Presentazione del rapporto sui farmaci in Toscana 2019

Firenze, 11 dicembre 2019

L'approvazione dei farmaci in Europa: dall'analisi sul rischio-beneficio al Risk Management Plan

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Università degli studi di Milano-Bicocca

Outline

- Introduzione sugli aspetti regolatori e sulle criticità relative al processo di approvazione dei farmaci
- Sottolineare il ruolo del Risk Management Plan come strumento di monitoraggio per la sicurezza post-autorizzazione
- Descrivere il ruolo della RWE nella conduzione dei PASS, inclusi gli studi di valutazione delle misure di minimizzazione del rischio

Approvazione dei farmaci:
framework regolatorio

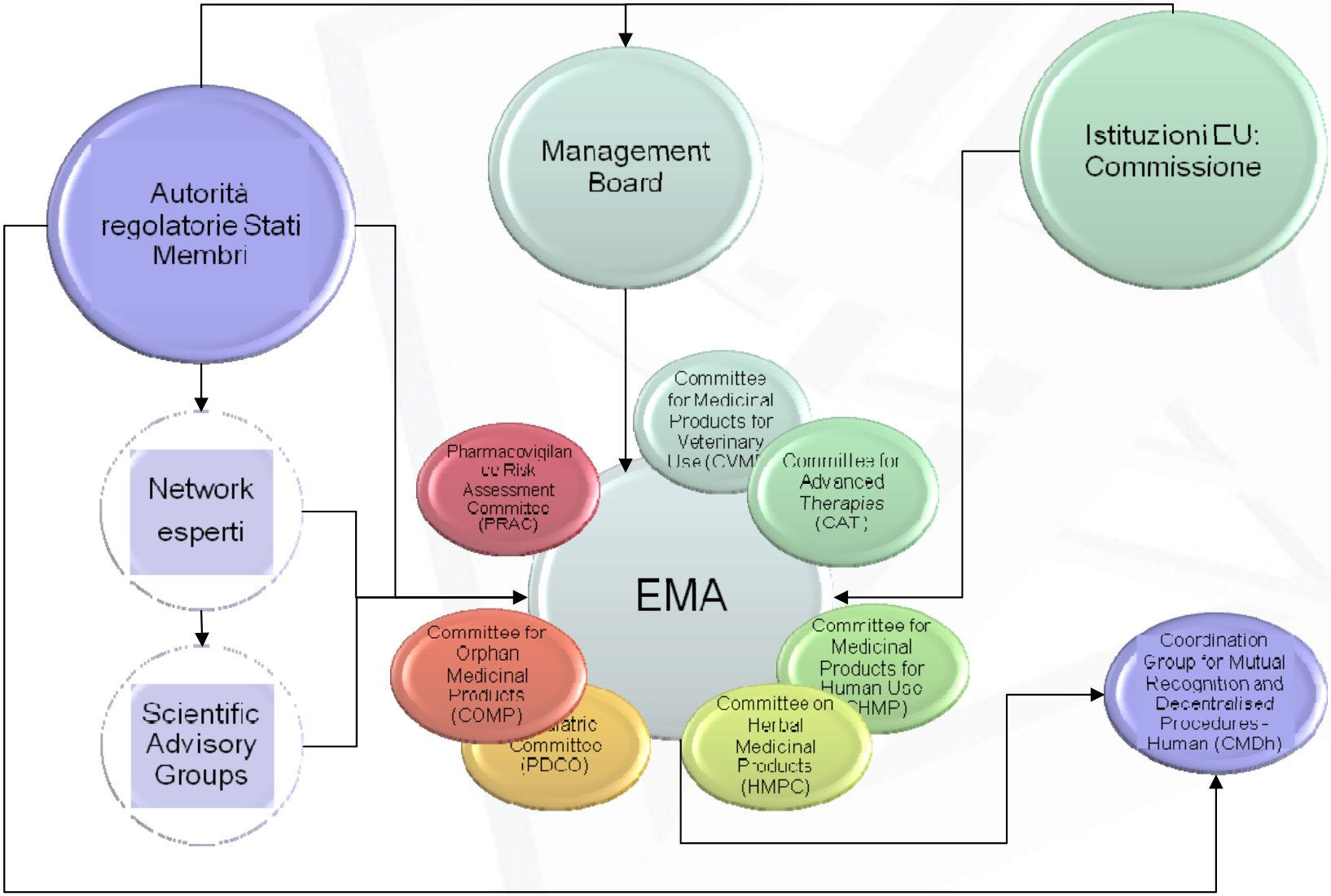
A medicinal product may only be placed on the market in the EU when a **Marketing Authorisation** has been issued by:

- the competent authority of the Member State(s) (MS)
- or by the European Commission (EC)

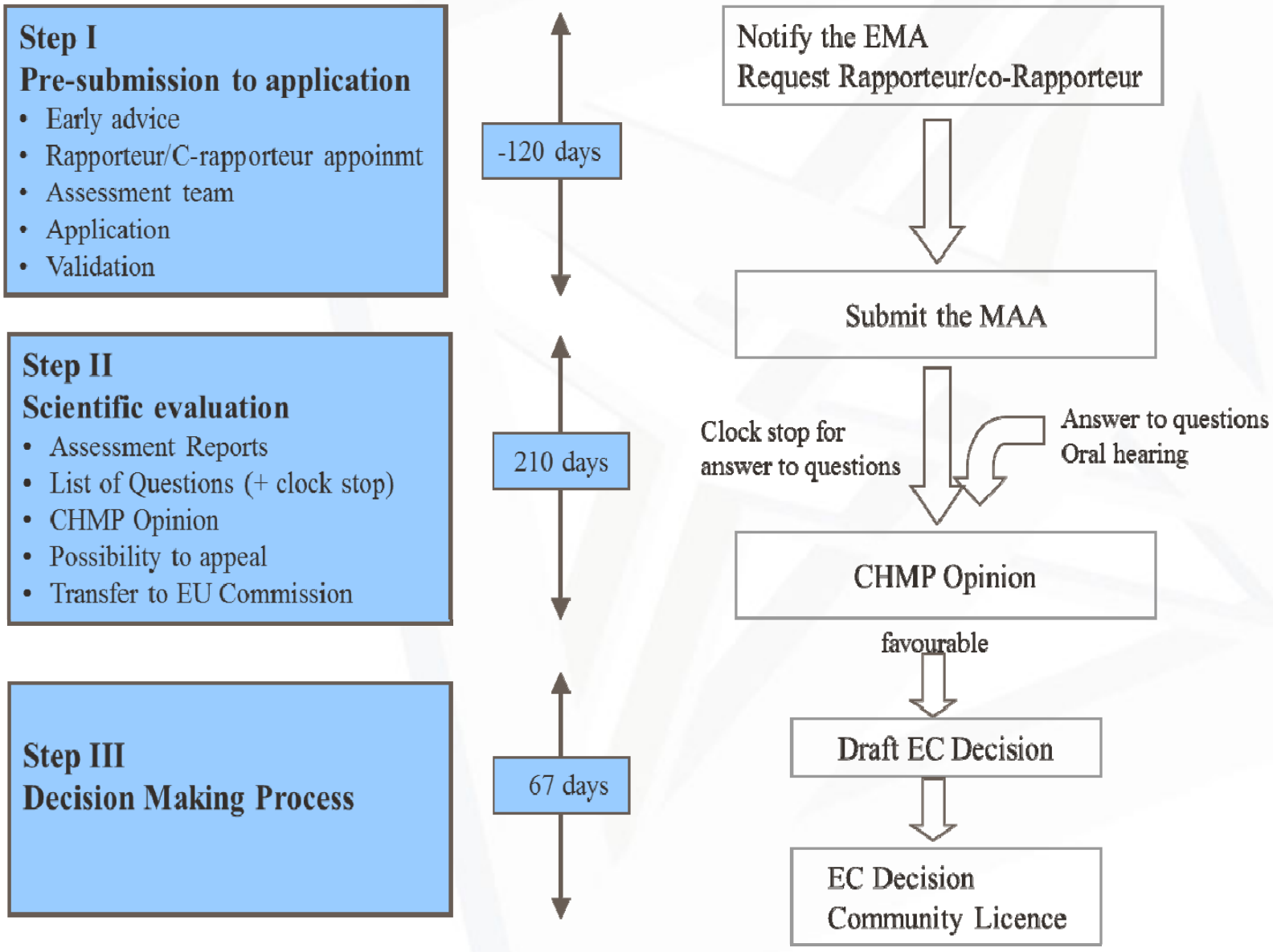
Same legal requirements irrespective of the route/procedure for the authorisations - granted on the basis of quality, safety and efficacy.

