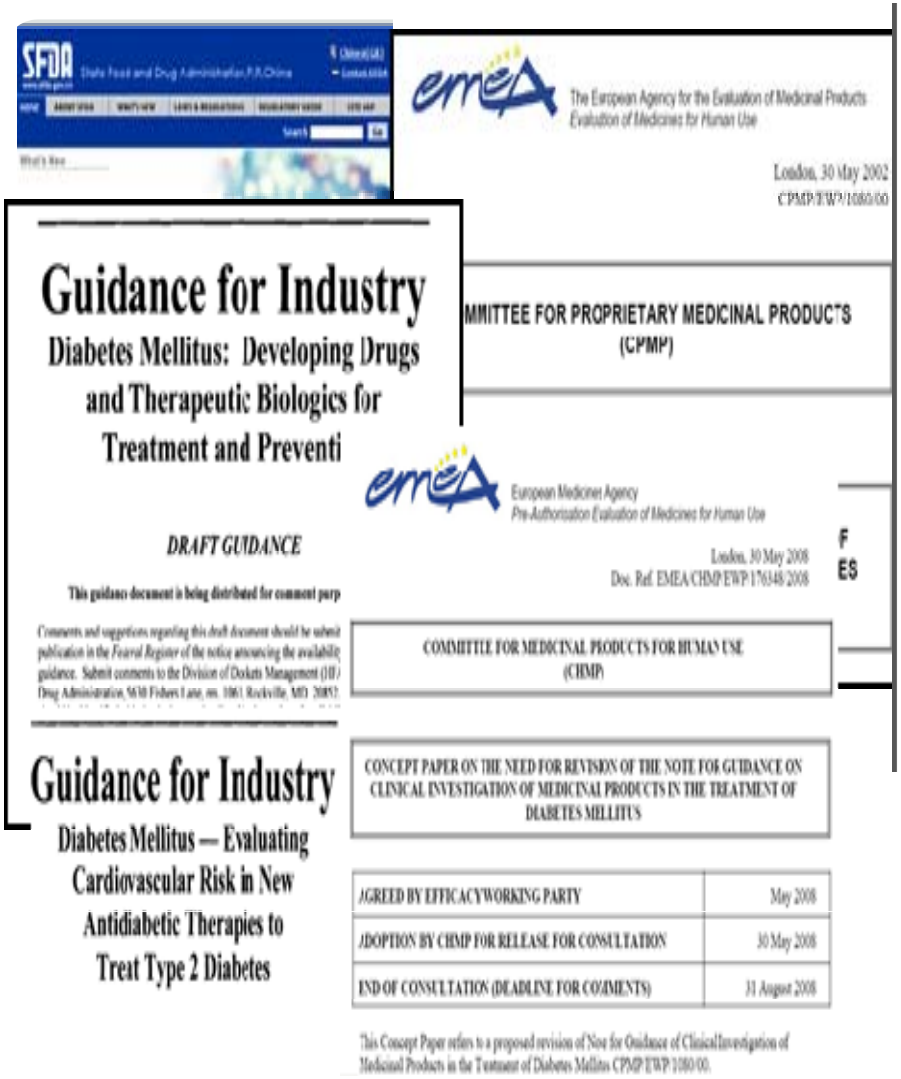


- Harmonised regulatory requirments for drug development.
- Harmonised regulations; GxP, GDP, GMP, GCP, GVP, GLP, GPP, etc.
- Common application files & data = CTD (Common Technical Document).
- Setting global standards and compliance requirements for Industry to protect patients

FDA: Food and Drug Administration
EMA: European Medicines Agency
PMDA: Pharmaceuticals and Medical Devices Agency - Japan

