

RISK MANAGEMENT LIFE CYCLE APPROACH – KEY POINTS

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RISK MANAGEMENT LIFE CYCLE APPROACH – KEY POINTS

Authorities measures in Benefit-Risk (B/R) Assessment

Effective interaction with all involved stakeholders during drug development process

Inter-authorities harmonisation with applicable effective regulations

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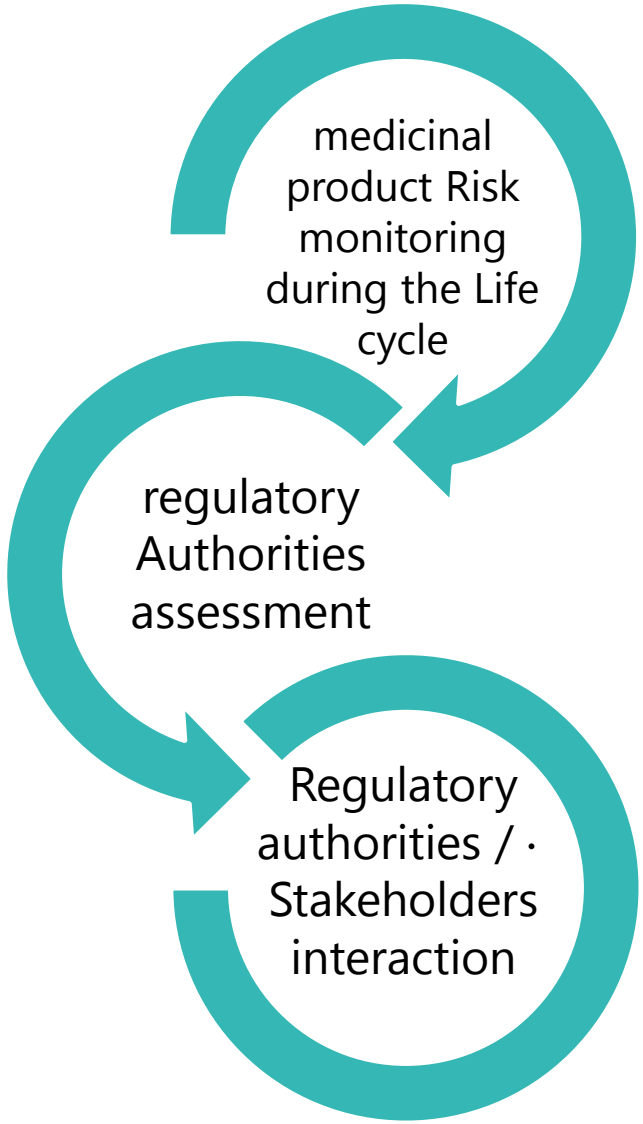
Authorities measures in Benefit-Risk (B/R) Assessment

Effective interaction with all involved stakeholders during drug development process

Inter-authorities harmonisation with applicable effective regulations

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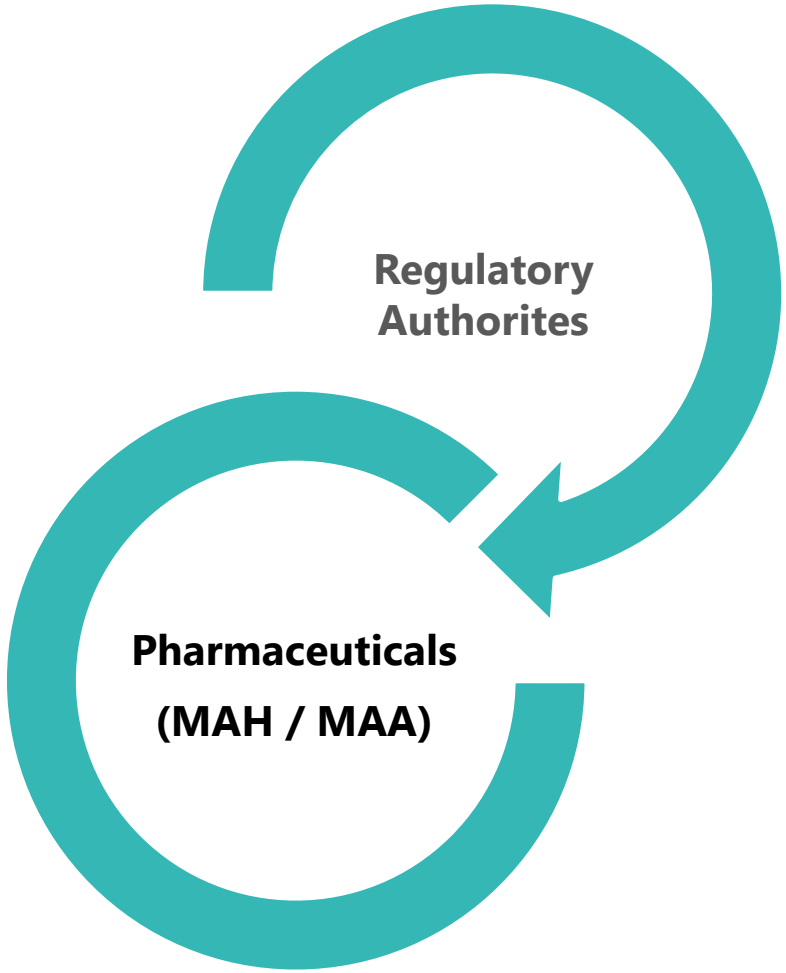


Product Life cycle

(Pre-/ post-authorisation phases)

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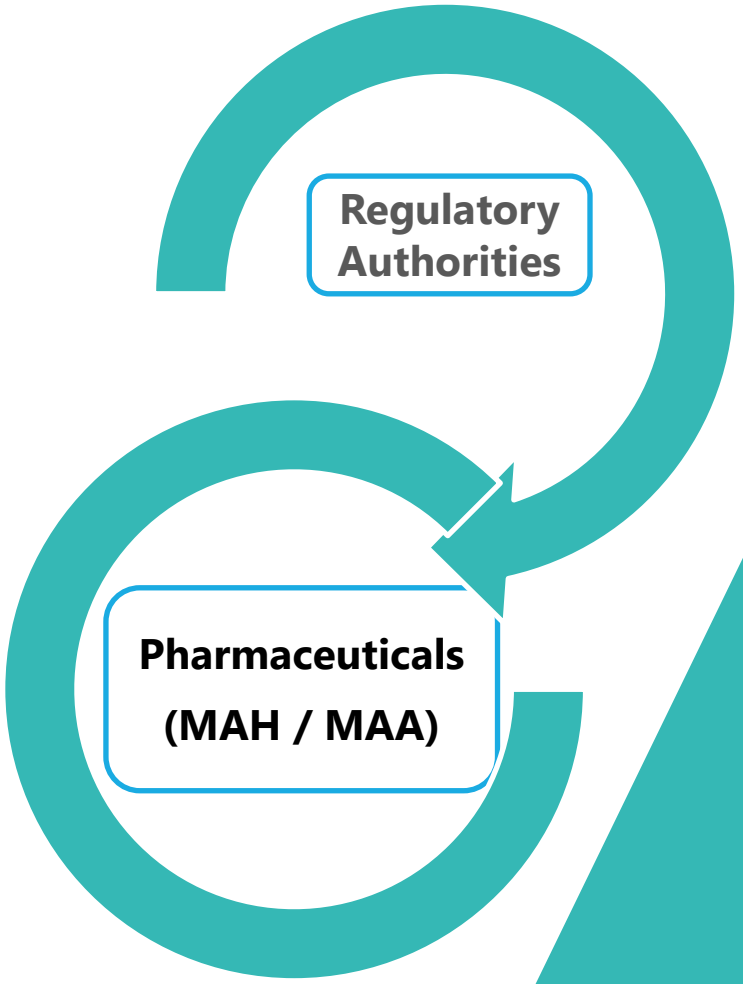
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Product Life cycle

(Pre-/ post-authorisation phases)

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Initial phase

initiating discussion with study' sponsor (designs, dose, endpoints)

MAA :

investigating uncertainties and their clinical consequences / Support B/R decisions

Anticipating and interpreting heterogeneity

Post Marketing:

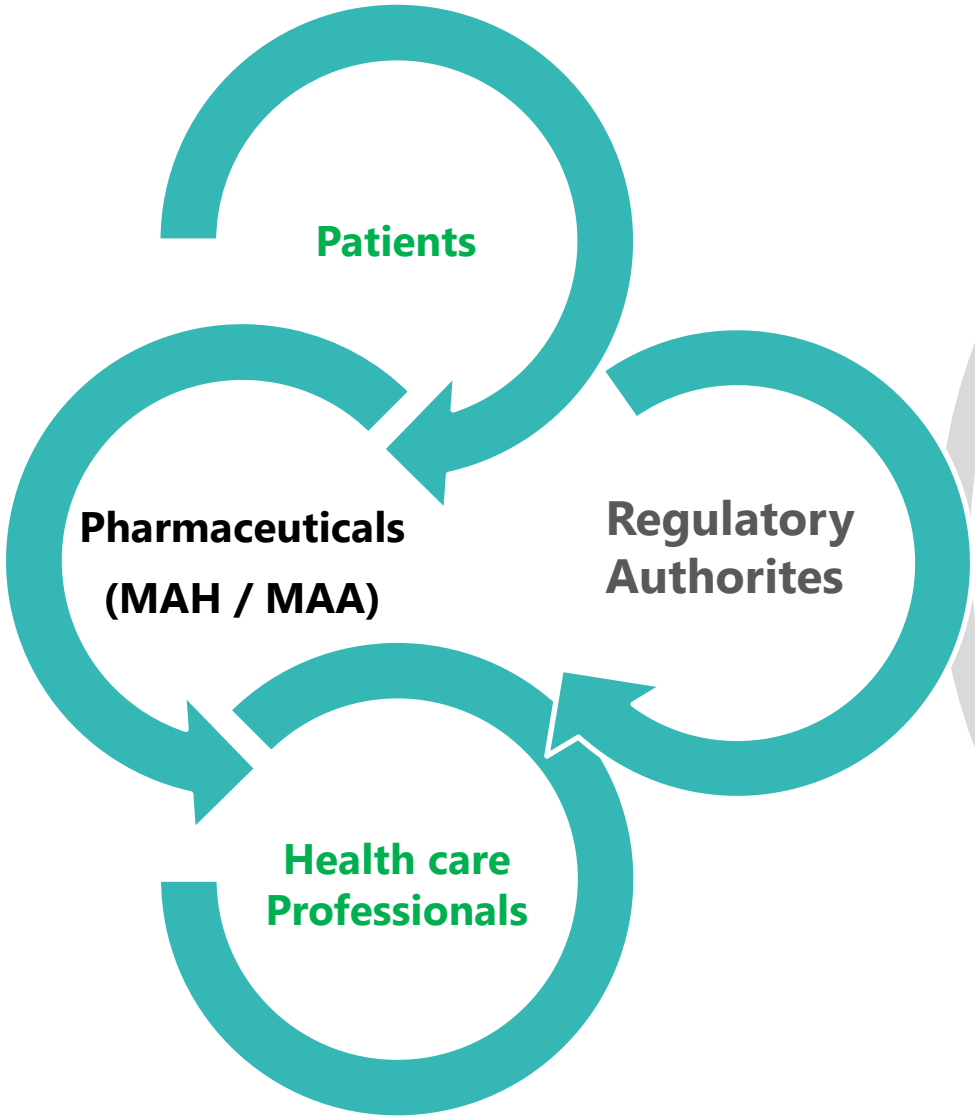
Identify risk groups (under/over exposure)

exposure-response relationship (PASS / PAES)

MHRA "BENEFIT-RISK MANAGEMENT PLANNING THROUGH THE LIFE CYCLE OF A PRODUCT" (Session 0101/0701/0901/1301) April 2016

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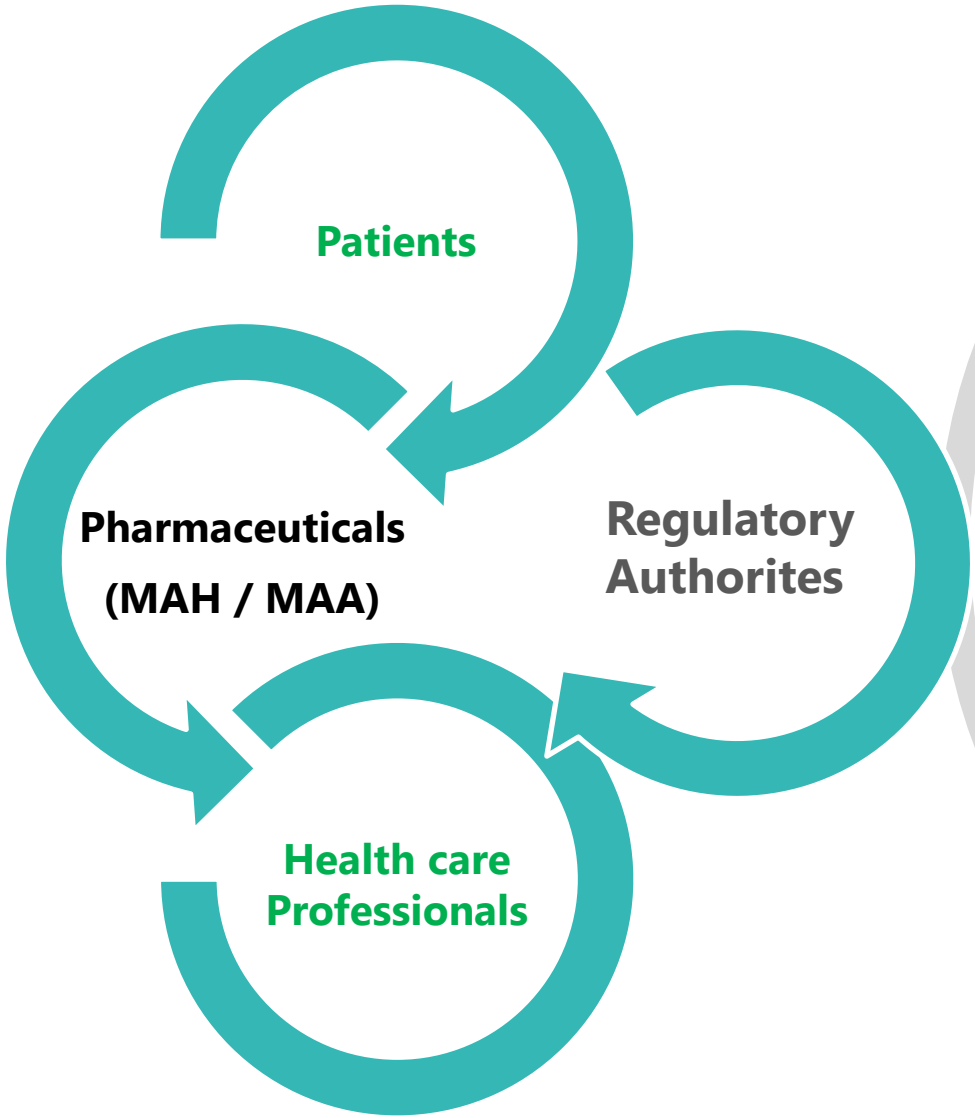


Product Life cycle

(Pre-/ post-authorisation phases)

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DECISION MAKER

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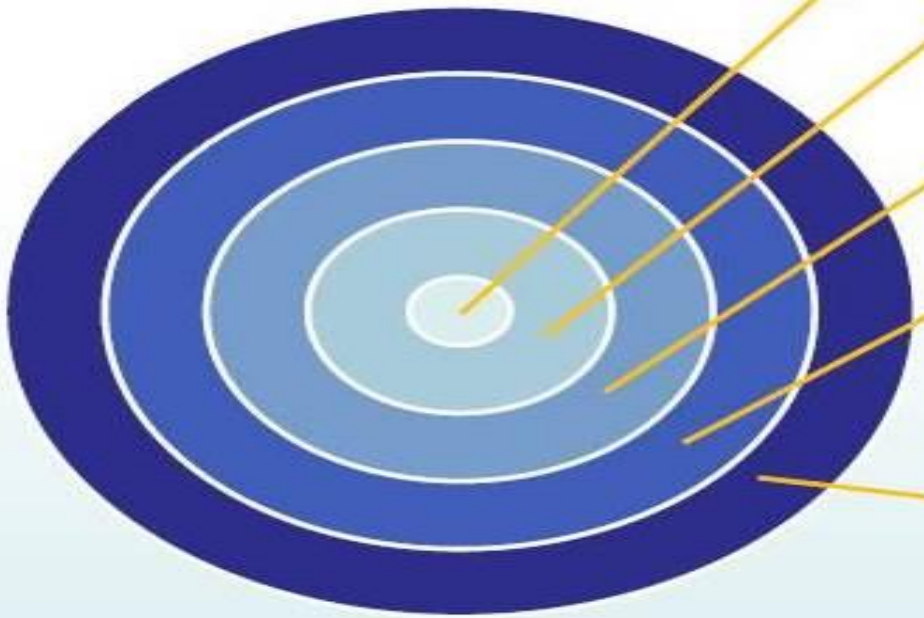
DECISION MAKING PROCESS



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Decision makers – hierarchical?



Patients
- Make decisions for themselves

Healthcare providers
- Make decisions based on prescribing lists

Health technology assessors
- Makes decisions on cost-effectiveness

Regulators
- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

Pharmaceutical companies
- Makes decisions on what to develop for which licenses to apply

PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

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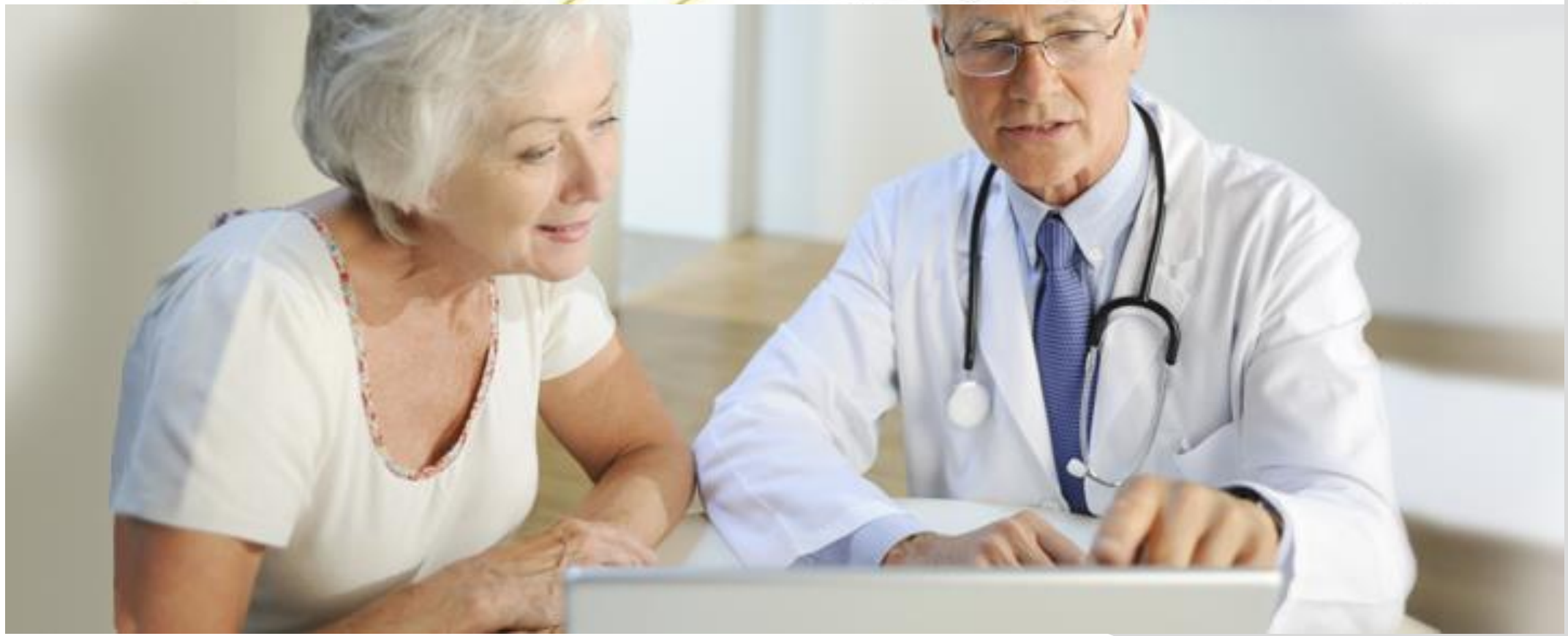
biopharma VIGI-CARE

RISK MANAGEMENT LIFE CYCLE APPROACH – KEY POINTS

Decision makers – hierarchical

Patients

Healthcare providers



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RISK MANAGEMENT LIFE CYCLE APPROACH – KEY POINTS

Decision makers – hierarchical

- Patients
- Healthcare providers



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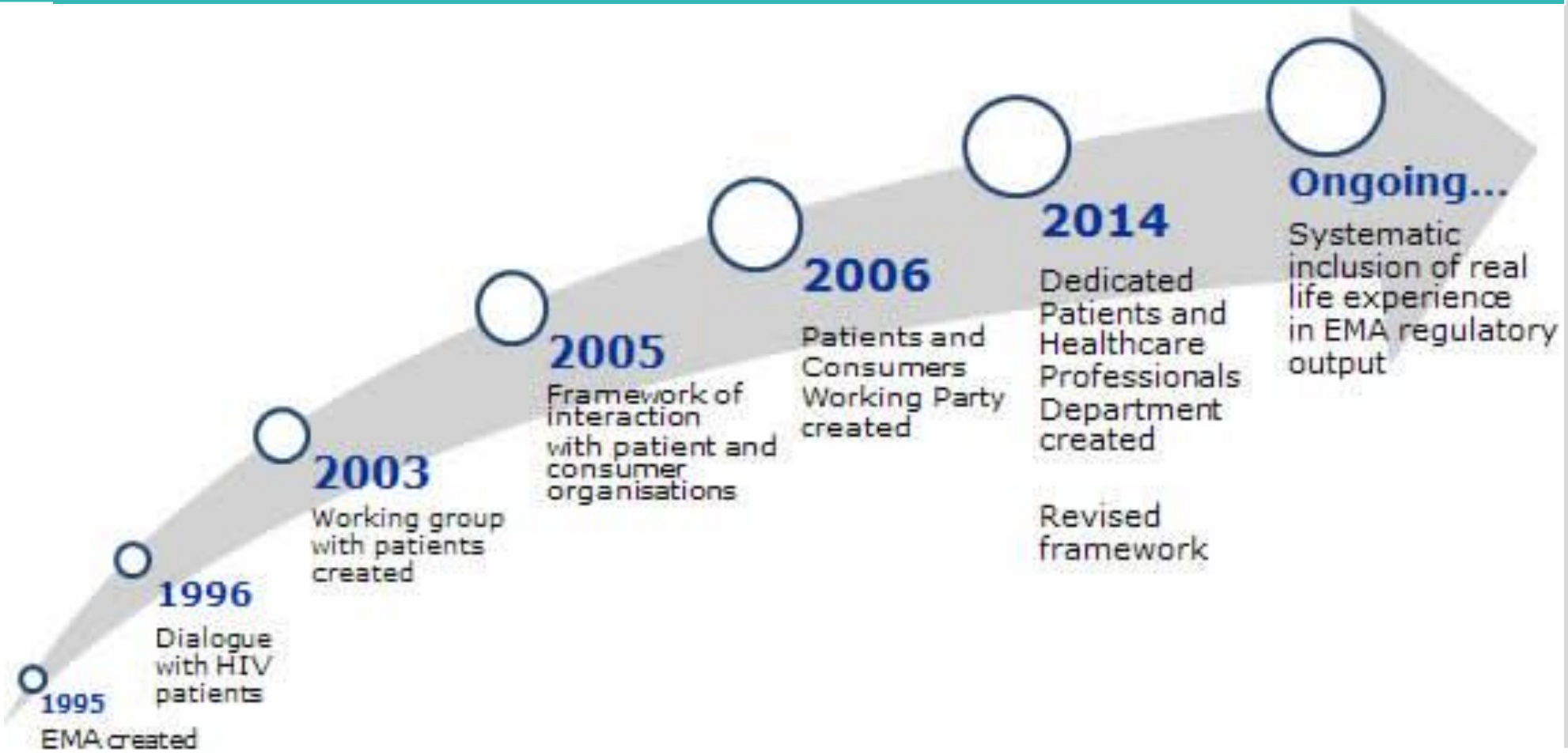
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EMA initiatives for patient Dialogue



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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2013
EMA/607864/2013
Stakeholders and Communication Division

The patient's voice in the evaluation of medicines

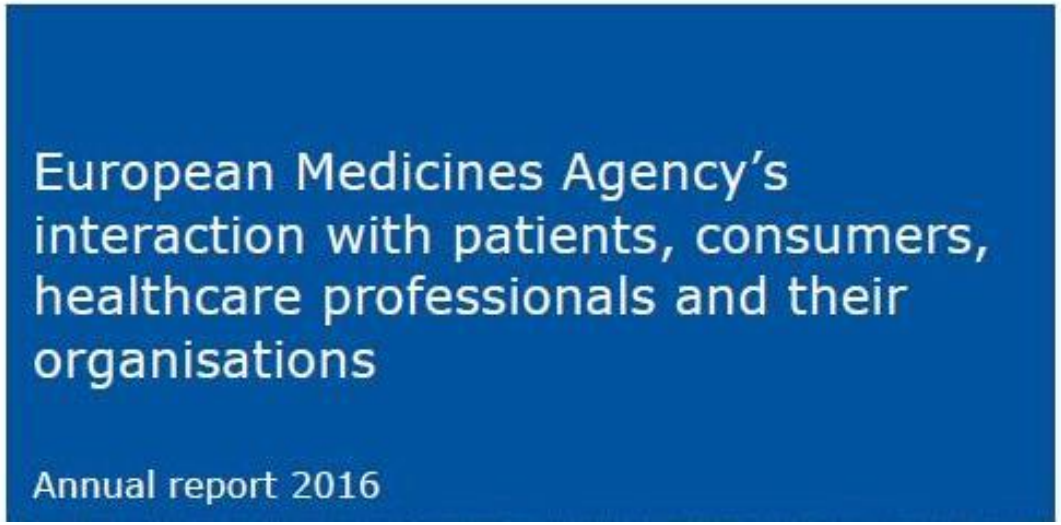
How patients can contribute to assessment of benefit and risk

Patient engagement initiatives

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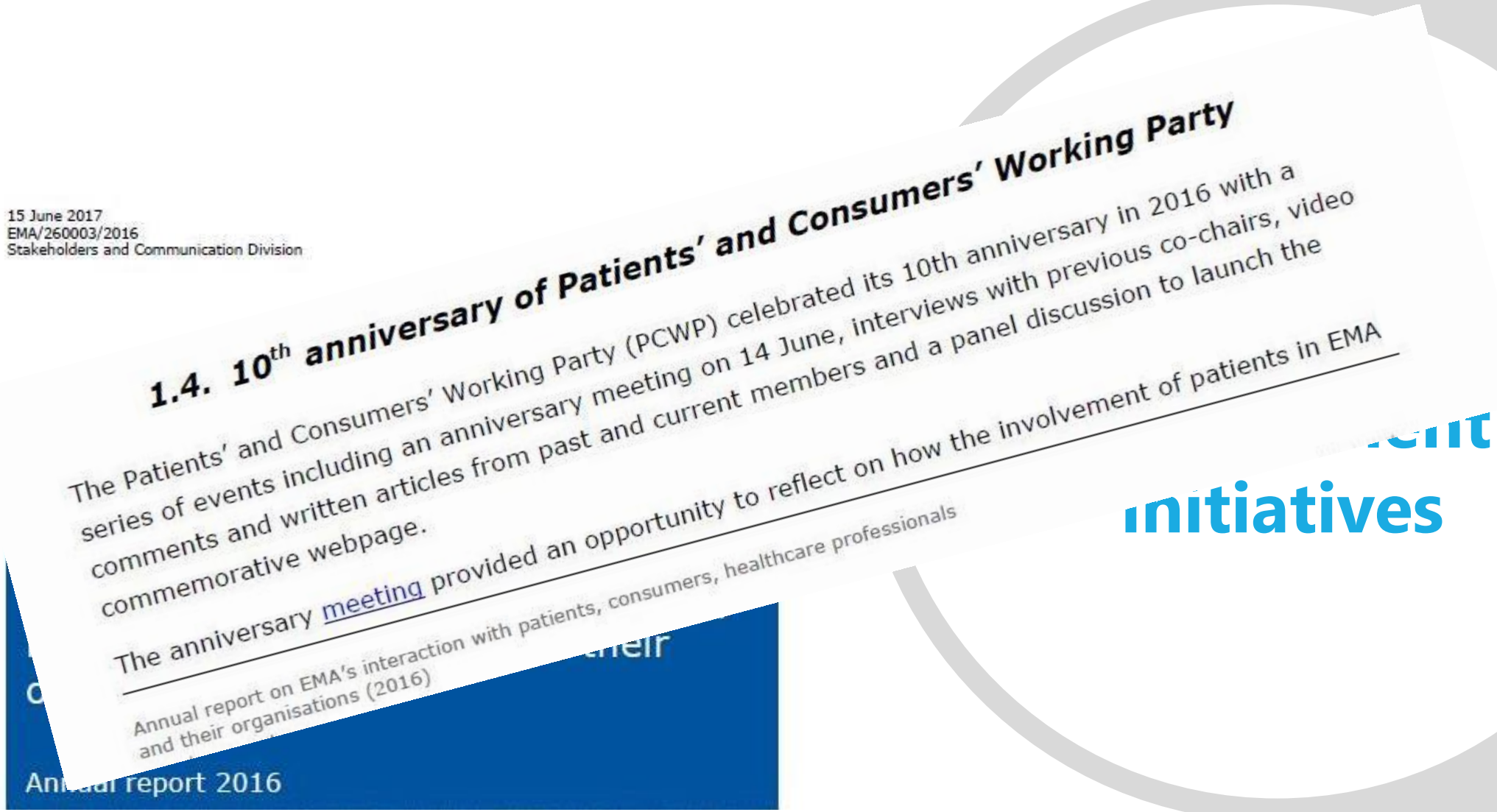
15 June 2017
EMA/260003/2016
Stakeholders and Communication Division



Patient engagement initiatives

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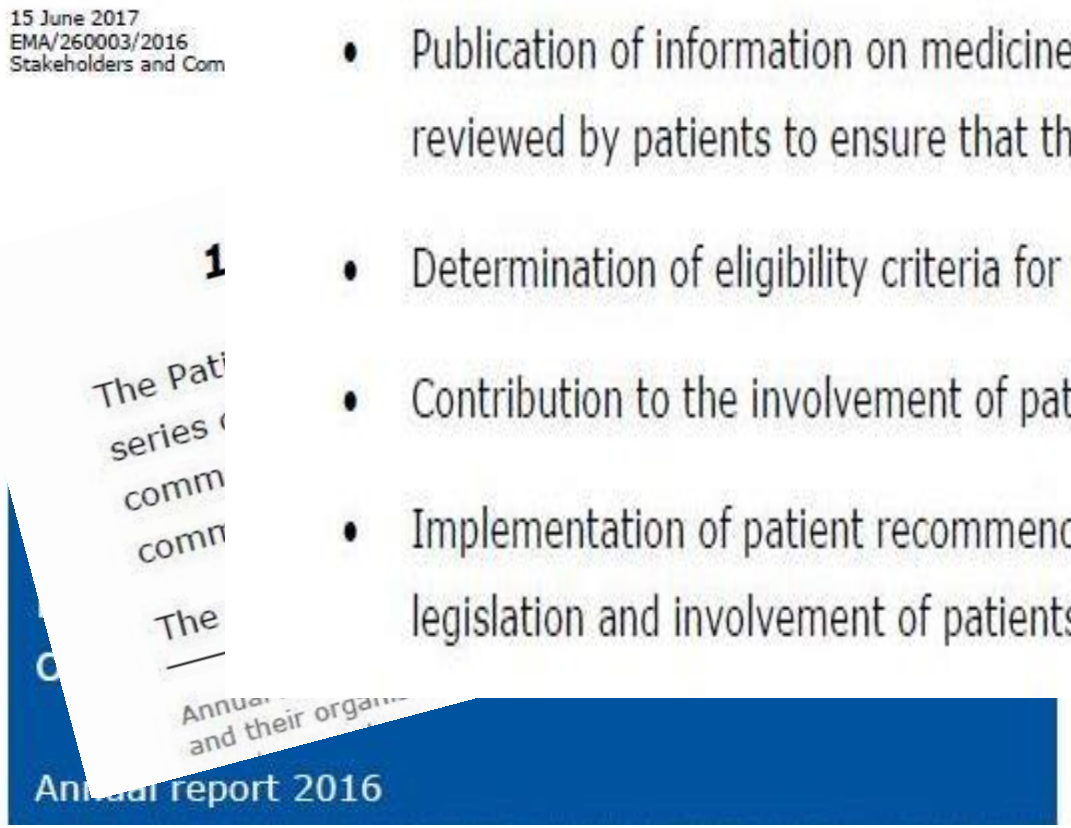
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initiatives

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recommendations made to EMA include:

- Publication of information on medicines addressed to the general public. These documents are reviewed by patients to ensure that the information is clear and relevant.
- Determination of eligibility criteria for patient and consumer groups working with the Agency;
- Contribution to the involvement of patients as experts in regulatory activities.
- Implementation of patient recommendations in the revision of the Pharmacovigilance legislation and involvement of patients as members in the PRAC.

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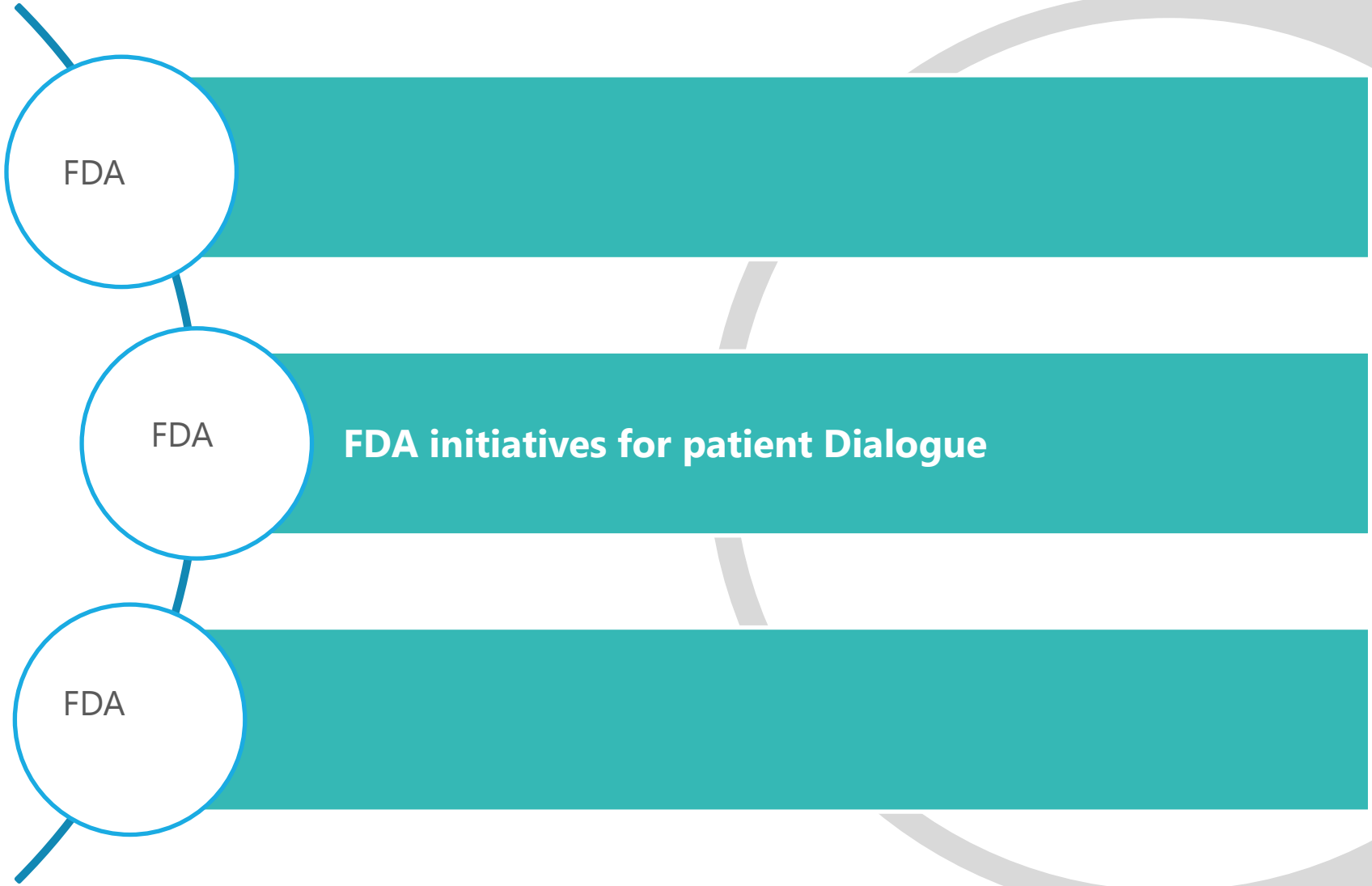
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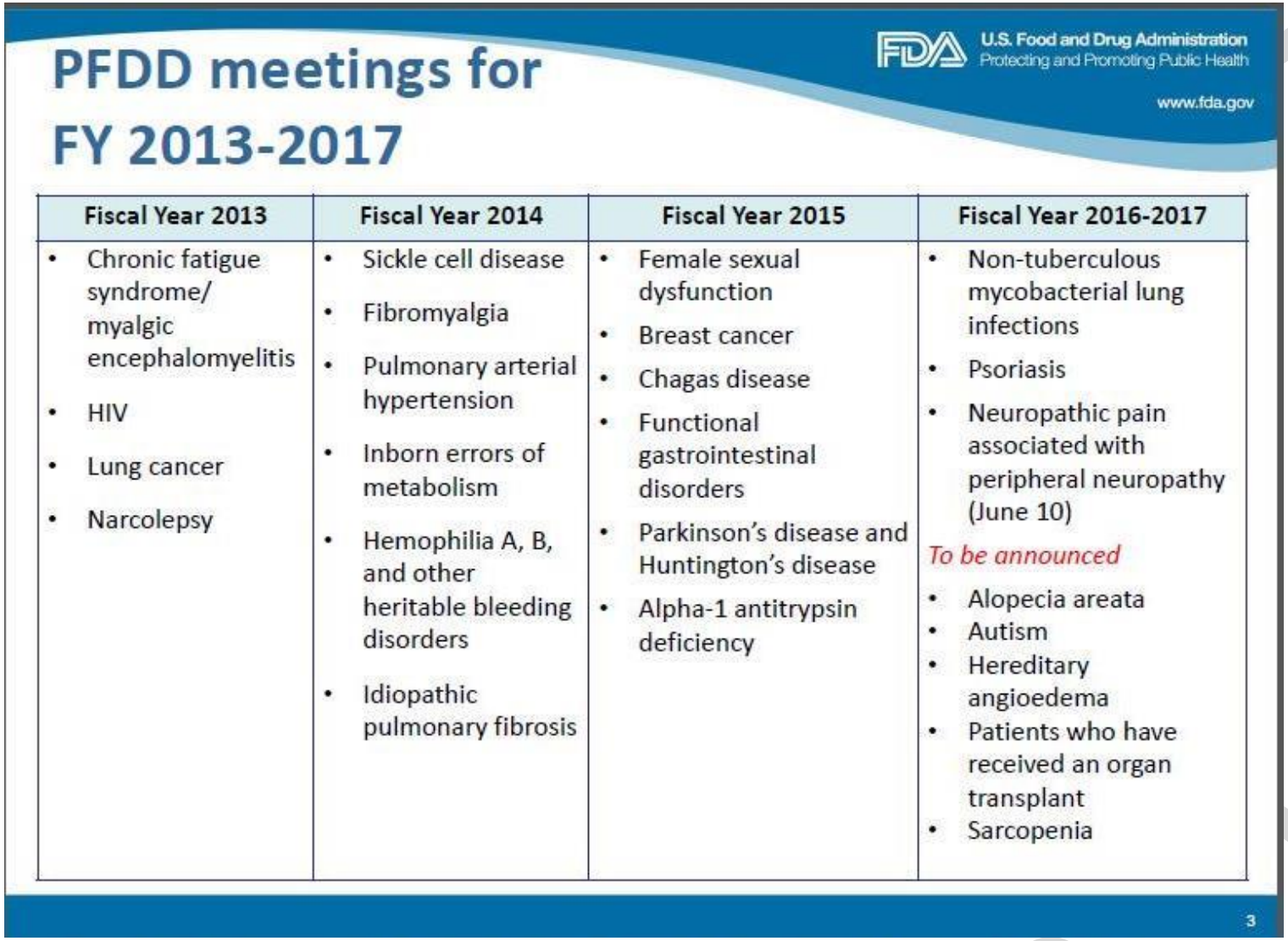
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PFDD meetings for FY 2013-2017

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Parkinson's disease and Huntington's disease • Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy (June 10) *To be announced* • Alopecia areata • Autism • Hereditary angioedema • Patients who have received an organ transplant • Sarcopenia

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Patient engagement initiatives

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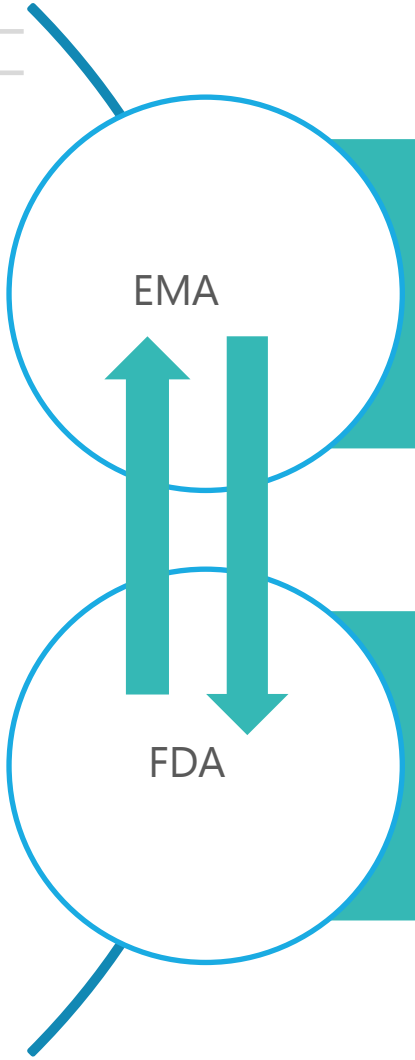
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EMA's pilot project on patient input for drug review

EMA's Patients' and Consumers' Working Party activities

CDER's Patient-Focused Drug Development

CDRH Patient Preference Initiative

Patient engagement initiatives

Center for Drug Evaluation and Research (**CDER**)
Center for Devices and Radiological Health (**CDRH**)

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Patient engagement initiatives

Cluster activities

EMA

- EMA's pilot project on patient input for [illegible] review
- EMA's Patients' and Consumers' W[illegible]y activities

FDA

- CDER's Patient-Focused Drug Development
- CDRH Patient Preference Initiative

Center for Drug Evaluation and Research (**CDER**)
Center for Devices and Radiological Health (**CDRH**)

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EMA – FDA Cluster activities



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Patient engagement initiatives

? What are authorites' strategies to minimise patient engagement obstacles?

? Is patient engagement had an impact on product approval decisions ?

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Inter-authorities harmonisation with applicable effective regulations

Challenges in Benefit-Risk (B/R) Assessment

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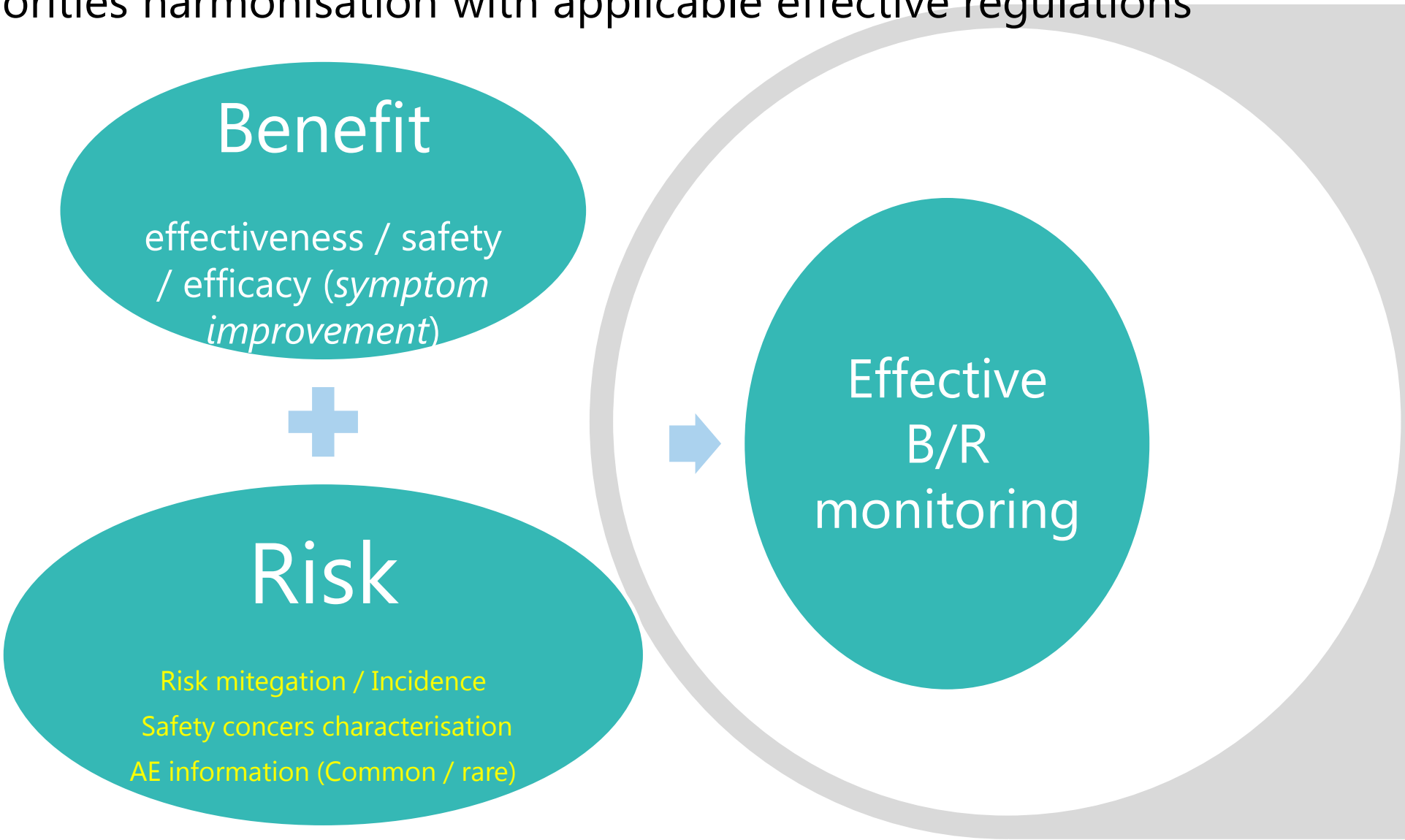
Inter-authorities harmonisation with applicable effective regulations



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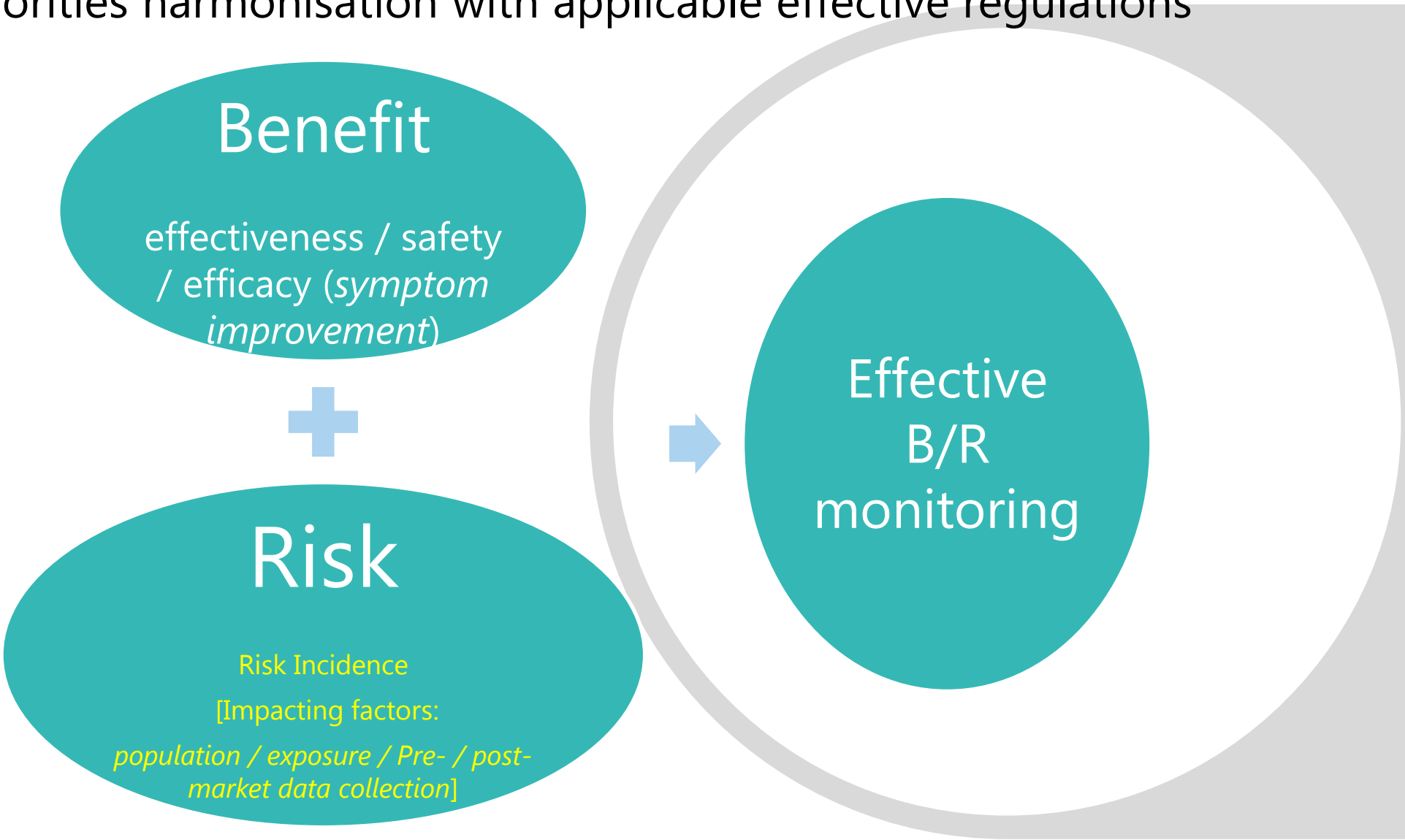
Inter-authorities harmonisation with applicable effective regulations



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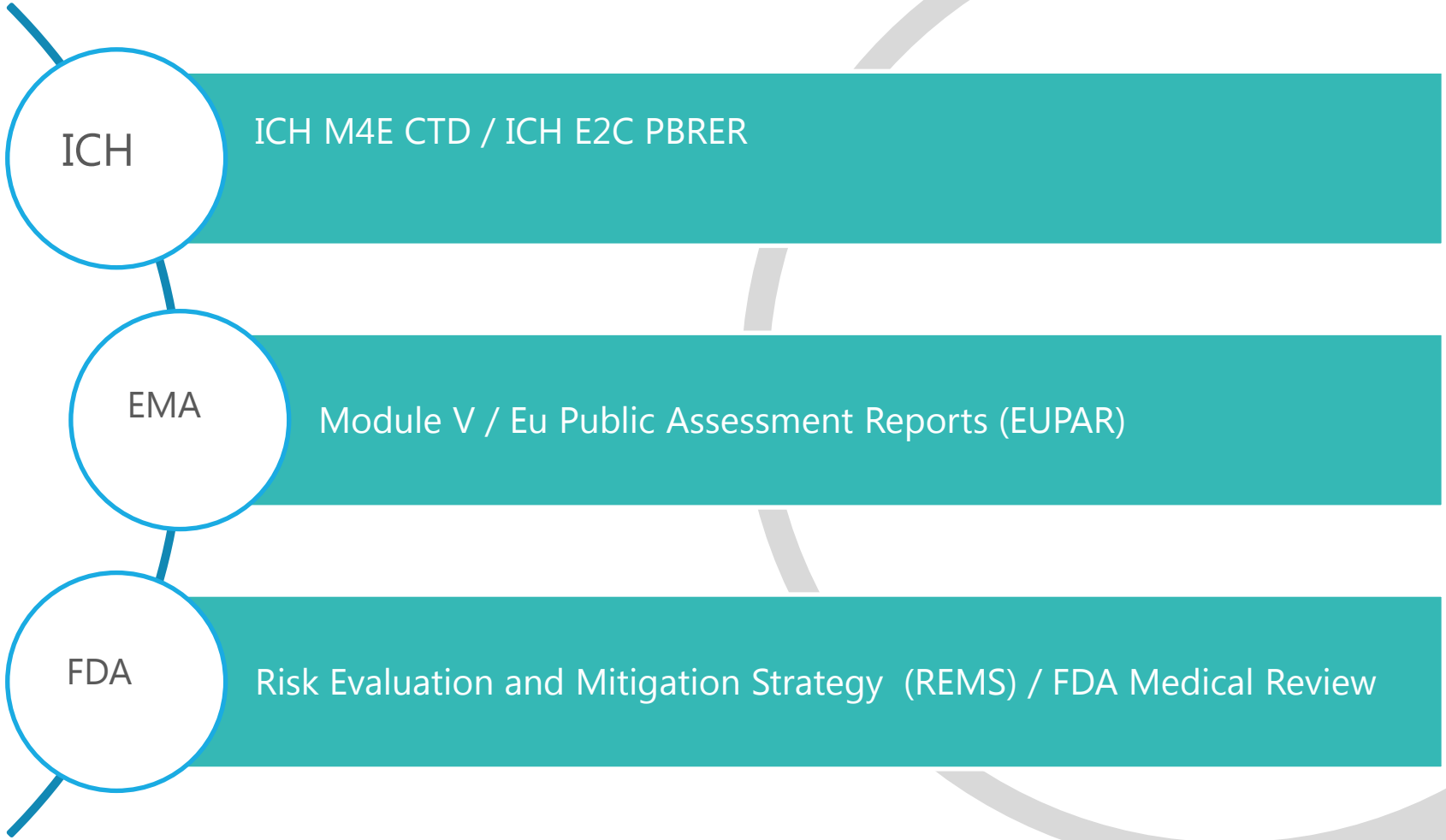
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Challenges in Benefit-Risk (B/R) Assessment
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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH

EFFICACY - M4E(R2)

Current *Step 4* version

dated 15 June 2016

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ICH M4E guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH

This document provides a succinct, integrated, and clearly explained benefit-risk assessment of the medicinal product for its intended use

- *Key benefits* ➔ the *favourable* effects generally assessed by primary and other clinically important endpoints across the studies in a development program
- *Key risks* ➔ the *unfavourable* effects that are important from a clinical and/or public health perspective in terms of their frequency and/or severity

The benefit-risk assessments of approved products are the subject of the ICH E2C(R2)

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

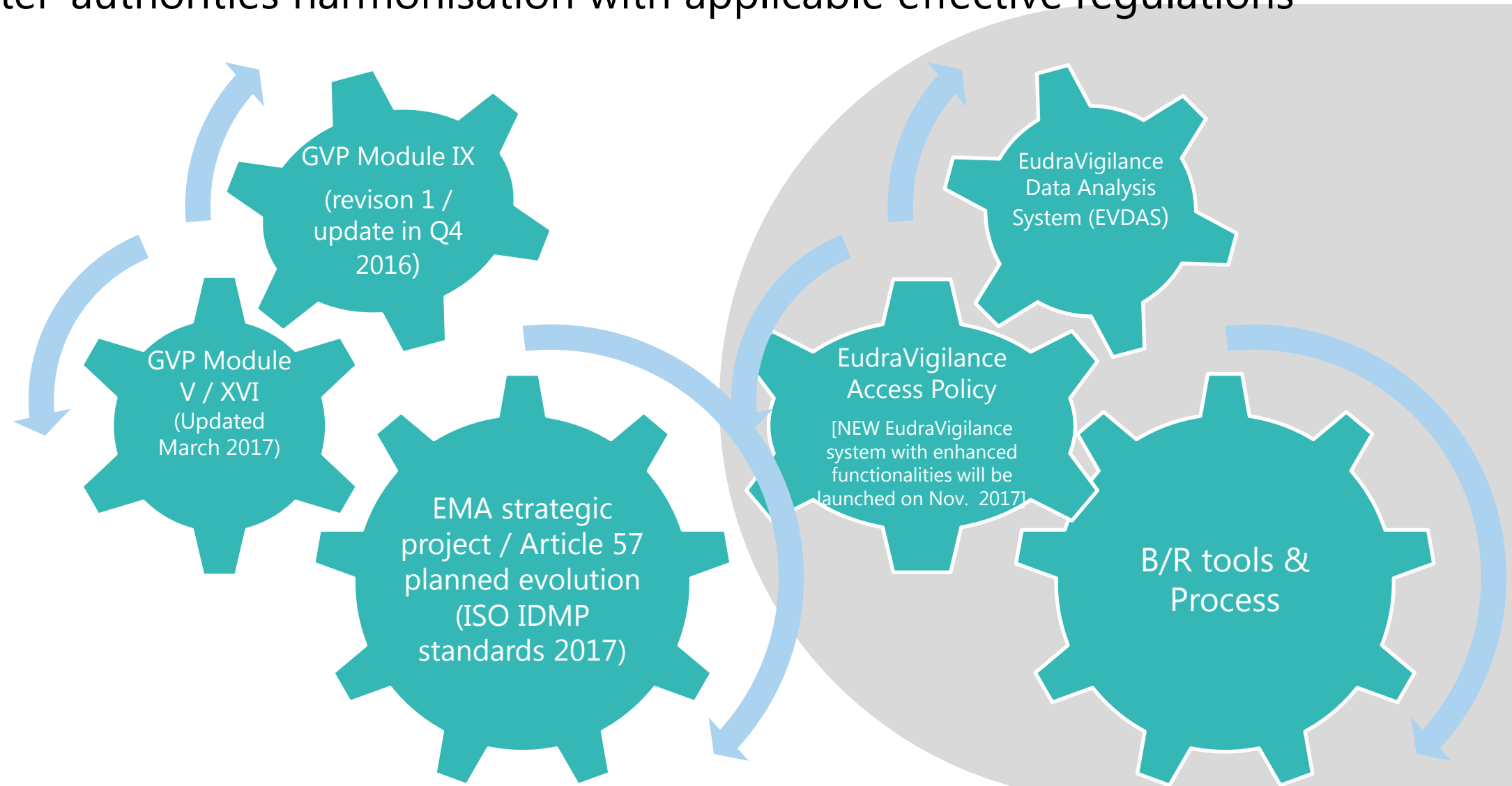
E2C(R2)

Current *Step 4* version
dated 17 December 2012

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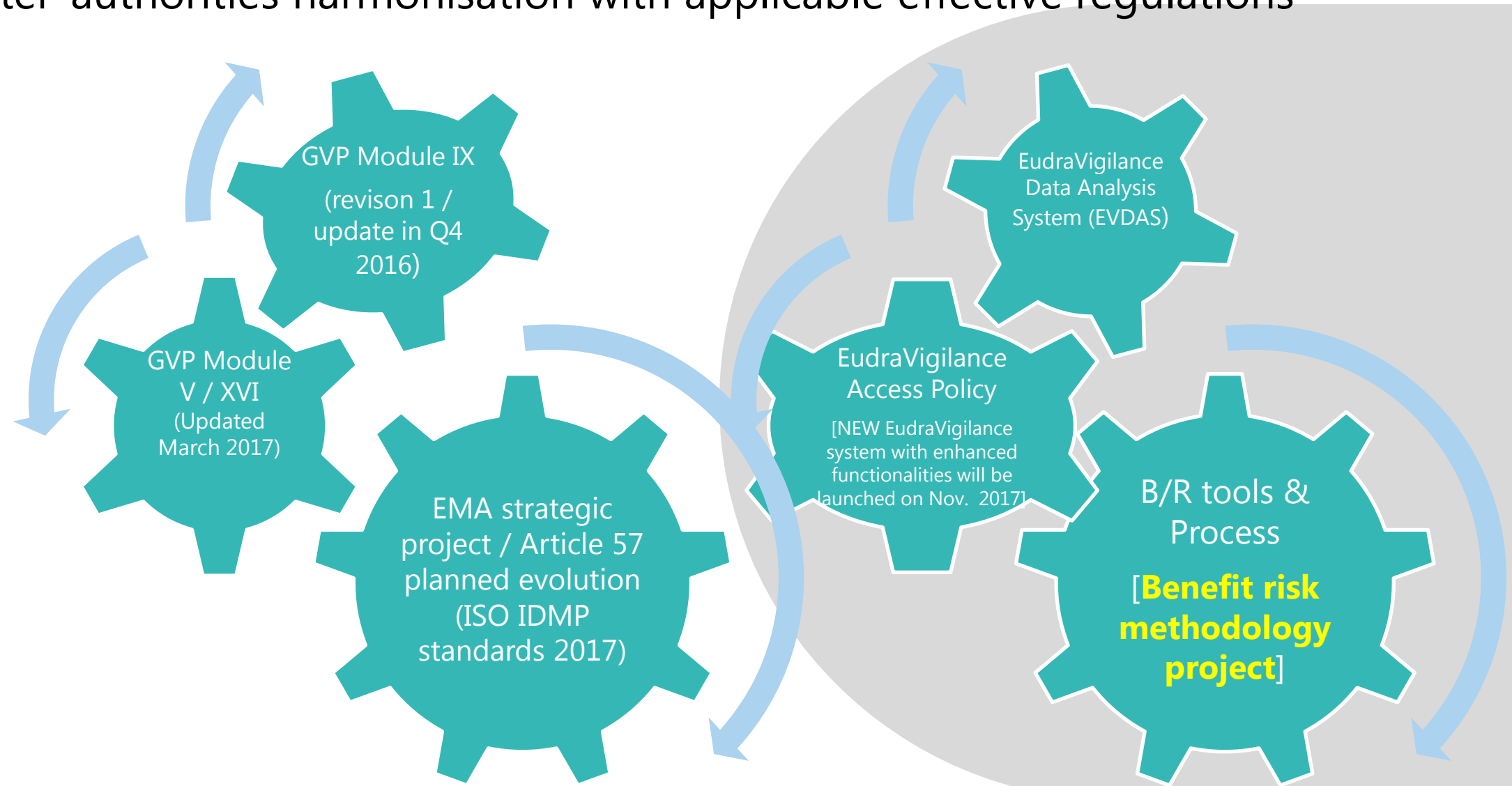
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Inter-authorities harmonisation with applicable effective regulations



9 May 2012
EMA/297405/2012 – Revision 1
Human Medicines Development and Evaluation

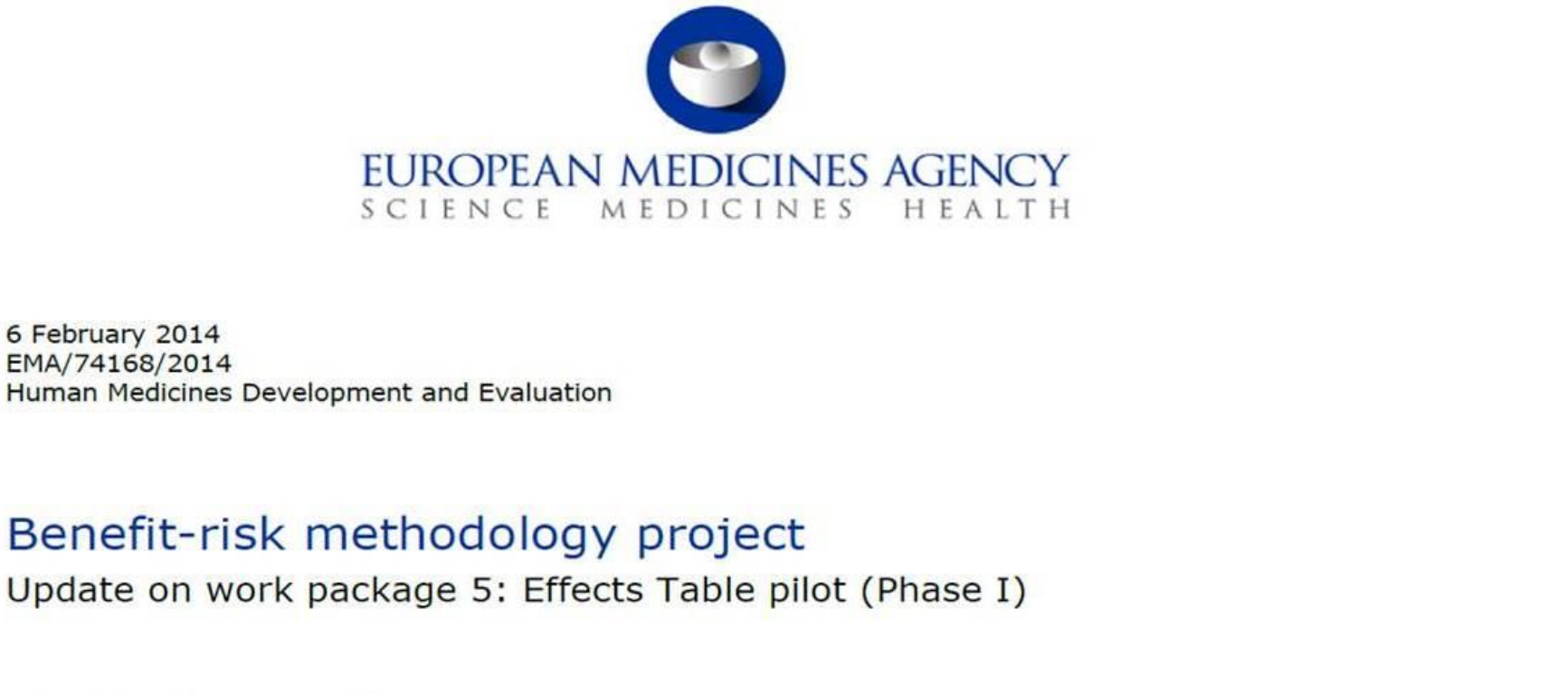
Benefit-risk methodology project

Work package 4 report: Benefit-risk tools and processes

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 February 2014
EMA/74168/2014
Human Medicines Development and Evaluation

Benefit-risk methodology project

Update on work package 5: Effects Table pilot (Phase I)

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Inter-authorities harmonisation with applicable effective regulations

Project Aim

Enhancing transparency of the benefit-risk decision-making process

Facilitating Rationale communication for each decision (within regulatory system / the public)

Project structure

ive consecutive work packages

-**Research phase** (first four work packages)

-Effects Table (ET) usage as an effective communication tool

-**Implementation** & **training** (fifth work package)

PRAC

explors ET implementation in post-authorisation B/R reviews

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EMA Benefit-Risk Methodology Project **(Effects Table example)**

Annex 1 - Hypothetical example of an Effects Table

Table 1. Effects Table for **vandetanib** / Based on the EPAR EMEA/H/C/002315 published on 02/03/2012

	Effect	Short Description	Unit	Placebo	Vandetanib	Uncertainties/ Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Mo	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

Abbreviations: PFS, progression-free survival; ORR objective response rate; Mo, months; OS, overall

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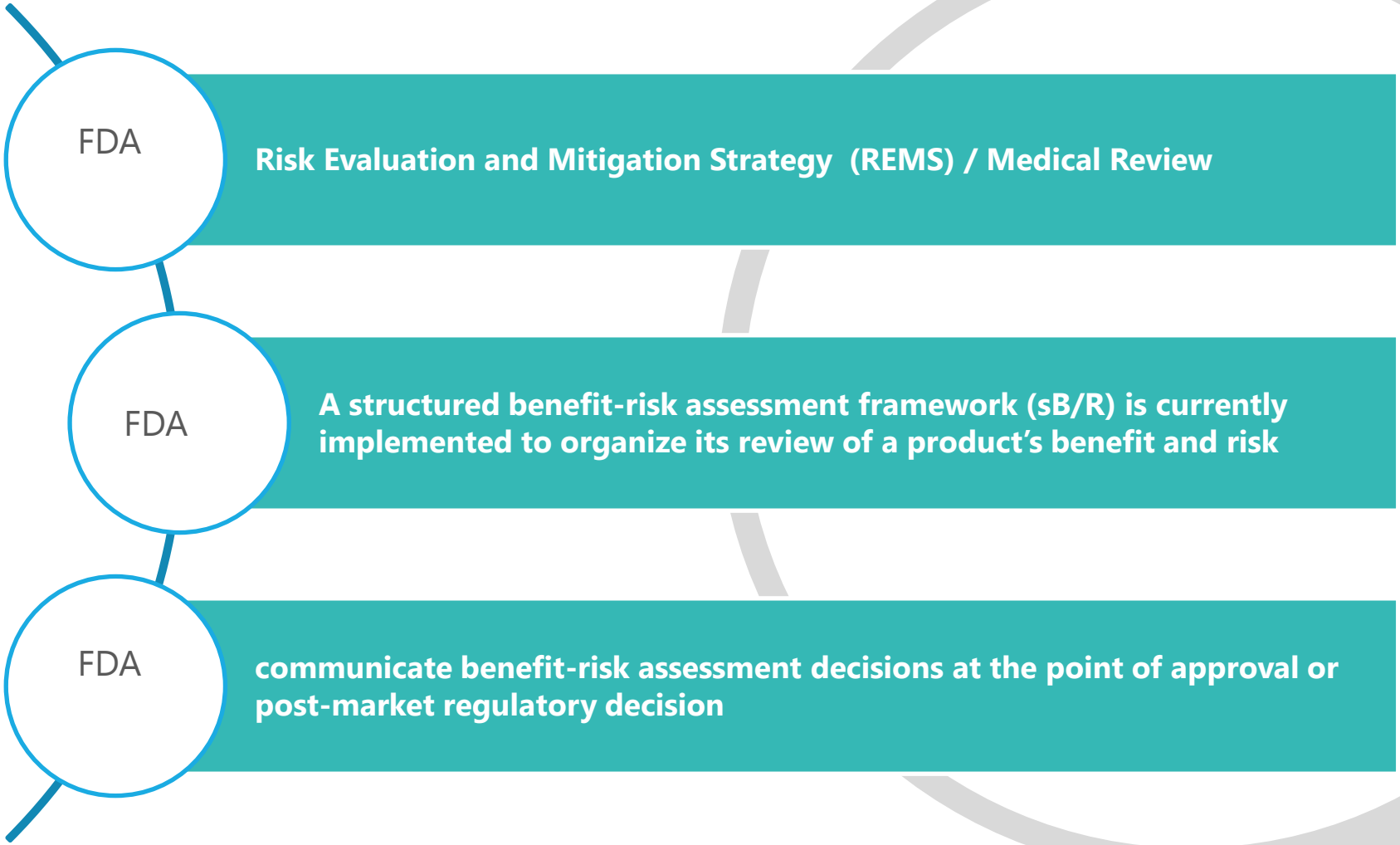
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Risk Evaluation and Mitigation Strategies: Modifications and Revisions
Guidance for Industry

The portion of this guidance document setting forth the submission procedures for risk evaluation and mitigation strategies revisions is being distributed for comment purposes only.

Comments and suggestions regarding this document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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 document contact (CDER) Kristen Everett at 301-796-0453, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-7800.

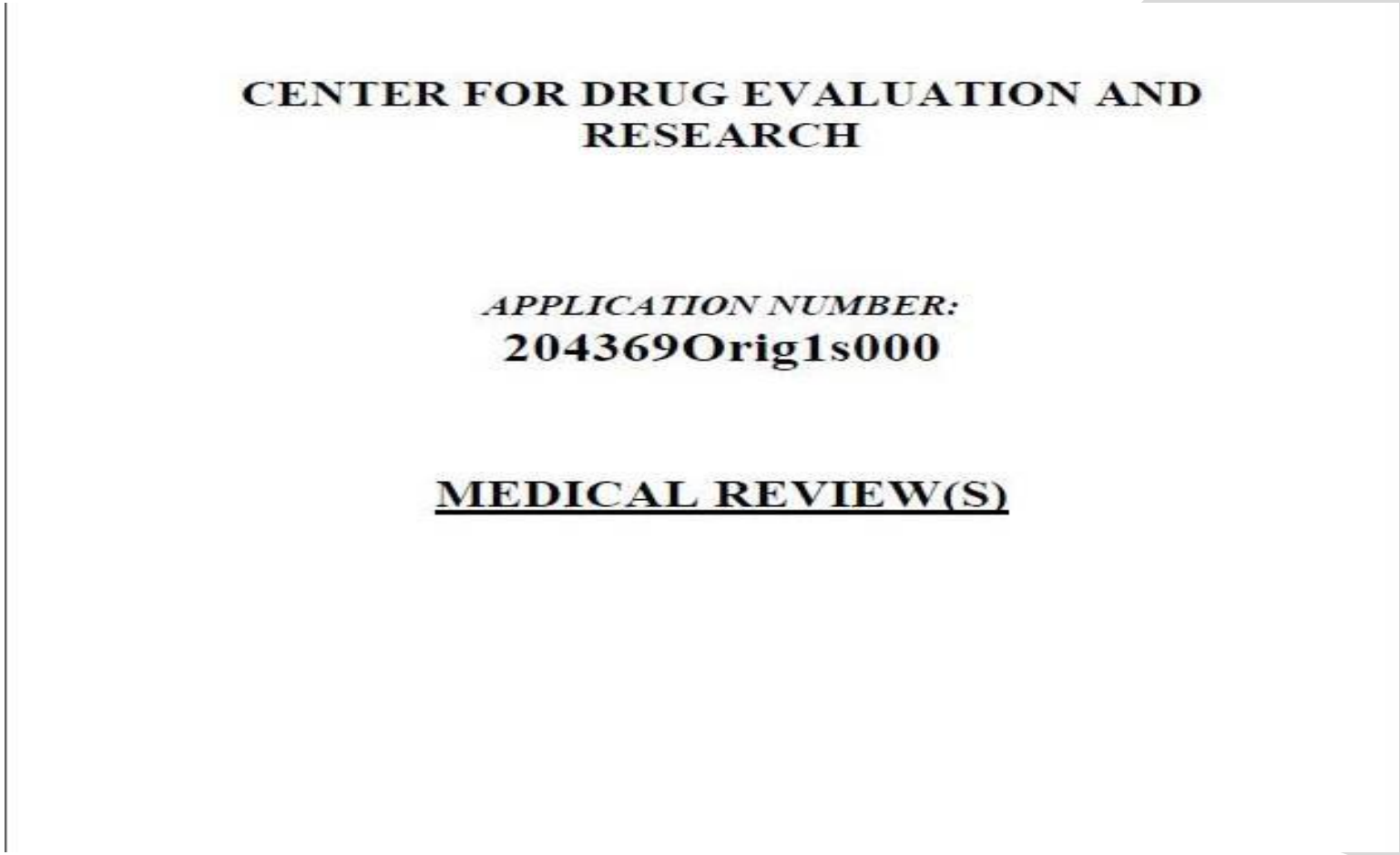
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2015

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CENTER FOR DRUG EVALUATION AND RESEARCH

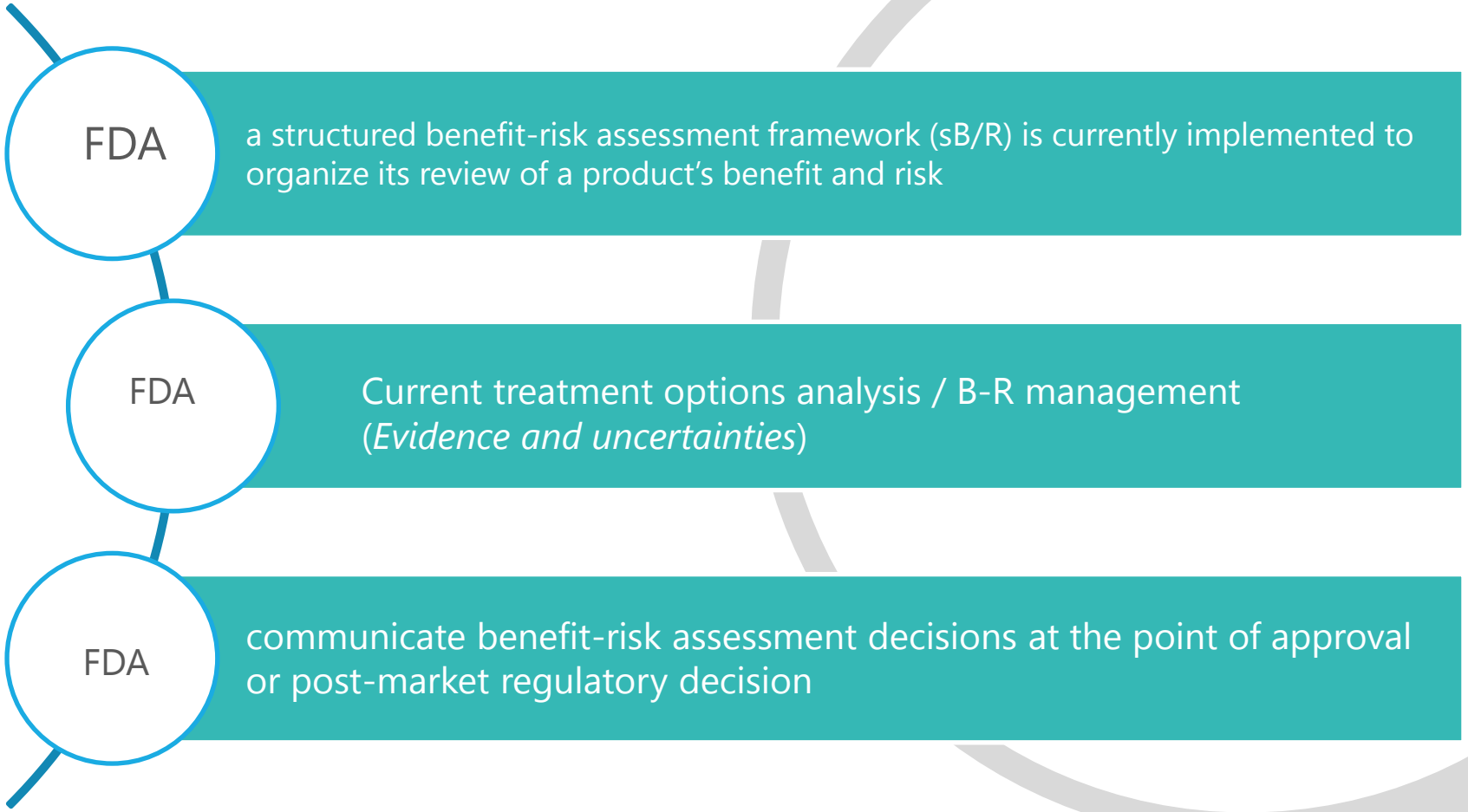
APPLICATION NUMBER:
204369Orig1s000

MEDICAL REVIEW(S)

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The Future of Population-Based Postmarket Drug Risk Assessment: A Regulator's Perspective

TA Hammad[1], GA Neyarapally[2], S Iyasu[3], JA Staffa[4] and G Dal Pan[2]

The US Food and Drug Administration emphasizes the role of regulatory science in the fulfillment of its mission to promote and protect public health and foster innovation. With respect to the evaluation of drug effects in the real world, regulatory science plays an important role in drug risk assessment and management. This article discusses opportunities and challenges with population-based drug risk assessment as well as related regulatory science knowledge gaps in the following areas: (i) population-based data sources and methods to evaluate drug safety issues; (ii) evidence-based thresholds to account for uncertainty in postmarket data; (iii) approaches to optimize the integration and interpretation of evidence from different sources; and (iv) approaches to evaluate the real-world impact of regulatory decisions. Regulators should continue the ongoing dialogue with multiple stakeholders to strengthen regulatory safety science and address these and other critical knowledge gaps.

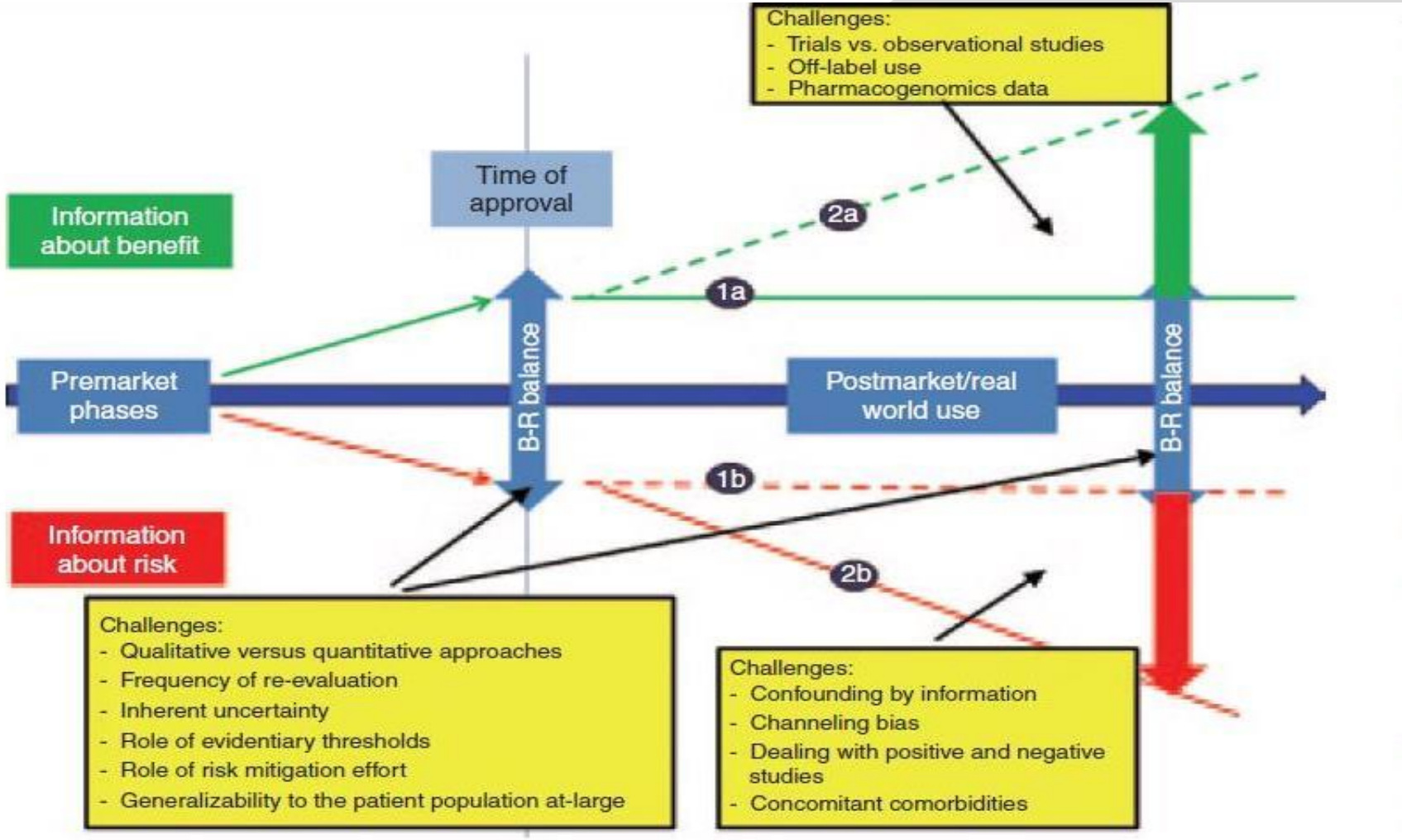
Drug regulation rests primarily on a population-based approach that seeks to ensure that, on a population level, the benefits of a

particular drug safety issue. By contrast, the postmarket drug risk assessment process involves an evaluation of the quality of

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(Hamada et al., 2013)

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Risk management during product life cycle requires:

Awareness of

* Integrating data from multiple sources
* Understanding the impact of risk management and real-world data
* Methods to balance benefit and risk (*Quantitative / qualitative approaches*)
* Applicable effective strategies

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RISK MANAGEMENT LIFE CYCLE APPROACH – KEY POINTS

ESSENTIALS IN STRATEGY

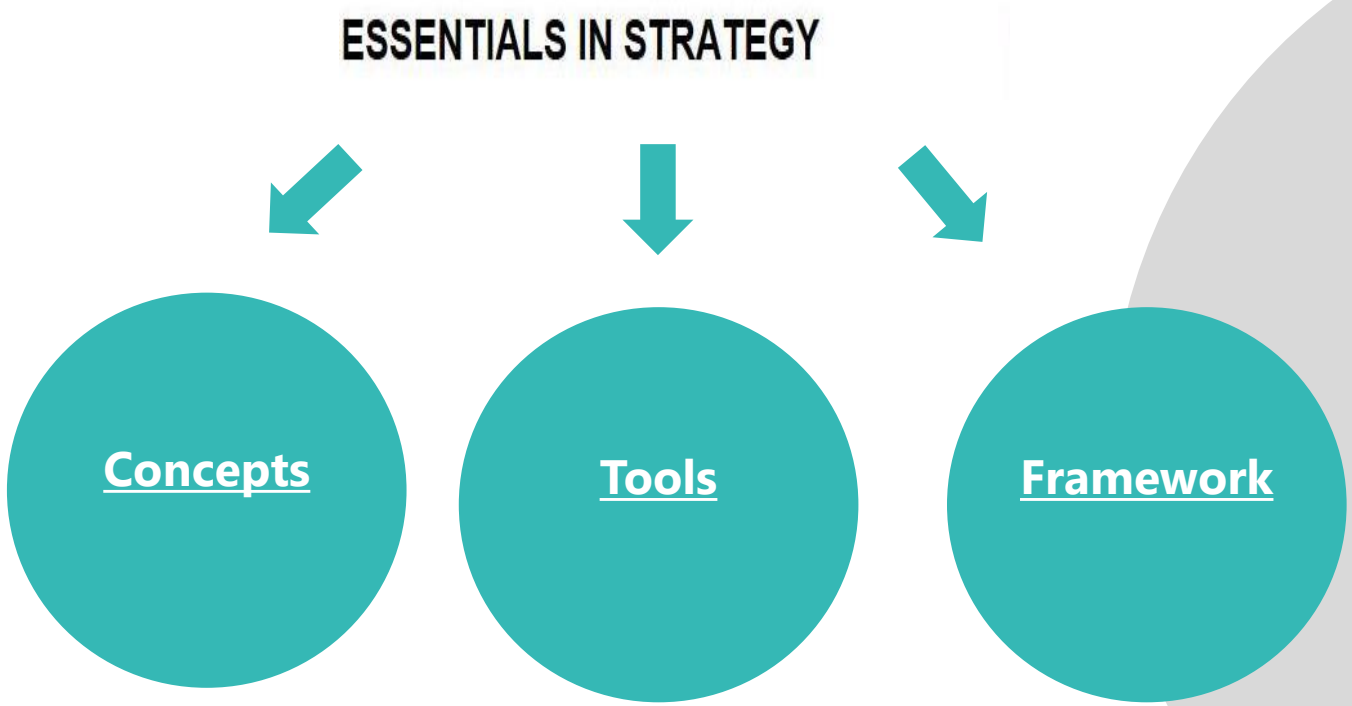
Concepts

Tools

Framework

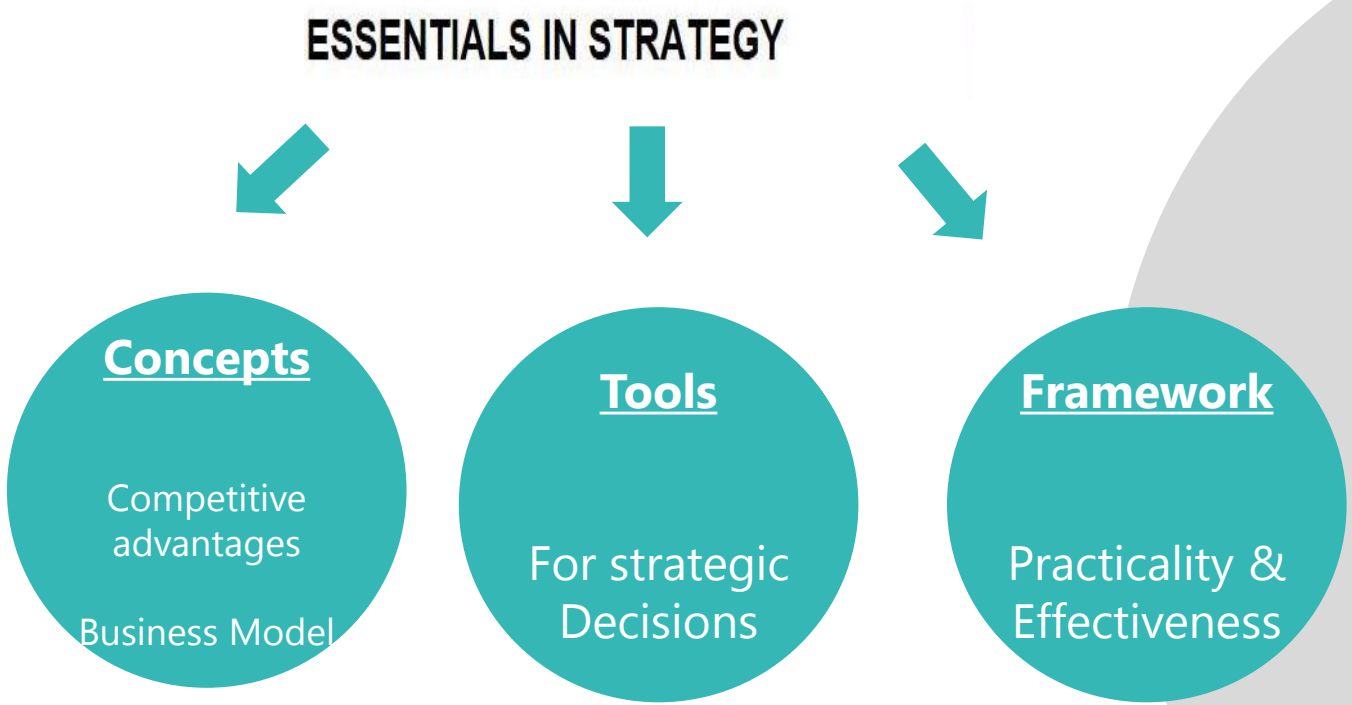
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Risk Management during product life cycle

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