- Centralised Procedure (CP)
- Mutual Recognition Procedure (MRP)
- Decentralised Procedure (DCP)
- National Procedure (NP)

Approvazione dei farmaci: il network Europeo



Approvazione dei farmaci



Approvazione dei farmaci:
sviluppo clinico

Preclinical studies ⟷ Clinical studies

Discovery | Early Clinical | Development

	Pre Clinical Testing	FILE IND	Phase I	Phase II	Phase III	FILE NDA	FDA/EMA/ NCAs	Approval
Years	**3.5**		**1 - 2**	**2 - 4**	**4 - 6**		**1.5**	**Total = 12 - 17**
Test Population	Laboratory and Animal Studies		20 to 100 Healthy Volunteers	100 – 300 Patient Volunteers	1,000 to 3,000 Patient Volunteers		Review Process	Post Marketing Safety Monitoring
Purpose	Assess Safety and Biological Activity		Determine Safety and Dosage	Evaluate Effectiveness. Look for Side Effects.	Verify Effectiveness, Monitor Adverse Reactions from Long-Term Use			Large Scale Manufacturing --- Distribution --- Education
% of all new drugs that pass			70% of INDs	30% of INDs	27% of INDs		20% of INDs	

Approximately 10–15 years from idea to marketable drug

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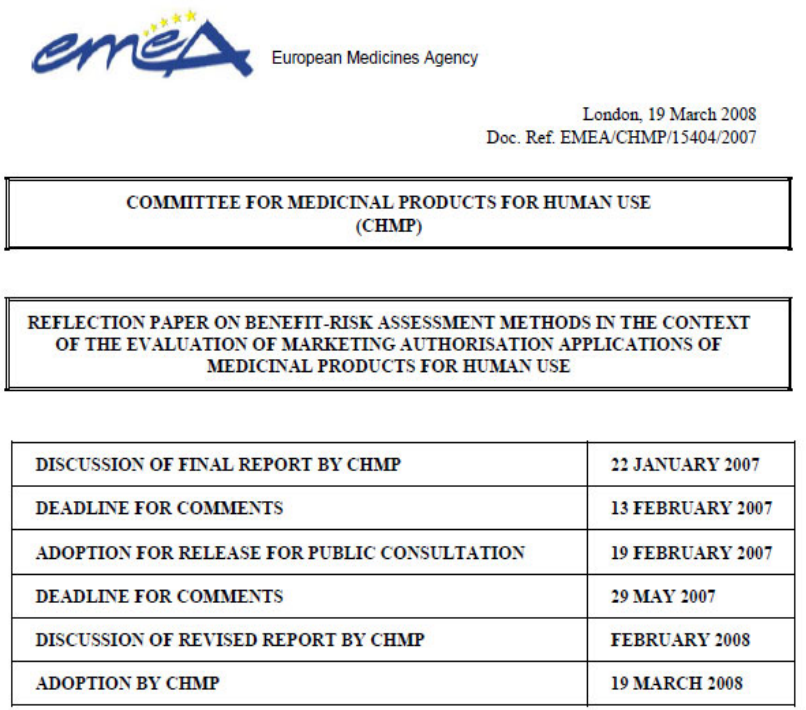
Analisi beneficio-rischio

*The assessment of the **benefits-risk profile** in the context of a new drug application is a **central element of the scientific evaluation** of a marketing authorisation application and related variations.*

*The assessment must reach a sufficient level of confidence that a set level of **quality**, **efficacy** and **safety** of the new medicinal product has been demonstrated.*

This requires evaluation of all relevant data as well as the use of judgement and arguments.



European Medicines Agency

London, 19 March 2008
Doc. Ref. EMEA/CHMP/15404/2007

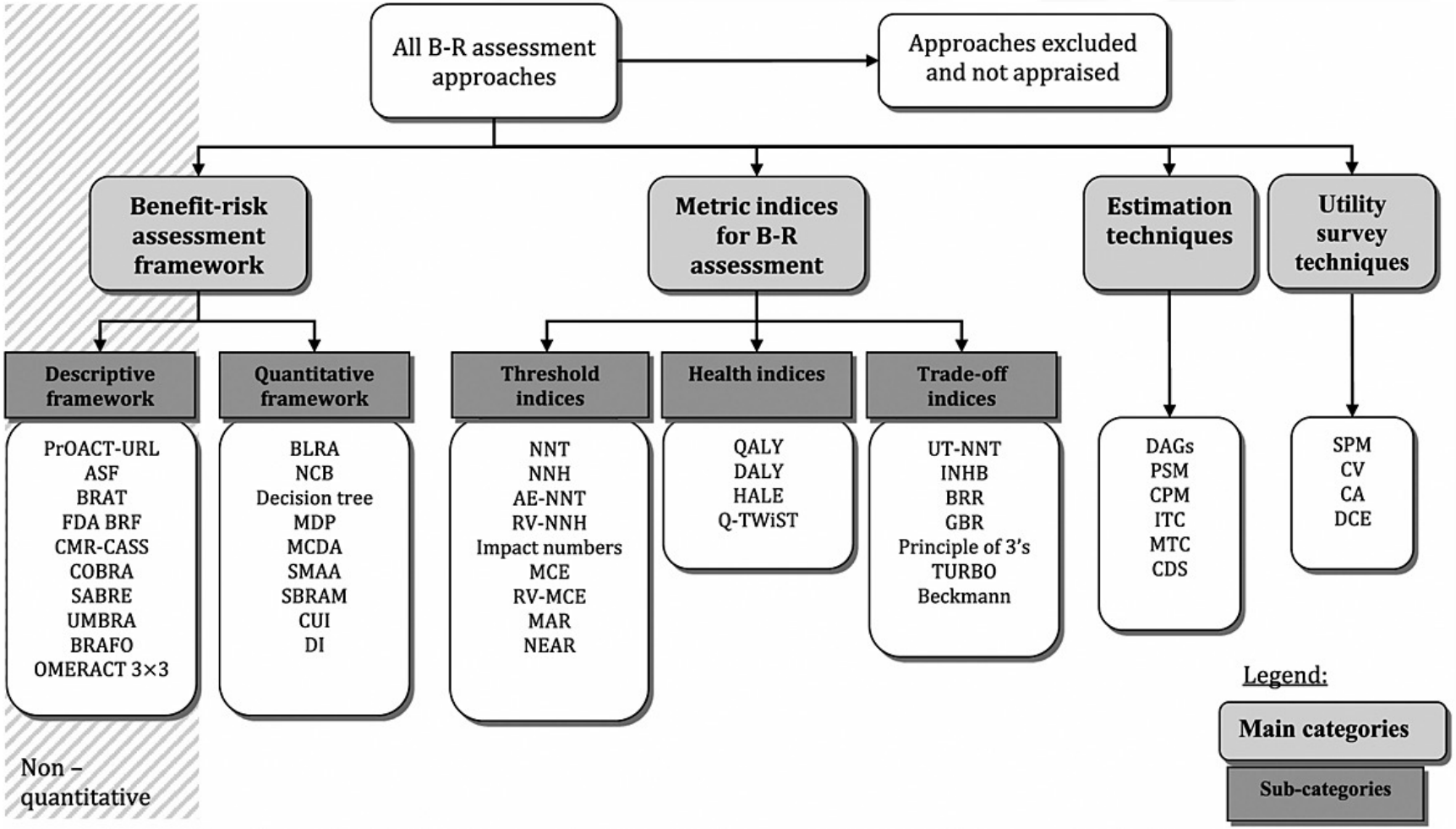
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE CONTEXT OF THE EVALUATION OF MARKETING AUTHORISATION APPLICATIONS OF MEDICINAL PRODUCTS FOR HUMAN USE

DISCUSSION OF FINAL REPORT BY CHMP	22 JANUARY 2007
DEADLINE FOR COMMENTS	13 FEBRUARY 2007
ADOPTION FOR RELEASE FOR PUBLIC CONSULTATION	19 FEBRUARY 2007
DEADLINE FOR COMMENTS	29 MAY 2007
DISCUSSION OF REVISED REPORT BY CHMP	FEBRUARY 2008
ADOPTION BY CHMP	19 MARCH 2008

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf

Analisi beneficio-rischio: metodi



Pharmacoepidemiol Drug Saf. 2014 Jul;23(7):667-78. doi: 10.1002/pds.3636.