Drug Development: The Regulatory Framework

Regulatory Guidelines



ICH
harmonisation for better health

Guidance for Industry

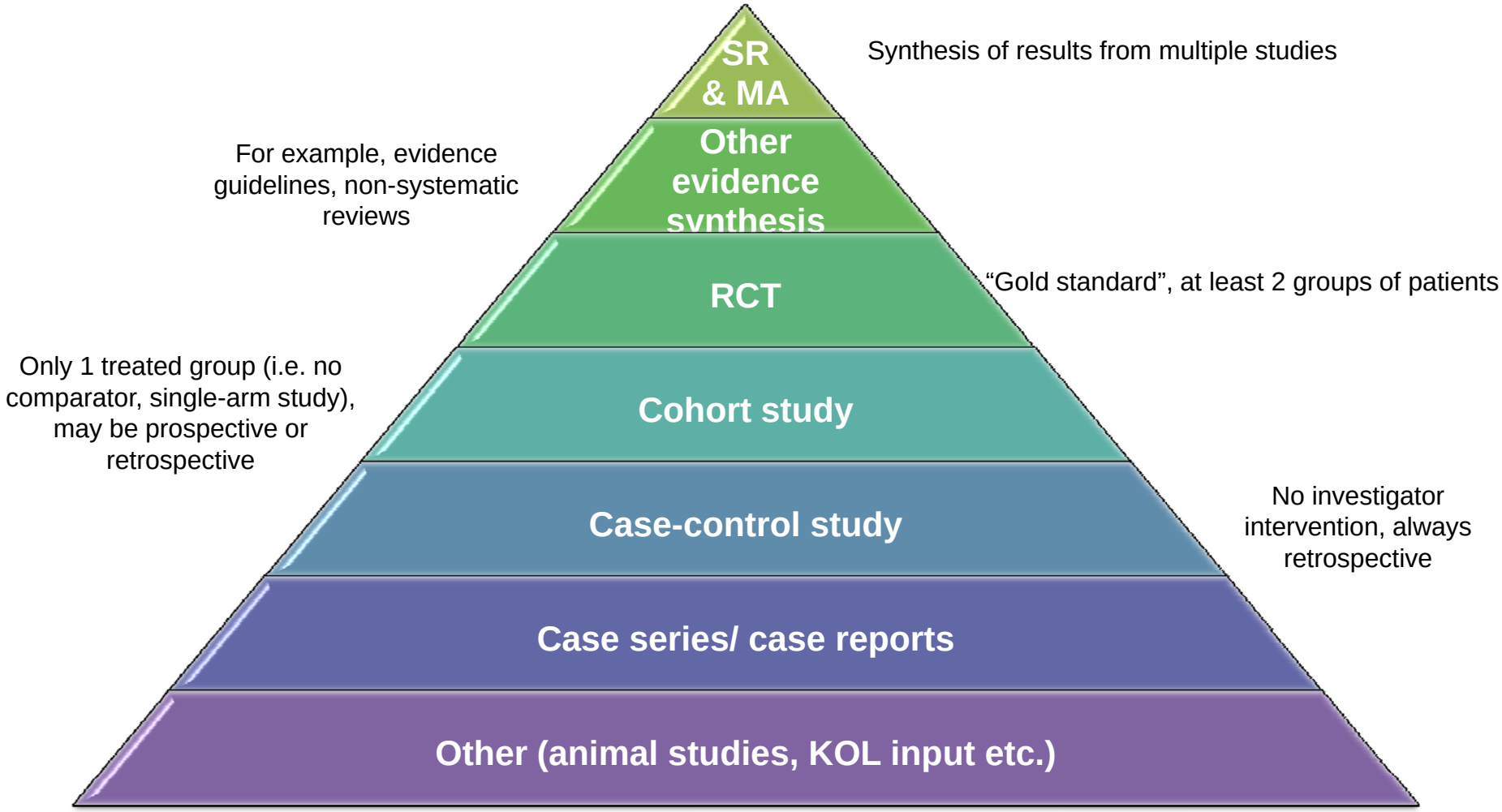
Q8(R2) Pharmaceutical Development

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CD
Center for Biologics Evaluation and Research (C

November 2009
ICH

Revision 2

What are the most common designs of clinical studies?

