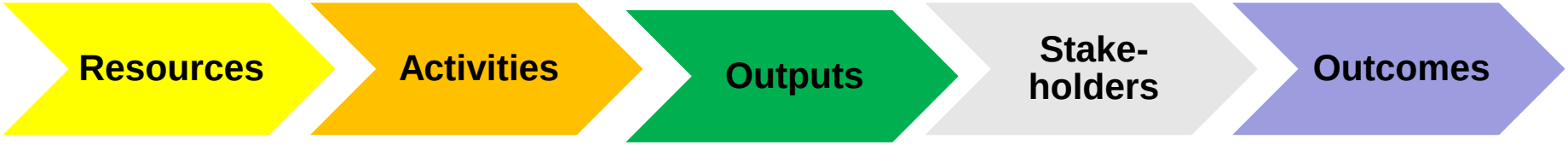
Is there a role for expert judgment in the medicines use process?

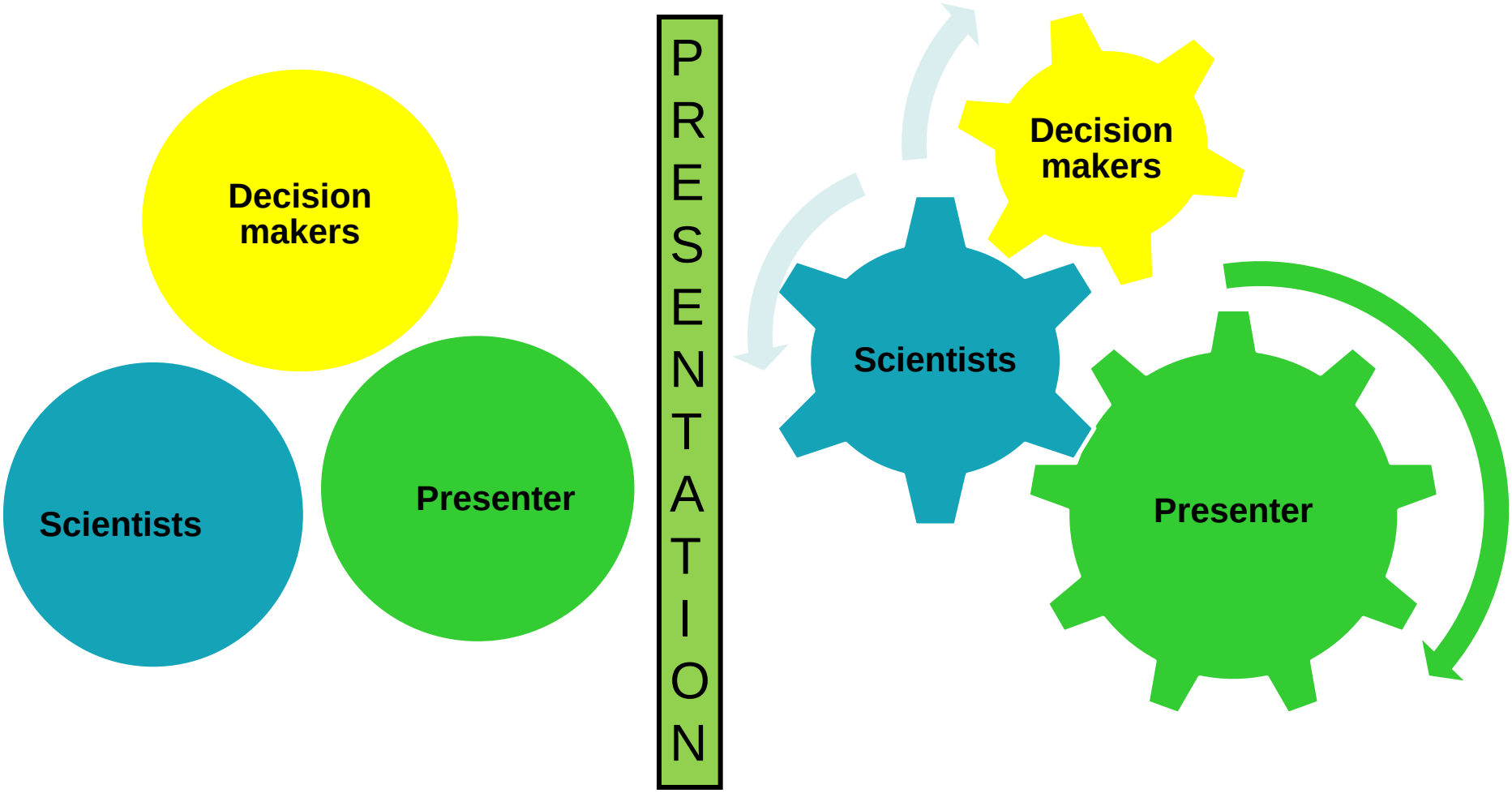


Dr Patricia Vella Bonanno

Using Expert Judgement to Enhance Health Decision Making

Malta 7-9th October 2015

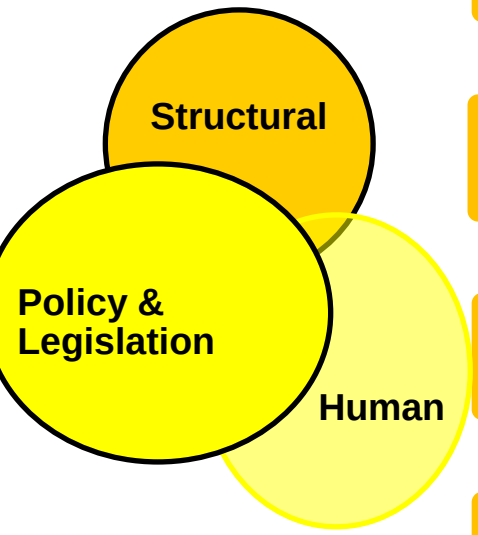
Objective of the presentation



The medicines use process - representation through a logic model

Medicines use process model

Resources → Activities → Outputs → Stake-holders → Outcomes



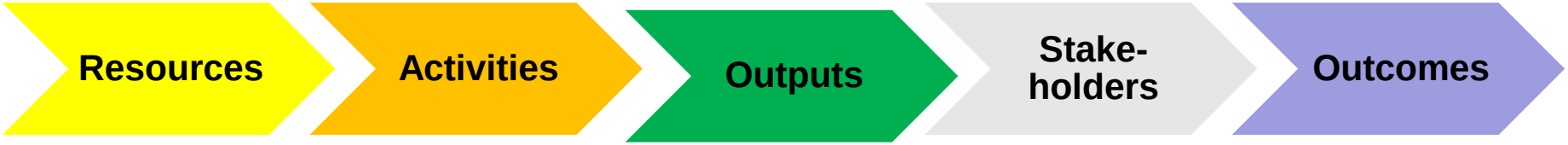
- Research and development
- Marketing authorisation
- Pricing and reimbursement
- Manufacturing and supply
- Prescribing and dispensing
- Administration and monitoring

Logic model for the framework

Resources	Activities	Outputs	Stake-holders	Outcomes				
				A	A	A	Q	R
Industry	Research and development	Public health Competition	Patients HCPs	X	X	X	X	X
Regulatory Authorities	Marketing Authorisation/ Post-licensing	Public health	Industry HCPs/Patients	X	X		X	X
Reimbursement authorities	Pricing and reimbursement	Competition Public health	Industry HCPs/Patients	X		X		X
Industry	Manufacturing and supply	Competition Public health	Industry	X	X	X	X	
HCP's	Prescribing and dispensing	Public health	Patients HCPs		X	X		X