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Analisi beneficio-rischio:
PrOACT-URL framework (qualitativo)

Problem	• Determine the nature of the problem and its context. • Frame the problem
Objective	• Establish objectives that indicate the overall purposes to be achieved. • Identify criteria for (a) favourable effects, and (b) unfavourable effects
Alternatives	• Identify the options to be evaluated against the criteria.
Consequences	• Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects.
Trade-off	• Assess the balance between favourable and unfavourable effects.
Uncertainty	• Report the uncertainty associated with the favourable and unfavourable effects. • Consider how the balance between favourable and unfavourable effects is affected by uncertainty.
Risk tolerance	• Judge the relative importance of the decision maker's risk attitude for this product. • Report how this affected the balance reported in step 9.
Linked decisions	• Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

http://protectbenefitrisk.eu/PrOACT-URL.html

Analisi beneficio-rischio:
Effect Table (quantitativo)

		Name	Description	Best[1]	Worst	Units	Placebo[2]	300 mg[2]	Uncertainties
Favourable Effects	Primary Endpoint	Progression-free survival Hazard Ratio	Date of randomization to the date of objective progression or death (blinded independent review)	0	1	unitless	1	0.46	Only a very low number of patients with definite RET negative status at baseline
	Secondary Endpoints	Progression-free survival (median)	Date of randomization to the date of objective progression or death (Weibull model)	60	0	months	19.3	30.5	
		Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter of target lesions compared to baseline)	100	0	%	13	45	
Unfavourable Effects		Diarrhoea CTC3 Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living; Life-threatening consequences (e.g., hemodynamic collapse)	0	100	%	2.0	10.8	Duration of follow up in the pivotal study is quite short with regard to the need for long duration of treatment and therefore the risk of developing further major Cardiac SAEs including Torsades de pointe.
		QTc related events CTC[3] Grade 3-4	QTc >0.50 second; life threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	0	100	%	1.0	13.4	
		Infections CTC[3] Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated; Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	0	100	%	36.4	49.8	

Hypothetical example of an Effects Table for Caprelsa (vandetanib, treatment of inoperable thyroid cancer)

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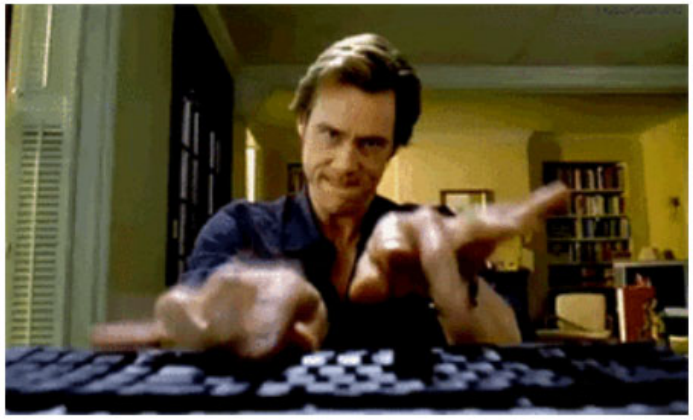
Analisi beneficio-rischio:
be creative!

Benefit-risk assessment and discussion

This is where we use value judgements! Interpretation of the results; possibility to be creative!!



LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Kristina Dunder 2018, SE CHMP

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Analisi beneficio-rischio:
Approccio quali-quantitativo

- *There are no agreed frameworks for the assessment of the B/R profile and/or accepted thresholds.*
- *Assessment of B/R is a **qualitative approach** that is grounded in **quantification** of various data elements:*
  - ***Benefits:** Efficacy endpoints from controlled clinical trials*
  - ***Risks:** Harms reported in clinical trials and other sources (in the post-marketing)*
- *Evaluation of B/R is **dynamic** as knowledge of benefits and risks evolves **over product life-cycle***

Jenkins J. A United States Regulator's Perspective on Risk-Benefit Considerations. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM210155.pdf. Rockville, MD: Shady Grove Conference Center; 2010.

CHMP opinion:

Strumenti che prevedono la valutazione del profilo beneficio-rischio post-autorizzazione

MA under exceptional circumstances	Conditional MA	Standard MA
• MA granting based on a *less comprehensive* data package • Comprehensive clinical data *not expected* • Post approval commitments (studies) *always* • *5 year validity* with annual reassessment of MA • Standard MA not envisaged	• MA granting based on a *less comprehensive* data package • Comprehensive clinical data *expected within defined timeframe* • Post approval commitments (studies) *always* • *1 year validity* with annual renewal of MA • Switch to standard MA envisaged	• MA granting based on *comprehensive* data package • Post approval commitments (studies) *possible* • *5 year validity* • Standard MA at approval

Gli studi randomizzati sono sempre l`opzione preferita.
L`uso RWD, in particolare registri, viene considerata come una possibile seconda scelta

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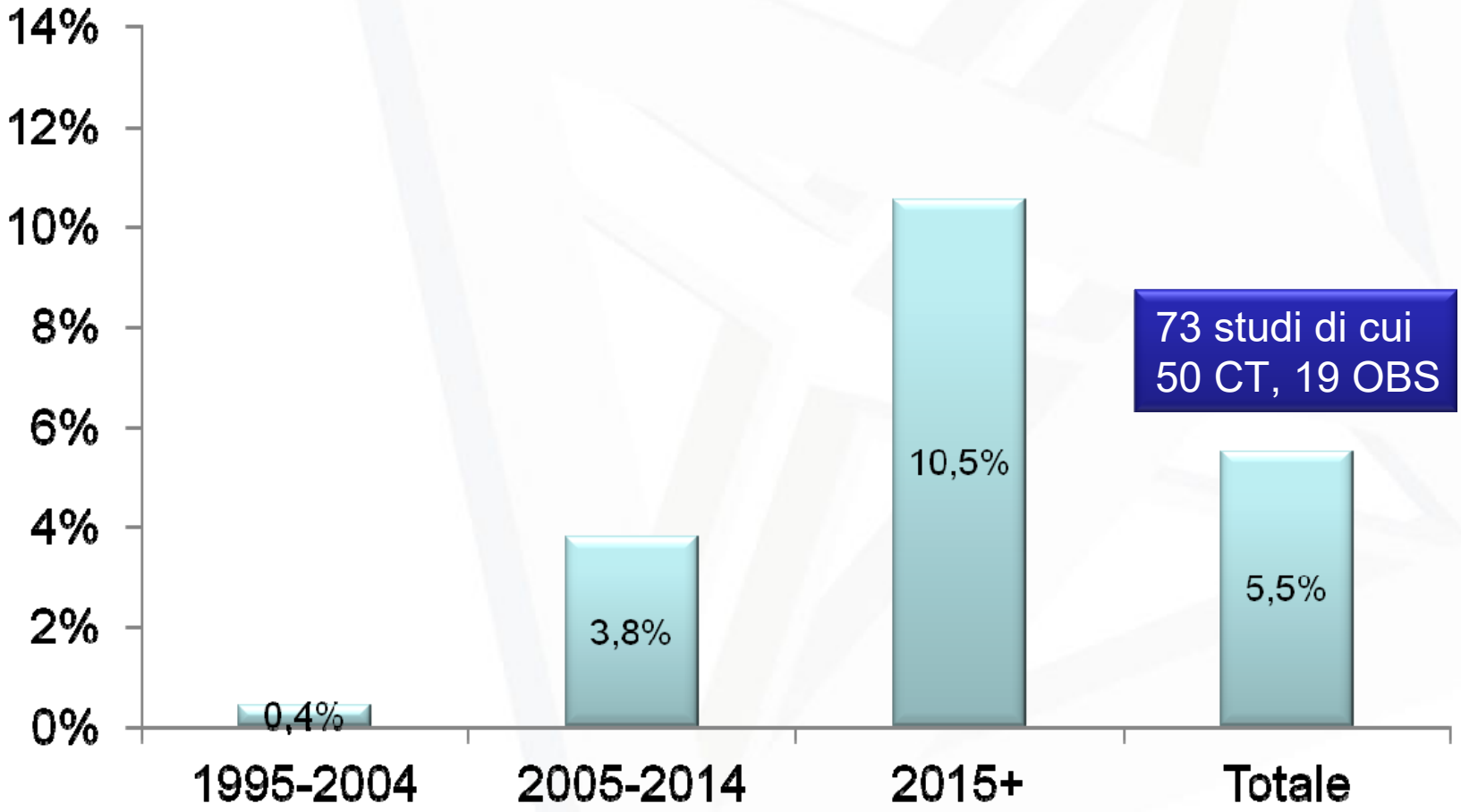
CHMP opinion:

Frequenza di studi post-autorizzazione imposti con richiesta di valutazione di efficacia (1328 farmaci autorizzati)