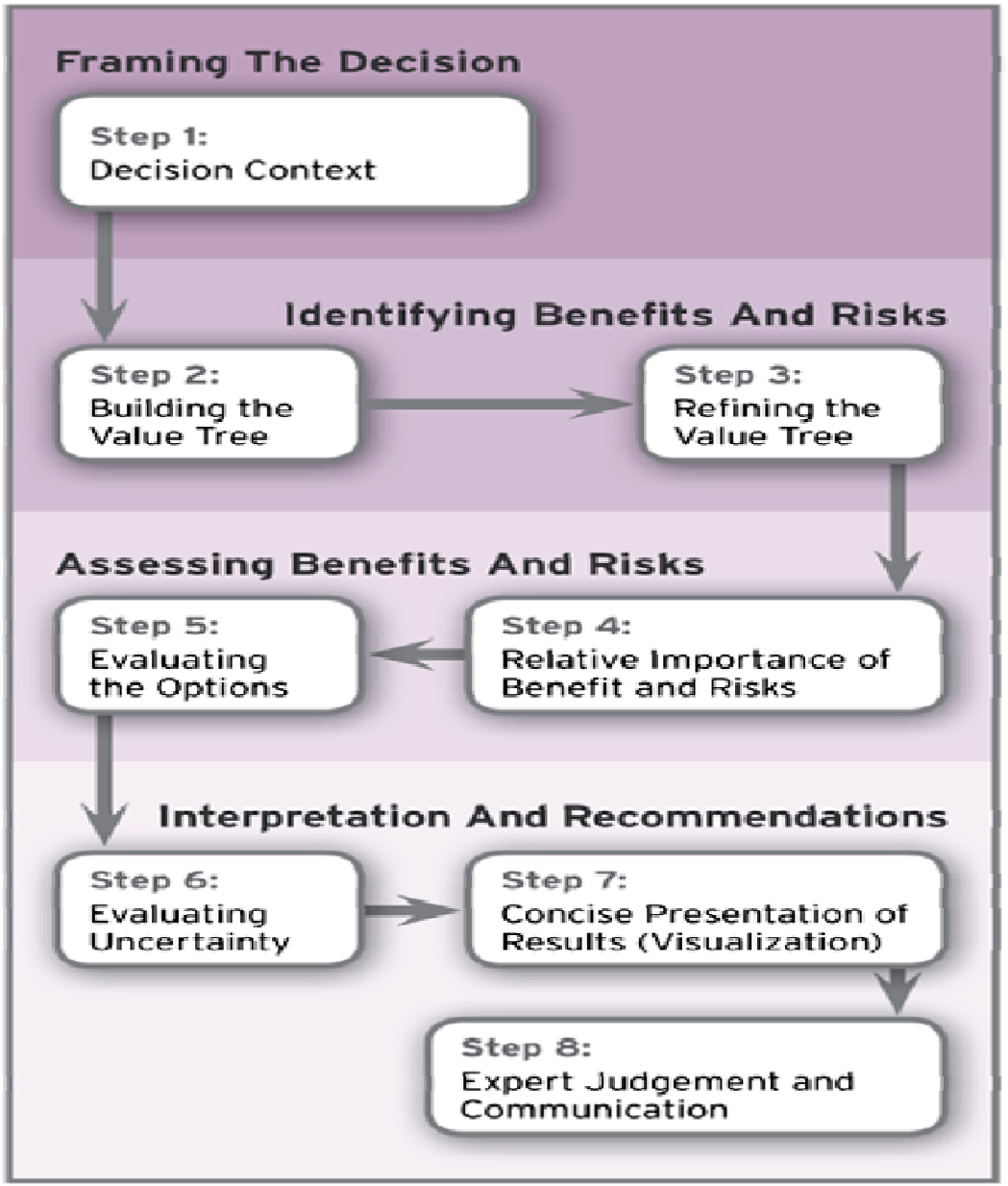


Key: MA, meta-analysis; RCT, randomised controlled trial; SR, systematic review.