HCP's Industry	Administration and monitoring	Public health Competition	Patients HCPs		X	X	X	X
External influences:								

Identification of risks/uncertainty in the medicines use process using the framework logic model

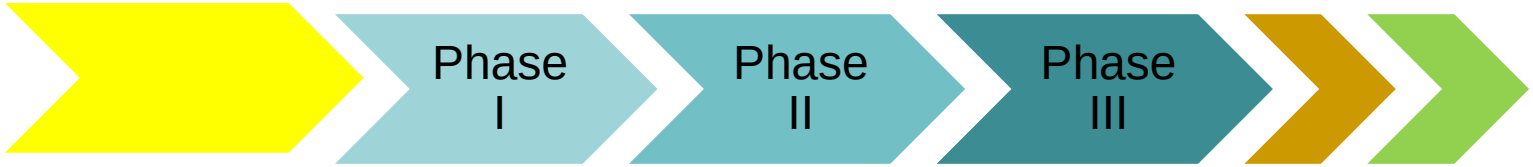
Activity 1



1.	Research and development
2.	Marketing authorisation/ Post-licensing
3.	Pricing and reimbursement
4.	Manufacturing and supply
5.	Prescribing and dispensing
6.	Administration and monitoring

Research and development

Medicinal product life-cycle



Stage	Discovery/ Pre-clinical		Clinical		MA	PL
Duration	3-6 years		6-7 years			
Compounds	5,000-10,000	250	Starting from 5 compounds going down to 1		1	
Patients/ subjects	Models		Volunteers 20-100	Patients 100-500 1,000-5,000		

The delivery of a new drug:
- a high risk investment; covered by IP protection
- is estimated at a cost of Euro 1 to 3.8 billion
- sponsorship: the pharmaceutical industry (64%), others (36%)

Clinical trials

• Produce information required for the evaluation of marketing authorisations.

• Objectives of the legislation:
- to protect clinical trial subjects
- to ensure that results are credible

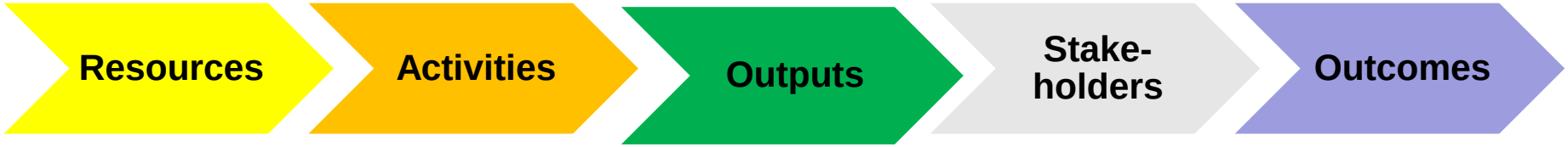
• Regulated since 2005.
New Regulations from 2016.