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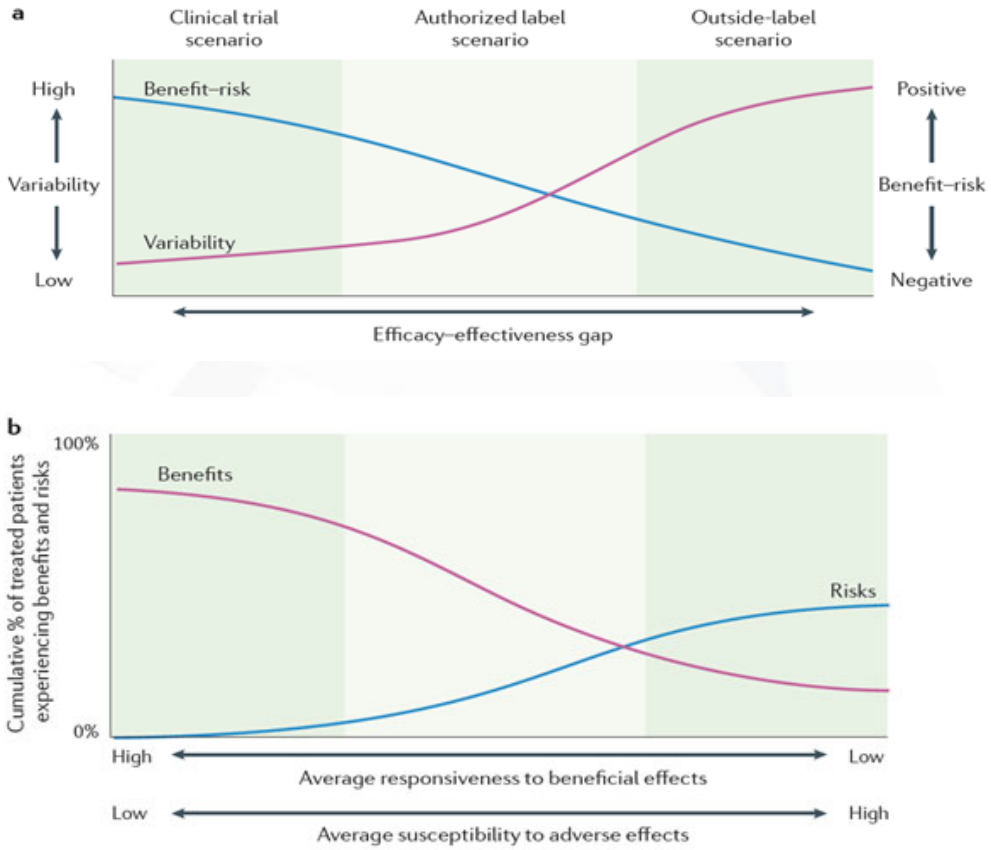
Analisi del rischio pre-approvazione: Limiti dei clinical trials

- Disegnati sull'efficacia, la sicurezza è un endpoint secondario non pre-definito
- Scarsa rappresentatività del campione selezionato
- Dimensione del campione e follow-up limitati



Nature Reviews Drug Discovery 10, 495-506 (July 2011)

Informazioni limitata su reazioni avverse: Rare, con lungo tempo di latenza, da effetto cumulativo, da interazioni, da uso off-label

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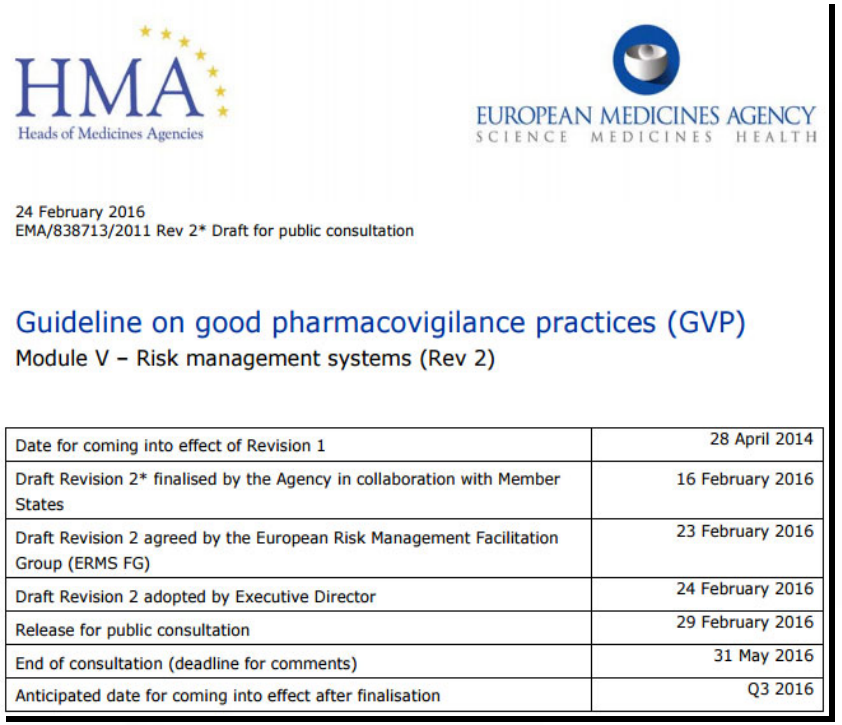
Gestione del rischio post-approvazione: Il Risk Management Plan

Nel 2005 viene introdotto in Europa il RMP, reso obbligatorio nel 2012 per tutti i farmaci approvati da EMA.

L`RMP descrive tutte le attività di Farmacovigilanza con l`obiettivo di gestione delle incertezze sul rischio dei farmaci al momento dell`approvazione. Le attività si esplicitano nell`identificazione, caratterizzazione e minimizzazione di tale rischio.



HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2016
EMA/838713/2011 Rev 2* Draft for public consultation

Guideline on good pharmacovigilance practices (GVP)
Module V – Risk management systems (Rev 2)

Date for coming into effect of Revision 1	28 April 2014
Draft Revision 2* finalised by the Agency in collaboration with Member States	16 February 2016
Draft Revision 2 agreed by the European Risk Management Facilitation Group (ERMS FG)	23 February 2016
Draft Revision 2 adopted by Executive Director	24 February 2016
Release for public consultation	29 February 2016
End of consultation (deadline for comments)	31 May 2016
Anticipated date for coming into effect after finalisation	Q3 2016

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/02/WC500202424.pdf

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News: Sudden withdrawal of cerivastatin by Bayer

The Pharmace

Rosiglitazone: recommended withdrawal from clinical use

Suspension of the marketing authorisations of rosiglitazone (Avandia, Avandamet) recommended across the European Union.