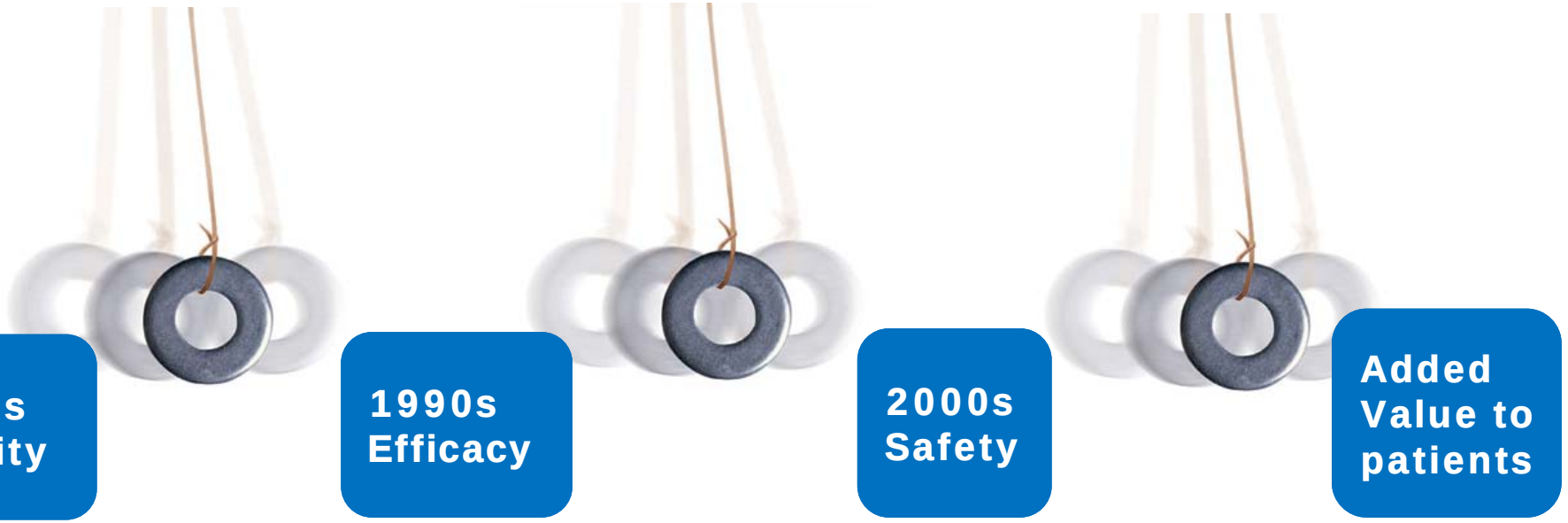
Drug Development: Decision-Making Process Matters

UMBRA 8-Step Benefit-Risk Framework

"An international group of regulators and drug companies have agreed in principle to a framework that sets out eight steps for assessing a drug's benefits and harms and could set the stage for a global approach to evaluating medicines" *Pink Sheet* August 2012



Rapidly Changing Environment
Health Authorities focus shifting

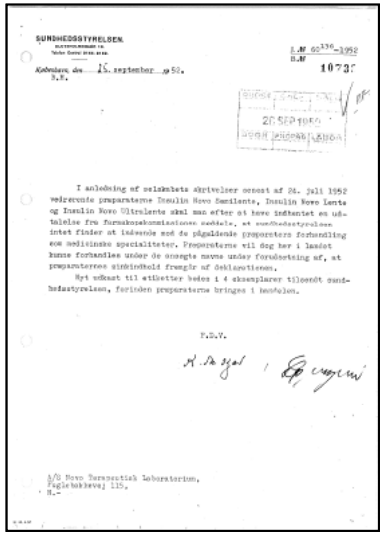


Consequence: It has become much more difficult to get drugs approved

Keeping up with increasing scope and complexity of global regulations for Drug Development

1952

Insulin products MAA
7 pages


SUNDHEDSSTYRELSEN

København, den 15. september 1950.

10737

I anledning af ovennævnte skrivelser oversat af 24. juli 1952 vedrørende præparaterne Insulin Novo Semilente, Insulin Novo Lente og Insulin Novo Ultralente skal man efter at have indhentet en udtalelse fra farmakopékommissionen meddele, at sundhedsstyrelsen intet finder at indvende mod de pågældende præparaters forhandling som medicinske specialiteter. Præparaterne vil dog her i landet kunne forhandles under de ovenfor nævnte navne under forudsætning af, at præparaternes sammensætning fremgår af deklarationen.

