EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

EUCOPE

Pricing & Reimbursement / Market Access Working Group Meeting

Brussels, 12 February 2019

Agenda (1/3)

I. **Welcome / Next Events / Working Groups**
Chairs

II. **Update on the Beneluxa initiative on pharmaceutical policy**
Diane Kleinermans, Belgian Ministry of Health
Francis Arickx, RIZIV

III. **France: The work of the comité économique des produits de santé – CEPS**
Jonathan Rodrigues, CEPS

Agenda (2/3)

IV. Germany:

- **New round in the Pharmadialog talks between the federal government and industry**
- **The draft bill on uptake of biosimilars and mandatory registries for OMPs**

Kevin Rieger, BPI e.V.

V. Market Access Challenges for Nanomedicines

Emanuele Degortes, Vifor Pharma

Agenda (3/3)

VI. **Dutch and European developments as regards to the use of unlicensed medicines**
Andrea Corazza, FTI Consulting

VII. **HTA Network Stakeholder Meeting: feedback and next steps**
Ana Palma, SOBI

VIII. **Further country updates**

IX. **AOB / Closure of meeting**

I.
Welcome / Next Events / Working Groups

Chairs

Upcoming Events

- 21 February: Life Sciences College, Brussels
- 21 - 22 February: ERA Conference on EU Law in the Pharmaceutical Sector, Brussels
- 26 February: EUCOPE Members' Meeting, Brussels
- 27 February: EUCOPE EP Breakfast Meeting on Gene & Cell Therapies, Brussels
- 19/20 March: Pharma pricing & market access Congress, Amsterdam
- 28/29 March: GIRP 4th Conference on Supply Chain, Cannes
- 10 - 12 April: World Orphan Drug Congress USA
- 2 May: Regulatory / PV / Medical Device Meeting, Brussels
- 15 May: OMP Meeting, Brussels
- 4 June: Market Access / Pricing & Reimbursement Meeting, Brussels
- 25 June: EUCOPE Members and General Meeting, Brussels

II.

Update on the Benelux initiative on pharmaceutical policy

Diane Kleinermans, Belgian Ministry of Health, **and**
Francis Arickx, RIZIV

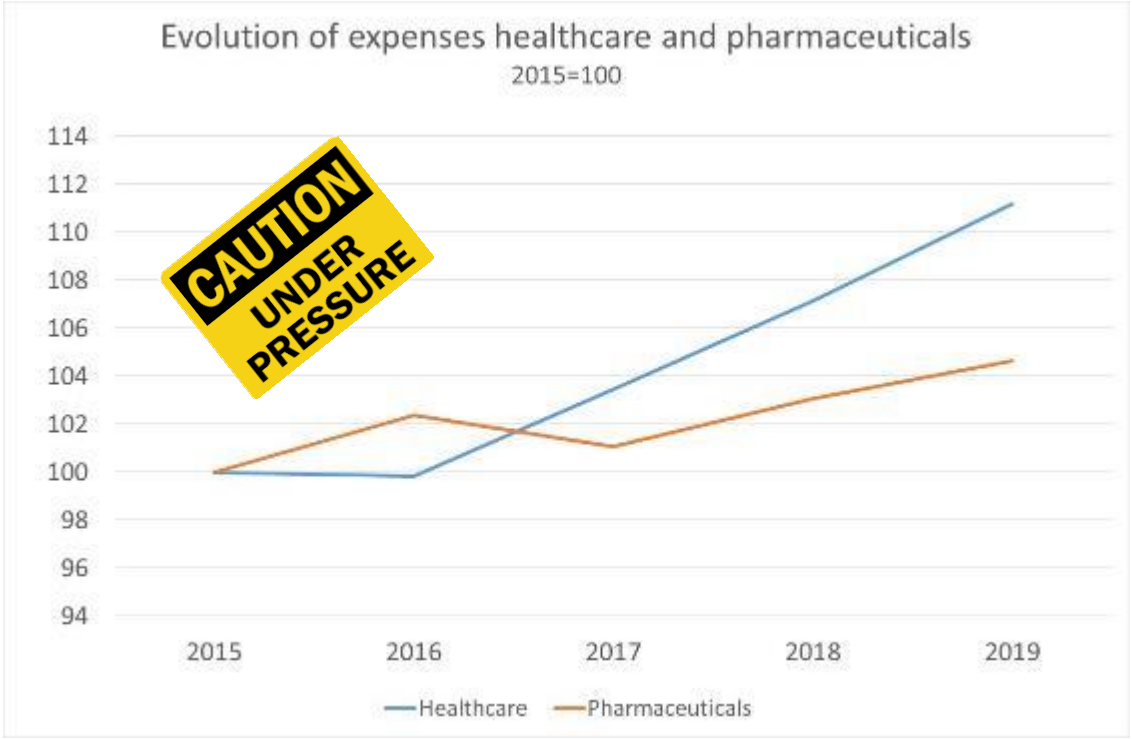
Ministre des Affaires sociales et de la Santé publique
MAGGIE DE BLOCK

BeNeLuxA
Stronger together in bringing solutions to the patient

Bart Vermeulen
Deputy Director Healthcare
Office of the Minister of Social Affairs and Public Health

.be

Challenges?!



Added Value and Effectiveness?

Pricing?

Managed Entry Agreements?

...

BeNeLuxA: stronger together

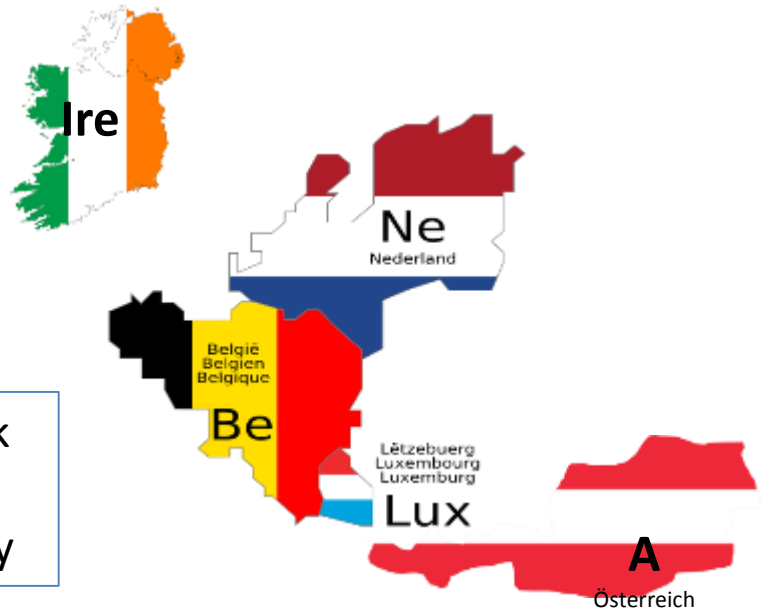
- Source?

  Government Agreement 2014: Samen met het Europese bestuursniveau zoeken we naar gemeenschappelijke oplossingen voor uitdagingen zoals zeldzame ziekten.

- **2014:** Rome, IT Presidency: NCAPR debate on collaboration and open invitation to form a 'coalition' on pharmaceutical pricing

- How did it begin?
  - 2015: Be+Ne
  - 2015: Be+Ne+Lux
  - 2016: Be+Ne+Lux+A
  - 2018: Be+Ne+Lux+A+Ire
  - …?

BeNeLuxA is currently the benchmark for European and international collaboration in pharmaceutical policy



BeNeLuxA: stronger together

Goal: 'The BeNeLuxA Initiative aims to ensure sustainable access to innovative medicine at affordable cost for our patients.'

- Scope: Expensive Medicines
  - High cost per patient
  - High budget impact
- Collaboration on:
  - Horizon Scanning
  - HTA
  - Information Sharing
  - Pricing and Reimbursement
- Working principle: Voluntary and learning by doing
  - Consensus based cooperation
  - Letter of intent and terms of reference
  - Price and reimbursement decisions are still national competence

What's in it for …

- **The authorities**:
  - Learning from your peers and best practices
  - Better policy:
    - Better alignment of HTA and P&R across borders
    - Coherent approach of cross-border development
  - More robust scientific evidence (clinical expertise, data gathering, HTA methods)
  - Stronger negotation position
  - Economies of scale might lead to lower prices and help the sustainability of our systems

- **The industry**
  - Insight into how to better prepare on an undeniable international trend
  - Economies of scale:
    - Instead of 28 evaluation dossiers, only 24…
    - Less costly registries
  - Less uncertainty and potential access to a bigger market (in our case 42 million citizens)

- **The patient**

  Earlier access to treatment

What's on the Menu?

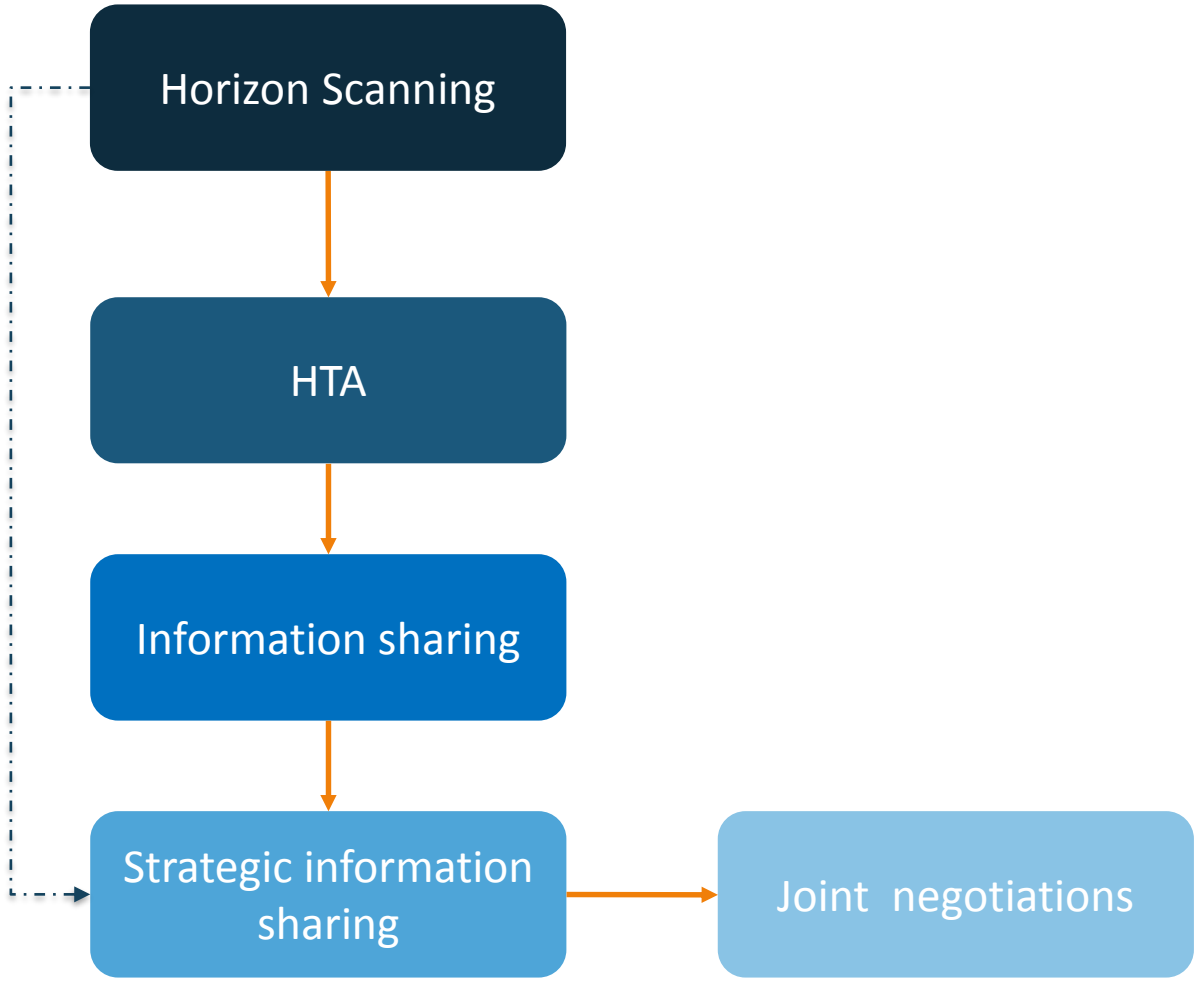
Collaborative approach to gathering information

Mutual recognition; Joint HTA

Best practices, registries, policy dilemmas

Horizon Scan interpretation; Strategic information exchange;

Input for Joint Negotiations



Information Exchange

Goals

1. To strength the position of the payer and patient through sharing intelligence by:
   - Organising sessions on important strategic issues, e.g. conditional reimbursement, evergreening, etc.
   - Exchanging information on pharmaceutical markets, patient groups, therapy guidelines, industry approach
   - Discussing best practices on policy issues

2. To serve as a platform for exploring cross-border data sharing (registries)

Information Exchange

Webinars:

- Twice a year
- Topics agreed by Steering Committee

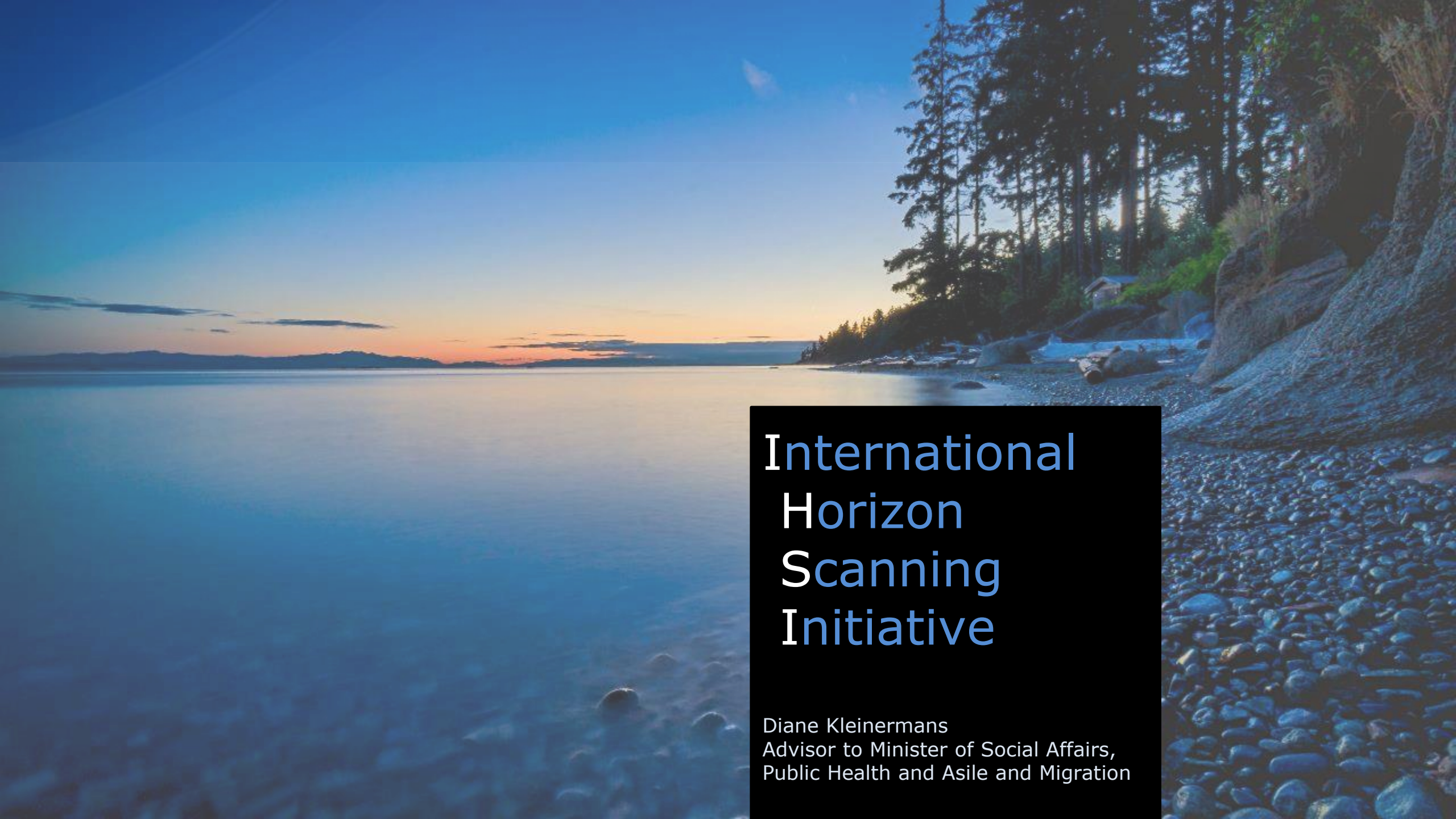
In 2018:

✓ Biosimilars

✓ Funding mechanisms of medicines in the outpatient and inpatient sectors

Strategic Information

- Creation of environment / platform for the exchange of strategic information
- To prepare joint negotiations/ negotiations for price and reimbursement
- Feasibility study on specific cross-border registries



International Horizon Scanning Initiative

Diane Kleinermans
Advisor to Minister of Social Affairs,
Public Health and Asile and Migration

Agenda

- Objectives
- Expected benefits
- Scope and Methodology
- Deliverables
- Potential collaborations
- Timelines

Objectives

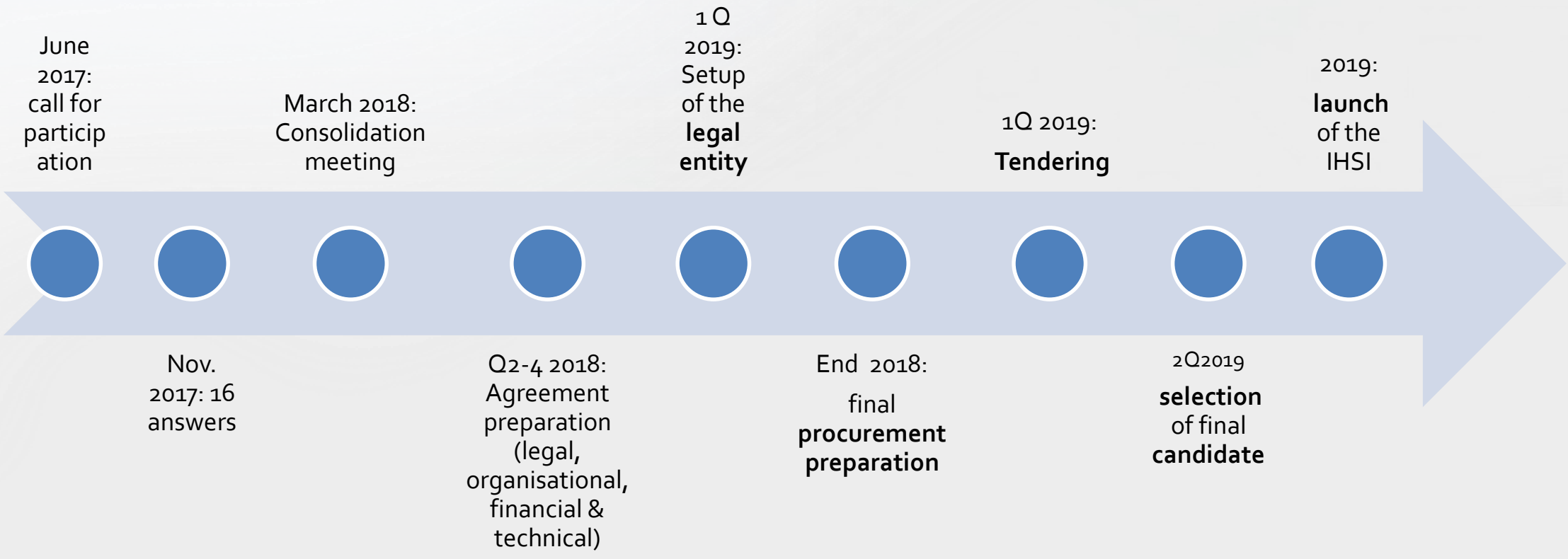
Aim of a joint horizon scanning database:

- To inform decision makers on emerging and new pharmaceuticals for reimbursement decisions and policy development on issues that are relevant for the managed introduction and monitoring of pharmaceutical products

- To enhance collaboration between member states by selecting relevant issues for collaboration

- *Design and methodology based on Belgian KCE study*
- *NL horizon scanning activity as temporary product*

Horizon Scanning



Scope and methodology

International unit - does and doesn't

Does

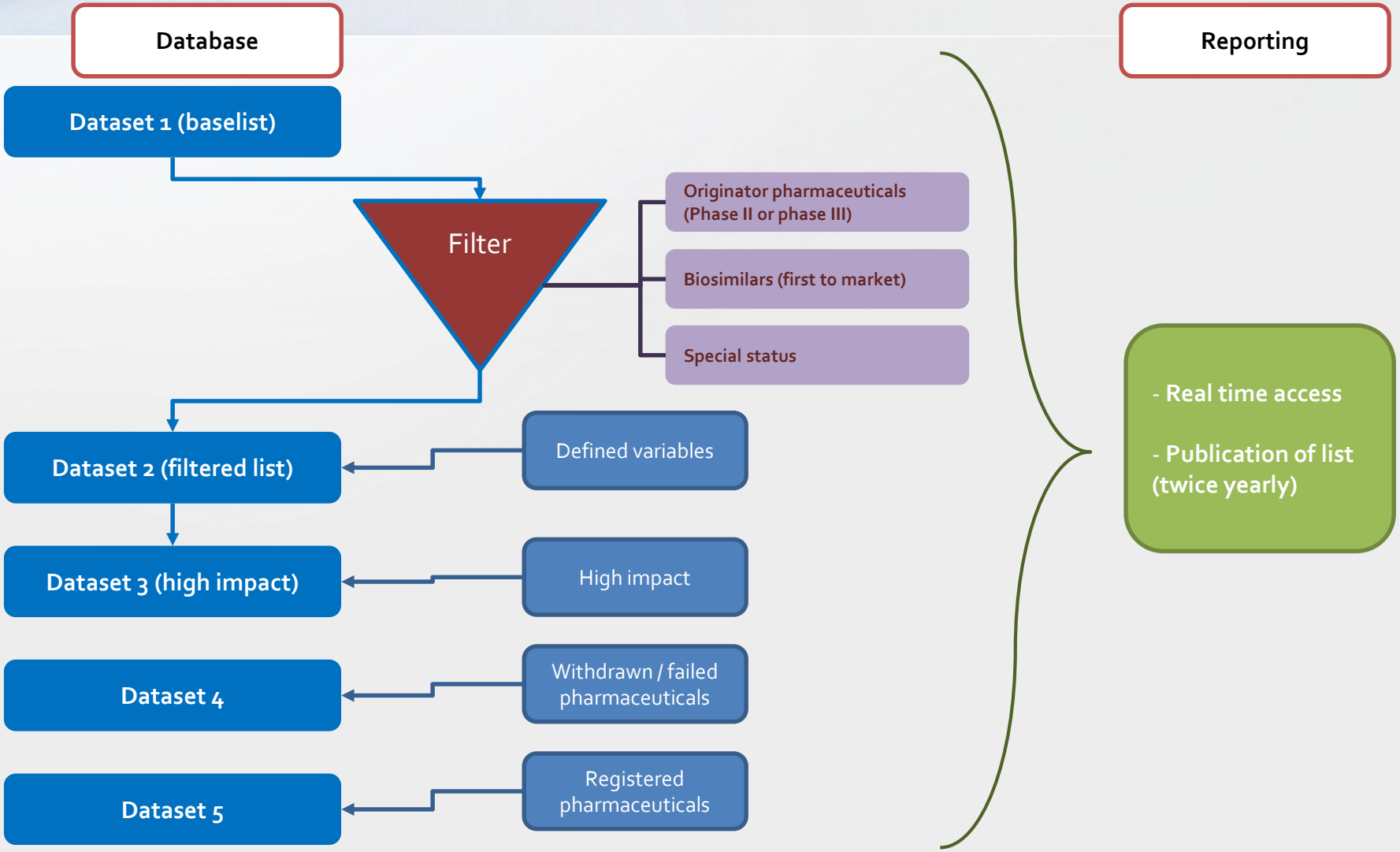
- The international horizon scanning database is like a library containing information based on publicly available data
- The data collected is factual
- Data collected is owned by paying participants

Does not

- The central unit does not prioritise for countries
- The central unit does not make any decisions on pricing and reimbursement, nor on market entry
- The data collected is not tailored to individual countries

- **It is up to users what to do with the data**

The database – 'must have'



Dataset 1 & 2

Dataset 1 (baselist)

- Aim: to provide an overview of all pharmaceuticals in development from phase I
  - Gives insight in the industry pipeline
  - Enables to identify gaps in research
  - Ties in with the European clinical trials register

Dataset 2 (filtered list)

- Aim: to provide an overview of all originator pharmaceuticals in development from phase II /phase III
  - Provides much more detailed insight into the pharmaceutical products coming to market from PHII/PIII
  - The filter enables payers to focus on those pharmaceutical products likely to come to market within the next 1-2 years and which are likely to have a higher impact
    - Originator pharmaceutical products PHII/PHIII
    - First to enter biosimilars
    - Pharmaceutical products with a special status

Dataset 3

Dataset 3 (high impact)

- Aim: to identify pharmaceutical products with a high impact
  - Enables payers to rank pharmaceutical products according to their impact
  - Enables countries to identify issues or pharmaceutical products for collaboration
  - Impact will be assessed using a validated methodology
    - A questionnaire will be developed for asking medical experts to assess pharmaceutical products on their impact
    - Pharmaceutical products will be divided into a number of disease areas
    - The following parameters will be used to assess impact
      - Potential importance of the unmet need it intends to address
      - Potential to improve patient health
      - Potential for acceptance/adoption by patients and clinicians
      - Potential impact on health care costs

Dataset 4 & 5

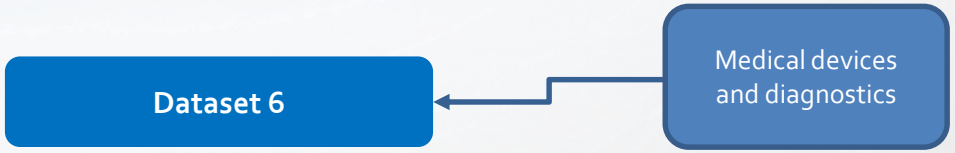
Dataset 4

- Aim: to provide insights into pharmaceutical products that, at any stage have failed or are withdrawn from FDA / EMA registration procedures
  - Data collected on pharmaceutical products, which have failed or are withdrawn from registration will migrate into a new dataset
  - Enables to identify disease areas where pharmaceutical products fail and investment potentially high

Dataset 5

- Aim: to enable users to see the data collected for pharmaceutical products once registered
  - Enables users to see the data also once a pharmaceutical product has been registered, however the data will no longer be updated

The database: dataset 6



Will be included later

- Aim: to provide insight in which medical devices and diagnostics are being developed
  - Enables users to identify not only pharmaceutical products, but all medical technology
  - Ties in with the EU initiative to include medical devices into a database (EUDAMED)
  - The data collected can be included in datasets 1-5

Potential benefits

Potential benefits

The benefits of an international database include:

- A more level playing field with the pharmaceutical industry – all have the same information
- More insight into what is coming and which pharmaceutical products may potentially have a high impact
- Insight into the potential costs of future pharmaceutical products
- Potential to identify gaps in research and development
- Potential for collaboration between countries in different ways:

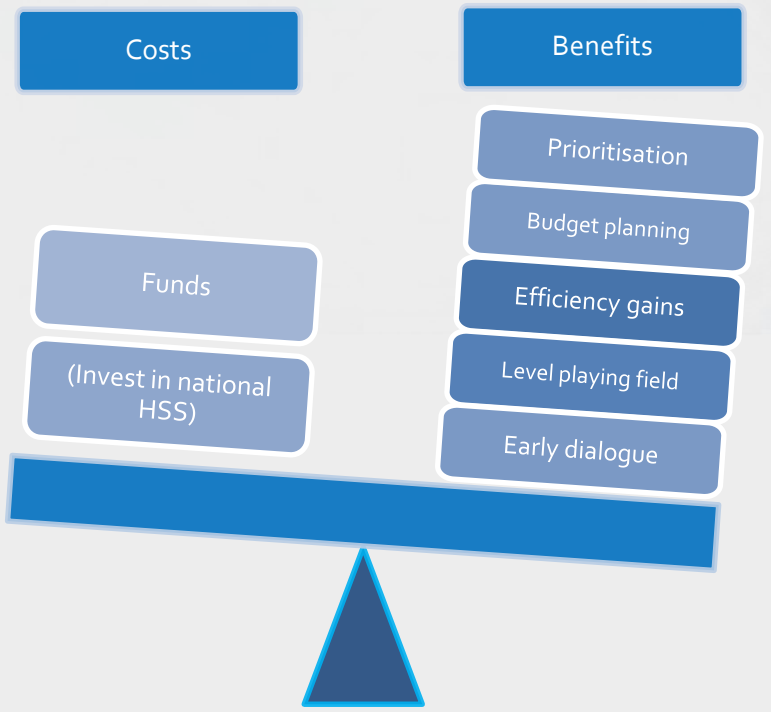
  ✓ Sharing of information with regards to prioritisation and decision-making
  ✓ Joint negotiations
  ✓ Collaboration between national scanning units and the sharing of national data

- Potential or early dialogue amongst different stakeholders

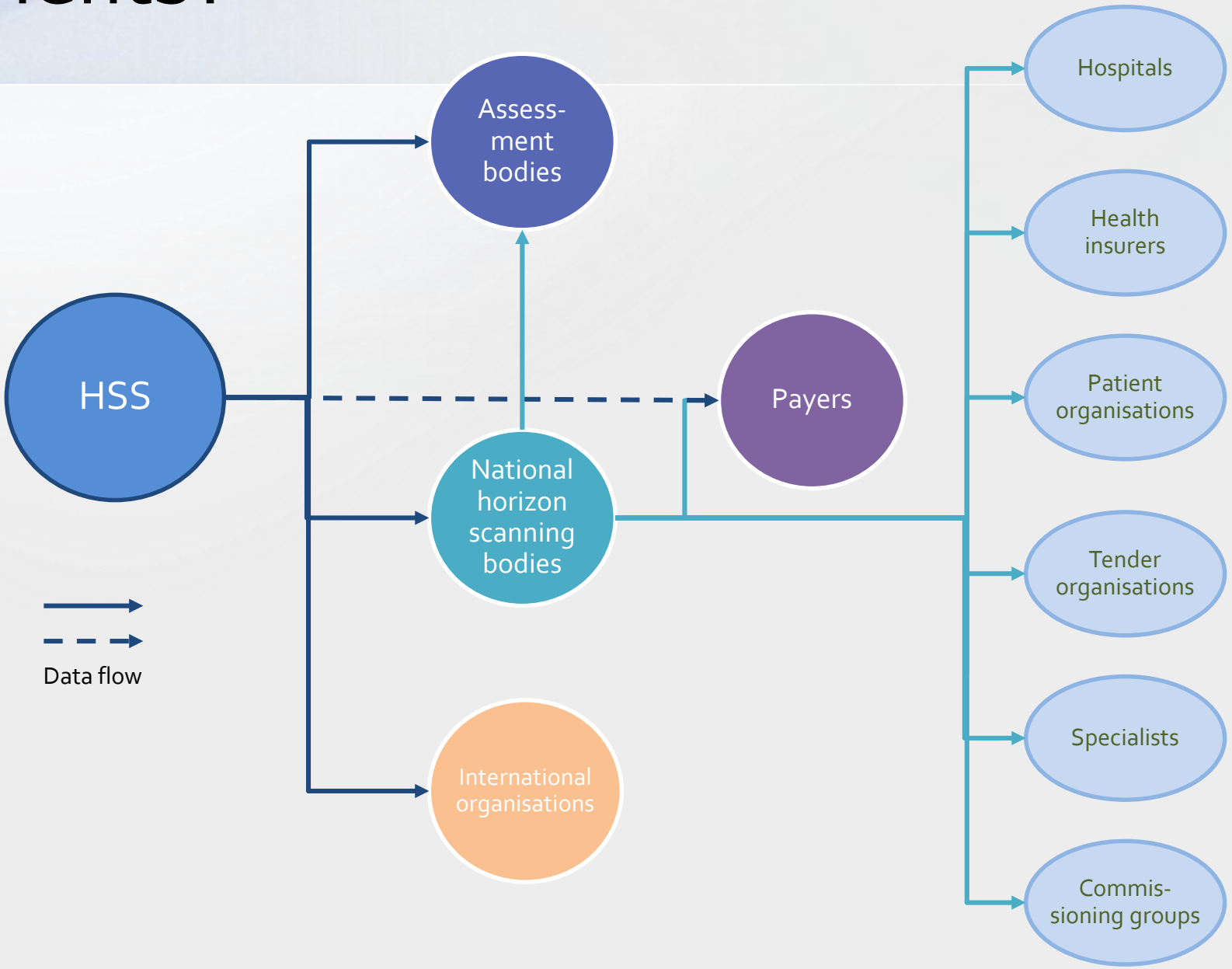
  ✓ With the European Medicines Agency
  ✓ With patient organisations
  ✓ With medical specialists
  ✓ With the pharmaceutical industry

Potential benefits

- Prioritisation – potential to improve access
  - Allows for prioritisation of policy-making
  - Allows for capacity planning for HTA bodies
  - Allows for earlier planning for guidelines and registries
- Budget planning – potential for savings
  - Flags potential issues of displacement. Allows for better tools for budget allocation
- Efficiency gains – potential to improve access
  - Allows for streamlining procedures
- Level playing field – potential for savings
  - Allows for sharing earlier and lessening the current information asymmetry with industry
- Early dialogue – strengthens collaboration
  - Allows for stakeholders to share information at an earlier stage, e.g. Beneluxa



Who benefits?



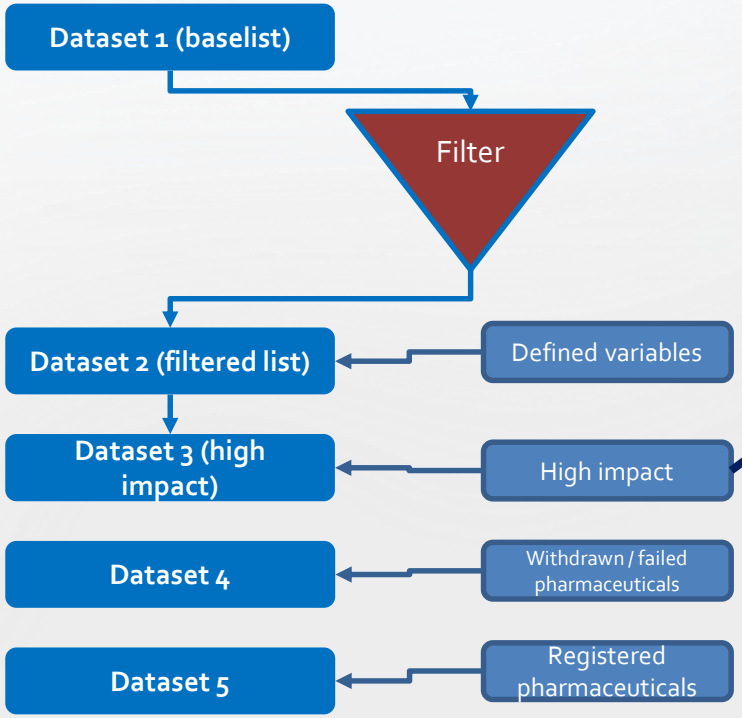
IHSI Database deliverables

Packer , C. 2012

Deliverables

- "EAA systems are guarantors of health care systems sustainability by supporting informed and accountable decisions based on the best available evidence along the life cycle of health technologies"*
- Advantages of early intelligence (deliverables IHSI):
  - The opportunity to plan future investments (real time database)
  - To ensure that health systems are able to embrace innovation in a sustainable way (high impact reports)
  - To decide where research and evaluation resources and efforts should be directed (long-term investments)

Overview of deliverables



High impact reports

Priority Area 02: Cancer

Topics	High-Impact Potential
1. Afatinib (Gilotrif) for treatment of advanced head and neck cancer	No high-impact potential at this time
2. Anamorelin for treatment of cancer-related cachexia/anorexia	No high-impact potential at this time
3. * Blinatumomab (Blincyto) for treatment of acute lymphoblastic leukemia	Lower end of the high-impact-potential range
4. Cabozantinib (Cometriq) for treatment of renal cell carcinoma	No high-impact potential; archived November 2015 on basis of experts' comments
5. Capsule endoscopy (PillCam Colon 2) for colorectal cancer screening	No high-impact potential; archived September 2015 on basis of experts' comments
6. * Crizotinib (Xalkori) for treatment of *ROS1*-positive nonsmall cell lung cancer	Lower end of the high-impact-potential range
7. * Daratumumab (Darzalex) for treatment of multiple myeloma	Moderately high
8. Denosumab (Xgeva) for treatment of refractory hypercalcemia of malignancy	No further potential for high impact; archived November 2015 on basis of being broadly diffused
9. * Dinutuximab (Unituxin) for treatment of neuroblastoma	Lower end of the high-impact-potential range
10. * Elotuzumab (Empliciti) for treatment of multiple myeloma	Moderately high

Real time database

*AHRQ high impact report 2015
https://effectivehealthcare.ahrq.gov/sites/default/files/cancer-horizon-scan-high-impact-1512.pdf

High impact reports

Priority Area 02: Cancer

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Lung Cancer

Checkpoint Inhibitors (Nivolumab [Opdivo], Pembrolizumab [Keytruda]) for Treatment of Nonsmall Cell Lung Cancer

- Key Facts: Lung cancer is the second most common cancer diagnosed in the United States and is the leading cause of cancer death. Lung cancer was expected to be diagnosed in an estimated 221,200 Americans and an estimated 158,040 were expected to die of the disease in 2014. NSCLC accounts for about 78% of lung cancers and has a 5-year survival rate of 3% to 13%. Also, a need exists for interventions that can improve patient outcomes. NSCLC among other types of cancer has adapted a mechanism to avoid being detected by the immune system by activating the checkpoint pathway via the programmed death 1 (PD-1) receptor. Cancer cells overexpress the ligand of PD-1 (PD-L1) and diminish the antitumor response of immune T cells upon binding to PD-1. Nivolumab (Opdivo) and pembrolizumab (Keytruda®) are monoclonal antibodies specific for PD-1 that prevent interaction with PD-L1, thus potentially improving patient survival by disrupting the tumoral blockade signal between PD-1 and PD-L1 in immune cell tumor cells, respectively. In February 2015 and after priority review, FDA approved nivolumab for treating NSCLC that has progressed after platinum-based chemotherapy. Results from the phase III CheckMate 017 and the phase II CheckMate 063 trials were the basis for nivolumab's approval. In October 2015, FDA granted accelerated approval to pembrolizumab based on results from the phase I KEYNOTE-001 trial after earlier granting breakthrough therapy status.

...Brahmer and coworkers and Paz-Ares and coworkers presented results from the phase III CheckMate 017 and CheckMate 057 trials at the 2015 American Society of Clinical Oncology annual meeting. Patients with squamous NSCLC enrolled in the CheckMate 017 trial were treated with nivolumab or docetaxel, and the nivolumab group showed a statistically significant improvement in overall survival (9.2 vs. 6.0 months), progression-free survival (3.5 vs. 2.8 months), and response rate (20% vs. 9%). Meanwhile, patients with nonsquamous NSCLC in the CheckMate 057 trial who received nivolumab had improved overall survival over patients given docetaxel (12.2 vs. 9.4 months) and improved response rate (19.2% vs. 12.4%), but not longer progression-free survival (2.3 vs. 4.2 months), which could be related to PD-L1 expression. Patients with NSCLC are treated intravenously with 3 mg/kg of nivolumab once every 2 weeks until disease progression or unacceptable toxicity. Results published by Gettinger and coauthors in 2015 demonstrated that patients treated with pembrolizumab (3 mg/kg once every 3 weeks, 10 mg/kg once every 2 weeks, or 10 mg/kg once every 3 weeks) who expressed PD-L1 in 50% or more of tumor cells had superior outcomes, as compared with all enrolled patients. The exhibition group (>50% PD-L1) experienced response rates of 46.2%, a median progression-free survival of 8.3 months, and had not reached median overall survival at the data cutoff point. The most common drug-related adverse events manifested by patients receiving pembrolizumab were appetite loss, fatigue, and pruritis.

Enhances collaboration internationally

- Provides payers with an overview of high impact products in terms of:
  - Potential importance of the unmet need it intends to address
  - Potential to improve patient health
  - Potential for acceptance/adoption by patients and clinicians
  - Potential impact on health care costs
  - Overall potential to fulfill the unmet need
- Use:
  - Governments will have a quick overview of those products that will have the potential to disrupt
  - Member states will be able to use this for collaboration and discussion on important topics
  - Tool for prioritisation

*AHRQ high impact report 2015
https://effectivehealthcare.ahrq.gov/sites/default/files/cancer-horizon-scan-high-impact-1512.pdf

Real time database

Enhances collaboration nationally

- Provides payers with detailed information on each product coming to market
  - Assessment bodies: will be able to anticipate products and prioritise
  - Health insurance institutions: budget allocation and negotiations with hospitals / care organisations
  - Hospitals (and other care institutions): budget allocation and/or restructuring care (e.g. CAR-T)
  - Medical specialists: start working on national guidelines at an earlier stage
  - Patients: helps them to understand the timelines for the product to enter the market
  - Pharmaceutical industry: allows for early dialogue and a central point of data-collection

Collaboration: Involvement of stakeholders

Involvement stakeholders

- EMA
  - Currently exploration of collaboration with EMA on sharing data:
    - During the regulatory process (e.g. decisions on accelerated assessment, prime, clock stop, etc.)
    - Products before entering the regulatory process
    - Sharing data on the future horizon, i.e. 3-10 years
  - Thoughts on collaborating with regards to data gathering
- Eudamet
  - Aim to meet with Eudamet to discuss incorporating medtech data in IHSI
- EUnetHTA
  - Support from EUnetHTA on IHSI
- Pharmaceutical industry

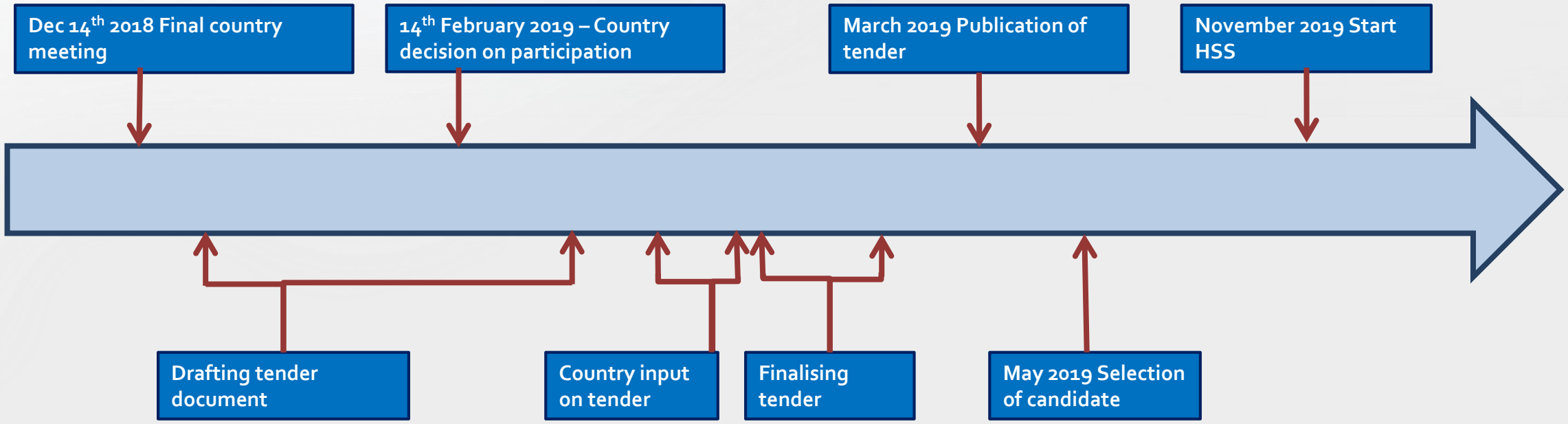
* Not an extensive list of potential partners

Input from the (pharmaceutical) industry

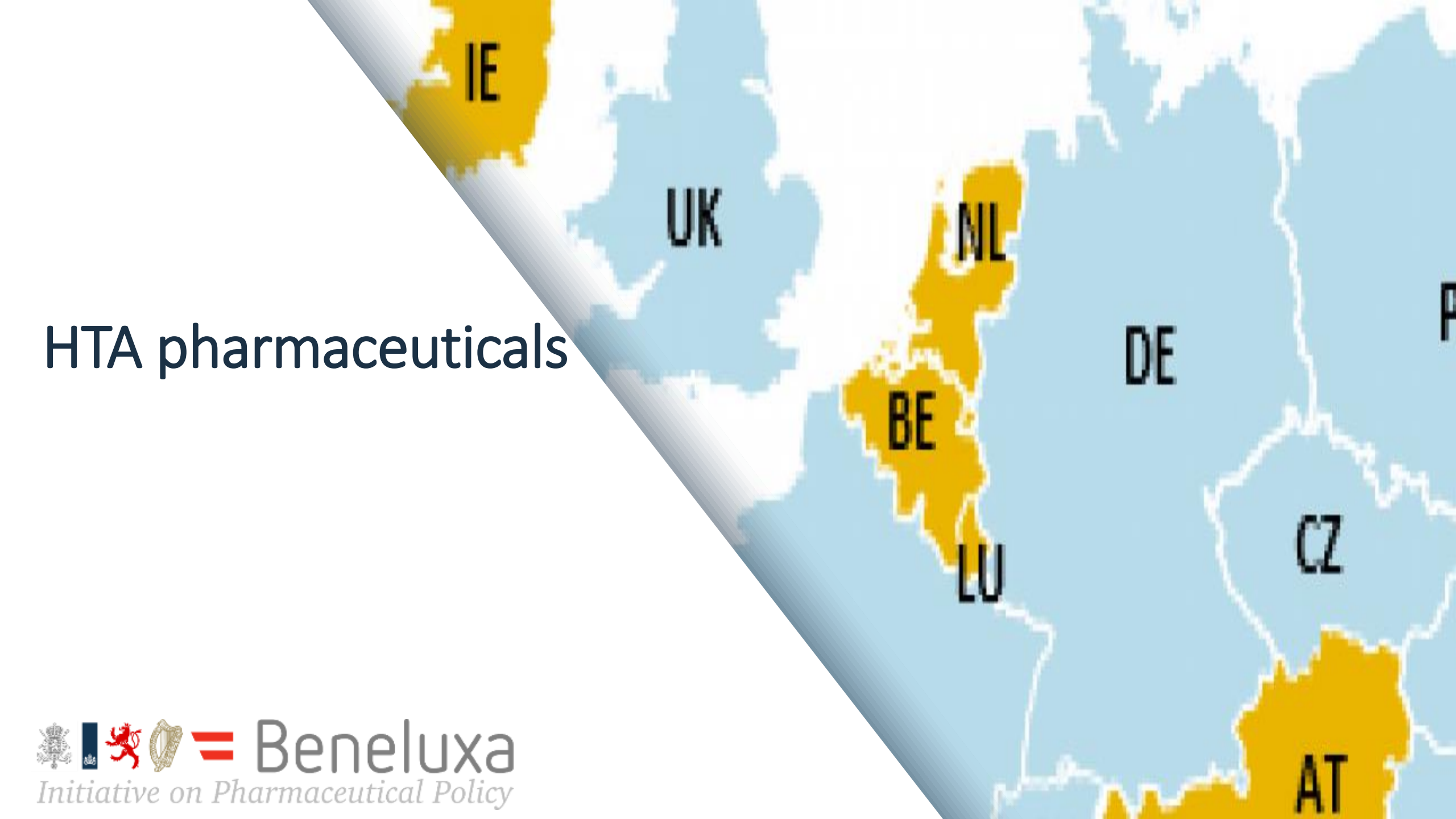
- Input from industry is important for data gathering and completion of the data
  - Data confidentiality
  - Type of data from industry
    - Expected launch
    - Future indications / discontinuation
    - Especially for medtech the only way to identify all products coming to market
    - Potential to work together on this with EMA and Eudamet
    - Price - Planning to have meeting with industry to explore possibilities
- Industry - IHSI
  - Pipeline meetings
  - Questionnaire
  - Direct contact with IHSI for product specific information
- Verification of data by IHSI

Timeline

Planning


Dec 14th 2018 Final country meeting
14th February 2019 – Country decision on participation
March 2019 Publication of tender
November 2019 Start HSS
Drafting tender document
Country input on tender
Finalising tender
May 2019 Selection of candidate

HTA pharmaceuticals



Beneluxa
Initiative on Pharmaceutical Policy

Agencies – Authorities involved

Cross-border HTA

B	RIZIV-INAMI KCE
NL	Zorginstituut Nederland, relationship with EUnetHTA
L	Contrôle Médical de la Sécurité Sociale
A	Hauptverband der Österreichischen Sozialversicherungsträger Ludwig Boltzmann Institut
IRL	National Centre for Pharmacoeconomics

1

Aims

Christ Church Cathedral, Dublin

Aims

to achieve:

- Insight in the timelines of ongoing and future assessments;
- HTA reports that are suitable for international use;
- Joint assessments, both bilateral as well as within EUnetHTA;
- The adoption of ‘non-national’ HTA-reports in national reimbursement decisions, by investigating and tackling the legislative hurdles.

2

How ?

Graslei, Gent (B)

Types of collaboration

Authoring reports, 3 formulas

- Joint writing
- Re-use
- Mutual recognition

External referee

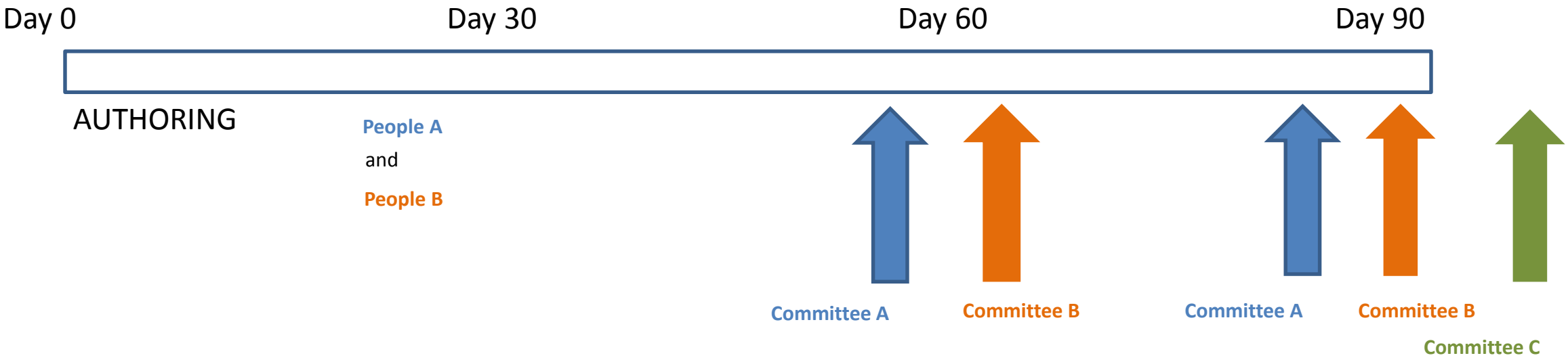
EUnetHTA Early Dialogues: NeBel

3

3 formulas

Beneluxa

Pfarrkirche Alpbach (AT)



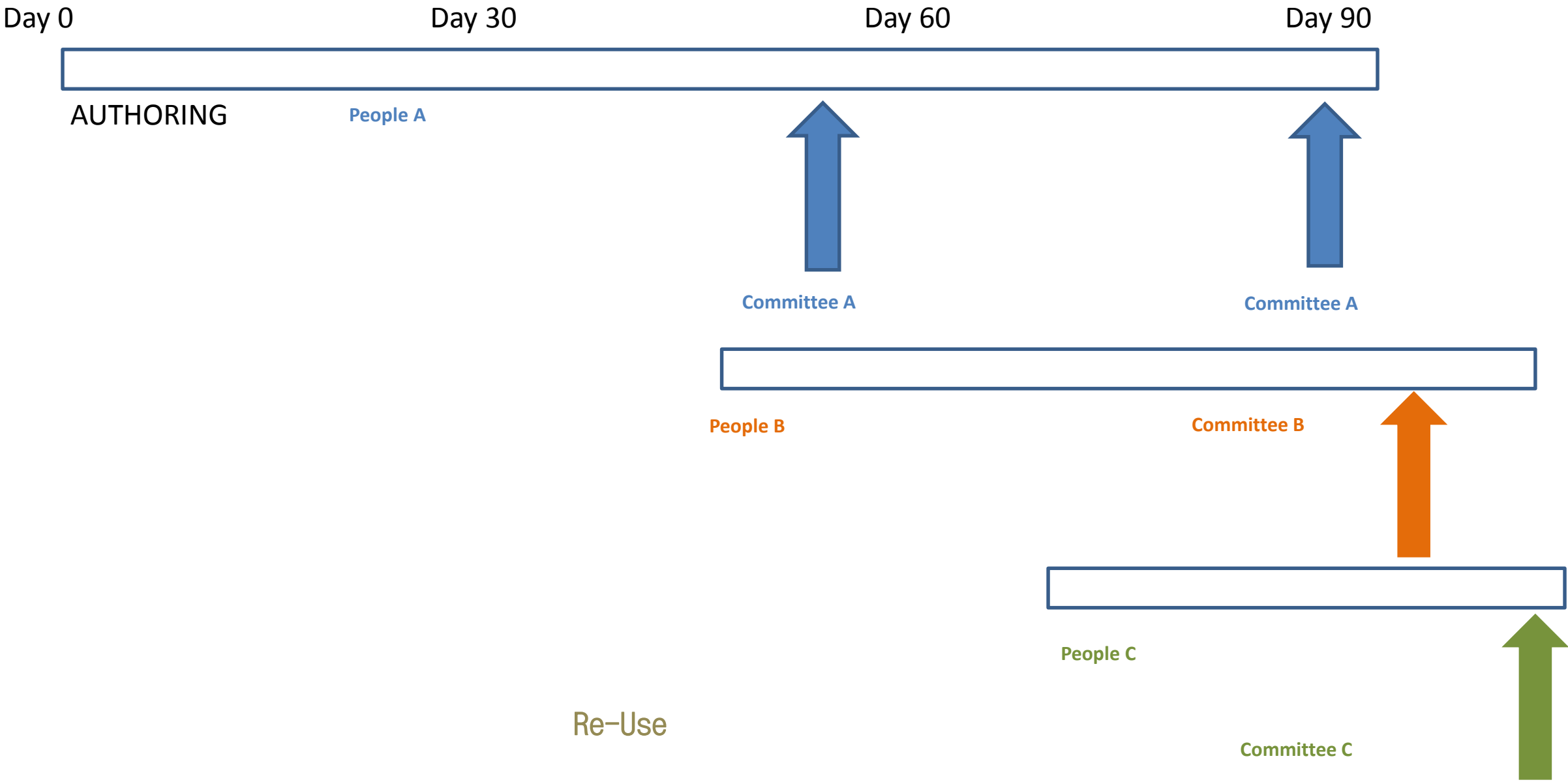
Joint Writing

Joint writing

- Synchronous
- Planified with company
- Adjustment of calendars
- Clear tasks
- Day minus 90: provisional file
- Fits with Joint P&R

Joint Writing of a report:
NL & BE

Pharmaceutical	Disease	Year	Reimbursement status
ORKAMBI	Cystic fibrosis	2x 2016+2017	NL: yes BE: no
OCALIVA	Primary biliary cholangitis (provisional report)	2017	NL: in procedure BE: in procedure


Day 0
Day 30
Day 60
Day 90
AUTHORING
People A
Committee A
Committee A
People B
Committee B
People C
Committee C

Re-Use

Re-use

- Not synchronous
- Full or partial re-use
- With company or without
- Day minus 90, with company
- Fits less well with Joint P&R

Re-use of a report:

NL -> BE

Pharmaceutical	Disease	Year	Reimbursement status
LOJUXTA lomitapide	Congenital lipid disorder	2016	NL: yes BE: no
SPINRAZA nusinersen	Spinal muscular atrophy	2018	NL: yes BE: yes
XERMELO telotristat	Carcinoid syndrome	2018	NL: yes BE: yes
RAVICTI glycerol phenylbutyrate	Urea cycle disorder	2018	NL: in procedure BE: in procedure

AT -> BE

Pharmaceutical	Disease	Year	Reimbursement status
TAGRISSO osimertinib	1st line NSC Lung Cancer	2018	BE: in procedure

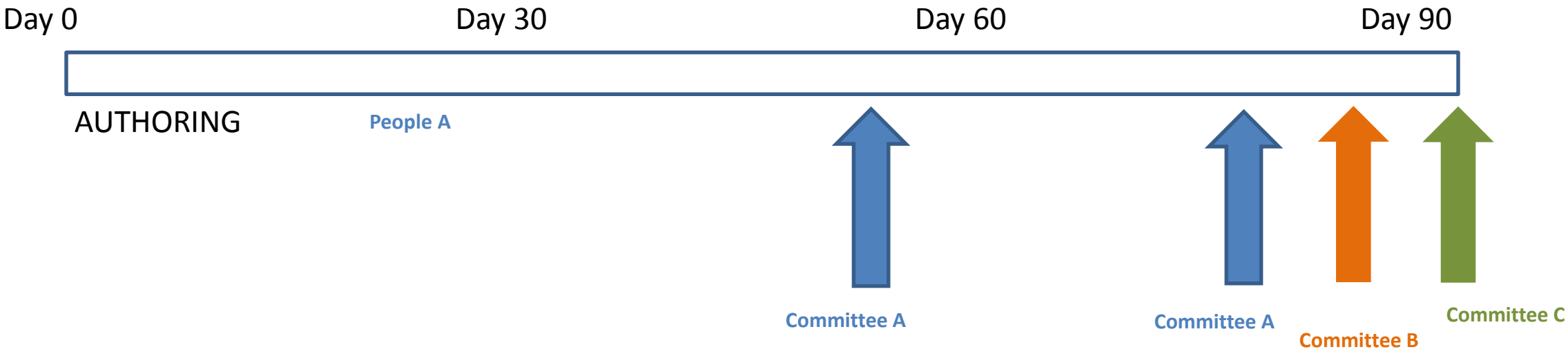
Re-use of a report:

EUnetHTA -> BE

Pharmaceutical	Disease	Year	Reimbursement status
RYDAPT midostaurin	Acute leucemia	2017	BE: yes

EUnetHTA -> AT

Pharmaceutical	Disease	Year	Reimbursement status
ALECENSA alectinib	First line ALK+ lung cancer	2018	AU: in procedure



Mutual Recognition

Mutual recognition:

No results			

To start with common denominator of all reports?

Quid stakeholders ?

4

General comments

Keizersgracht, Amsterdam

General comments

National procedures and commissions

National rules COI and confidentiality

Active and passive roles 5 countries

Clock-stops possible

Timelines fixed in synchronous procedure

CTG CRM : loop procedure since 2018

Cost-effectiveness: model agreed on beforehand

Pricing & Reimbursement
including joint negotiations

Beneluxa
Initiative on Pharmaceutical Policy

1

Aims

Christ Church Cathedral, Dublin

Aims

- Objective is

to create an overall ‘win’ situation:

  - for patients: accelerated and affordable access
  - for authorities: economy of scale (not only financially), knowledge building (joint registries), joining expertise
  - for companies: faster access, lower administrative burden

2

Selection of pharmaceuticals

Graslei, Gent (B)

Eligibility for a joint procedure

- An assessment and if applicable, a negotiation should fit within the national legislations, eg:
  - intramural (hospital) pharmaceuticals eligible for the “lock procedure” in the Netherlands
  - pharmaceuticals submitted as Class 1 or orphan application in Belgium
  - ..
- Pharmaceutical not explicitly reimbursed for that particular indication in a country of the collaborating HTA partners
- The Steering Committee needs to agree with the selection of the pharmaceutical

Positive elements in selection

- high unmet medical need
- recent date of EMA-registration/EMA-positive opinion
- expected added value
- satisfactory degree of evidence
- willingness of the manufacturer to submit a draft submission file
- ..

Negative elements in selection

- previous refusal of reimbursement in a country of the collaborating HTA partners
- unwillingness of the manufacturer to commercialize the pharmaceutical in a country of the collaborating HTA partners after a positive decision on reimbursement
- ..

Contact procedure

- Start of early dialogue on a possible joint HTA & joint negotiation - two scenario's

Company - driven

Company contacts one of the country coordinatiors

Company expresses willingness to collaborate
on a joint assessment and negotiations procedure, or
only on a joint assessment

Company identifies possible dates for an (informal) orientational meeting

BeNeLuxA - driven

Selection of pharmaceutical as a possible candidate for a joint HTA & joint negotiation based on Horizon Scan

One of the country coordinators reach out to the pharmaceutical company

Invitation for an (informal) orientational meeting

exploratory meeting

3

The Process

Beneluxa

Pfarrkirche Alpbach (AT)

The Process – general information

- No joint ‘BeNeLuxA’ reimbursement regulation - **national regulation will be followed**
- In case of a successful joint assessment and negotiation, a **decision on reimbursement** will be made **simultaneously but separately in the participating countries**.
- A joint reimbursement negotiation without a joint HTA will not be accepted
- **Opt out** possibility
  - Any reached milestones, such as the result of the joint assessment will still stand, and both countries commit to upholding the projected timelines to the best of their abilities in separate procedures.
  - Day 0 of the joint procedure will still count as day 0 in both countries if the procedures are separated.

➢ In general, Luxembourg does not (yet) actively participate in any joint HTA & negotiations pilot. Luxembourg can act as an observer or an external expert opinion. Luxembourg will receive the joint assessment report (day 90).

Requirements for joint reimbursement file

- Around time of CHMP opinion: draft submission file in all implied countries
- Day 0: (simultaneous) submission of the identical reimbursement claims in the implied countries
- The dossier must contain all necessary documents for participating countries according to national legislations
- In general:
  - A country specific budget-impact analysis is required in all cases.
  - The obligation of a pharmaco-economic report depends on national legislation. However, it is highly recommended to include one model split out using country specific data.

Language

- The Belgian procedure legally requires that submission files, assessments and appraisal reports are written in a Belgian national language (French, Dutch, German).
- In the Netherlands, submissions should be filed in Dutch.
- However, both in Belgium as in the Netherlands, an exception can be made for international joint assessments, which can be filed in English

  → cover letters need to be in national language, annexes can be in English

Joint submission files, assessments and appraisal reports can be written in English.

4

Timing & Procedure

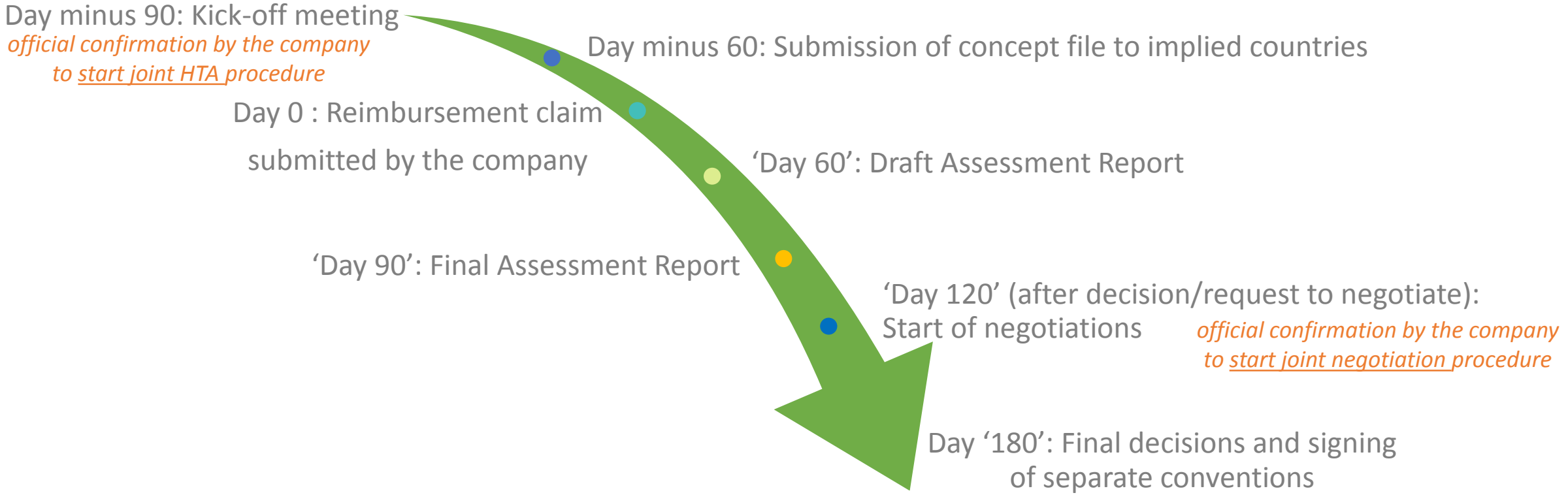
Keizersgracht, Amsterdam

Start the clock

- **Day minus 180: exploratory meeting**
  - The exploratory meeting will be an informal meeting, based on trust and openness.
  - Information on choice on assessment process, language, confidentiality and communication will be touched during the exploratory meeting.
  - The 'driver' country will be the single point of contact for the company with questions on the procedure. *This is independent of all formal communication related to the official national reimbursement procedure.*
- **Day minus 90: kick-off meeting**
  - The objective of the meeting is to obtain the official confirmation by the company of the willingness to collaborate by means of a formal letter with signature addressed to the country coordinators of the implied countries (can be send in the weeks after the kick-off meeting) → step in on a voluntary basis

Projected timing

- A timeline will be established taking into account national procedures and calendars of implied countries. ‘Days’ mentioned below act as an indication. Timing in all implied countries will be aligned.
- All parties commit to give maximum effort to reach on optimal timing.



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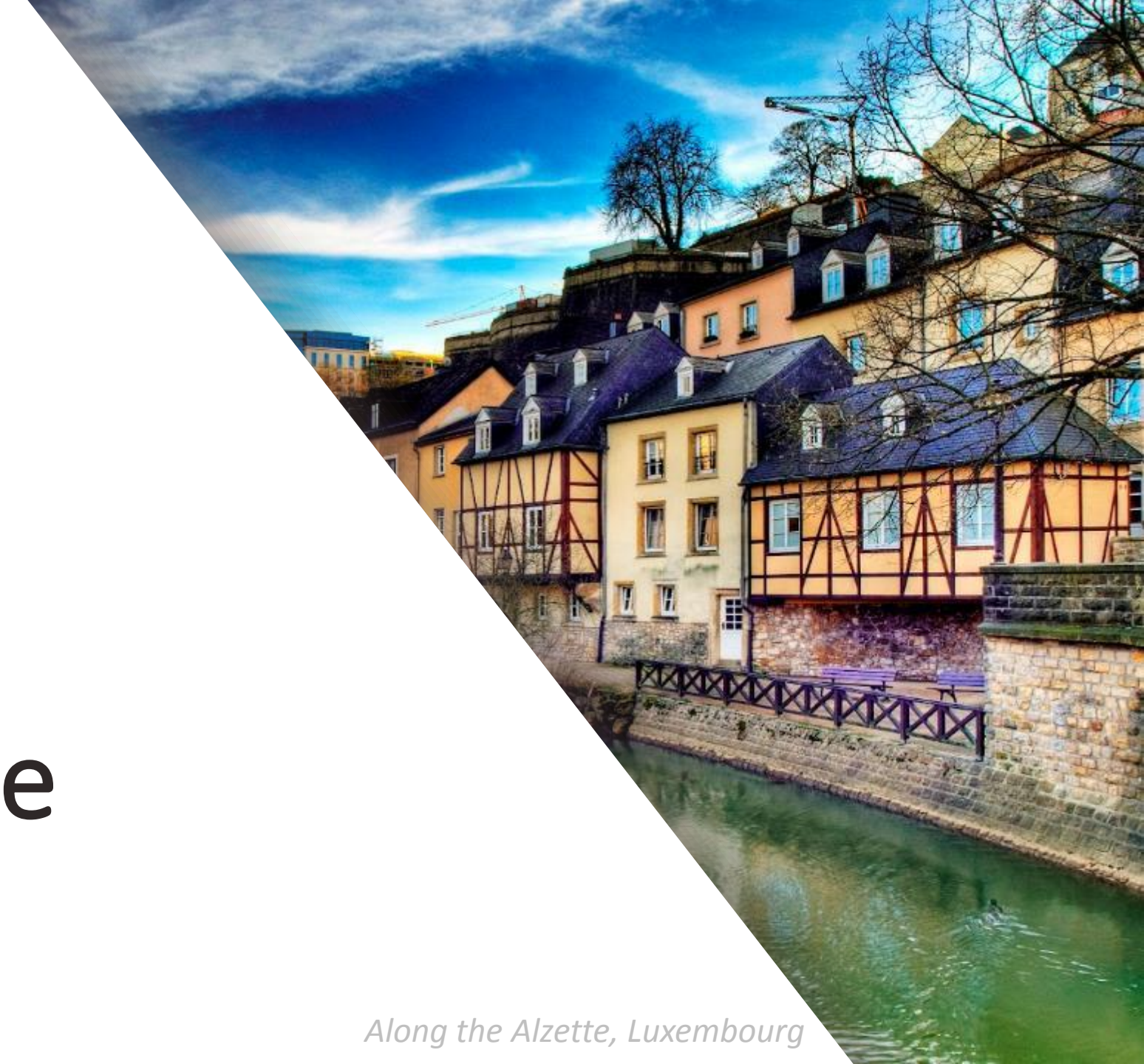
In practice



Along the Alzette, Luxembourg

the Negotiation framework of participating countries

- Negotiation framework is set up in close collaboration with all participating countries
  - All participating countries have **equal 'say'** in setting up negotiation framework
  - Target of framework = **same negotiation strategy /principles valid for all participating countries**
    - Framework leads most often to country specific net budget
    - Not a bargaining negotiation process
    - Arguments are given why deal is fair and defensible
  - **Implementation may differ** (eg in absolute number of discount or net budget)
- All participating negotiators ask for a "mandate" from their decision making authorities
- All participating countries give their agreement to written proposals sent to company and representatives of all participating countries are present in face to face meetings with company

➔ **Challenge on organization and coordination**

Key learnings on joint P&R for both countries & companies

- Early alignment on local procedures
  - Timing of (joint) decision-making on mandate/WTP
  - Manage expectations
  - Communication ‘rules’

- Early alignment on a joint framework for WTP
  - Early alignment on what elements to consider, e.g. cost-effectiveness, ’fairness’

- Early discussion on country-specific differences
  - Differences in local (reimbursement) policy or geographic differences may affect the WTP

III.

France: The work of the *comité économique des produits de santé* – CEPS

Jonathan Rodrigues, CEPS

COMITÉ ÉCONOMIQUE
DES PRODUITS DE SANTÉ

The work of the French Pricing Committee

EUCOPE P&R/MA Working Group Meeting
12 February 2019

Fundamentals in France

> Positive reimbursement list;

> Price and Reimbursement are published in the official journal;

> Price setting is a separate process from reimbursement.

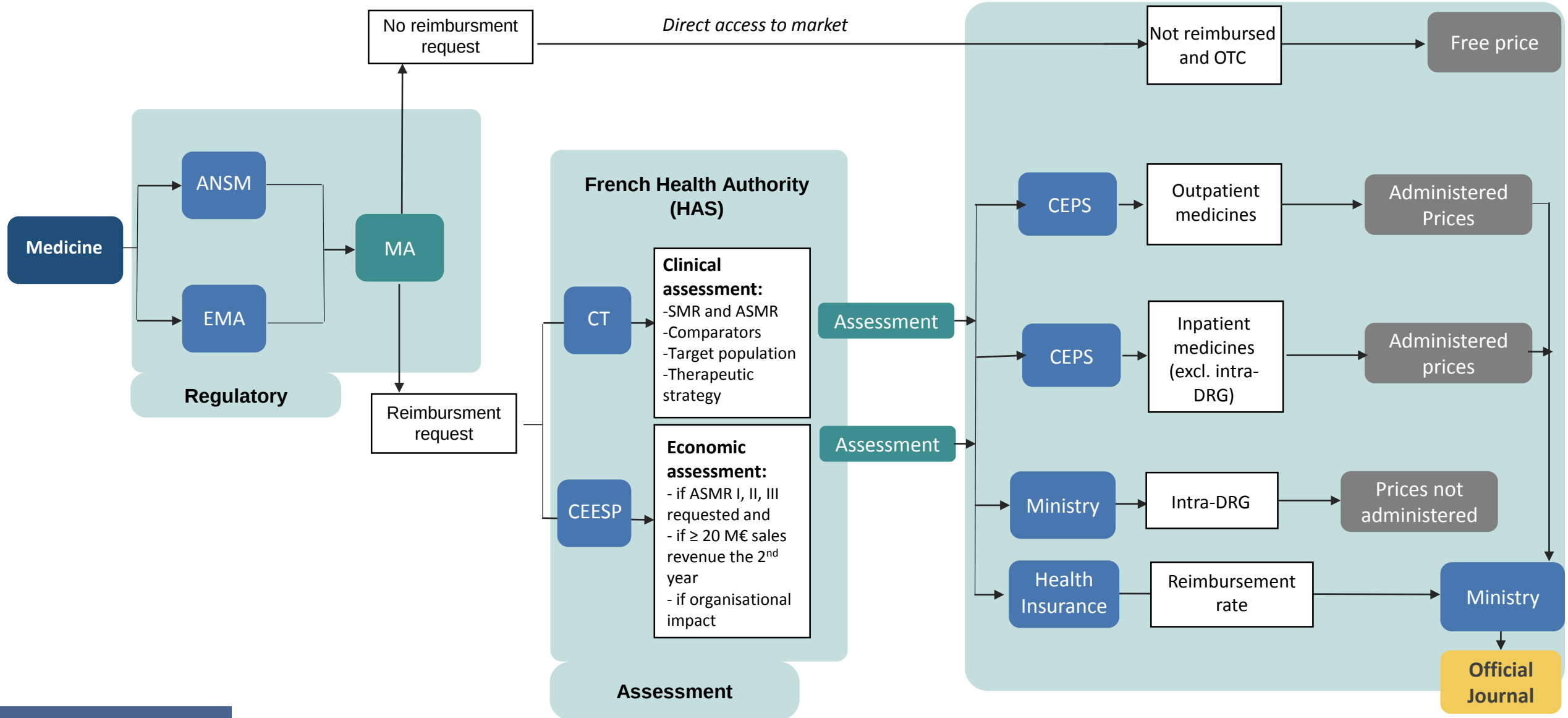
Reimbursed medicines prices are :

> Administered : publication in the Official Journal;

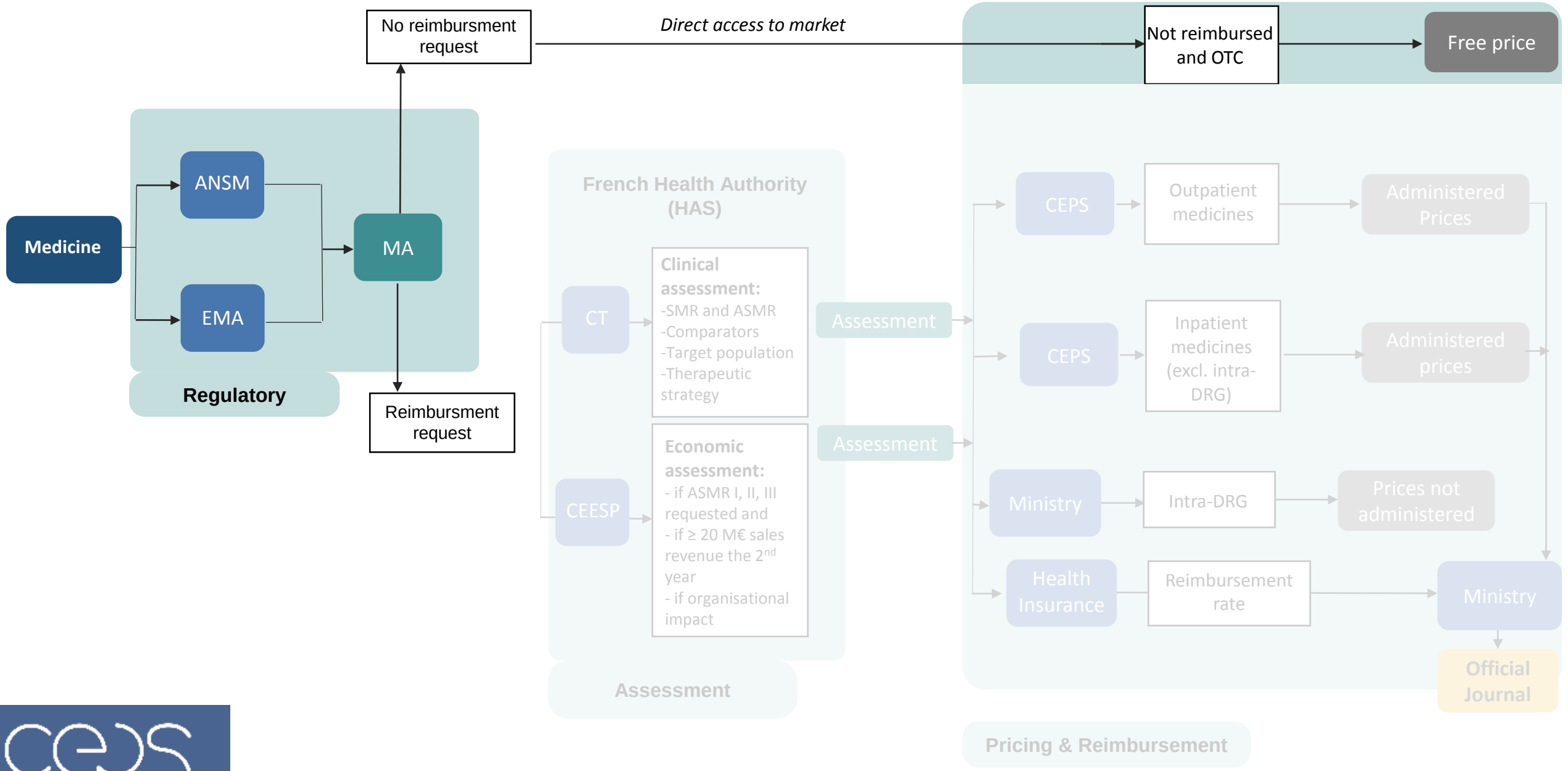
> Negotiated : by the CEPS (initial price and price decreases conventionally agreed);

> Regulated (conventional and legislative financial regulation).

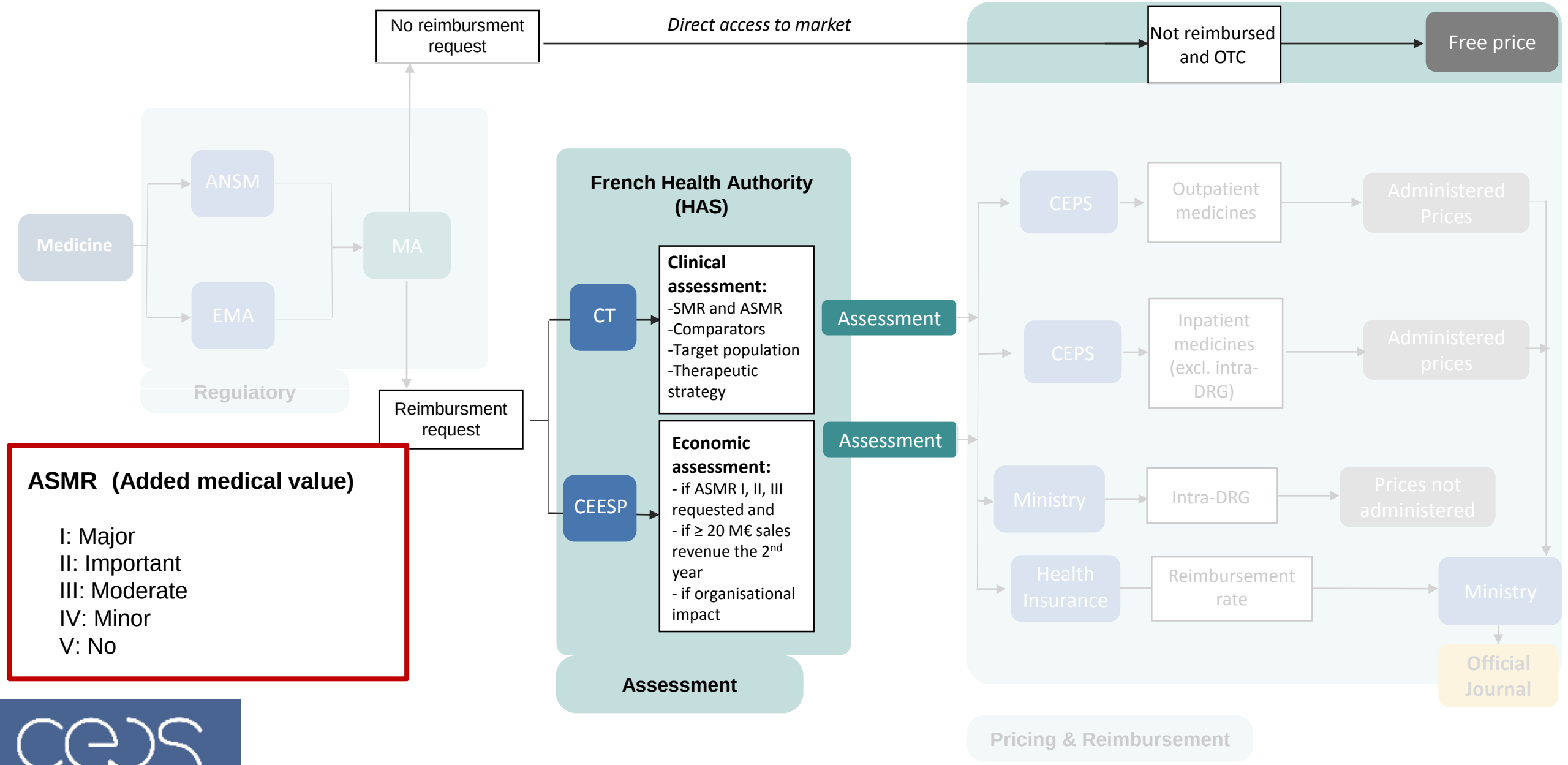
Steps to access French market



Steps to access French market



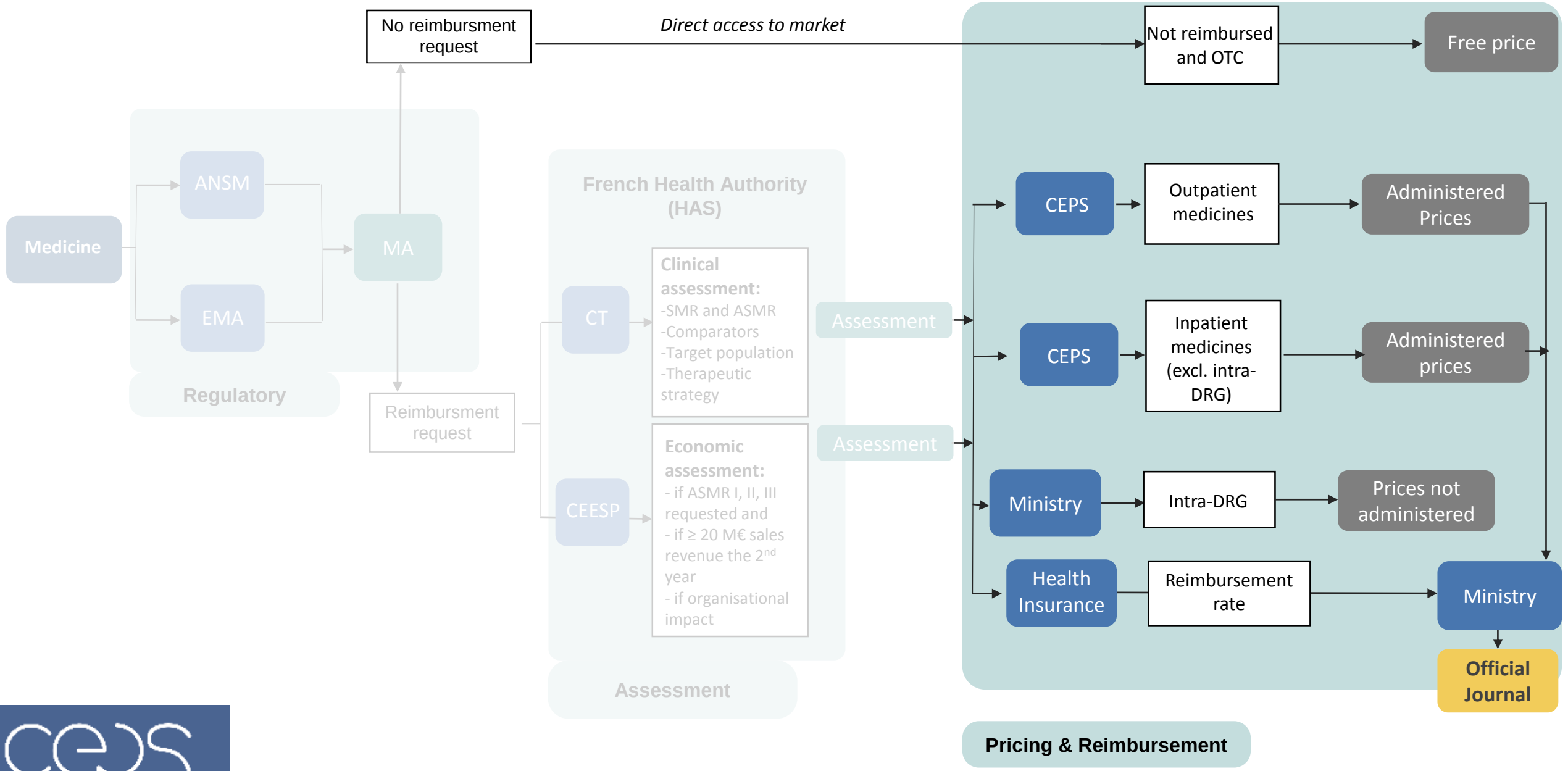
Steps to access French market



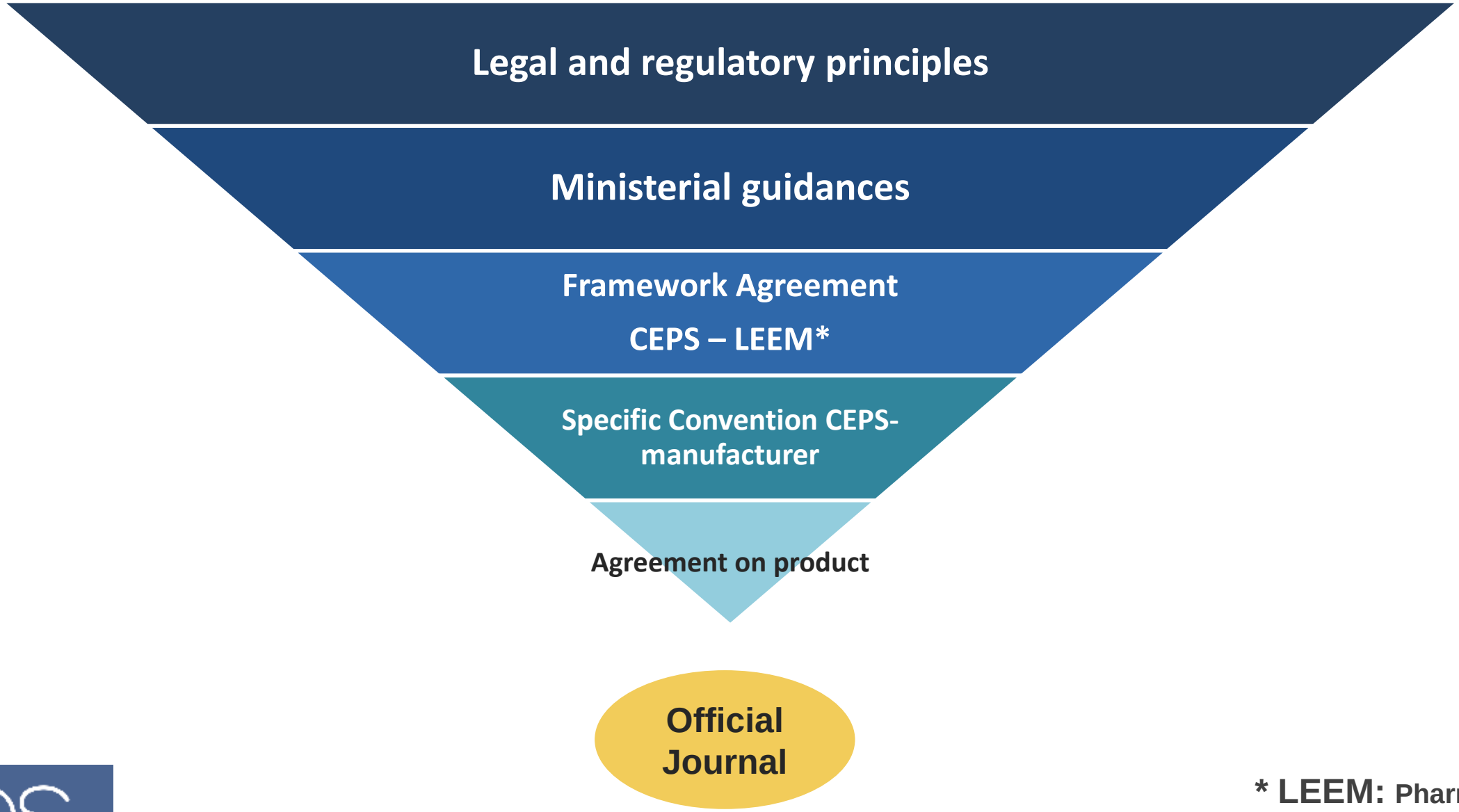
ASMR (Added medical value)

I: Major
II: Important
III: Moderate
IV: Minor
V: No

Steps to access French market



Pricing Framework



* LEEM: Pharmaceutical Industry representative

Legal and regulatory principles

BY WHO?

Conventionally agreed between the CEPS and the manufacturer

↓

If the negotiations fail, the CEPS can unilaterally decide a price

BASED ON WHAT?

1. Added medical value (score ASMR)
2. Economic assessment results
3. Prices of equivalent medicines
4. Forecasts or observed volumes
5. Predictable and actual conditions of use

FRAMEWORK AGREEMENT

- Agreement between CEPS and the pharmaceutical industry representative (LEEM);
- Validity of 3 years;
- Act in addition to the other dispositions and not in subsitution;
- Create the framework for the pluriannual CEPS – manufacturer conventions…
- … which will include the agreements per products;
- Version in effect : 31 December 2015 valid until 2018.

Why a Framework Agreement?

- Define rules to specific situations which are not stated in other reference documents
- Way to formalise a doctrine
- Provides predictability and transparency in the decisions
- Allows faster negotiations (reimbursement agreement and price decrease)
- Win – win situation

FRAMEWORK AGREEMENT - Articles

CHAPTER I: GENERAL PROVISIONS
Art. 1 – Governance and joint monitoring group
Art. 2 – Information exchange
Art. 3 – Intellectual property
Art. 4 – Horizon scanning

CHAPITER II: GENERAL PROVISIONS ON CONVENTIONS
Art. 5 – Conventions framework
Art. 6 – Conventional amendments revision

CHAPTER III: PRICE SETTING
Art. 7 – General provisions on new medicines
Art. 8 – Accelerated approval for innovative medicines
Art. 9 – Price guarantee for ASMR I, II and III
Art. 10 – Economic assessment consideration
Art. 11 – Hospital-purchased medicines
Art. 12 – Outcome-based contract
Art. 13 – Paediatric medicines
Art. 14 – Orphan medicines
Art. 15 – Medicines associated to a technology
Art. 16 – Price increase conditions – essential medicine

CHAPTER IV: PRICE REGULATION AND EFFECTIVE USE
Art. 17 – Price decrease and predictability
Art. 18 – Investments
Art. 19 – Generics
Art. 20 – Prices consistency
Art. 21 – Transformation of rebate into price decrease
Art. 22 – Biosimilars
Art. 23 – Volume clause
Art. 24 – Medicines without ASMR
Art. 25 – Rebates categories
Art. 26 – Information for prescribers, promotion and advertisement
Art. 27 – Cooperative action to medicine effective use
Art. 28 – Structure effect correction
Art. 29 – Real-world date of new medicines
Art. 30 – Extension of indication assessment

CHAPTER V: ANNUAL FINANCIAL REGULATION
Art. 31 – Annual financial regulation
Art. 32 – Post ATU allowance
Art. 33 – W contribution
Art. 34 – L contribution
Art. 35 - Credits on discounts

CHAPTER VI: AGREEMENT SCOPE
Art. 36 – Agreement scope

ANNEX 1: Pluriannual CEPS – manufacturer convention template

ANNEX 2: Generics pricing rules and regulation

ANNEX 3: Annual sales revenue declaration template

ANNEX 4: List of acronyms

Art. 9 – Price guarantee for ASMR I, II and III

> An innovative medicines is qualified by an ASMR I, II or III

> Eligibility conditions:
  - Require and obtain an ASMR I, II or III
  - Valid economic assessment
  - New antibiotics API obtaining an ASMR IV

> The Framework Agreement provides an « European price stability »
  - French price won't be lower than the lowest price among the four main EU markets (Germany, Italy, Spain and the UK)
  - Validity of 5 years

> At the end of a « price guarantee » period (Art. 9) or after 3 years of commercialisation, the CEPS will request a partial or total transformation of the rebates into price decrease.

Art. 24 – Medicines without ASMR

> ASMR V = no added medical value

> Objective: faster and simplified pricing track for medicines with an ASMR V

> Conditions: - Obtained an ASMR V
- No comparator out-patented
- Daily treatment cost inferior to the comparators

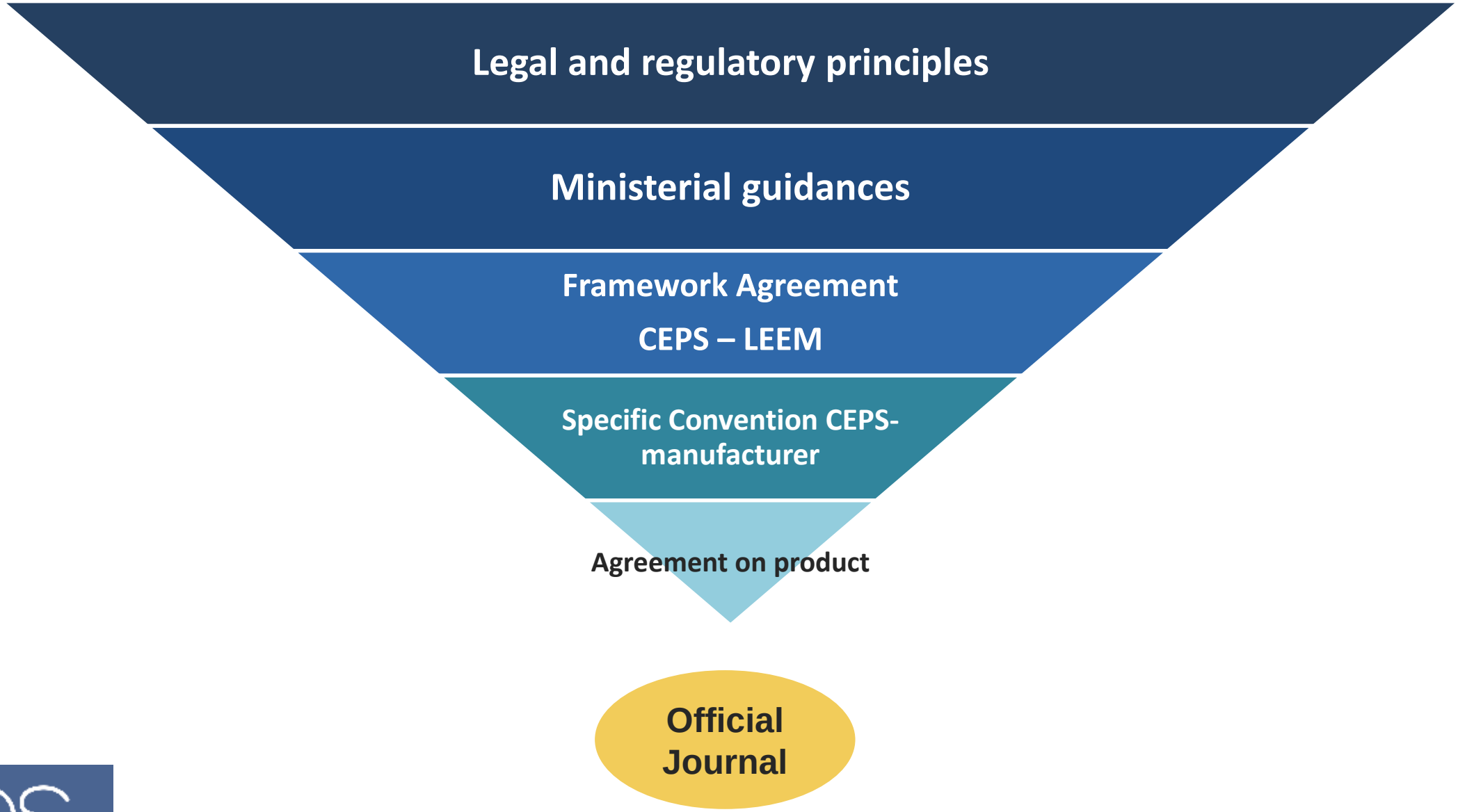
> Pricing agreement within two weeks after the HTA process

Link to the Framework Agreement:

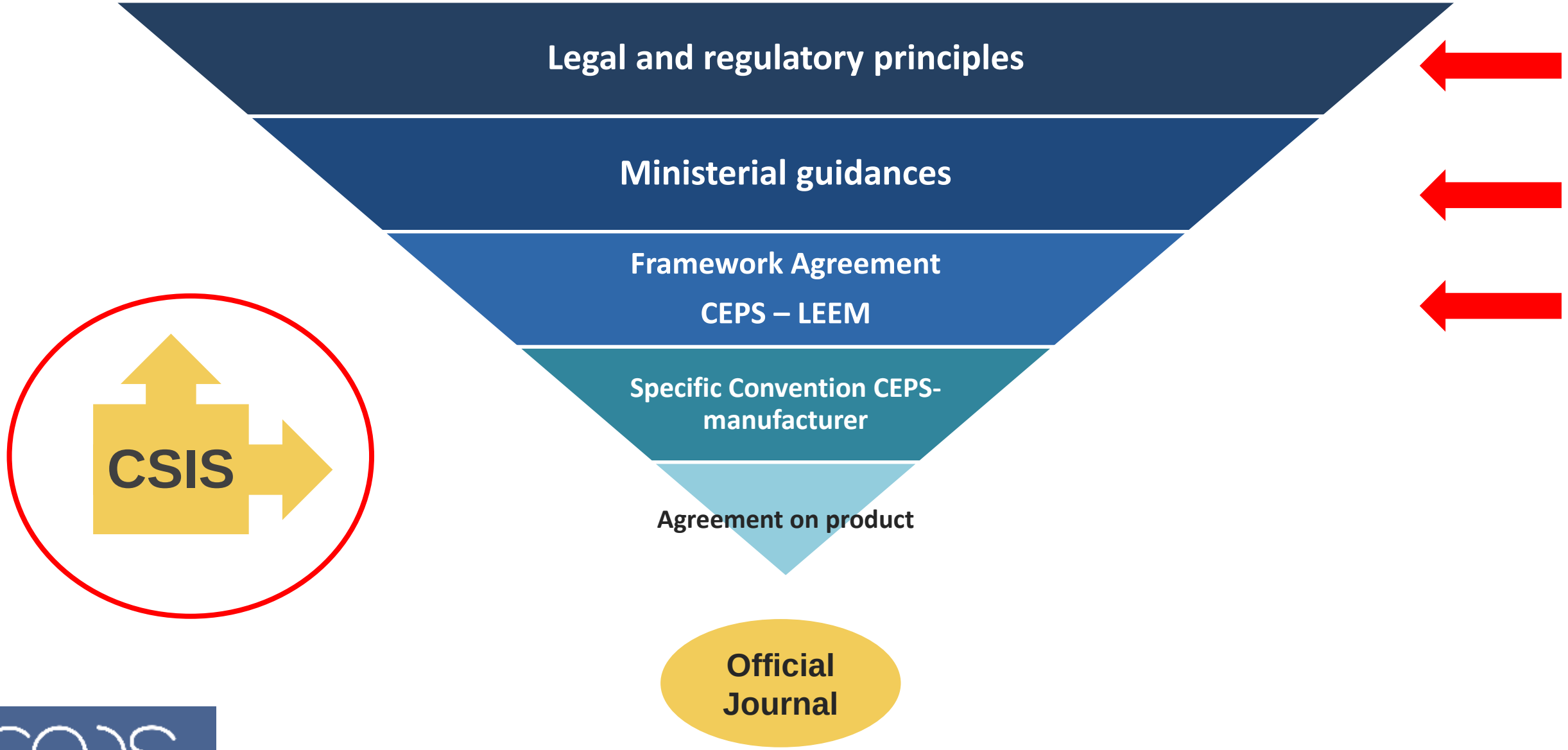
(only in French)

http://solidarites-sante.gouv.fr/IMG/pdf/accord_cadre_version_definitive_20151231.pdf

Pricing Framework



Pricing Framework



CSIS measures

Aiming at ensuring France maintains his “business friendly” attitude towards the Health Industry.

Measures are set to:

Ensure patients get a faster access to innovation

> Reducing the timeframe to access the market to 180 days
> Broadening the early access programme not only to new products but also to new indications of products already reimbursed
> Clarifying the early access programme to medical devices (the “forfait innovation”)

Enhance public-private partnerships in research and training

> Launching the “Health Data Hub” aiming at collecting health data available in France

Maintain France as a centre of excellence

> Launching the venture capital “Innobio II” – budget of 150 to 250 M€

Foster a more stable and predictable pharmaceutical regulation

> Allowing a pharmaceuticals spending increase by at least 0,5% for the global market
> Updating the HTA procedure (new criterion?)

Link to access to the report:
http://m.enseignementsup-recherche.gouv.fr/cid132716/8eme-conseil-strategique-des-industries-de-sante-csis.html

Social Security Financing Act for 2019

L rate becomes M amount in 2019:

> L rate: level of evolution of the turnover of the pharmaceutical industry beyond which it must pay a contribution
> In 2018, L rate was split between the Lv (for the outpatient sector) and Lh (for the inpatient sector);
> In 2019, L rate will merge and and become the M amount.
> It will be set at + 0,5 % for the three coming years;
> Exemptions (orphan drugs and generics) will be removed;
> M amount will be only based on net annual revenue of each manufacturer regardless of its growth.

Hybrids medicines substitution:

> From 2020, a registry will be launched allowing the substitution between originators and hybrids medicines.

Reimbursement rate if no substitution:

> From January 1st 2020, patients refusing the substitution to a generic will be reimbursed on the basis on the generic price and no longer the originator price.

Early access scheme “ATU”:

> New indication and medicines with a MA are eligible from the 1st of March to the ATU.

New ministerial guidances

- Jointly signed by the Ministries of Economy, of Health and Public Accounts
- Sent on the 4th February 2019 to the reelected CEPS President
- Reaffirms CSIS conclusions and provides orientations for the coming Framework Agreement negotiations
- To be updated after the new Framework Agreement is signed

Link: https://solidarites-sante.gouv.fr/IMG/pdf/lettre_d_orientation_ministerielle_du_4_fevrier_2019.pdf

New ministerial guidances

1. **An ASMR IV medicine price is neutral for the national budget and lower than ASMR III price.**

2. **Investments and exports could be taken into consideration during the negotiation of an updated Article 18 (price stability).**

3. **Decreasing the negotiation and instruction time while ensure it does not lead to additional cost to the Statutory Health Insurance.**

Link: https://solidarites-sante.gouv.fr/IMG/pdf/lettre_d_orientation_ministerielle_du_4_fevrier_2019.pdf

New framework agreement

- The framework agreement of 31 December 2015 has been extended until the 31 December 2019.

- Negotiations did not started yet.

- Some amendments of the current framework agreement are being discussed :
  - Biosimilars
  - Negotiations delays
  - “ M” amount

https://solidarites-sante.gouv.fr/IMG/pdf/avenant_a_l_accord_cadre_du_31-12-2015_entre_le_ceps_et_le_leem_20181207.pdf

Thank you

Jonathan Rodrigues
jonathan.rodrigues@sante.gouv.fr

Pricing process for a new medicine

The manufacturer submits at the same time a clinical and in some cases an economic report to HAS and a pricing report to CEPS

Once the CEPS receives the HTA conclusions, it can start the price negotiation.

The CEPS set a price proposal based on the HTA conclusions, the manufacturer request and the pricing rules (comparators, target population, market share…). The CEPS' proposal is taken by the majority. In case of a tie, the chairman has a casting vote.

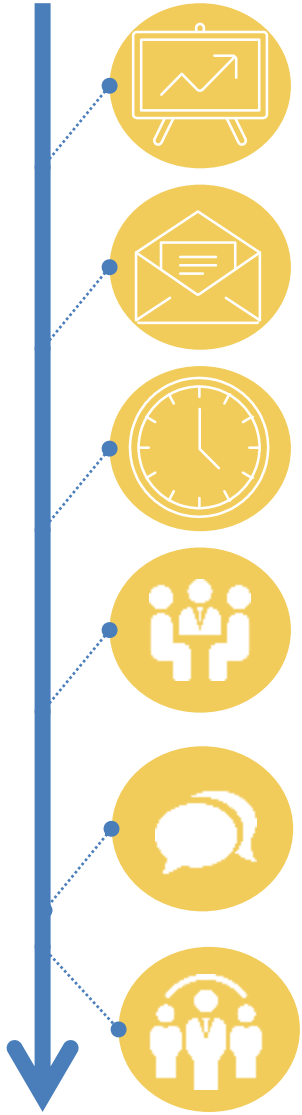
Several iterations with the manufacturer can be necessary. The CEPS' General Secretariat acts as a mediator. Each new manufacturer's proposal is submit to the Committee who analyses it when it meets every week.

Once the CEPS and the manufacturer agree on a price, a contract (which may include a MEA) is signed and the price is published in the official journal.

What happens if the negotiation fails? Two possible solutions:

- Rare situation → Price is set unilaterally. The ministers can oppose it and set another one within 15 days.
- More frequent situation → The company may decide not to market the product.

Pricing process for already commercialised medicines



Every year, the Parliament defines an objective of savings on health spendings including on medicines prices decreases.

Based on the pricing rules and the market dynamics, the CEPS send to the manufacturer a contract for the decrease of a medicine's price.

The manufacturer has one month to reply or to ask for an audition. If the manufacturer does not agree with the new price, he can present his arguments and suggestion another option.

The CEPS consideres the manufacturer's arguments and might maintain or amend his request accordingly.

Several iterations with the manufacturer can be necessary. The CEPS' General Secretariat acts as a mediator. Each new manufacturer's proposal is submit to the Committee who analyse it when it meets every week.

Once the CEPS and the manufacturer agree on a new price, a contract is signed (which may include a MEA) and the price is published in the official journal.

> Conditions:
  - a manufacturer considers to stop to produce or commercialise a medicine
  - The medicine addresses an unmet medical need which will not any longer be convered (no comparators)

> The manufacturer can request a price increase based on the financial conditions of operation

> In case of price increase, the manufacturer has to ensure the market provision

ANNEX 2: Generics pricing rules and regulation

> Prices of out-patent medicines and generics sold in the outpatient sector are still administrated but not negociated.
> Annex 2 establishes an automaticity in in prices dynamic.
> The CEPS is implementing an equivalent approach for the inpatient sector.

	Outpatient only
Initial price decrease	- 20% for the brand product - 60% for the generics
Following price decrease	at 18 months : - 12,5% for the brand product - 7% for the generics
Brand/generics price convergence	after 5 years

IV.
Germany

Priorities in the “Pharma-Dialog 2.0”

Topics, Participants, Perspectives

Kevin Rieger, Head of European Affairs, BPI e.V.

Outlook

- Current Situation
- Competence Teams
- Participants
- Topic suggestions
- High-level meetings
- Conclusions

Current Situation

April 2016: Results of „Pharma-dialog 1.0“ presented in BMG

March 2017: AMSVG presented as the implementation of the results of the “Pharma-Dialog“

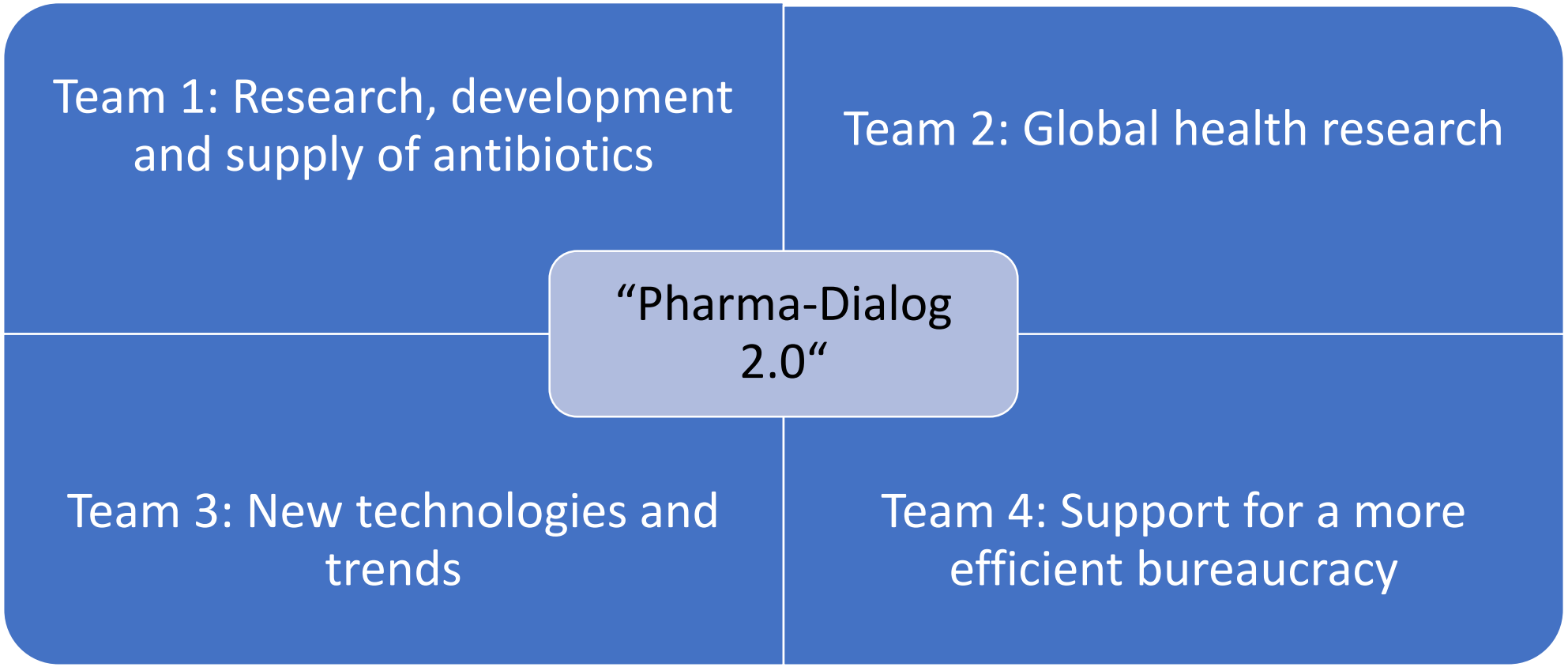
2017: German parliament elections lead to difficult government formation

October 2018: Draft of a legal ordinance of the BMG concerning the physician information system

2018: Government parties agree to continue “Pharma-Dialog“ in coalition treaty

Between the two phases the “Pharma-Dialog“ was continued on working levels within the competence teams

Competence Teams



- Competence teams have held meetings up to the restart of “Pharma-Dialog 2.0“
- Results are saved and can be further developed in “Pharma-Dialog 2.0”, if needed

Participants

Participants “Pharma-Dialog 1.0“	New Participants “Pharma-Dialog 2.0“
Producer associations	Representatives of the “Länder“
Research institutes	Governing parties of the German Parliament
Labour union “IG BCE“	
Federal institutions “BfArM“, “PEI“	
Representatives of the “Länder“	
Experts of the included resorts “BMG“, “BMWi“, “BMBF“	
Chancellor‘s office as a guest	
Depending on the topic: “G-BA“, “RKI“, “GKV-SV“	

Topic suggestions

- The pharmaceutical industry associations have handed in their topic suggestions for the 19th legislative period in a common paper
- Topics
  - Research networks and location policy
  - Innovations and quality of care
  - Security of supply
  - New supply concepts
- All these topics are integrating the aspect of digitalization
- 16 subtopics have been suggested

Topic suggestions (cont‘d)

Selection of subtopics

1. Production site as well as production and supply security
2. Research promotion financing through taxes
3. Strengthening medium-sized businesses
4. Recognize research on known active ingredients and in the field of OTC medicines
5. Europe and the background of progress and regulation (Europe-wide consultations, joint advisory services G-BA, BfArM and PEI)
6. Digitalization and new supply concepts
7. Consideration of bureaucratic aspects
8. Antimicrobial Resistance (AMR) (especially translation and new funding measures)

Topic suggestions (cont‘d)

- Based on the experiences of “Pharma-Dialog 1.0” the industry associations have decided not to prioritize social rights questions
- Due to the diversity of participants the industry associations will not be the only ones influencing the agenda
- The labour union “IG BCE” will continue to focus on the topic of skilled personnel
- Research institutes will focus on the topics of translation and framework conditions for research
- “Länder” and parliamentary fractions will make own topic suggestions
- The diversity of participants and the different interests will be a new challenge

High-level meetings

- First meeting was held on the 16.11.2018
- Title: „Chances of new technologies and trends for pharmaceutical research, best possible patient supply and using the strong innovation location Germany“
- Two meetings are planned in every year in the ongoing legislative period
- Working topic spring 2019: „Supply security and quality“
- Working topic fall 2019: „Technology transfer and translation“
- 36 people expected at the table, two from each institution
- One representative from the preparation group per institution in the background

Example: Competence Team 3

New Techniques and Trends

- Develop a German Biotech Agenda
- Tax reductions on research activities
- Better Translation processes
- Better use of Real World Data

Future tasks of the competence teams

- Competence teams will also function as technical working level
- Working independently on focus topics, formulating recommendations, accepting tasks from high-level meetings
- Professional knowledge of competence teams should complement political format of the dialog
- Continuation of the work in competence teams 1-3
- Competence team 4 has had a successful conclusion → work should be continued directly between “Länder“ and the industry

Conclusion

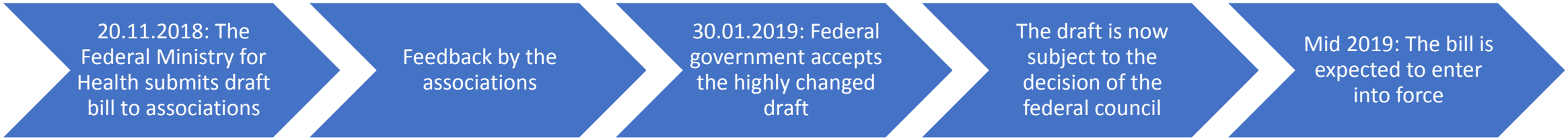
- “Pharma-Dialog 2.0“ is a continuation and not a restart
- Producer associations act in agreement
- Multiple new partners in dialog → new positions and questions
- Results are supposed to be saved in the process and not in a final legal document
- BPI will continue to collect data and present it

“GSAV“

Outlook

- Status quo
- Content Summary
- Orphan Drugs

Status quo



- GSAV → Law for more safety in the supply of medicines
- The law is a consequence of recent medicine scandals (e.g. Lunapharm, Valsatan)
- Goal: Enhanced control and safety

Content summary

Topic	News
Cannabis	Simplification for approval reservations for cannabis therapy
Recalls	No additional costs for the patients if the medicine was recalled due to minor quality
Discount contracts	Diversity of producers and adequate supply should be taken account of
Products for new therapies	New regulation competencies with the G-BA in order to set out expectations for the quality of medication for new therapies
Imports	Tiered minimum price intervals
Biosimilars	The exchange with biosimilars will enter into force three years after the GSAV
Haemophilia	Subject to pharmacy obligation, price moratorium for haemophilia products
„AMNOG“	New regulations concerning revenue threshold for orphan drugs

Orphan drugs

- Additional benefit threshold: 50 million €
  - Now including in- and outpatient care
  - → Pharmaceutical companies have to present full dossiers earlier

- G-BA can order extra data collections
  - During treatment
  - Additional to EMA controls

- Considerable sanctions

Thank you for your attention!

V.

Regulatory and market access challenges with nanomedicines and nanosimilars

Emanuele Degortes, Vifor Pharma

What are nanomedicines?

- Nanomedicines are medicinal products that have at least one dimension in the nanoscale range (1nm to 100nm).
- The small size of nanomedicines allows for preferential crossing of specific barriers within the body (e.g. cell membranes) to reach the drug target (e.g. enzymes).
- Nanomedicines exhibit phenomena and properties, attributable to their size and morphology, that are relevant to their safety, effectiveness and quality.
- Due to their unique physicochemical features, nanomedicines have the potential to offer treatment options for previously untreatable diseases.

Some examples

[1]AmBisome®
- Fungal/Protozoal infections
- Liposomal amphotericin B
- Gilead Sciences

[4]Rapamune®
- Immunosuppressant
- Sirolimus
- Wyeth Pharmaceuticals

[7]Restasis®
- Chronic dry eye disease
- Cyclosporine ophthalmic emulsion
- Allergan

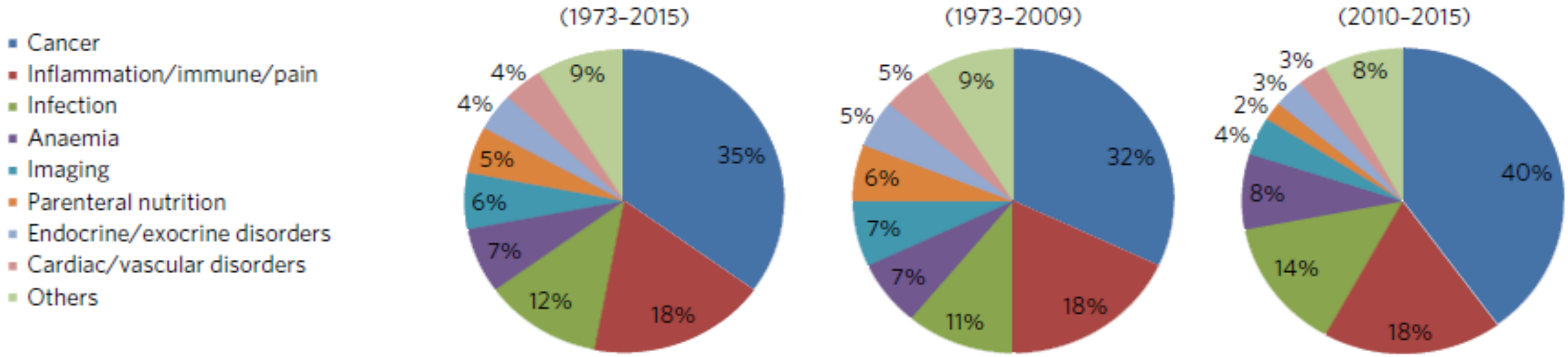
[5]Venofer®
- Anaemia
- Iron sucrose
- Vifor Pharma

[3]Copaxone®
- Multiple sclerosis
- Glatiramer acetate
- Teva Pharmaceuticals

[2]Doxil®
- Cancer
- Doxorubicin liposomal
- Janssen

[6]Abraxane®
- Cancer
- Albumin-bound paclitaxel
- Celgene

Indications nano medicines are used in

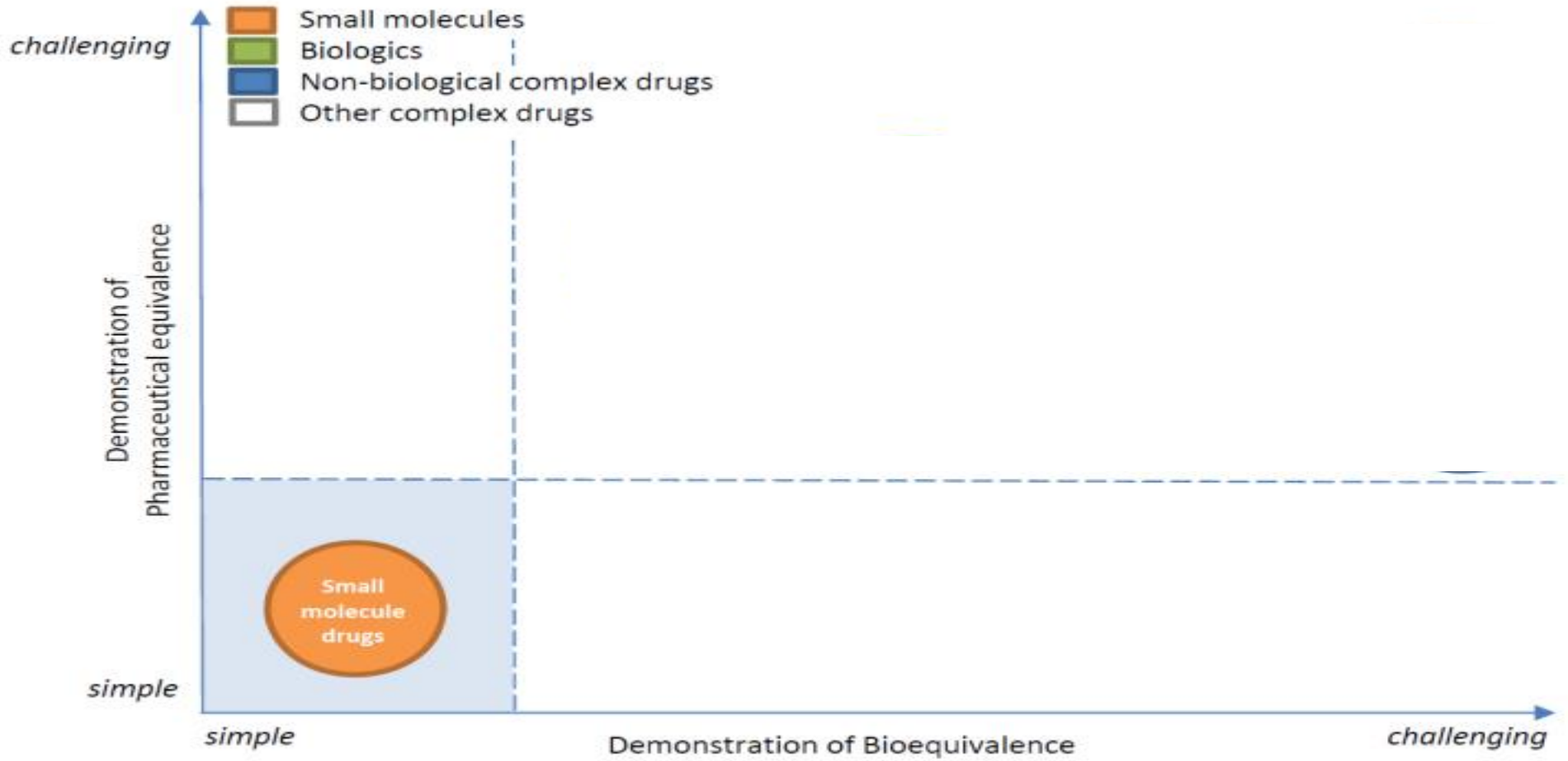


D'Mello, S. R., Cruz, C. N., Chen, M. L., Kapoor, M., Lee, S. L., & Tyner, K. M. The evolving landscape of drug products containing nanomaterials in the United States. *Nat. Nanotechnol.* **12**, 523-529 (2017).

Nanomedicines are highly complex

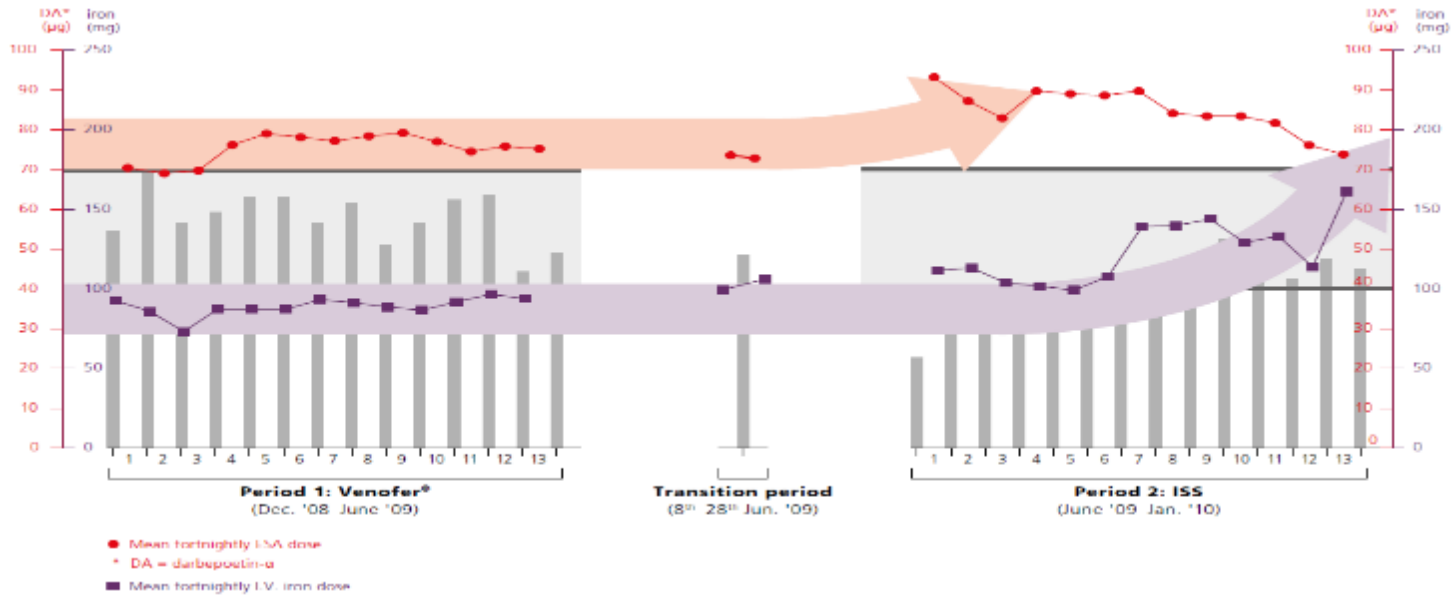
- Due to their size, nanomedicines differ from small molecule drugs in two critical ways:
  - their properties cannot be fully characterized, and
  - the entire nanomedicine product is regarded as the active pharmaceutical ingredient (API).
- The complexity of a nanomedicine does not allow for full physicochemical characterisation. Nanomedicine follow-on sameness cannot be demonstrated, unlike that of “regular” generics.
- Minor changes in manufacturing can affect size and/or morphology of nanomedicines. These differences can substantially influence quality, biological properties and therapeutic profiles. Therefore, nanosimilars may exert clinically relevant differences compared with the originator products and should not automatically be considered to be interchangeable.
- Clinical differences were observed with nanomedicine follow-ons, confirming the expected challenges in making identical copies of nanomedicines.
- This sets nanomedicines apart from small molecules and their generic follow-on products.

Complex Landscape

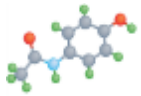
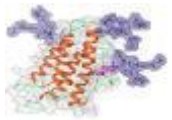


Impact on patients

- One determinant for the fate of nanomedicines is the interaction of the biological environment with their surface.
- Surface modification of nanoparticles can lead to change in:
  - Pharmacokinetics
  - organ disposition
  - Pharmacodynamics



Nanomedicines share many characteristics with biologics

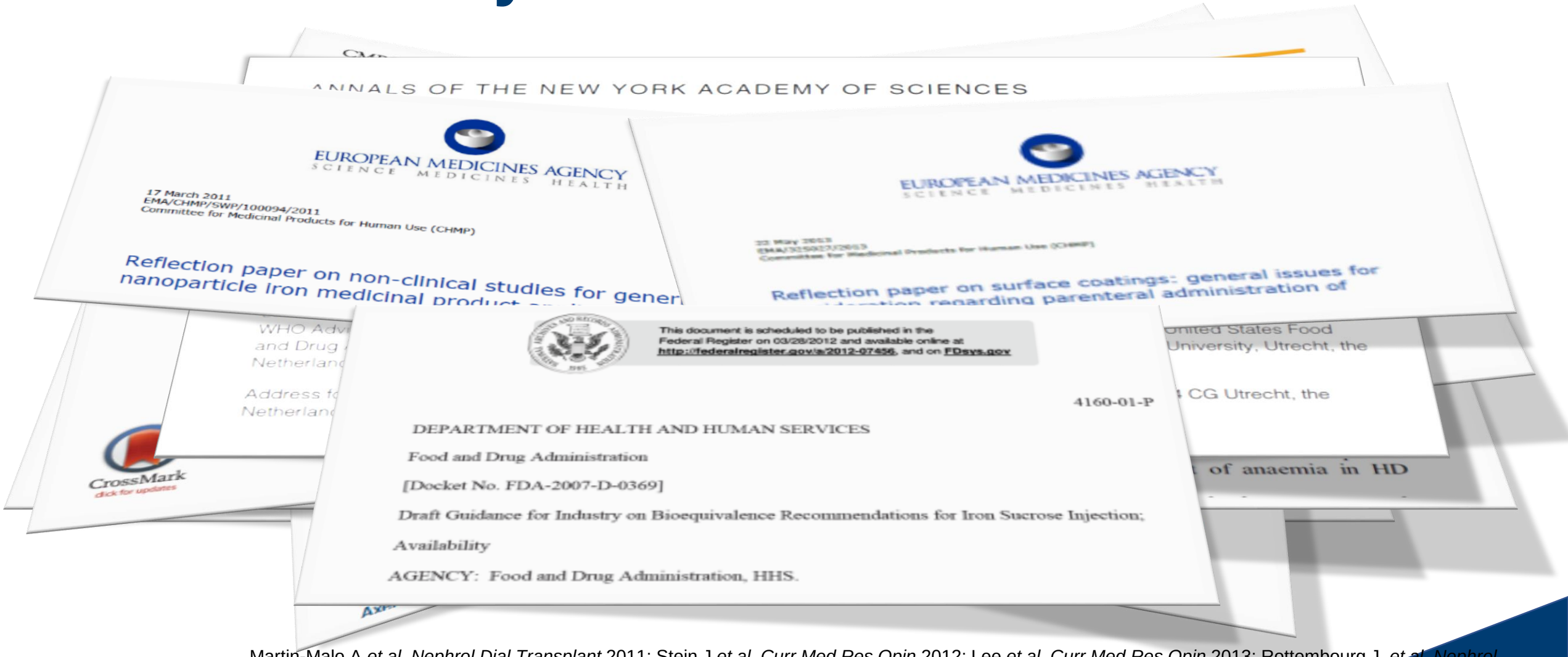
	 SMALL MOLECULE DRUGS	 BIOLOGICS	 NANOMEDICINES
Molecular weight	Low (<500 Da)	High (5-900 kDa)	
Structure	Well defined	Complex, heterogeneous, defined by manufacturing process	
Manufacturing	Chemical synthesis	Produced in living cells or organisms	Synthetic technologies
Characterization	Complete characterization	Not fully characterized	
Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	

Based on Schellekens et al; Regul Toxicol Pharmacol. 2011 Feb;59(1):176-83

Regulatory Challenges

- The complexity of nanomedicines prevents sufficient proof of pharmaceutical equivalence, when comparing a follow-on product to a reference product.
- Hence, the current EU application procedures are not suitable for nanomedicines:
  - Generic application: Article 10(1) Directive 2001/83/EC is inappropriate, as acknowledged by the EMA in different reflection papers.
  - Biosimilar application: Article 10(4) Directive 2001/83/EC is not an option, as most nanomedicines are not biologic.
  - Hybrid application: Article 10(3) Directive 2001/83/EC could potentially serve as an alternative but lacks adequate guidance.

Regulators acknowledge challenges but still no clarity in how to deal with them



Martin-Malo A *et al. Nephrol Dial Transplant* 2011; Stein J *et al. Curr Med Res Opin* 2012; Lee *et al. Curr Med Res Opin* 2013; Rottembourg J *et al. Nephrol Dial Transplant* 2011: Agüera ML *et al. PLoS One*. 2015 Aug 31;10(8):e0135967. doi: 10.1371/journal.pone.0135967; Hussaart *et al. Ann N Y Acad Sci*. 2017 Nov;1407(1):39-49doi: 10.1111/nyas.13347

Market Access Challenges

- In the absence of a robust regulatory pathway able to demonstrate therapeutic equivalence, it is important for payers, pharmacists and physicians to recognize that follow-on nanomedicines may not offer the same level of efficacy and safety as their originators. Therefore:
  - Follow-on products should not be interchangeable with their originators.
  - Automatic substitution should be avoided as it could harm patient safety or result in lower patient outcomes.
  - Specific therapeutic needs of patients and potentially negative consequences of changing treatment for non-medical reasons should always be taken into.

Similarities and differences with biosimilars

INTERCHAGEABILITY	SWITCHING	SUBSTITUTION
Europe has developed a robust regulatory biosimilars framework but not nanosimilars one. In the absence of it (or a very clear EMA guidance) it is important for payers, pharmacists and physicians to recognize that nanosimilars may not offer the same level of efficacy and safety as their reference product and should therefore not be considered interchangeable	Switching should always be considered carefully and decided by the prescriber, all the more so given the complexity of nanomedicines and the absence of a targeted regulatory approach for nanosimilars. As experience with biologics has shown, patients, who are being switched to a similar product during the course of an ongoing treatment, might demonstrate lack of adherence. Switching to a nanosimilar could affect future treatment options.	Automatic substitution at the pharmacy level should not be allowed under any circumstance, and all the more so given the complexity of nanomedicines and the absence of a targeted regulatory approach for nanosimilars. Automatic substitution at the pharmacy level is not even widely permitted for biologics/ biosimilars, where a robust regulatory pathway is already in place.

Q&A

VI.

Dutch and European developments as regards to the use of unlicensed medicines

Andrea Corazza, Senior Director, FTI Consulting
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What is compounding?

- Compounding is a practice in which a licensed pharmacist prepares medicinal products in a pharmacy by **combining, mixing, or altering pharmaceutical ingredients**.
  - Compounding of a licensed medicine to prepare for a different route of administration or dosage;
  - Preparation of a new compound by combining two or more active ingredients.
- A legitimate practice and justified when needed to tailor a medication to the specific needs of an individual patient, or when a licensed product is not available / unsuitable.
- Compounding vs Authorised Medicines:
  1. No **clinical trial** (not demonstrated their efficacy or safety profile);
  2. Quality of the **active ingredient** (pharmacist is not obliged to disclose the source);
  3. Not subject to **GMP** requirements (stability and quality of the product);
  4. Not subject to **pharmacovigilance** practice in contrast to commercial drugs;
  5. Act of compounding increases the **risk of contamination**.

EU regulatory framework

- Article 3(1) and (2) of Directive 2001/83 provides an exemption from the requirement to obtain marketing authorisation for the sale of compounded drugs.
  1. *Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient* (commonly known as the magistral formula).
  2. *Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question* (commonly known as the officinal formula).
- In addition, Article 5(1) of the same Directive provides that:
  - *A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.*
- CJEU strict interpretation: the prescription for a compounded drug must be for a particular named patient and that the patient must be identified before the medicinal product is produced.
- However, national practice is sometimes in contradiction with this court ruling and fragmented across Europe.

Compounding trends in Europe

- Compounded products being used in hospitals instead of available licensed medicines without any medical rationale but purely to save costs.
- Pharmacies started large-scale compounding to replicate existing authorised products, using the same active substance and the same mode of administration.

This is known as **economic compounding**.

- During regulatory / HTA / P&R process, increased pressure on pharmaceutical companies bringing to the market new, licensed products replacing existing hospital preparation.

Recent developments – the Netherlands

- 19/11/2018 - IGJ Decision (Health inspectorate) about **OMP compounding to be considered small scale**, and thus compliant (Laediant's CDCA case) – this was openly supported by Minister Bruins
- 18/12/2018 - New KNMP (Dutch pharmacist association) guideline: **allowing for compounding high costs products** (before only if available products weren't satisfactory for patients)
- 19/12/2018 - NZa (Dutch Healthcare Authority) confirms **reimbursement for compounded products** even if authorised alternatives area available (from 1/01/2019)
- 20/12/2018 - Minister Bruins saying **compounding is an alternative to licensed product even if there is no excessive pricing**
- 1/02/2019 - Entry into force of "pharmacist exception" to patent law which allows pharmacies to prepare patented drugs (**DPA exception**)
- 7/02/2019 - **Parliamentary debate** in the Netherlands on framework for compounding

➢ **Compounding is allowed and reimbursed small and large scale in disregard of any authorised product being available in the market**

  ➢ *De facto*, **new regulatory framework in the NL** until the court will step in and block these decisions

Recent developments – rest of Europe

Belgium

Laediant

- **Test-Aankoop** to sue Laediant “for making a medicine 335 times more expensive than the pharmaceutical preparation” (Het Laatste Nieuws).
- Fagron, which offers compounding services, is looking for the **raw material to compound** Laediant’s product at the UZ Leuven.

Beyond Laediant

- **Journalist investigation** into presenting seven pharmaceutical orphan products that they believe could be replaced by hospital preparations. 120 million euros in 2018 vs 10 million euros if produced by pharmacists. Products include: Afinitor, Revatio, but also Litak and Tepadina.
- The **Belgian Pharmacists Association (Apothekersbond APB) and the Christian Mutuality** are demanding more government support for hospital preparations.

Spain

- Increasing challenges faced by some EUCOPE members in relation to compounding of their products.

EUCOPE's position

- Against prescribing compounded products in place of equivalent licensed products for reasons other than the medical need of a patient:
  - **Exposes patients to unnecessary risk,**
  - **Creates double standards for patients in Europe**
  - **Produces a negative effect on innovation** and long-term access to safe and innovative medicines.
- Limit pharmacy compounding operations to situations where a suitable medicinal product with a marketing authorisation is unavailable and in order to meet the special medical needs of individual patients.
- Ensure that healthcare professionals educate and inform patients about the rationale behind the prescription of a compounded product as well as its potential risks, and put in place the tools needed to monitor the effect of the medication on patient and report any potential adverse event.

EUCOPE WG on Unlicensed Medicines

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

Who we are?

- The group was created in 2016 to tackle economic off-label and compounding.
- Coordinated by the EUCOPE Secretariat with the support of FTI Consulting.
- All funding for this Working Group is provided through additional members' financial contributions from the group's members.
- Members include: Biogen, Novartis, CTRS, Santhera, Oprhan Europe, and any interested EUCOPE member.

On compounding:

- EUCOPE position paper in June 2016 and a policy paper in November 2017.
- Educating stakeholders through a number of meetings and a roundtable in Brussels.
- Commissioned to Springer Medical a report on patient safety issues associated with the use of compounded medicines as alternatives to approved pharmaceutical products in Europe.
- Support to individual members' responses to compounding affecting their products.
- More to be done at national level to protect the regulatory framework…

VII.

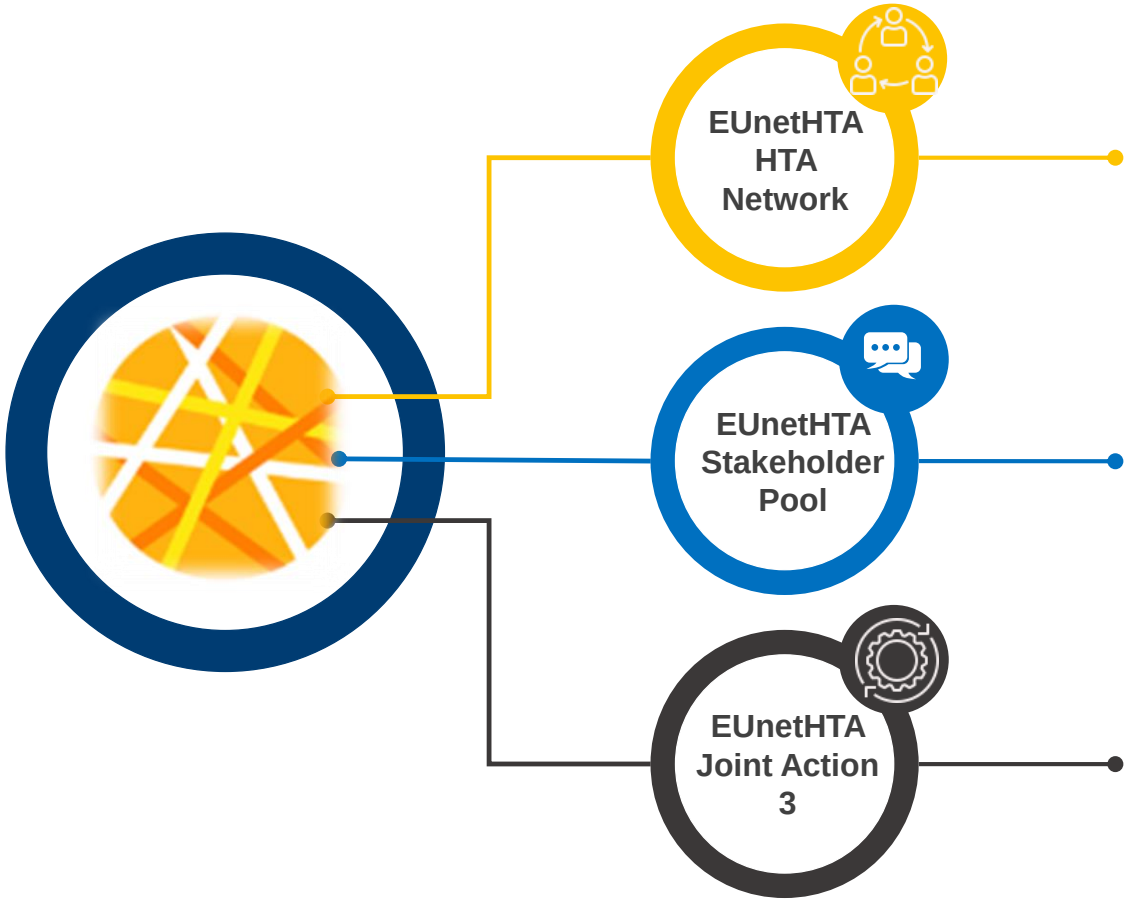
1st Stakeholder Pool Meeting of the EUnetHTA Network

- an update -

Ana Palma, SOBI

EUnetHTA Network + Stakeholder Pool Meeting

Background



01

- Representatives of national members of the EUnetHTA initiative. Provides the political and strategic guidance for EU-level coordination on HTA.
- HTA network supported by a “scientific and technical cooperation mechanism” -> Joint Action (now: JA3).
- 1 or 2 meetings / year

02

- Representatives of the stakeholders (patients and consumers, payers, HCPs and industry).
- 1 voice for pharmaceutical industry (EFPIA)
- 1 meeting a year (normally).

03

- Objectives: define and implement a sustainable model for the scientific and technical cooperation. build on the lessons, success and products of the earlier EUnetHTA Joint Actions.
- 7 Work Packages : Network coordination; Dissemination; Evaluation; Joint production; Lifecycle approach to improve evidence generation; Quality management, scientific guidance & tools; National implementation & impact

EUnetHTA Network + Stakeholder Pool Meeting

Draft Position Paper EUnetHTA

June 2018

Draft Paper published in June 2018 by WP4 on joint production of HTAs

Q4 2018

Pilot project plan

Objective

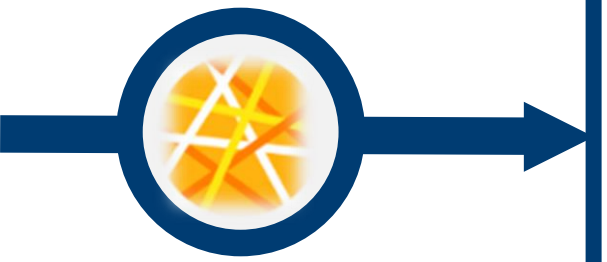
provide recommendations for horizon scanning system to serve joint HTA beyond 2020, as well as a work flow for topic identification, selection and prioritisation to support ongoing JA3 WP4 activities

July 2019

Finalisation of recommendations

EUnetHTA Network + Stakeholder Pool Meeting

Draft Position Paper EUnetHTA

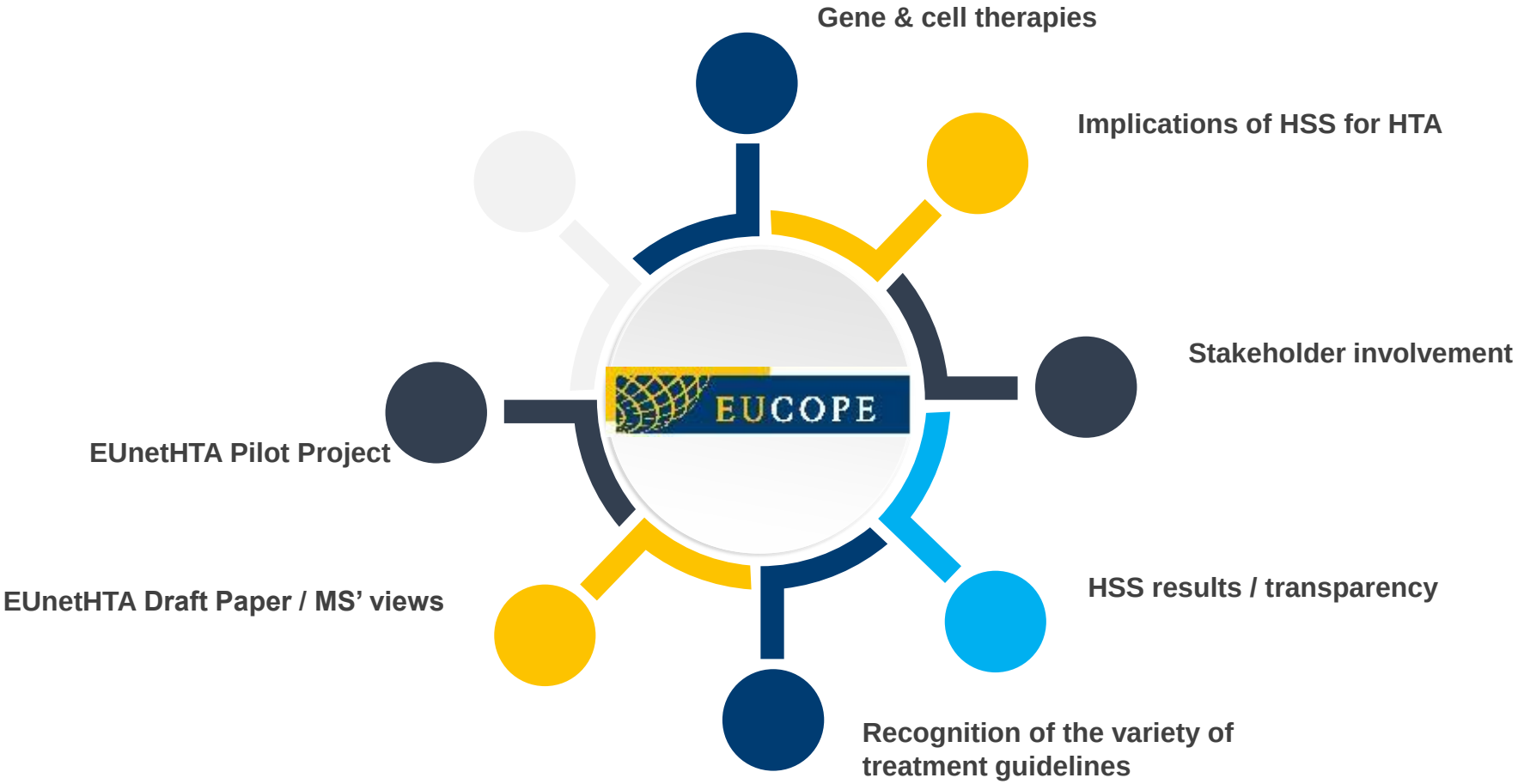


Recommendations

- to establish a cooperative HSS following standard operational procedures (SOPs) and a coordinating secretariat to act at the central level of the system. Cooperation with existing HSS, HS initiatives and scientific networks should be explored to avoid duplication of work
- that the purpose of the HSS should be to support planning, timeliness and relevance of the HTA network's activities in a technology lifecycle perspective
- that the target of the HSS should be those planning and prioritising HTA activities at any level of the network, including individual HTA agencies and stakeholders
- to at least start with pharmaceuticals (medicinal products), medical devices (MDs) and in vitro diagnostics (IVDs), with possibilities of further extension to any potential high impact (innovative), transformative or disruptive technologies as well as obsolete technologies with 296 the focus being on patient needs
- to deliver minimal data-sets for monitoring, and filtration of identified technologies according to pre specified selection criteria and more comprehensive datasets for planning and prioritisation according to pre specified prioritisation criteria
- Timeframe: no later than when a pharmaceutical enters the list of medicines under evaluation in EMA; no later than six months before the time when pivotal trial data are anticipated to become available.

EunetHTA Network + Stakeholder Pool Meeting

EUCOPE speaking points



EUnetHTA Network + Stakeholder Pool Meeting

Agenda

1. **Update on EU Cooperation on HTA**
2. **Update on ongoing & future stakeholder involvement**
3. **Parallel sessions**
   - a Patient & healthcare professional experts involvement
   - b Cooperation on identification and prioritisation of health technologies for Joint Work (=Horizon Scanning)

EUnetHTA Network + Stakeholder Pool Meeting

Session summary

1 Update on EU Cooperation on HTA

EC Presentation:

- overview of EC commitment to stakeholders' involvement in HTA cooperation
- Update on the status of the inter-institutional negotiations of the EC proposal for EU cooperation on HTA

Stakeholders' feedback:

- Call for continued EU HTA cooperation post 2020;
- Importance of involvement of all stakeholder groups;
- Need for a transparent & solid conflict of interest policies vis-à-vis industry and all stakeholders

Note: the EUnetHTA Joint Action will shortly publish their Conflict of Interest Policies.

EUnetHTA Network + Stakeholder Pool Meeting

Session summary

2 Update on ongoing & future stakeholder involvement

EunetHTA Presentation:

- Focus on early dialogues and joint assessments

Stakeholders' feedback:

- Opportunities for stakeholder contributions to early dialogues & Joint Assessment

Group discussion:

- challenge is to ensure stakeholder involvement in a way that it provides high quality input within the tight timeframe of the joint work – the timely
- .

EUnetHTA Network + Stakeholder Pool Meeting

Session summary

3 Parallel sessions

Group discussion

- Agreement that horizon scanning needs to have a pragmatic approach to identify relevant technologies.
- The importance of using an agreed definition for unmet medical needs
- Timelines: horizon scanning should look at medicinal products 6-12 months prior to EMA submission
- Industry open to exploring whether they could share with EUnetHTA information on medicinal products that they plan to submit to EMA. Objective: allow EUnetHTA a more timely planning and preparation for joint clinical assessments and give a longer term perspective to the work.

Next steps:
Opportunities for written input

VIII.
Further country updates

IX.

AOB / Closure of meeting

Thank you for your time