Published 11 December 2014

EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta

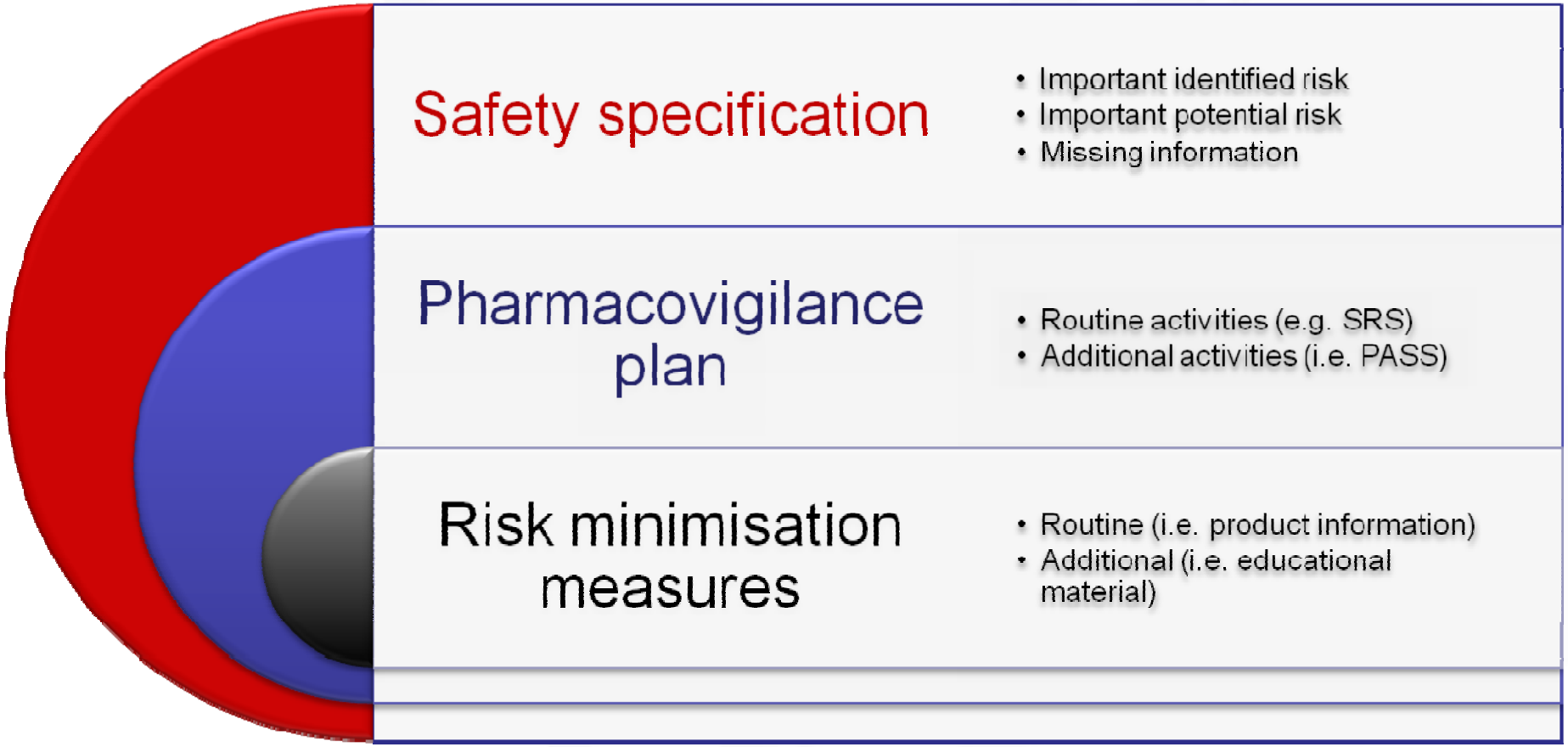
Share

Press release 07/03/2018

Evidence indicates risk of serious inflammatory brain disorders

The European Medicines Agency (EMA) has recommended the immediate suspension and recall of the multiple sclerosis medicine Zinbryta (daclizumab beta) following 12 reports of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis. Three of the cases were fatal.

Principali componenti del Risk Management Plan



http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/02/WC500202424.pdf

L'importanza della segnalazione spontanea

Table 2 List of evidence used to support medicinal product withdrawals in all EU member states between 2002 and 2011 derived from EMA reports, PubMed literature search and websites of competent authorities

Drug name	Case reports	Animal studies	Case–control	Cohort	RCTs	Meta-analysis	*Others
Rofecoxib	X		x	x	x	X	
Thioridazine	X	X	x		x	X	
Valdecoxib	X				x	X	
Rosiglitazone	X		x	x	x	X	
Sibutramine	X				x		x
Orciprenaline	X				x		
Benfluorex	X		x	x	x		
Clobutinol	X	X			x		
Buflomedil	X	X					
Veralipride	X						
Rimonabant	X				x	X	
Carisoprodol	X	X		x	x		x
Aceprometazine+Acepromazine +Clorazepate	X						x
Dextropropoxyphene	X						x
Nefazodone	X						x
Ximelagatran/melagatran					x		
Lumiracoxib	X				x		
Sitaxentan	X	X					
Bufexamac	X	X					x

*Other studies include non-randomised and/or not controlled clinical trials and incidence studies.
EMA, European Medicines Agency; EU, European Union.

BMJ Open 2014;4:e004221.

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Post-authorisation safety studies

"Any study relating to an authorised medicinal product conducted with the aim of ***identifying****,* ***characterising*** *or* ***quantifying*** *a safety hazard,* ***confirming*** ***the safety profile*** *of the medicinal product, or* ***measuring the effectiveness of risk management measures****."*

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 3 August 2015
2 EMA/813938/2011 Rev 2* - Draft for public consultation

3 Guideline on good pharmacovigilance practices (GVP)
4 Module VIII – Post-authorisation safety studies (Rev 2)

Date for coming into effect of first version	2 July 2012
Date for coming into effect of Revision 1	25 April 2013
Draft Revision 2* finalised by the Agency in collaboration with Member States	23 June 2015
Draft Revision 2 agreed by the European Risk Management Facilitation Group (ERMS FG)	16 July 2015
Draft Revision 2 adopted by Executive Director	3 August 2015
Release for public consultation	11 August 2015
End of consultation (deadline for comments)	9 October 2015
Anticipated date for coming into effect	Q1 2016

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/08/WC500191779.pdf

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Post-authorisation safety studies

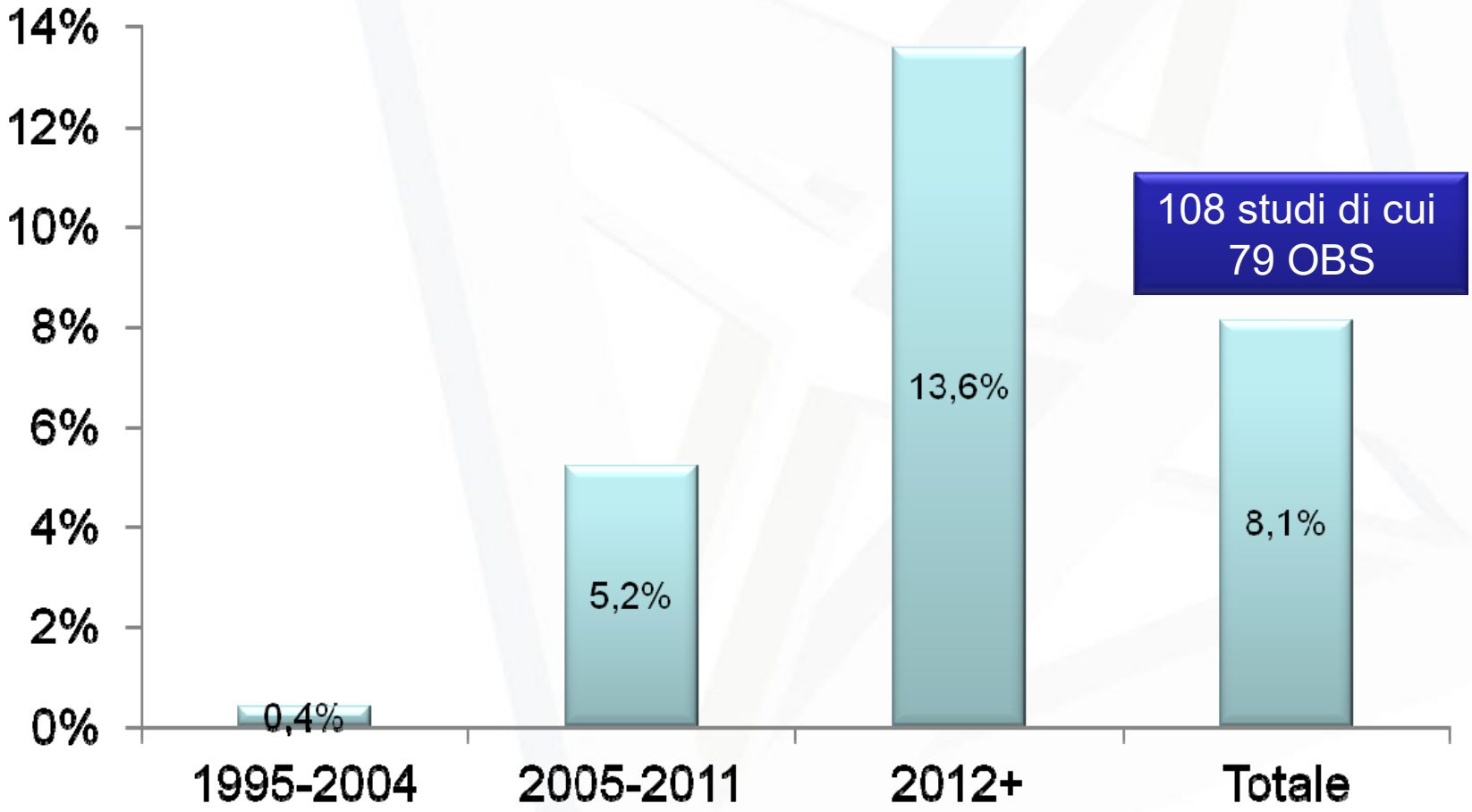
PASS initiated, managed or financed by a MAH

- **Pursuant to an obligation imposed by a competent authority**
  - as a condition of the marketing authorisation if **their results are key to assess the benefit-risk profile** of the product **(category 1)**
  - as part of a marketing authorization granted **under exceptional circumstances (category 2)**

- Studies **required in the risk management plan** "*to investigate a safety concern or evaluate the effectiveness of risk minimisation activities*" **(category 3)**

CHMP opinion:

Frequenza di studi post-autorizzazione imposti con richiesta di valutazione di sicurezza (1328 farmaci autorizzati)



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PASS: alcuni esempi di studi imposti

Description	Due date
The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP. The applicant should submit yearly interim analyses and the final CSR by December 2017	December 2017
The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis by December 2015. The applicant should also submit yearly interim reports within PSURs.	December 2015

"Ivacaftor has convincingly shown clinically relevant efficacy in patients with cystic fibrosis and a G551D mutation. The safety profile is acceptable. Also considering the high unmet medical need in this population, the benefits of ivacaftor clearly outweighs their risks. ***Limited information is available on long-term safety and efficacy*** *hence further data should be obtained on the safety and efficacy of ivacaftor in long term use."*

PASS: alcuni esempi di studi imposti

Thorax. 2018 Aug;73(8):731-740. doi: 10.1136/thoraxjnl-2017-210394. Epub 2018 May 10.

Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor.

Bessonova L[1], Volkova N[1], Higgins M[2], Bengtsson L[1], Tian S[1], Simard C[1], Konstan MW[3], Sawicki GS[4], Sewall A[5], Nyangoma S[6], Elbert A[7], Marshall BC[7], Bilton D[6,8].

Author information

Abstract

BACKGROUND: Ivacaftor is the first cystic fibrosis transmembrane conductance regulator (CFTR) modulator demonstrating clinical benefit in patients with cystic fibrosis (CF). As ivacaftor is intended for chronic, lifelong use, understanding long-term effects is important for patients and healthcare providers.

OBJECTIVE: This ongoing, observational, postapproval safety study evaluates clinical outcomes and disease progression in ivacaftor-treated patients using data from the US and the UK CF registries following commercial availability.

METHODS: Annual analyses compare ivacaftor-treated and untreated matched comparator patients for: risks of death, transplantation, hospitalisation, pulmonary exacerbation; prevalence of CF-related complications and microorganisms and lung function changes in a subset of patients who initiated ivacaftor in the first year of commercial availability. Results from the 2014 analyses (2 and 3 years following commercial availability in the UK and USA, respectively) are presented here.

RESULTS: Analyses included 1256 ivacaftor-treated and 6200 comparator patients from the USA and 411 ivacaftor-treated and 2069 comparator patients from the UK. No new safety concerns were identified based on the evaluation of clinical outcomes included in the analyses. As part of safety evaluations, ivacaftor-treated US patients were observed to have significantly lower risks of death (0.6% vs 1.6%, p=0.0110), transplantation (0.2% vs 1.1%, p=0.0017), hospitalisation (27.5% vs 43.1%, p<0.0001) and pulmonary exacerbation (27.8% vs 43.3%, p<0.0001) relative to comparators; trends were similar in the UK. In both registries, ivacaftor-treated patients had a lower prevalence of CF-related complications and select microorganisms and had better preserved lung function.

CONCLUSIONS: While general limitations of observational research apply, analyses revealed favourable results for clinically important outcomes among ivacaftor-treated patients, adding to the growing body of literature supporting disease modification by CFTR modulation with ivacaftor.

PASS: alcuni esempi di studi imposti

Description
Non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice, patterns of use and cardiovascular risk. After approval of the protocol, annual reports from this study shall be provided within the PSUR until submission of the final study report, which is due by December 2017.

"The CHMP considered that these show a clear tendency towards neutralisation of the cardiovascular risk when the population is restricted to patients with severe osteoporosis without contraindications.

***The CHMP acknowledged that implementation of all the proposed risk minimisation measures is challenging**. Repeated risk assessment was nonetheless considered to be feasible within normal clinical practice*

The CHMP requested that the MAH shall conduct a post-authorisation safety study to assess whether there is compliance with the restrictions introduced, and to collect further information on the risks of the medicinal product and on the effectiveness of the risk minimisation measures."

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Conclusion/human/000560/WC500169913.pdf

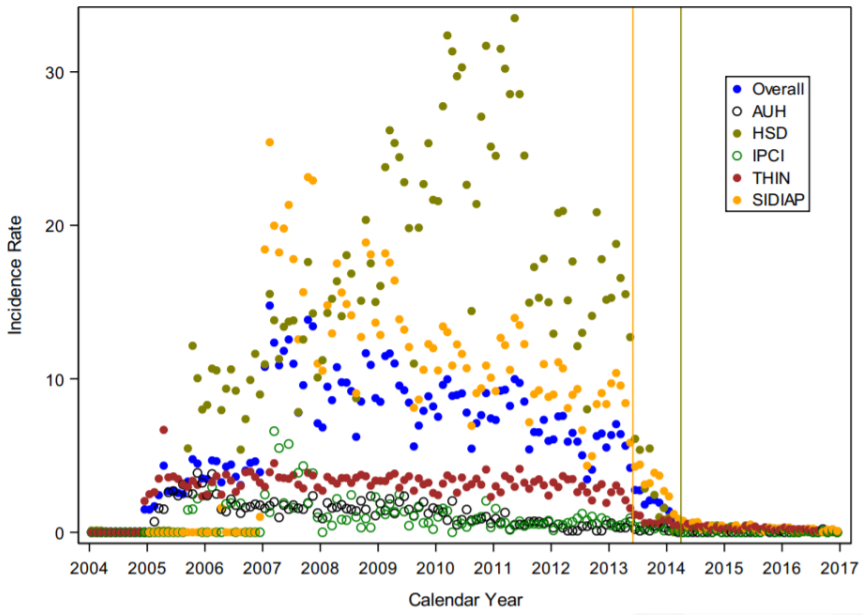
PASS: alcuni esempi di studi imposti

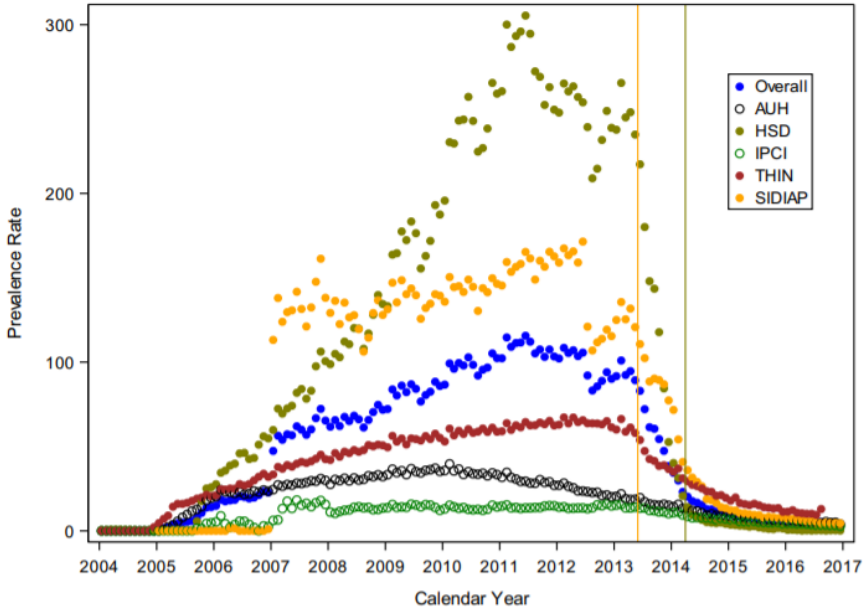
Osteoporosis International
https://doi.org/10.1007/s00198-019-05181-6

ORIGINAL ARTICLE

Check for updates

Impact of risk minimisation measures on the use of strontium ranelate in Europe: a multi-national cohort study in 5 EU countries by the EU-ADR Alliance





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PASS: studi di valutazione delle misure di minimizzazione del rischio

Routine RMM

(Informazioni sul prodotto [SmPC, PIL])

Possono essere inseriti nel RMP immediatamente dopo l'approvazione oppure durante la fase di post-approvazione

Additional RMM

(Informazioni aggiuntive per HCP e pazienti; accesso controllato)

OBIETTIVI

Stabilire se un intervento richiesto dalle autorità regolatorie per minimizzare un rischio è risultato efficace; nel caso contrario per stabilire le cause del fallimento e quali azioni correttive dovrebbero essere implementate

PASS: studi di valutazione delle misure di minimizzazione del rischio

BMJ

RESEARCH

Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis

Keith Hawton, professor of psychiatry and director,[1] Helen Bergen, researcher,[1] Sue Simkin, researcher,[1] Anita Brock, senior research officer,[2] Clare Griffiths, principal research officer,[2] Ester Romeri, research officer,[2] Karen L Smith, senior medical statistician,[3] Navneet Kapur, professor and honorary consultant in psychiatry, head of research,[4] David Gunnell, professor of epidemiology[5]

ABSTRACT

Objective To assess the effect of the UK Committee on Safety of Medicines' announcement in January 2005 of withdrawal of co-proxamol on analgesic prescribing and poisoning mortality.

Design Interrupted time series analysis for 1998-2007.

Setting England and Wales.

Data sources Prescribing data from the prescription statistics department of the Information Centre for Health and Social Care (England) and the Prescribing Services Unit, Health Solutions Wales (Wales). Mortality data from the Office for National Statistics.

Main outcome measures Prescriptions. Deaths from drug poisoning (suicides, open verdicts, accidental poisonings) involving single analgesics.