Nyt udkast til etiketter bedes i 4 eksemplarer tilsendt sundhedsstyrelsen, førinden præparaterne bringes i handelen.

P.M.V.

A/S Novo Therapeutisk Laboratorium,
Tagtækkevej 115,

2008

antidiabetic BLA submitted to FDA / EMA

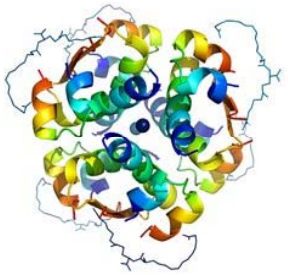
930.000 pages

2011

Next Generation Insulin BLA

14,000,000 Pages

Distance from NY - California



2018

MAA / BLA

Millions of Pages

?

WHAT ABOUT THE COST

&

ACCESS TO MARKET

PHARMACO-ECONOMIC EVALUATION vs. MARKET ACCES

The process of comparing the value of one drug or therapy to another in terms of costs, benefits, efficacy, contribution to quality of life, etc.

Why Important?	* Applicants to consider investment & development efforts
	* Payers are increasingly incorporating pharmaco-economic evaluations into their reimbursement decision processes

PHARMACO-ECONOMIC EVALUATION

- BUDGET IMPACT ANALYSIS
- COST-EFFECTIVENESS ANALYSIS – INCREMENTAL COST-EFFECTIVESS RATIO
- COST-UTILITY ANALYSIS
- CLINICAL EFFECTIVENESS
- COMPETITIVE RATIONALIZATION
- COST-CONSEQUENCE ANALYSIS
- COST-BENEFIT ANALYSIS

MARKET ACCESS STRATEGIES

- STAKEHOLDER MAPPING AND ENGAGEMENT
- ACCOUNT MANAGEMENT
- DECISION-MAKING PROCESS MAPPING
- HEALTH TECHNOLOGIES ASSESSMENT (HTA)
- VALUE DEVELOPMENT
- VALUE COMMUNICATION
- INTERNATIONAL REFERENCE PRICING
- ECONOMICALLY JUSTIFIABLE PRICING

Market Access and Reimbursement Schemes

FINANCIAL-BASED SCHEMES*

SIMPLE / CONFIDENTIAL NET DISCOUNTS

FREE PRODUCTS

VOLUME-DEPENDENT PRICING

- *Volume-dependent pricing*
- *Volume-dependent rebates / refund*

CAPPING

- *Budget cap*
- *Dosage cap*
- *Patient volume cap*
- *Utilization cap*

PORTFOLIO PRICING

- *Fixed price for portfolio*
- *Bundled products*

PERFORMANCE- / OUTCOMES-BASED SCHEMES (VBC)

EVIDENCE DEVELOPMENT

- *Real world evidence (RWE) generation*
- *Clinical endpoint achievement*

OUTCOMES-BASED CONTRACTING

- *Outcomes-based refunds / rebates*
- *Conditional Treatment Continuation*
- *Global response-based scheme (GBRS)*

ALTERNATIVE APPROACHES

DISEASE AWARENESS & SCREENING

PATIENT SUPPORT PROGRAM (PSP)