Evaluation

• **Evaluation:**
New drug vs. placebo / alternatives
- Risk-benefit assessment
- Ethical aspects
- Local aspects

• Limitations: controlled environment, numbers, limited groups

Activity 2



1.	**Research and development**
2.	**Marketing authorisation/ Post-licensing**
3.	Pricing and reimbursement
4.	Manufacturing and supply
5.	Prescribing and dispensing
6.	Administration and monitoring

Medicinal product life cycle

Medicinal product life-cycle

Discovery/ Pre-clinical	Clinical	MA	Post-licensing
3-6 years	6-7 years	0.5-2	Up to withdrawal

Phase I | Phase II | Phase III | Phase IV

In vitro *In vivo* Process development GMP production	Safety Tolerability Pharmaco-kinetics/ dynamics Dose response	Dosing Efficacy	Efficacy compared to gold standard treatment	**Regulatory review** **Scale up manufacture**	Post marketing surveillance Pharmaco-vigilance

Marketing Authorisation

Benefits

Efficacy

Indications for use

Evaluation

Risks

- Safety
- Side effects
- Adverse drug reactions
- Medication errors
- Contra-indications

Quality

Expiry dates

Active ingredients

Inactive ingredients

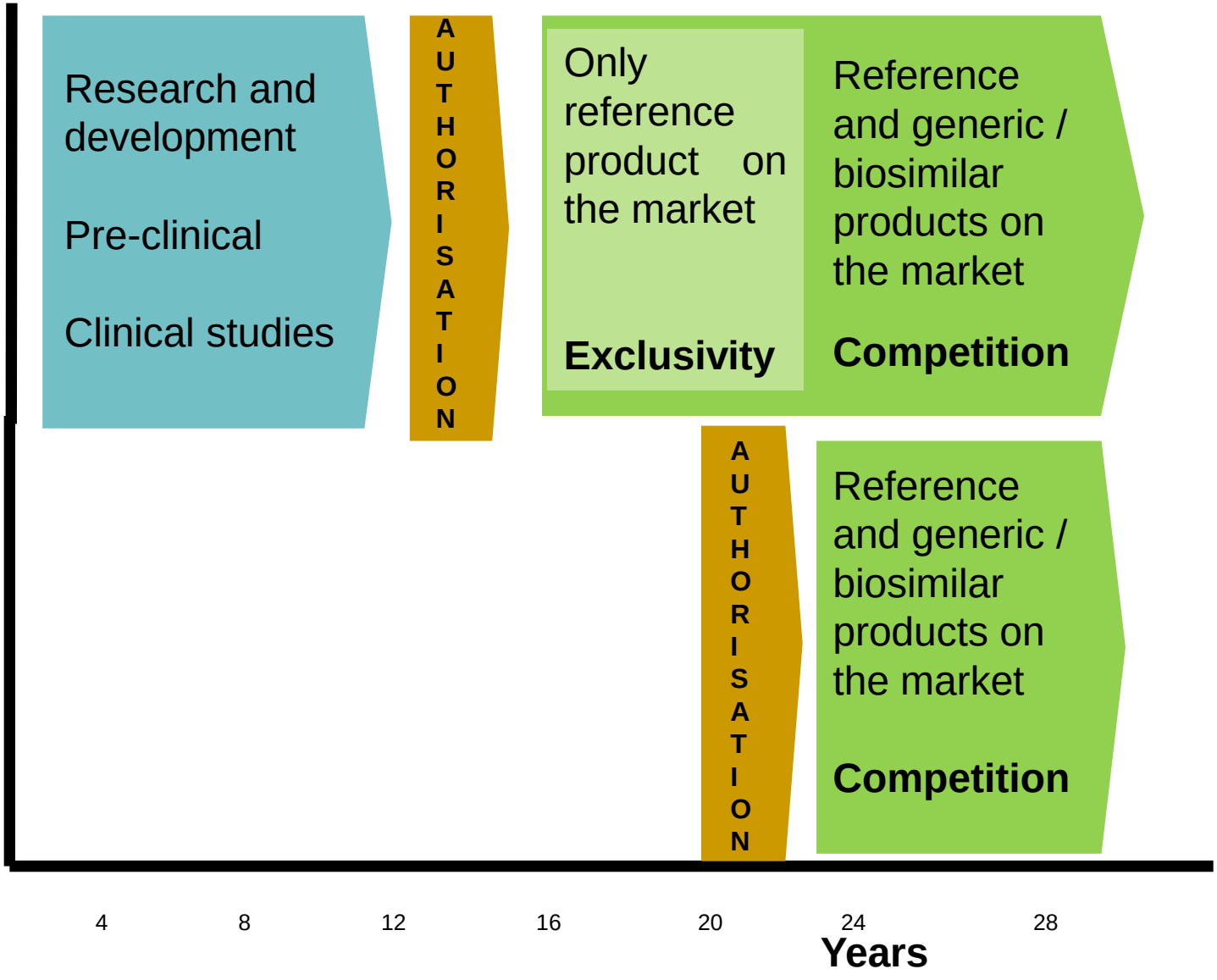
Storage conditions

- Classification (OTC/POM)
- Bioequivalence / biosimilarity
- Labeling
- Patient leaflet
- SmPC – official document, legal implications

- Evaluation based on pre-clinical and clinical data (limited)
- Evaluation for early access of new products:

Accelerated assessment procedure, adaptive pathways, conditional approval

Reference vs. generics /biosimilars



Post-licensing: Pharmacovigilance

pharmacovigilance data and activities

ADR reports, post-authorisation safety studies,
risk-management plans, risk-minimisation measures

Evaluation

evaluation of the risk/benefit balance

Variations to marketing authorisations

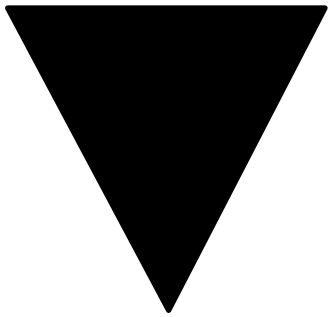
Suspension or withdrawal of marketing authorisations

Pharmacovigilance

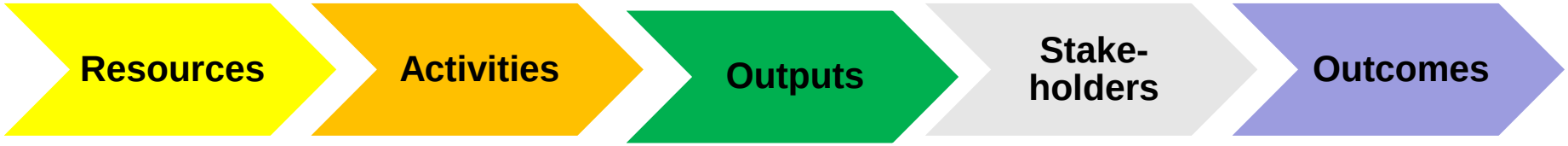
- Limitation of pre-clinical and clinical data on safety
- New risks identified with the use of a product in clinical practice:
new side-effects, perceived efficacy not achieved, teratogenicity and carcinogenicity
- New legislation on Pharmacovigilance (July 2012)

Adverse drug reaction (ADR):
- a response to a medicinal product which is 'noxious and unintended':
- ADRs from the authorised use of products
- Medication errors that result in an ADR
- Uses outside the terms of the SmPC

- Centralised EU database for ADRs and MEs
- Black triangle for additional close monitoring
- HCPs are encouraged to report ADRs
- Patients can report ADRs



Activity 3



1.	Research and development
2.	Marketing authorisation/ Post-licensing
3.	**Pricing and reimbursement**
4.	Manufacturing and supply
5.	Prescribing and dispensing
6.	Administration and monitoring

Pricing of medicinal products

External price referencing

- Prices of medicines vary across MS's.
- Most MS use external price referencing to determine prices

Health systems use a variety measures to control spending:	
Supply side	**Demand side**
- Determination of prices - Share of prices that are reimbursed	- Policies to encourage prescribing and dispensing of lower-priced products - Cost-sharing

Health Technology Assessment

- Systematic evaluation of properties, effects, impacts
- Applicable to health interventions and technologies
- Limited data on outcomes in practice – effectiveness
- Objective to distinguish, reward meaningful innovation
- Appraisal of additional clinical benefit of new technologies against alternatives and resulting costing
- Social, economic, organisational and ethical issues

Evaluation

Reimbursement of medicines

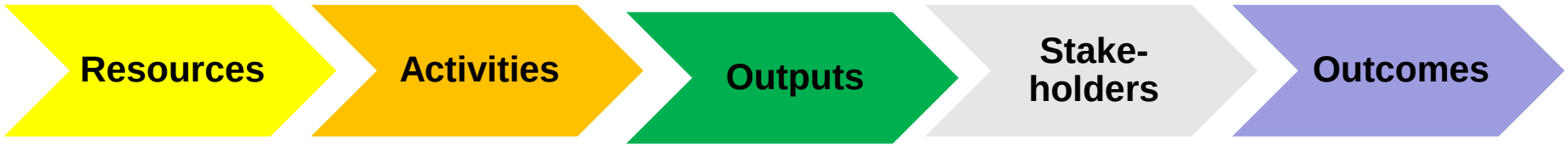
- Payers (public and/or private)
- Eligibility within national health systems / insurances (entitlement)
- Prioritisation and allocation of resources, budgetary allocation, equity
- Positive and negative lists, formularies, protocols, guidelines
- Reimbursement and pricing are a challenge for the industry (providers) – affect market entry
- Providers valuate prices relevant to the reimbursement expected from payers
- Conditional reimbursement, monitoring

Access to medicines in EU MS's

- Access to new medicines varies across EU Member States
- Reimbursement of new medicines is in competence of MS's
- Not all centrally authorised products are available in all MSs

Source: A call to make valuable innovative medicines accessible in the European Union, Belgian Presidency of the EU, Sept 2010

Activity 4



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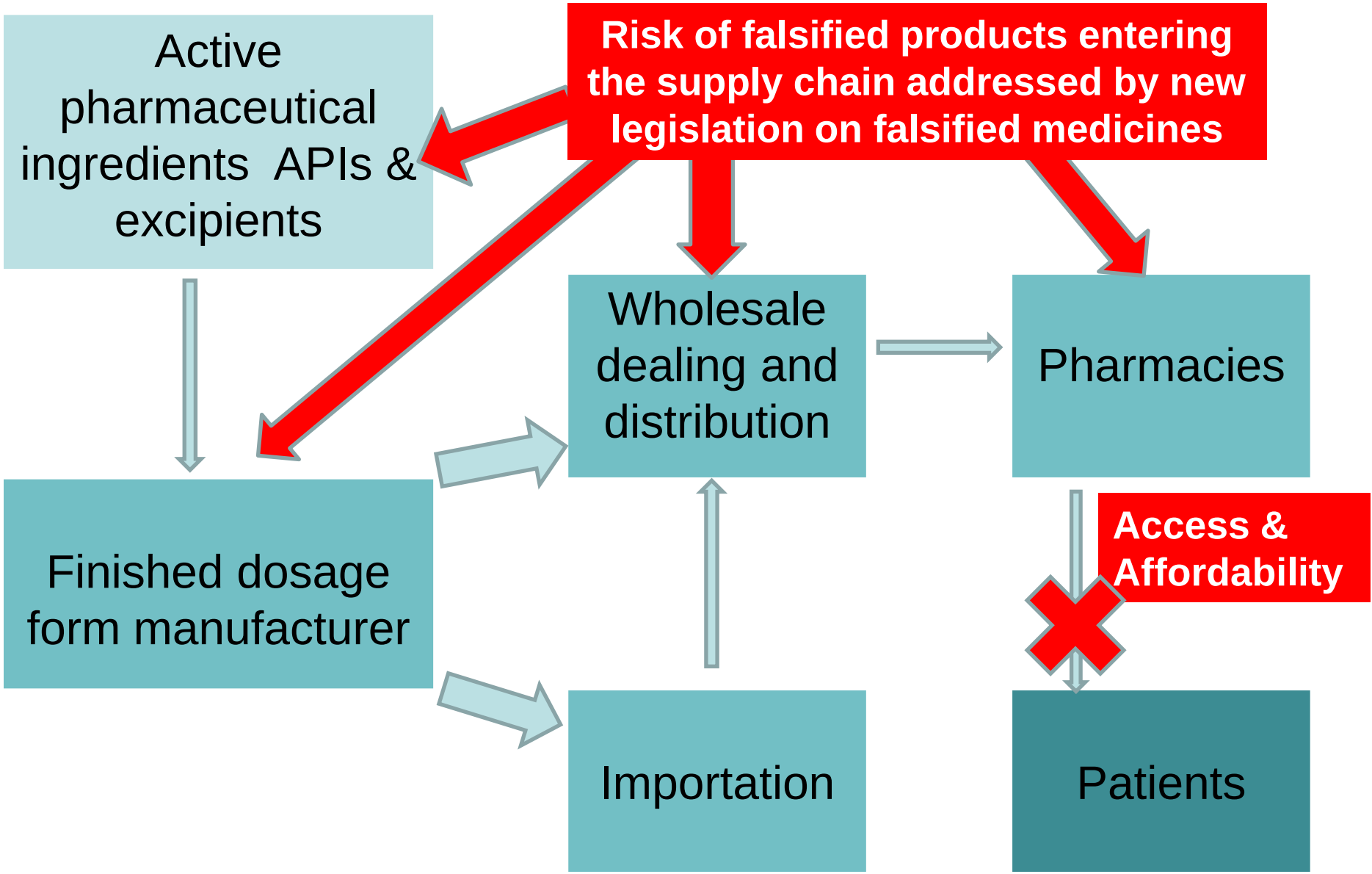
The medicines supply chain



Falsified medicines legislation

New legislation for the prevention of the entry of falsified medicines into the legal supply chain:

- defines falsified medicines as:

any medicinal product with a false representation of:

a) its identity, packaging and labelling, name or its composition
b) its source, manufacturer, country of manufacturing, country of origin
c) its history, records and documents relating to distribution channels

- quality of active ingredients, excipients, finished products
- strengthens the legal supply chain - safety features

- regulates sales of medicines over the internet (established authorised internet sites)

Activity 5

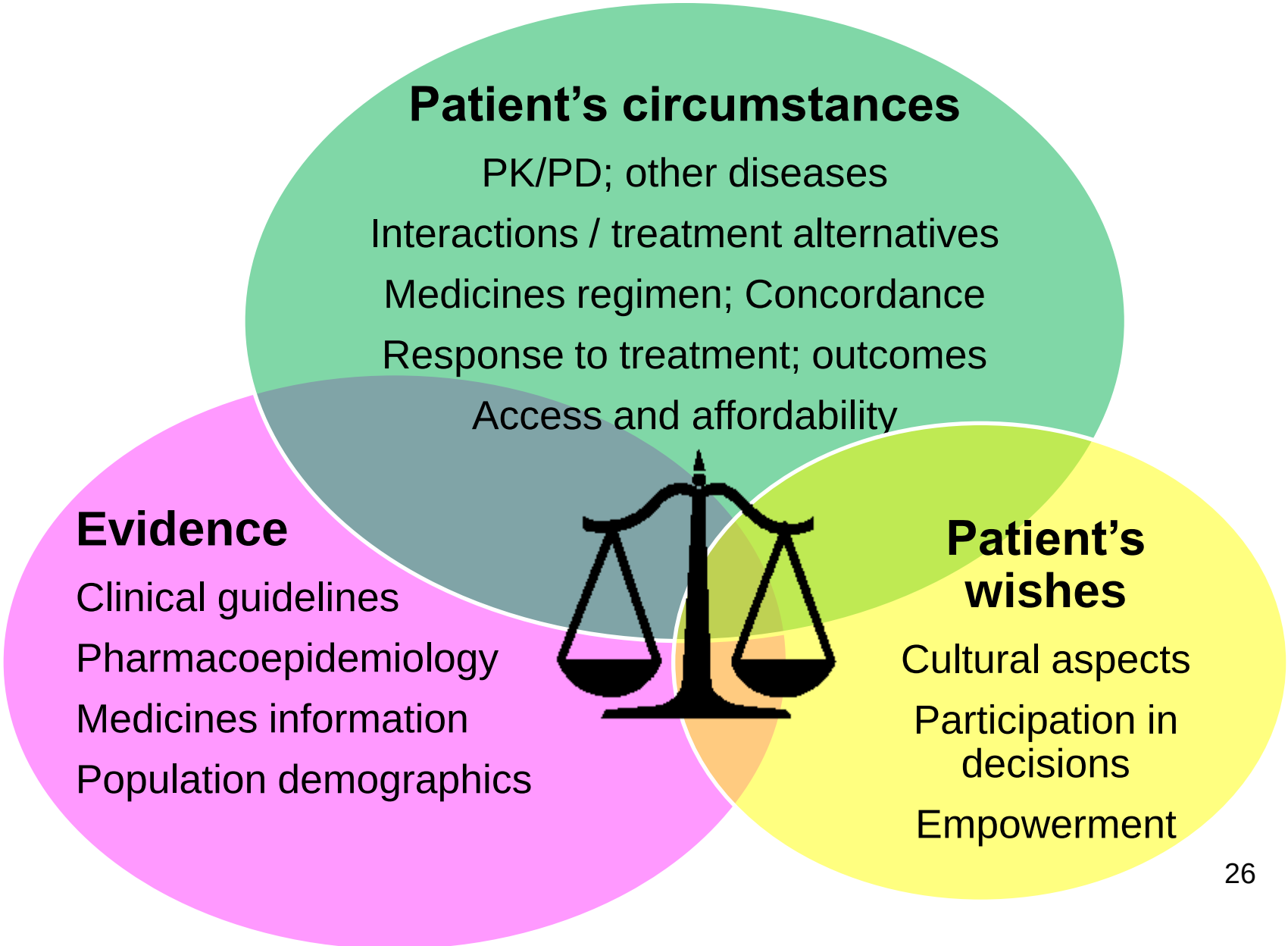
1.	Research and development
2.	Marketing authorisation/ Post-licensing
3.	Pricing and reimbursement
4.	Manufacturing and supply
5.	**Prescribing and dispensing**
6.	Administration and monitoring

Application of clinical evidence

1. evidence from research → 2. evidence synthesis → 3. forming clinical policy → 4. applying policy → 5. making clinical decisions

- New knowledge & updates
- SmPC (product-specific)
- Clinical guidelines, protocols
- Decision support systems
- Influences on prescribing
- Risk management plans

Clinical decision making



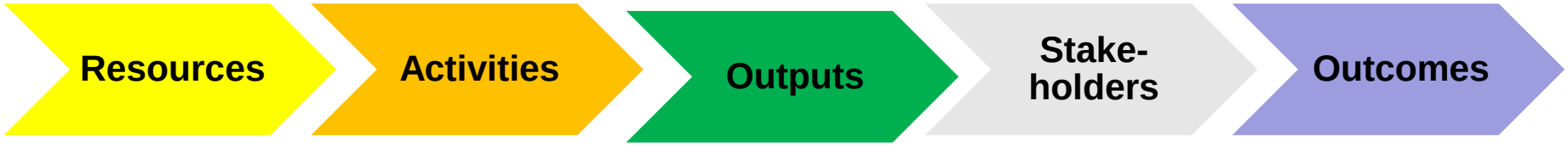
Factors affecting prescribing

- Inter-changeability of bioequivalent and biosimilar products
- Therapeutic alternatives
- Communication, negotiation with patient
- Protocols, clinical decision support systems
- Advertising and medical representatives
- Responsibility and liability

Legal status for use of a medicinal product:

- Use of medicinal product in line with SmPC
- **Compassionate use** – product in the process of being authorised through centralised procedure
- **Off label use** – not in accordance with the SmPC
- **Unlicensed:** without a marketing authorisation

Activity 6



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3.	Pricing and reimbursement
4.	Manufacturing and supply
5.	Prescribing and dispensing
6.	**Administration and monitoring**

Administration and monitoring

- **Administration**

- Right medication
- Right patient
- Right time

- **Monitoring**

-Monitoring and documenting response

-Reporting adverse ADRs and Medication errors

-Re-evaluating medicines regimen

- **Supporting patient participation**

-Information about the medicines and their use

-Advertising, information over the internet

-Tools to support the administration of medicines

- Empowerment of patients to participate

Concordance

Risks:
- medicines are prescribed but not dispensed
- medicines are dispensed but not taken properly

Factors affecting concordance:
- Level of patient-centred approach
- Polypharmacy
- Complication of the dosage regimen
- Dosage form and presentation of drug
- Knowledge on medicines and diseases
- Patient's perception of benefits and risks
- The patient's disease condition
- Patient's ability to administer medicine
- Access and affordability

Impact of adverse drug reactions

ADR's :

- expected/unexpected
- severity of ADRs

Other impacts of ADRs:

0.12 – 0.22% of hospital admissions result in death due to ADR

3 – 10% of hospital admissions are caused by ADRs

2.1 – 6.5% of hospitalised patients suffer from an ADR

ADR related costs (other than hospitalisation) €63.2 billion annually

Total societal costs of ADRs in the EU €79 billion annually

European Commission, Pharmacovigilance Assessment Report (SEC(2008) 2671)

Medication errors

‘a failure in the treatment process that leads to or has the potential to lead to, harm to the patient’

- **Types of errors:**

- Prescribing
- Omission
- Wrong time
- Wrong dosage form
- Wrong drug preparation
- Wrong administration technique
- Deteriorated drug
- Monitoring
- Adherence

- **Reporting of medication errors**

‘blame free culture’

External influences

Resources	Activities	Outputs	Stake-holders	Outcomes

External influences:

Regulatory and policy framework

- Legislation
  - EU and national legislation
  - Impact of the legislation
- Regulatory framework and risk governance
- Cultural influences
- Health care systems and practice
- Stakeholder perspectives/interests

50 years of EU pharmaceutical legislation

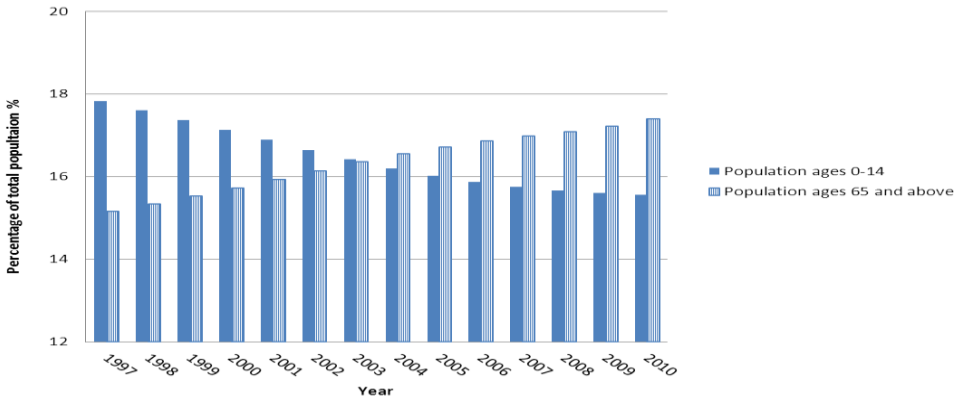
Significant achievements

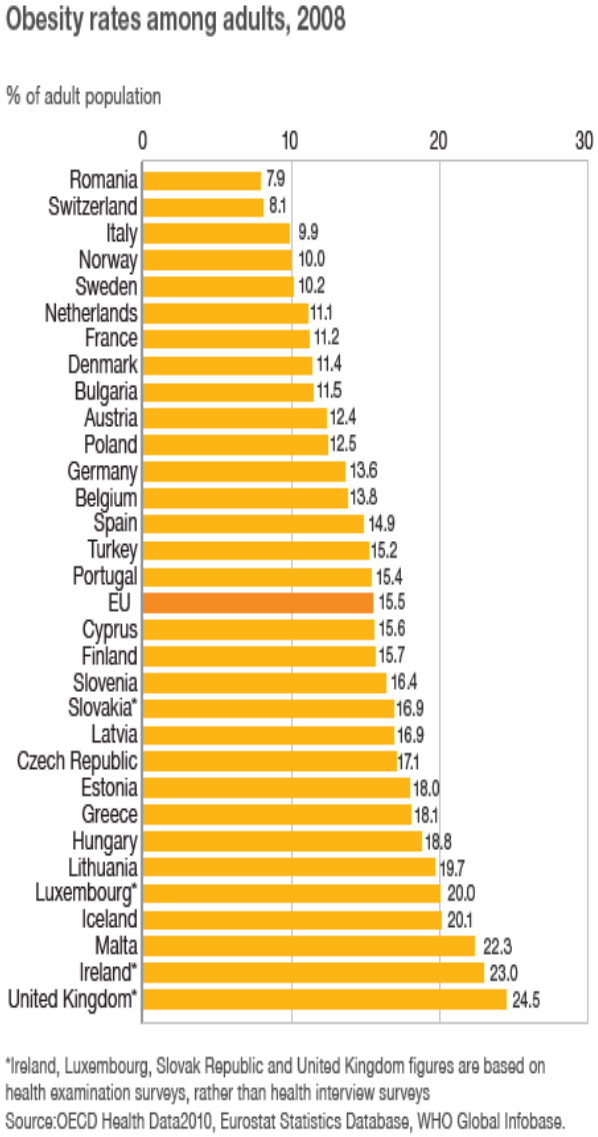
Gaps remain
- Access
- Single market

New challenges have arisen

Public health considerations

- New disease conditions
- Incidence and prevalence of diseases
- Risk factors and prevention of disease
- Access and affordability of treatment
- Demographic changes
- Public health considerations





Source: Priority Medicines for Europe and the World, Update 2013 Report, cited from Data from the World Bank

Challenges and initiatives

Initiatives for early access

- **Regulatory initiatives for early access:**

- accelerated assessment procedure
- conditional MA approval
- Adaptive Pathways Project
- Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP)

- **National early access programmes (different MSs)**

- **World Health Organisation, Europe**

Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research (WHO Regional Office for Europe, WHO, 2015)

Research initiatives – access

Innovative Medicines Initiative projects:

IMI 2 3rd Call for proposals

RADAR Remote Assessment of Disease and Relapse Key objective: to develop the foundational components to improve patient outcomes through remote assessment.

PROTECT (ongoing project)

Pharmaco-epidemiological Research on Outcomes of Therapeutics by a European Consortium

AdaptSmart project (launched in September)

To create EU practices and build methodologies and tools to make MAPPs a viable alternative to the current methodology of bringing new medicines on the market.

Stakeholders in decision making

Can EJ be used as a tool to involve different stakeholders in decision making?

Can EJ serve as a tool to enable balanced stakeholder involvement / influence in decision making?

Research initiatives - stakeholders

Innovative Medicines Initiative projects:

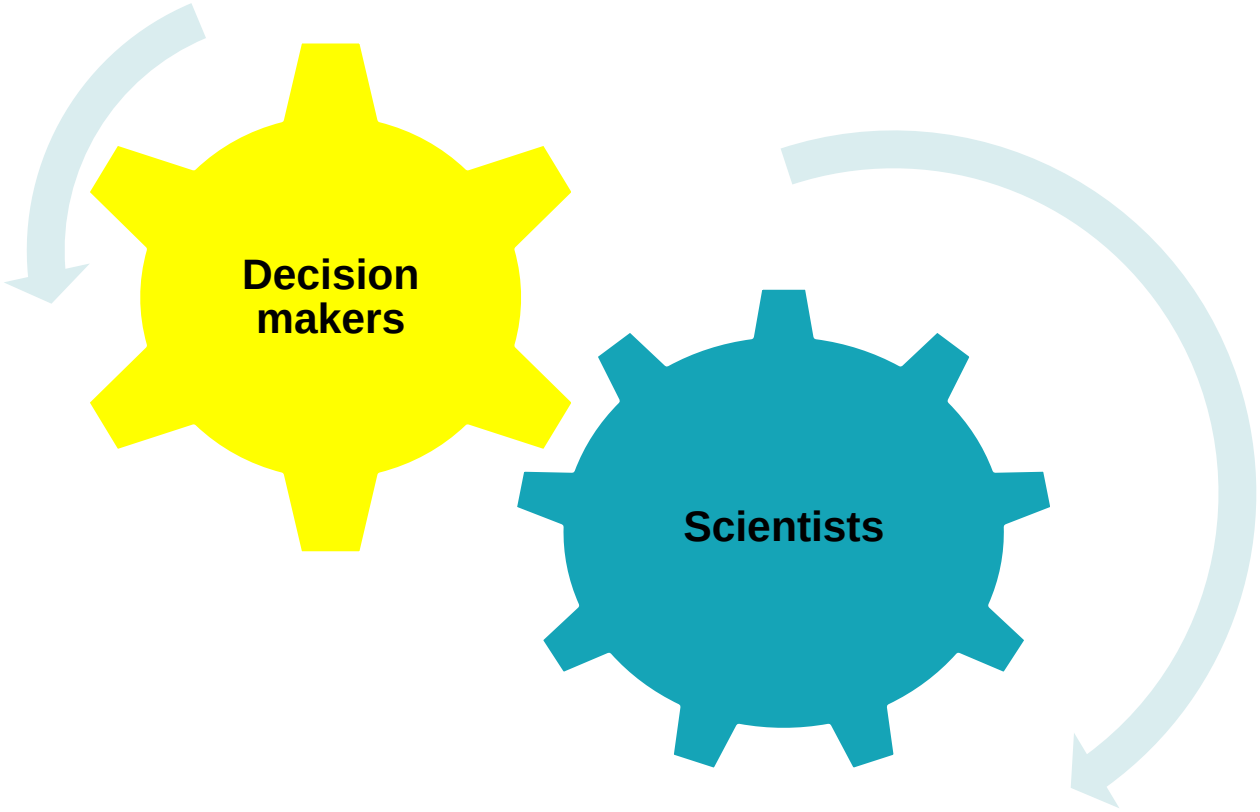
IMI 2 5th Call for proposals

Patient perspective elicitation on benefits and risks of medicinal products, from development through the entire life cycle, to inform the decision-making process by regulators and health technology bodies.

Stage 1 deadline 13th October 2015

Increased interest in direct patient involvement in research initiatives and clinical trials:
- the way studies are designed
- assessment of benefits and risks
- meaningful perspective to process

Looking forward to …..



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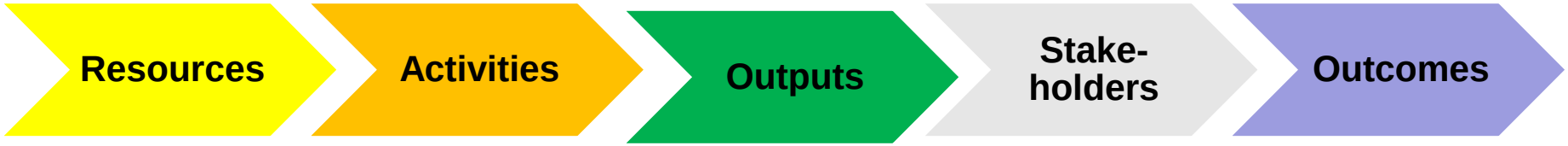
Discussion



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