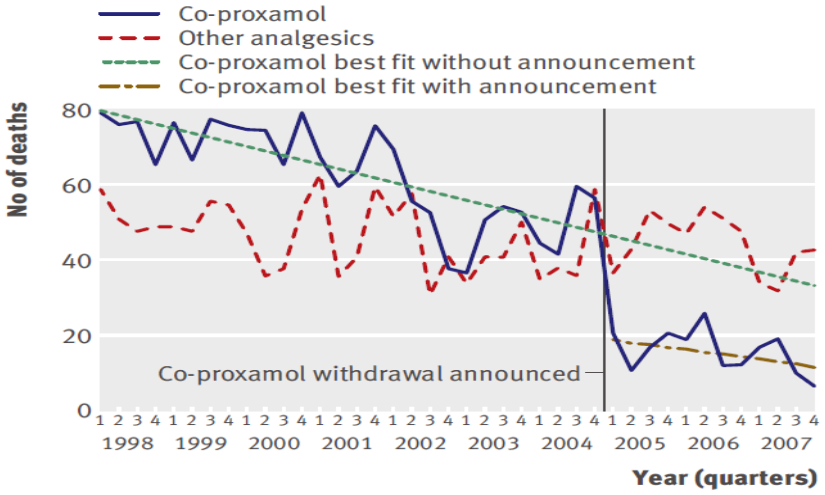

Fig 2 | Mortality in England and Wales from analgesic poisoning (suicide and open verdicts), 1998-2007, for people aged 10 years and over (substances taken alone, with or without alcohol)

BMJ 2009;338:b2270

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Elementi di analisi per gli studi di valutazione

- Analisi sull'incidenza degli eventi avversi complessa o impraticabile: la valutazione di efficacia dei programmi può partire dall'interpretazione dei dati ricavati da misure di processo
- Bisogna considerare con la dovuta attenzione le misure di processo che possono essere analizzate e che forniscono informazioni utili per le decisioni regolatorie

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 April 2014
EMA/204715/2012 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

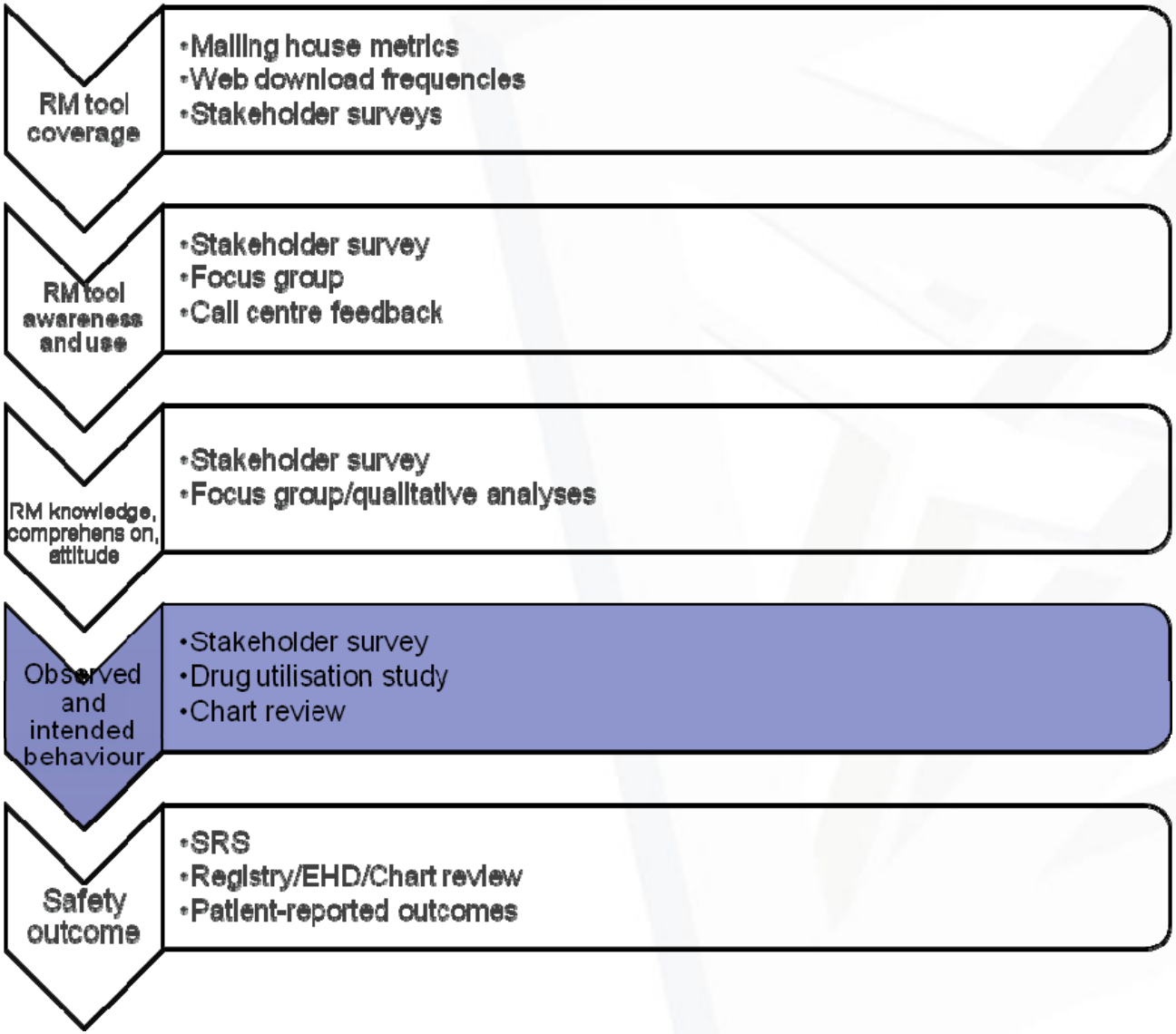
Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators (Rev 1)

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	21 March 2013
Draft agreed by ERMS FG	27 March 2013
Draft adopted by Executive Director	6 June 2013
Released for consultation	7 June 2013
End of consultation (deadline for comments)	5 August 2013
Revised draft finalised by the Agency in collaboration with Member States	15 January 2014
Revised draft agreed by ERMS FG	29 January 2014
Revised draft adopted by Executive Director as final	21 February 2014
Date for coming into effect	1 March 2014
Revision 1 adopted by Executive Director as final	15 April 2014
Date for coming into effect of Revision 1*	28 April 2014

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Elementi di analisi per gli studi di valutazione



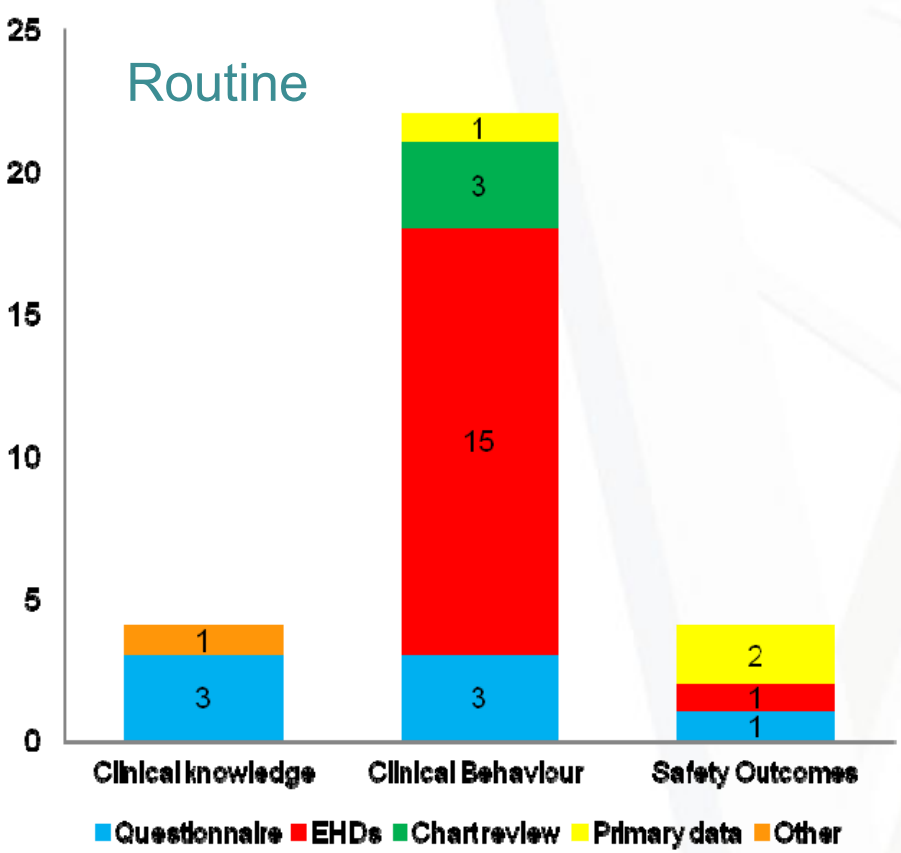
Aderenza dei comportamenti di erogatori di prestazioni sanitarie e pazienti rispetto alle informazioni contenute nella scheda tecnica e/o in altri strumenti di risk minimization