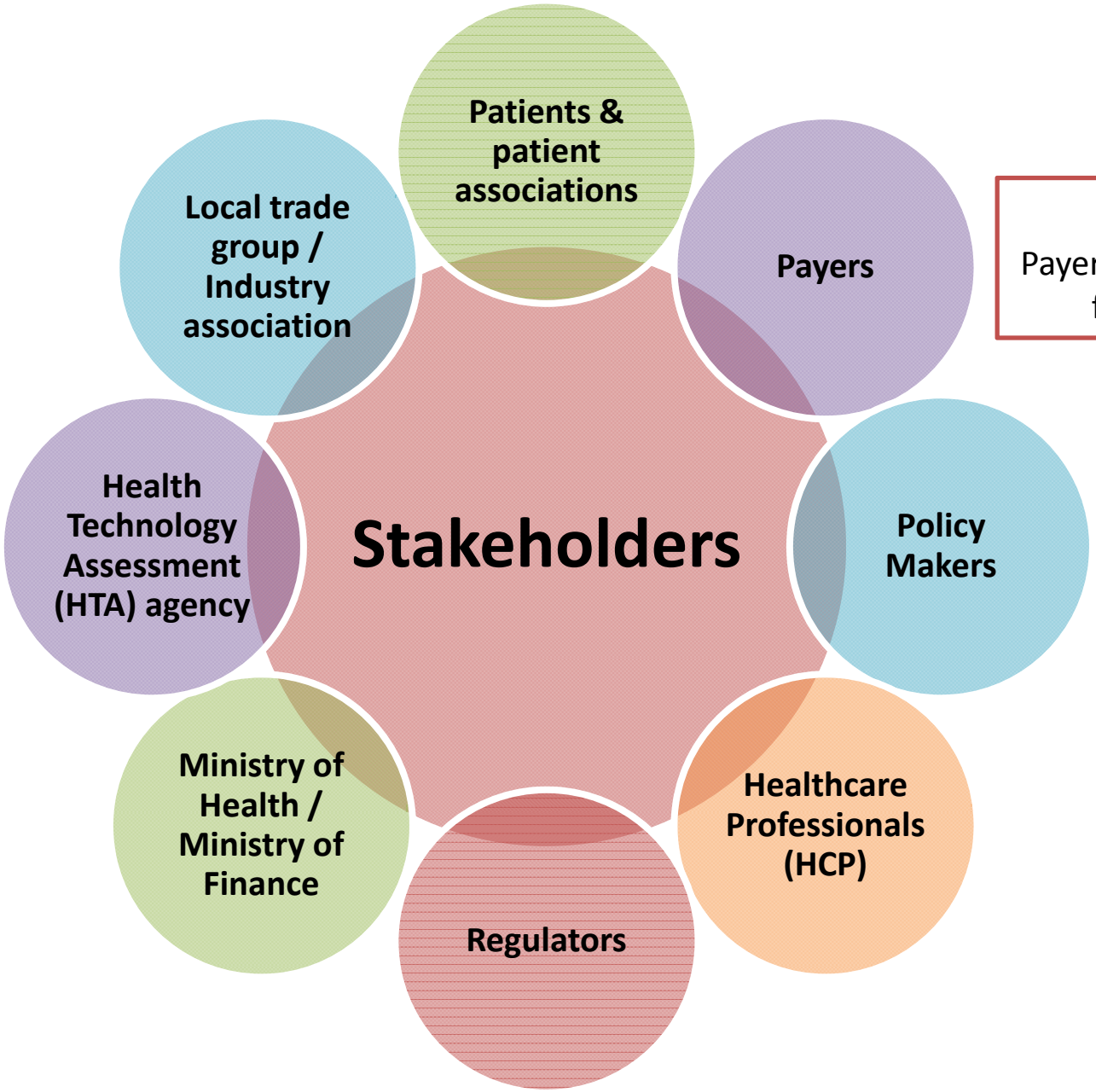
INDICATION-SPECIFIC SOLUTIONS

- *Indication-based pricing*
- *Indication reimbursement restriction*

MEANS-TESTED PATIENT ASSISTANCE PROGRAM

TECHNOLOGY TRANSFER

STAKEHOLDER MAPPING AND ENGAGEMENT



Example:

Payers can approach pricing decision from two key perspectives:

Cost-effectiveness

Clinical effectiveness

Health Technology Assessment 2004; Vol. 8: No. 36

Review of guidelines for good practice in decision-analytic modelling in health technology assessment

Z Philips, L Ginnelly, M Sculpher, K Claxton, S Golder, R Riemsma, N Woolacott and J Glanville

September 2004

Health Technology Assessment 2004; Vol. 8: No. 36

Abstract

Review of guidelines for good practice in decision-analytic modelling in health technology assessment

Z Philips,[1] L Ginnelly,[1]* M Sculpher,[1] K Claxton,[1,2] S Golder,[3] R Riemsma,[3] N Woolacott[3] and J Glanville[3]

[1] Centre for Health Economics, University of York, UK
[2] Department of Economics, University of York, UK
[3] Centre for Reviews and Dissemination, University of York, UK
* Corresponding author

Objectives: To identify existing guidelines and develop a synthesised guideline plus accompanying checklist. In addition to provide guidance on key theoretical, methodological and practical issues and consider the implications of this research for what might be expected of future decision-analytic models.
Data sources: Electronic databases.
Review methods: A systematic review of existing good practice guidelines was undertaken to identify and summarise guidelines currently available for assessing the quality of decision-analytic models that have been undertaken for health technology assessment. A synthesised good practice guidance and accompanying checklist was developed. Two specific methods areas in decision modelling were considered. The first method's topic is the identification of parameter estimates from published literature. Parameter searches were developed and piloted using a case-study model. The second topic relates to bias in parameter estimates; that is, how to adjust estimates of treatment effect from observational studies where there are risks of selection bias. A systematic literature review was conducted to identify those studies looking at quantification of bias in parameter estimates and the implication of this bias.
Results: Fifteen studies met the inclusion criteria and were reviewed and consolidated into a single set of brief statements of good practice. From this, a checklist was developed and applied to three independent decision-analytic models. Although the checklist provided excellent guidance on some key issues for model evaluation, it was too general to pick up on the specific nuances of each model. The searches that were developed helped to identify important data for inclusion in the model. However, the quality of life searches proved to be problematic: the published search filters did not focus on those measures specific to cost-effectiveness analysis and although the strategies developed as part of this project were more successful few data were found. Of the 11 studies meeting the criteria on the effect of selection bias, five concluded that a non-randomised trial design is associated with bias and six studies found 'similar' estimates of treatment effects from observational studies or non-randomised clinical trials and randomised controlled trials (RCTs). One purpose of developing the synthesised guideline and checklist was to provide a framework for critical appraisal by the various parties involved in the health technology assessment process. First, the guideline and checklist can be used by groups that are reviewing other analysts' models and, secondly, the guideline and checklist could be used by the various analysts as they develop their models (to use it as a check on how they are developing and reporting their analyses). The Expert Advisory Group (EAG) that was convened to discuss the potential role of the guidance and checklist felt that, in general, the guidance and checklist would be a useful tool, although the checklist is not meant to be used exclusively to determine a model's quality, and so should not be used as a substitute for critical appraisal.
Conclusions: The review of current guidelines showed that although authors may provide a consistent message regarding some aspects of modelling, in other areas conflicting attributes are presented in different guidelines. In general, the checklist appears to perform well, in terms of identifying those aspects of the model that should be of particular concern to the reader. The checklist cannot, however, provide answers to the appropriateness of the model structure and structural

European Medicines Agency

London, 23 June 2009
Doc ref.: EMEA/40926/2009

Information on benefit-risk of medicines: patients', consumers' and healthcare professionals' expectations

ary

ncreasingly involved in discussing with healthcare professionals about their choice of
cial that there is a clear understanding of the benefits and risks of medicines to help
on on the most suitable treatment for the individual patient. Following a request from
and healthcare professionals, the European Medicines Agency carried out a survey to
prove the information it provides on the benefits and risks of medicines.

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3752

ORIGINAL REPORT

Factors influencing quality decision-making: regulatory pharmaceutical industry perspectives†

Ronan Donelan[1], Stuart Walker[2] and Sam Salek[3]*

[1] *Global Regulatory Affairs, Quintiles, Dublin, Ireland*
[2] *Centre for Innovation in Regulatory Science, London, UK*
[3] *Department of Pharmacy, University of Hertfordshire, Hatfield and Institute for Medicines Development, Car*

ABSTRACT

Purpose Currently, there is no qualified understanding of the influences, behaviours and other factors that imp individuals and organisations involved in the development of new medicines. The aim of this qualitative study wa the important issues that influence quality decision-making.

Methods Semi-structured interviews were carried out with 29 senior decision-makers from the pharmaceutical thorities. The study participants were invited to discuss and review their perception of decision-making within t drug development and the regulatory review and their awareness and use of decision-making techniques and th decisions.

Results The analyses (using NVivo 8© software) resulted in the identification of 32 major and 97 sub-themes 19 overarching themes. These included items such as quality and validity of data, time considerations, organisatic analytical and logical approach, qualification and experience, subjective and personal considerations, political infl ilar previous decisions, understanding of the decision in question, impact analyses, audit trail, education and a corporate decision-making and frameworks. Relationships between themes were identified. The 19 overarchir were integrated into a framework for quality decision-making.

Conclusion This study has achieved its aim of exploring decision-making from the perspective of the indiv working in drug development and the regulatory review and has identified issues and considerations relating to sions and allowed for the generation of a framework to aid quality decision-making. Copyright © 2015 John W

KEY WORDS—qualitative; interviews; decision-making; quality; regulatory agencies; pharmaceutical industry framework; pharmacoepidemiology

Eur J Clin Pharmacol
DOI 10.1007/s00228-010-0848-8

SPECIAL ARTICLE

Risk Management Plans: are they a tool for improving drug safety?

Serena Frau · Maria Font Pous · Maria Rosa Luppino · Anita Conforti

Received: 18 March 2010 / Accepted: 20 May 2010

Abstract
Purpose In 2005, new European legislation authorised Regulatory Agencies to require drug companies to submit a risk management plan (RMP) comprising detailed commitments for post-marketing pharmacovigilance. The aim of the study is to describe the characteristics of RMP for 15 drugs approved by the European Medicines Agency (EMA) and their impact on post-marketing safety issues.
Methods Of the 90 new Chemical Entities approved through a centralised procedure by the EMA during 2006 and 2007, 15 of them were selected and their safety aspects and relative RMPs analysed. All post-marketing communications released for safety reasons related to these drugs were also considered.
Results A total of 157 safety specifications were established for the drugs assessed. Risk minimisation activities were foreseen for 5 drugs as training activities. Post-marketing safety issues emerged for 12 of them, leading to 39 type II variations in Summary of Product Characteristics (SPC). Nearly half of such variations, 19 (49%), concerned safety aspects not envisaged by the RMPs. Besides this, 9 Safety Communications were published for 6 out of 15 drugs assessed.
Conclusion The present study reveals several critical points on the way RMPs have been implemented. Several activities proposed by the RMPs do not appear to be adequate in dealing with the potential risks of drugs. Poor communication of risk to practitioners and to the public, and above all limited transparency for the total assessment of risk, seem to transform RMPs into a tool to reassure the public when inadequately evaluated drugs are granted premature marketing authorisation.

Keywords Risk management · Risk assessment · Safety management · Surveillance programs · Hazard · Postmarketing product surveillance

S. Frau
Dialogo sui Farmaci, Pharmaceutical Department,
Verona Local Health Unit,
Verona, Italy

KEY MESSAGES

- Regulatory and parmacoeconomic evaluation as well as Benefit-Risk Assessment of medicines is a an ongoing process both in the pre and post authorisation period

- Clear frameworks and motives should be there for:
  - ❑ discovery
  - ❑ research and development
  - ❑ sound regulatory decision-making
  - ❑ rapid registration decisions
  - ❑ post-approval change and controls
  - ❑ optimal pricing/payment strategies
  - ❑ evidence-based health care delivery based on outcomes/pharmacoeconomic studies,
  - ❑ quality of care
  - ❑ safe medicine use

- Ultimate consolidation is based on a vision of a collaborative structured approach and close involvement of all stakeholders throughout the overall process.

- promote, as overarching strategic objectives, rational use of medicines and good, cost-effective health care delivery practices.

Regulatory Challenges…


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
спасибо
dank je
tapadh leat
mochchakkeram
bedankt
dziękuje
go raibh maith agat
obrigado
sukriya
kop khun krap
grazie
arigatō
dakujem
terima kasih
merci
감사합니다
мерси