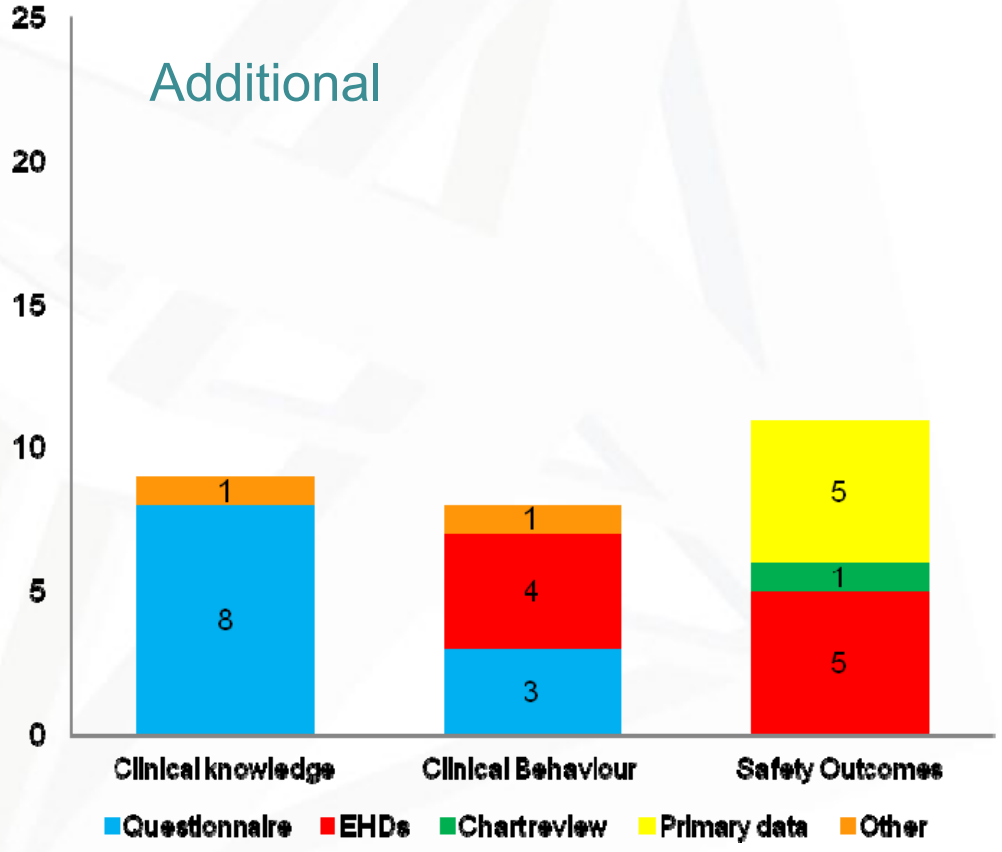
Proporzione di pazienti esposti ad un farmaco in accordo all'indicazione clinica autorizzata

Proporzione di pazienti esposti ad un farmaco in presenza di controindicazioni

Proporzione di pazienti sottoposti a test raccomandati prima, durante o dopo l'esposizione ad un farmaco

RWE e studi di valutazione





Drug Saf. DOI 10.1007/s40264-017-0604-4

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Real-World Evidence — What Is It and What Can It Tell Us?

N ENGL J MED (2016) 375;23: 2293

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Barriers and Opportunities for Use of Patient Registries in Medicines Regulation

Carla Alonso Olmo[1], Patricia McGettigan[1,2] and Xavier Kurz[1,*]

The European Medicines Agency (EMA) established the Patient Registry Initiative to explore ways of supporting the use of patient registries in generating high-quality data for regulatory decision making and to enable a systematic approach to their use. We review barriers and opportunities for using patient registries in medicines regulation. A key aspect is that early discussions between all parties may often help address concerns including heterogeneity of data collection, data quality, data sharing, or questions on safety reporting.

Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe

Alison Cave[1,*], Xavier Kurz[1] and Peter Arlett[1]

Real-world data (RWD) offers the possibility to derive novel insights on the use and performance of medicines in everyday clinical use, complementing rather than competing with evidence from randomized control trials. While Europe is rich in healthcare data, its heterogeneous nature brings operational, technical, and methodological challenges. We present a number of potential solutions to address the full spectrum of regulatory use cases and emphasize the importance of early planning of data collection.

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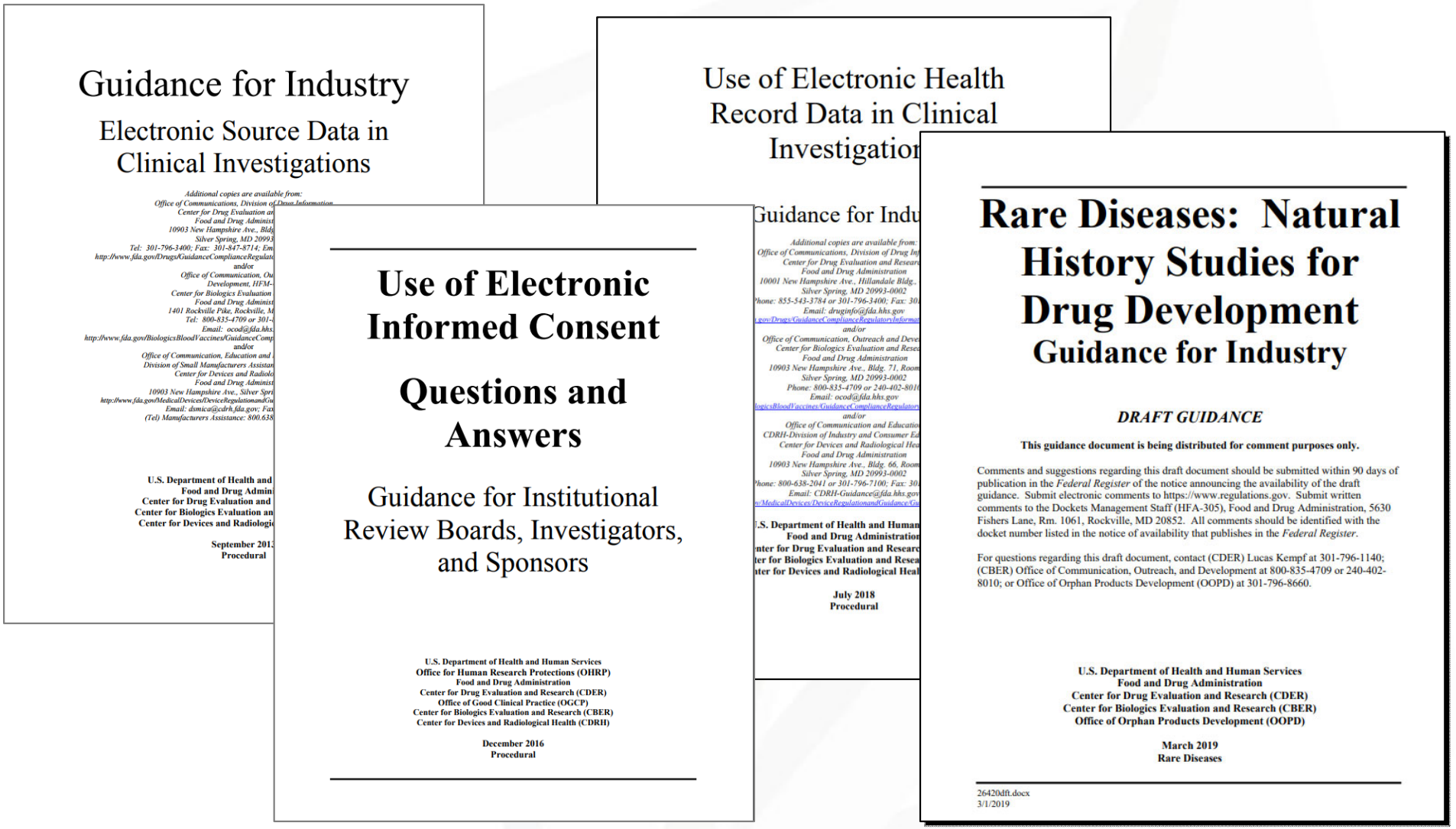

Guidance for Industry

Electronic Source Data in Clinical Investigations

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

Use of Electronic Informed Consent

Questions and Answers

Guidance for Institutional Review Boards, Investigators, and Sponsors

U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2016
Procedural

Rare Diseases: Natural History Studies for Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140; (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010; or Office of Orphan Products Development (OOPD) at 301-796-8660.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Orphan Products Development (OOPD)

March 2019
Rare Diseases

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obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos