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THE NEW QUESTIONS ON THE SAFETY AND RISK OF MEDICINES

Meeting in Lisbon

February 16th, 2018

Portuguese Pharmaceutical Society

Veronique Lamarque-Garnier, MD

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AGENDA

- Strengthening of the PV legal framework
- PV process improvements
- Involvement of patients
- Social media a new actor
- New challenges

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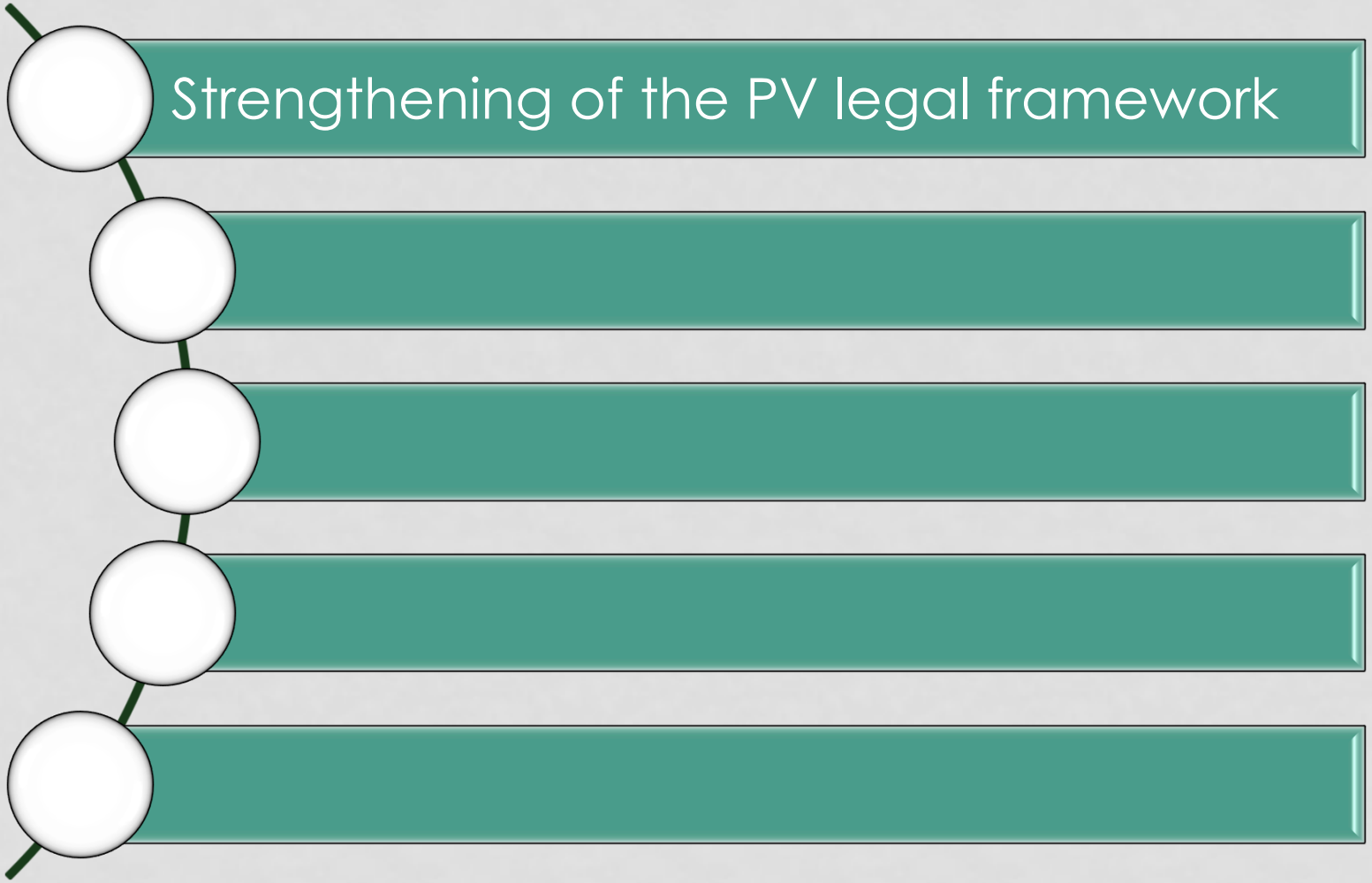

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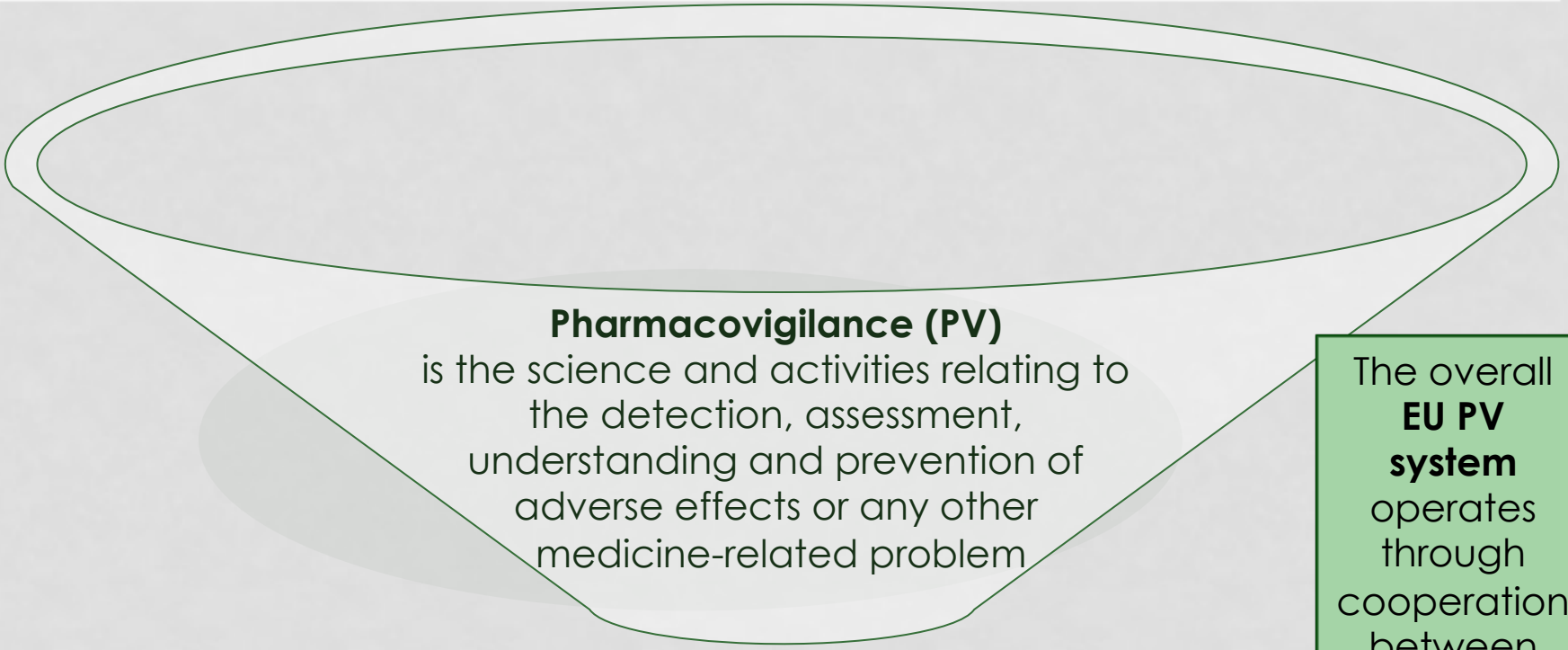
SAFETY AND RISK OF PHARMACEUTICAL PRODUCTS



Pharmacovigilance (PV)
is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem

PHARMACOVIGILANCE, SAFETY OF THE PHARMACEUTICAL PRODUCTS, SURVEILLANCE OF THE RISKS

The overall **EU PV system** operates through cooperation between the EU Member States, EMA and the European Commission

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FEW KEY EVENTS

Withdrawal of cerivastatin in August 2001
Withdrawal of rofecoxib in September 2004

→ **Regulation** amended in 2004, new guidelines on **Risk Management Plan** (RMP)

Audit of the EU PV system in 2005 and **public consultation** in 2006

→ New 2008 **Pharmaceutical Legislation**, adopted in 2010, effective in **2012**

Mediator (benfluorex) in France in 2010-2011

→ **Law of health safety strengthening** (France) in 2011 and adoption of new **measures by the EU parliament** (2012)

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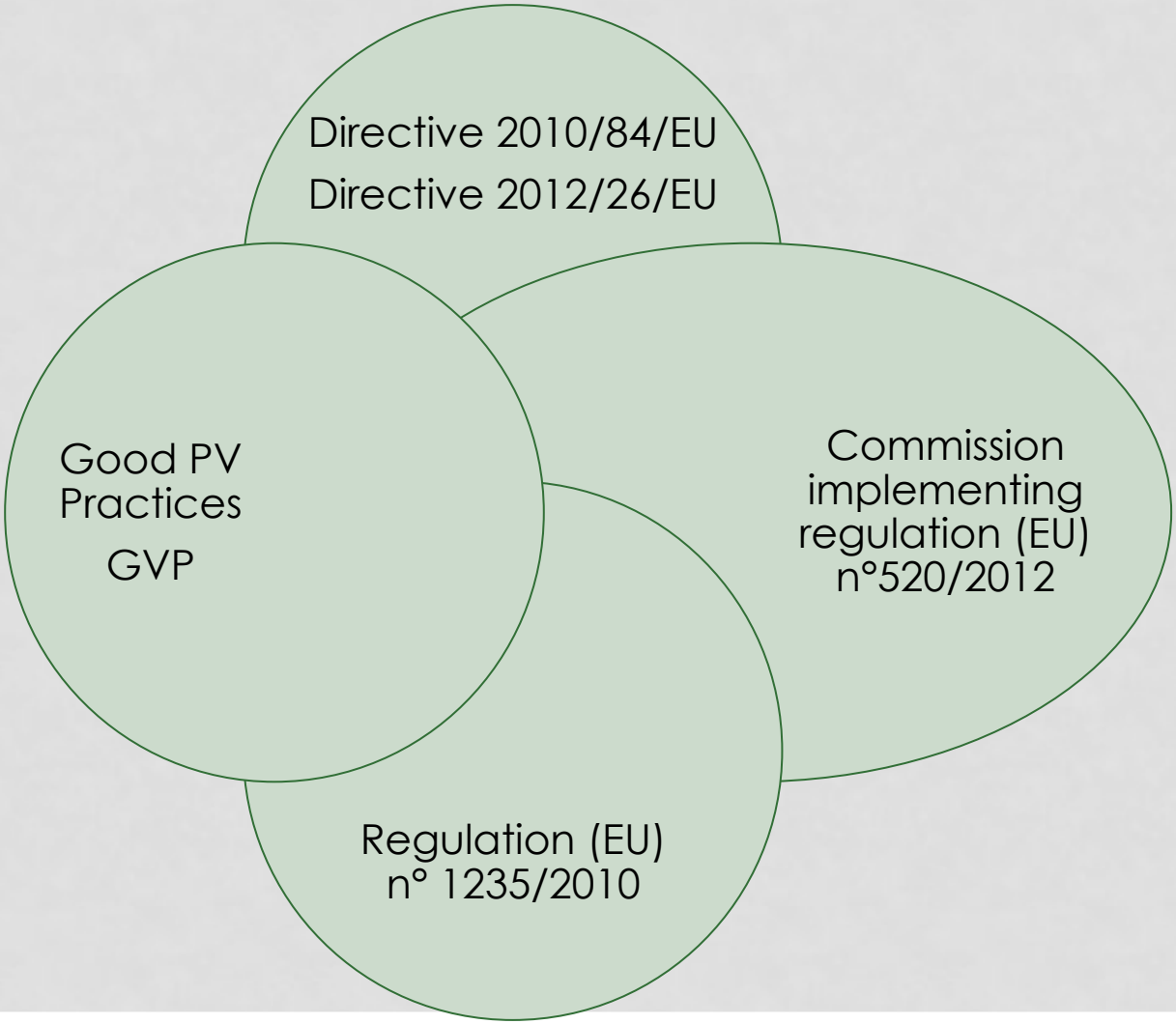
STRENGTHENING OF THE EUROPEAN LEGAL FRAMEWORK



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STRENGTHENING OF THE EUROPEAN LEGAL FRAMEWORK – NEW PHARMACEUTICAL LEGISLATION IN 2010

Better definition of **roles and responsibilities** of the stakeholders

Collection of **better data on medicines and their safety**

Rapid and robust assessment of issues related to the safety of medicines

Effective regulatory action to deliver safe and effective use of medicines

Empowerment of patients through reporting and participation

Increased levels of **transparency and better communication**

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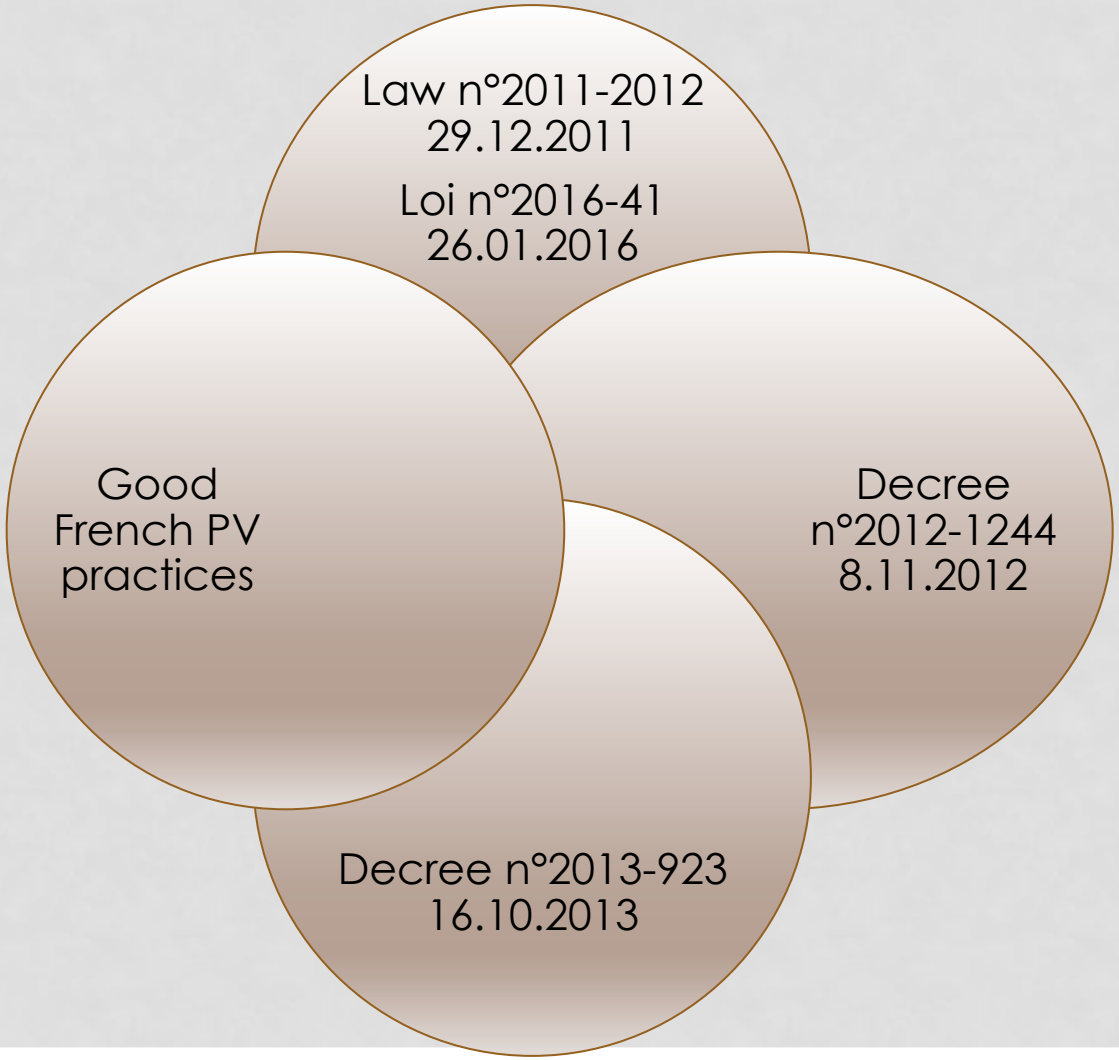
STRENGTHENING OF THE FRENCH LEGAL FRAMEWORK



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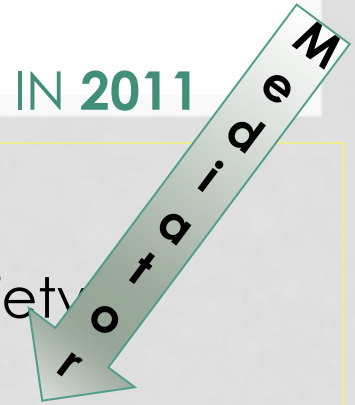
STRENGTHENING OF THE FRENCH LEGAL FRAMEWORK –

« LOI DE RENFORCEMENT DE LA SÉCURITÉ SANITAIRE » IN **2011**



- **Among several issues**
  - Strengthening of the pharmaceutical product safety

Mainly transposition into the French law of the EU 2010 Directive

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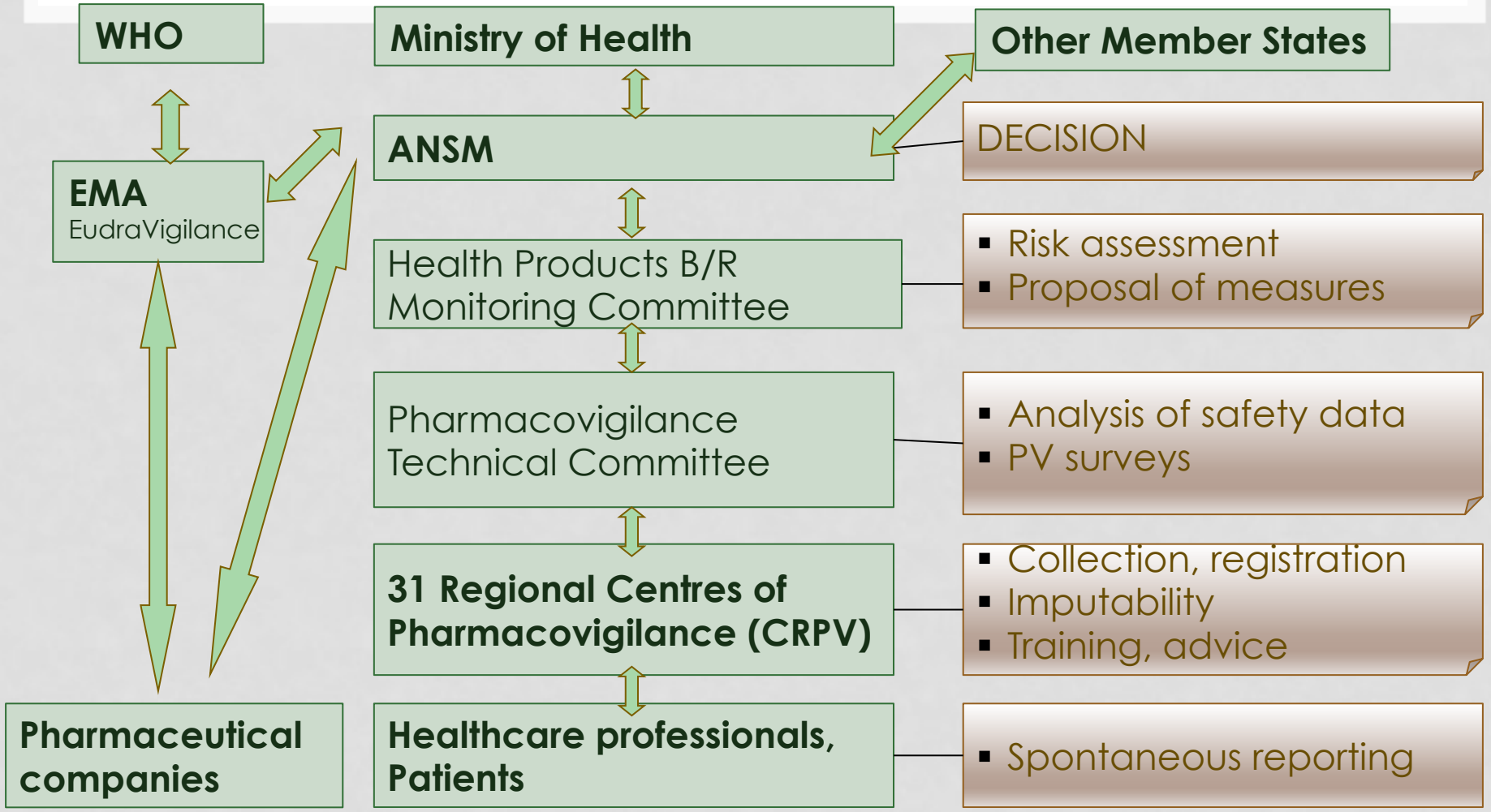
INTERACTION BETWEEN NATIONAL AND EUROPEAN PV SYSTEM



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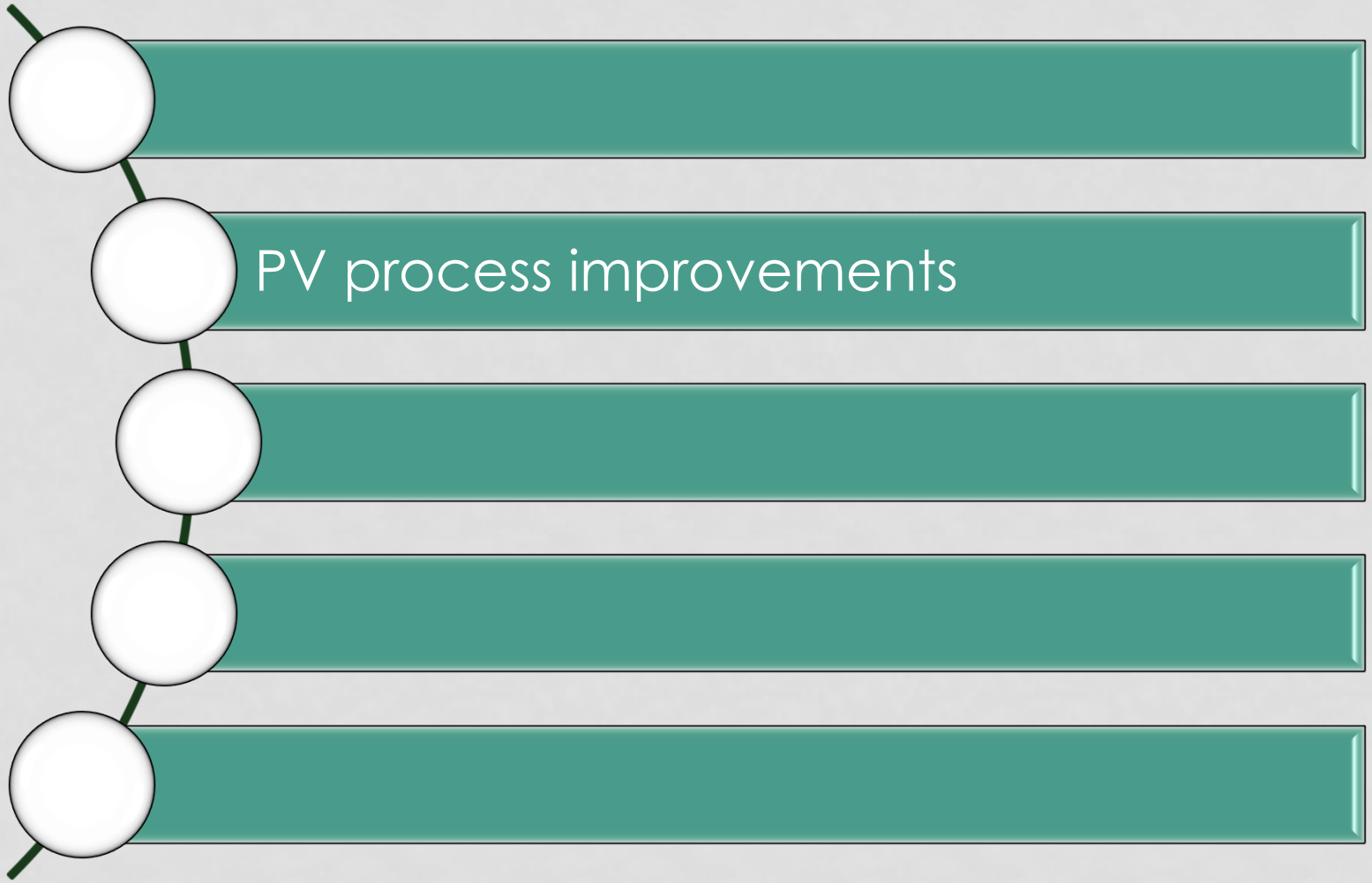

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SOPHISTICATED EU PV SYSTEM

Strengthened monitoring of medicines throughout lifecycle in clinical practice
through improved processes and EU initiatives

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EMA-ANNUAL REPORT 2016

Number of RMP :

266

Number of safety studies

(imposed PASS) : 10

Number of product withdrawals for safety reasons

Notifications of withdrawn products for safety reasons		
2014	2015	2016
132	160	118

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EMA-ANNUAL REPORT 2016

Number of signals :

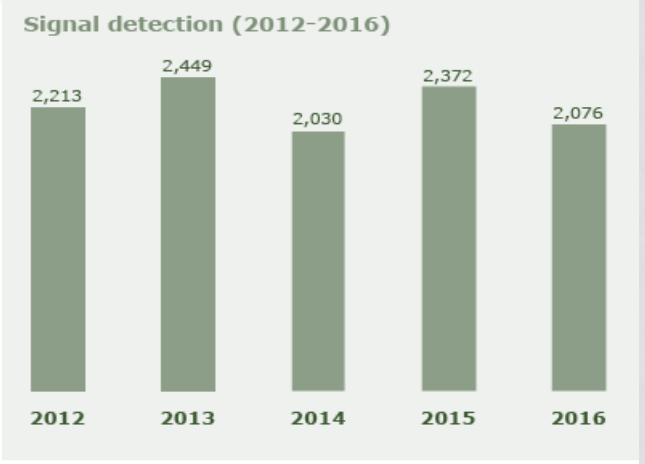
94 confirmed signals prioritised and assessed by the PRAC

48 signals detected and validated by EMA

46 signals detected and validated by EU Member States

- 4 signals led to a referral procedure to further investigate the issue
- 2 signals triggered another regulatory action such as a recommendation to update the risk management plan (RMP) or assessment through a study
- 28 signals led to an update to the product information

  3 of these also included a Direct Healthcare Professional Communication (DHPC) to highlight important new safety information to prescribers
- 30 signals were still under review by the PRAC at the end of 2016 as further data were required
- 30 signals led to recommendation for routine pharmacovigilance



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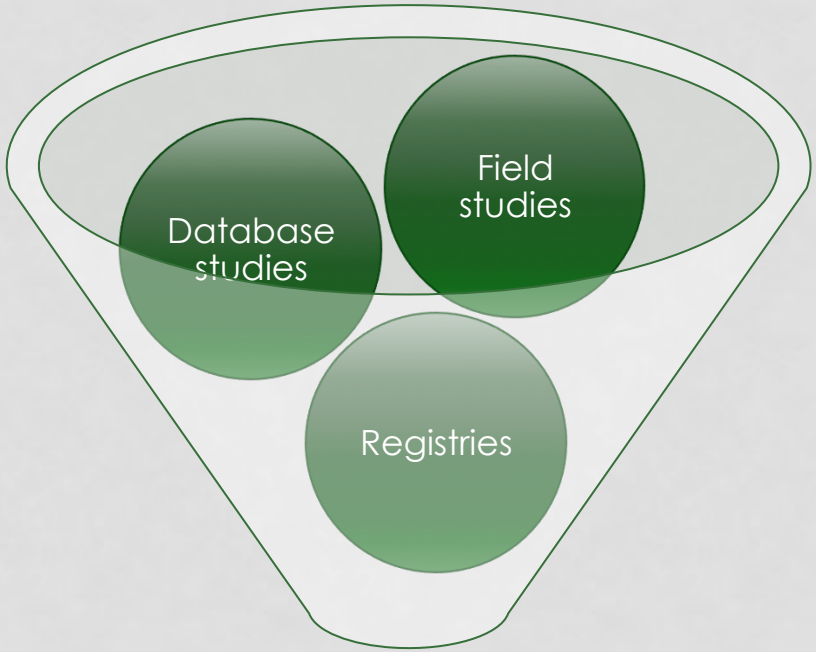
MORE REAL WORLD DATA IN PHARMACOVIGILANCE



Patient support programmes

More safety data under real conditions of use

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EU NETWORK PROJECTS ON PV

Since 2009

- **PROTECT :**
  - Objective :
    - Pharmacoepidemiological Research on Outcomes of Therapeutics by the IMI (Innovative Medicines initiatives) European Consortium: collaborative European project that comprises a programme to address limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance
      - New methods for data collection from consumers, Adverse Drug Reactions Reference Dataset, Drug Consumption Databases, Signal detection algorithm performance…
        > 74 articles

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EU NETWORK PROJECTS ON PV

- **SCOPE** « Strengthening Collaboration to Operate Pharmacovigilance in Europe » :
  - SCOPE gathered information and expertise on how regulators in Member States run their national PV systems. Using this information, a variety of tools were developed including guidance documents, PV training materials and other tools to support best practice.
    - 5 PV work packages
      - WP4 ADR collection
      - WP5 Signal management
      - WP6 Risk communication
      - WP7 Quality Management systems
      - WP8 Lifecycle PV

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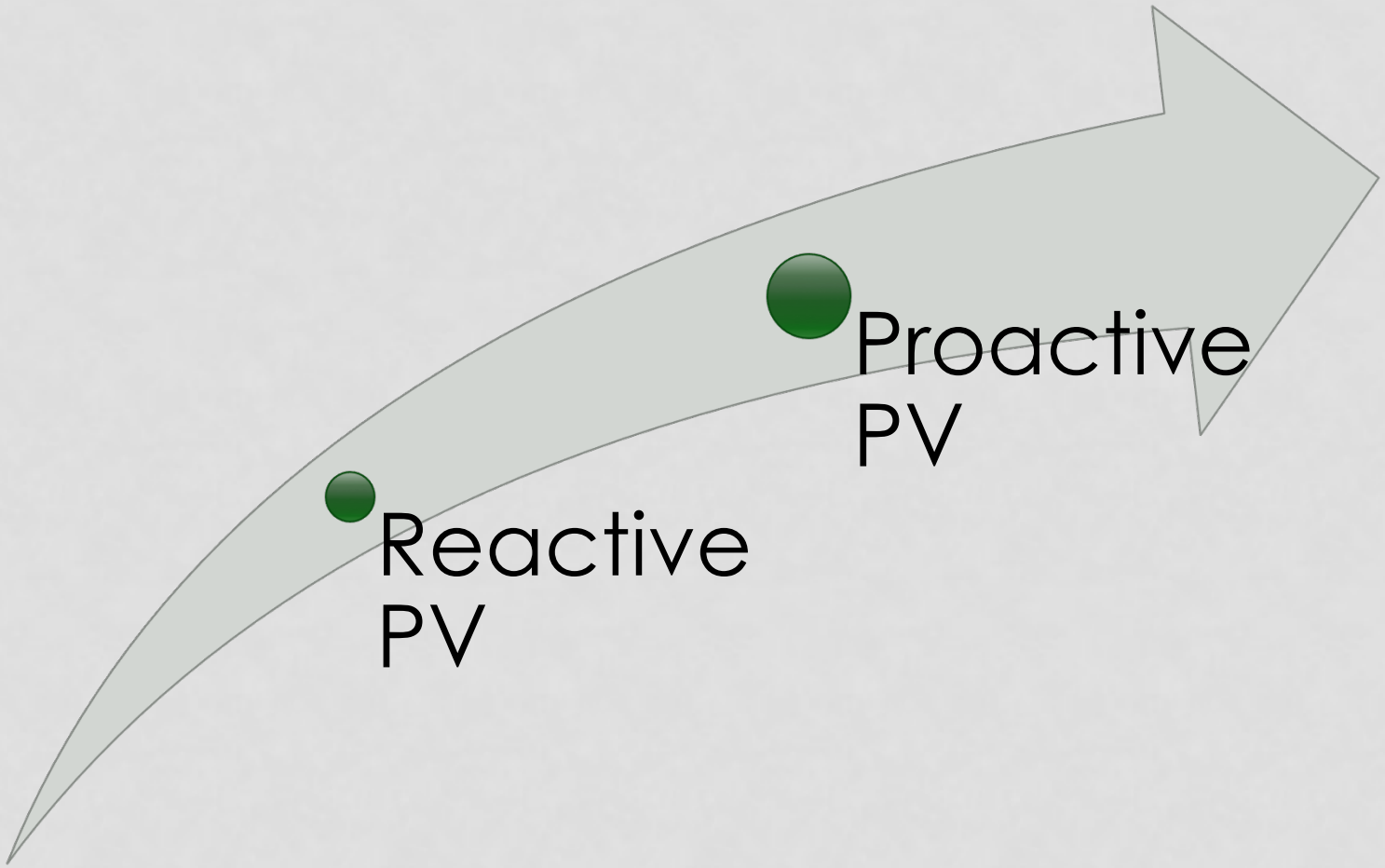
EVOLUTION OF THE PHARMACOVIGILANCE



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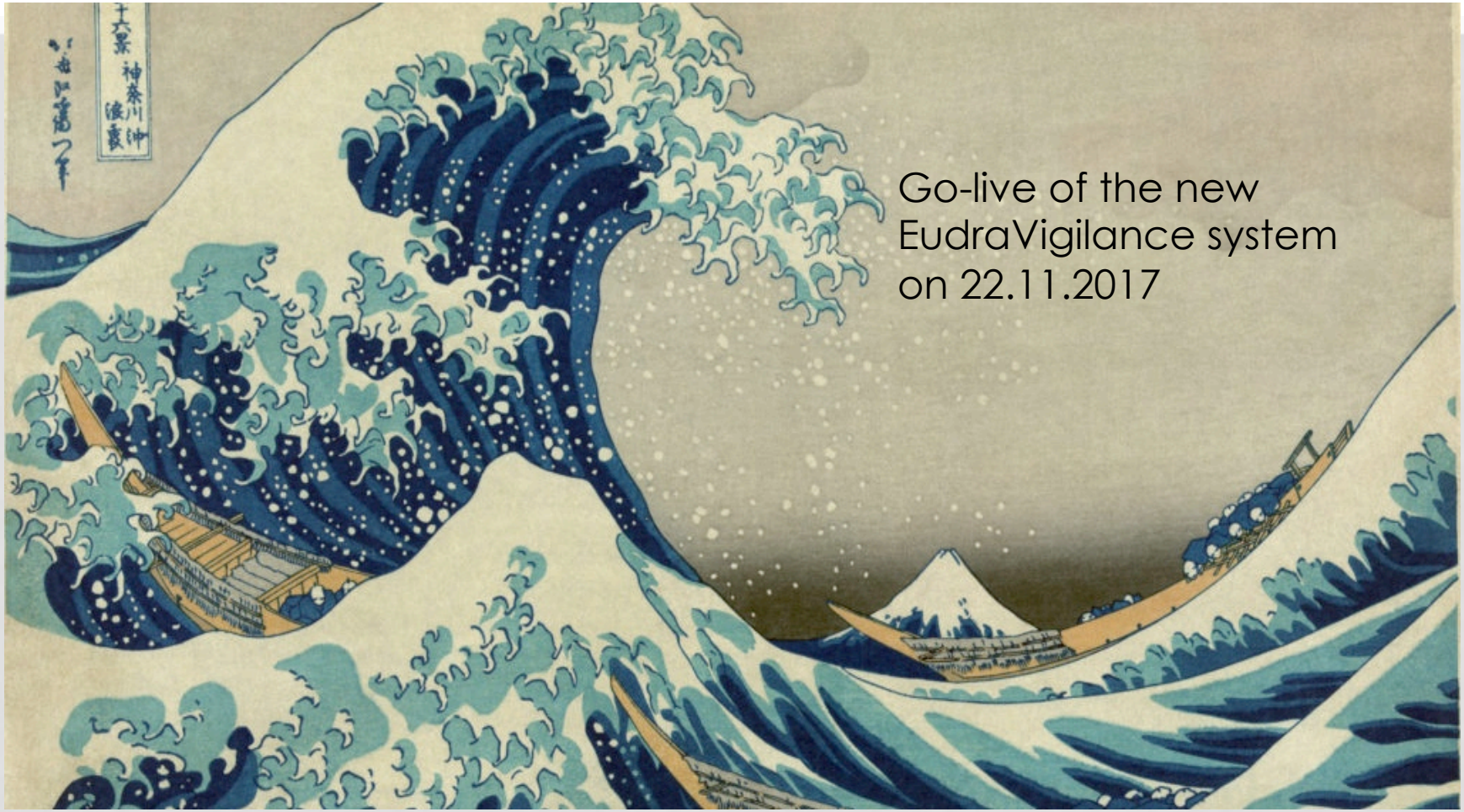
STENGTHENING AGAIN



La Grande Vague de Kanagawa-Hokusai

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WHY A NEW EUDRAVIGILANCE SYSTEM?

Benefits of the new EudraVigilance system

The new EudraVigilance system will have several significant benefits, including:

New feature	Benefit
Enhanced signal-detection and data-analysis tools to support safety monitoring directly by Member States and marketing authorisation holders	Better detection of new or changing safety issues, enabling rapid action to protect public health
Improved quality and completeness of ICSR data	Better searchability and more efficient data analysis
Enhanced scalability of the EudraVigilance system	Able to support an increased number of ICSRs due to the new requirement to report non-serious cases to EudraVigilance
Simplified reporting of ICSRs to EudraVigilance and the rerouting of ICSRs to Member States	Reduced duplication of efforts Marketing authorisation holders no longer have to provide ICSRs to national competent authorities, they have to submit these to EudraVigilance only
EMA will provide data to the World Health Organization (WHO) Uppsala Monitoring Centre directly from EudraVigilance	Enhanced collaboration between EMA and WHO Member States will no longer need to carry out this task

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HEALTH AUTHORITIES STAND POINT

- More proactive PV (impact of the risk management plans..)
- Strenghtening of signal detection
- Improvement of the benefit/risk ratio of medicines
- Greater patient involvement
- Greater transparency, more safety communication

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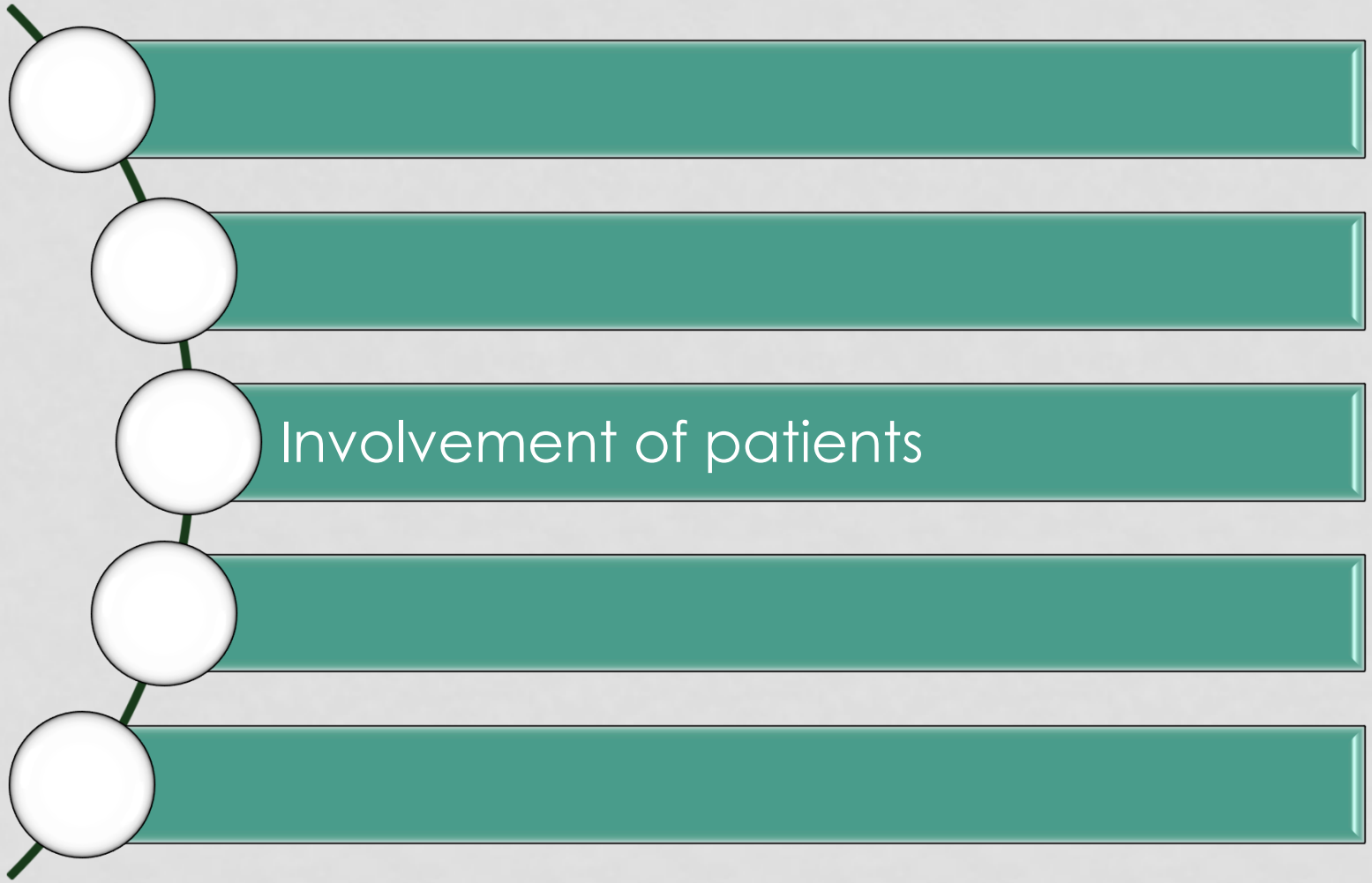

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INVOLVEMENT IN PV OF PATIENTS AND PATIENT ASSOCIATIONS

- At French level
  - Incentivise to report AEs to regional PV centres
  - Participation in advisory committees and board of directors of ANSM
  - Contribution to the review of risk minimization measures (RMPs) or the review of patient learning programs or the development of public information documents
  - Transmission to ANSM of any new information on the safety of medicines
  - Dissemination and relay to members of patient associations of safety information

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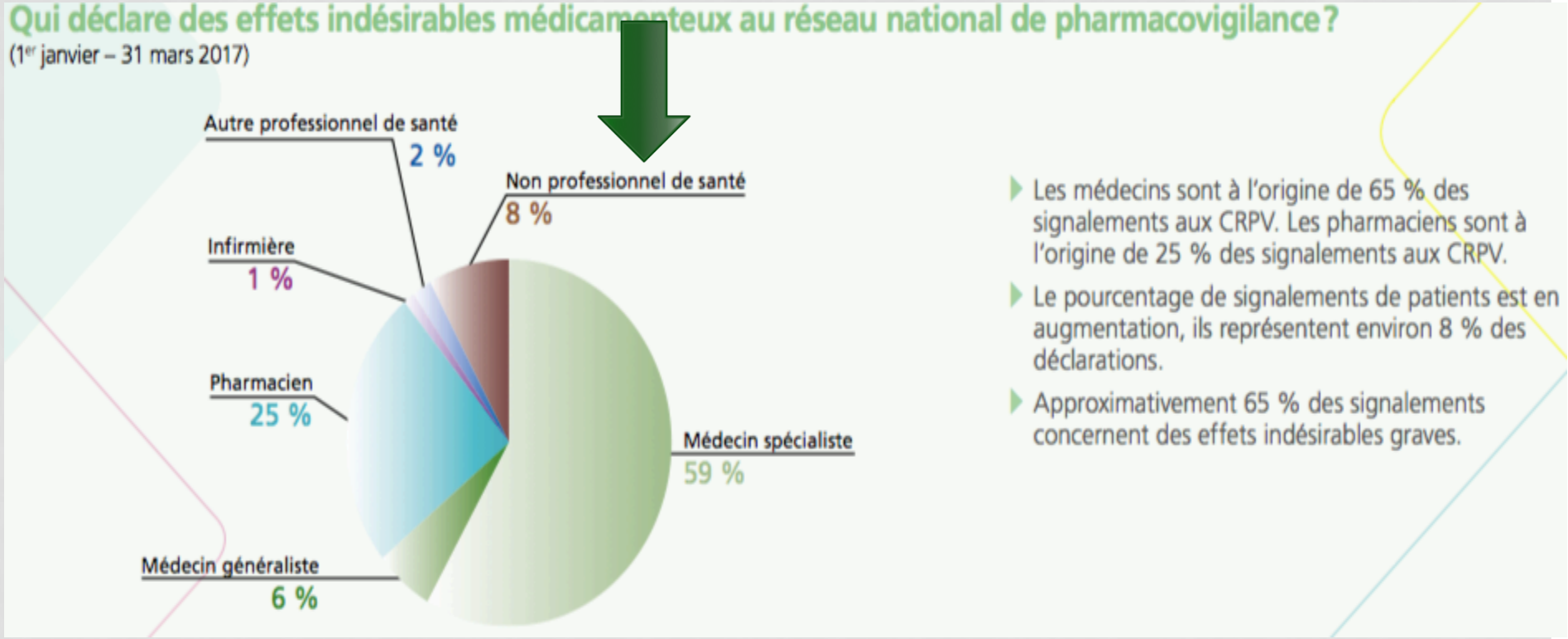
SPONTANEOUS CASES TO REGIONAL PV CENTRES (CRPV)



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INVOLVEMENT IN PV OF PATIENTS AND PATIENT ASSOCIATIONS

- At European level
  - Incentivise to report AEs
  - Participation in several committees including the Pharmacovigilance Risk Assessment Committee (PRAC)
  - Public hearing
  - Involvement in several IMI projects and European initiatives; POTECT, WEB-RADR, PREFER, SCOPE, graphic visualisation of risk, electronic package leaflet…
  - Thinking on having a PV contact in patient associations

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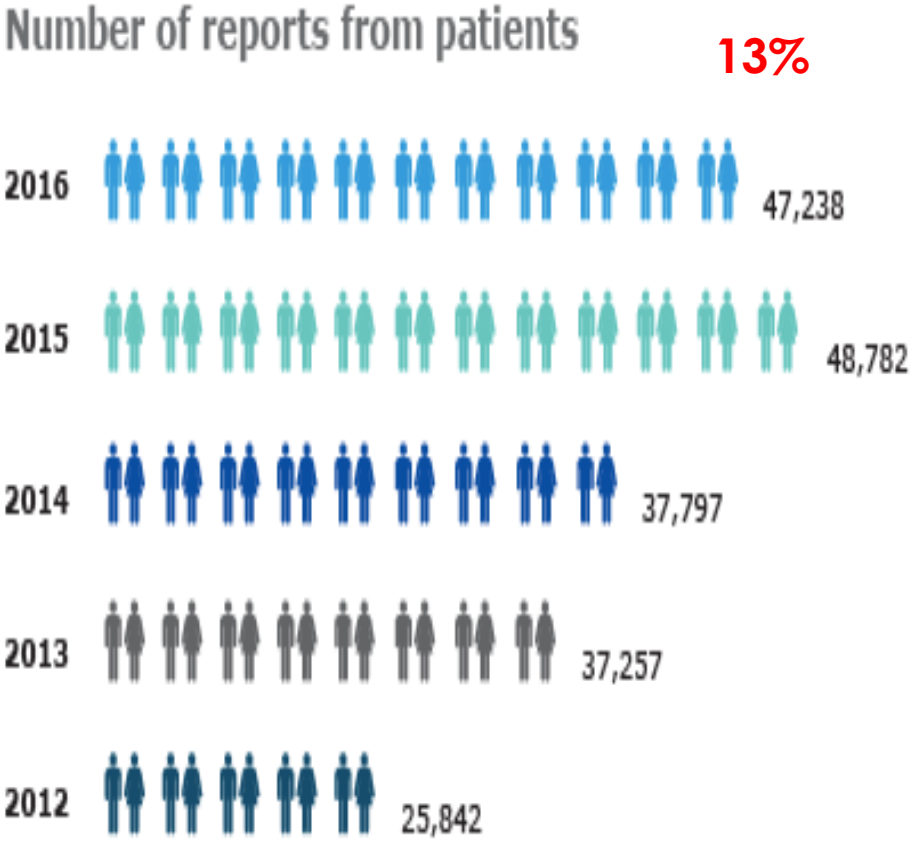
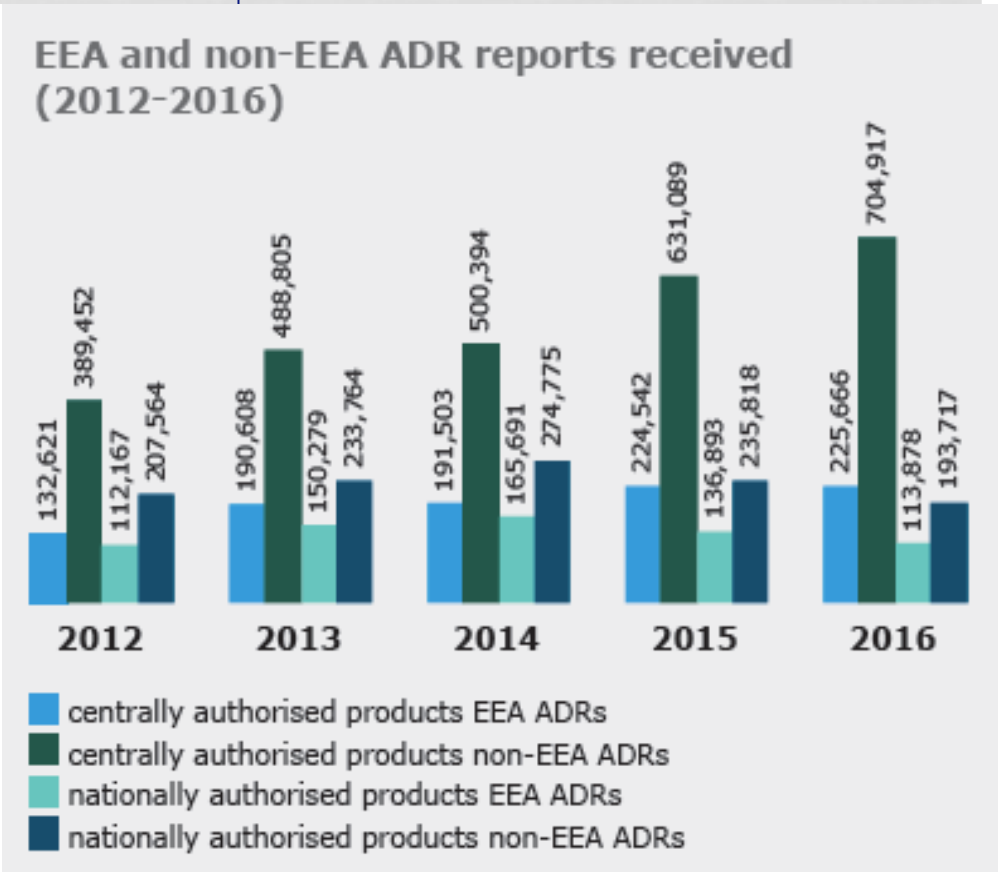
EMA-ANNUAL REPORT 2016

EudraVigilance

> 12 millions of Individual case safety reports





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INVOLVEMENT IN PV OF PATIENTS AND PATIENT ASSOCIATIONS

- **First public hearing** on valproate risk minimisation at EMA (26.09.17)
  - Objectives
    - Perception of risks by patients
    - Evaluation of risk minimization measures
  - Attendees:
    - during the public hearing, speakers from six EU Member States shared their experience directly with the members of the PRAC. A total of 25 speaker contributions, grouped into 16 speaker slots. An additional number of individuals attended the hearing as observers, making a total of 84 participants

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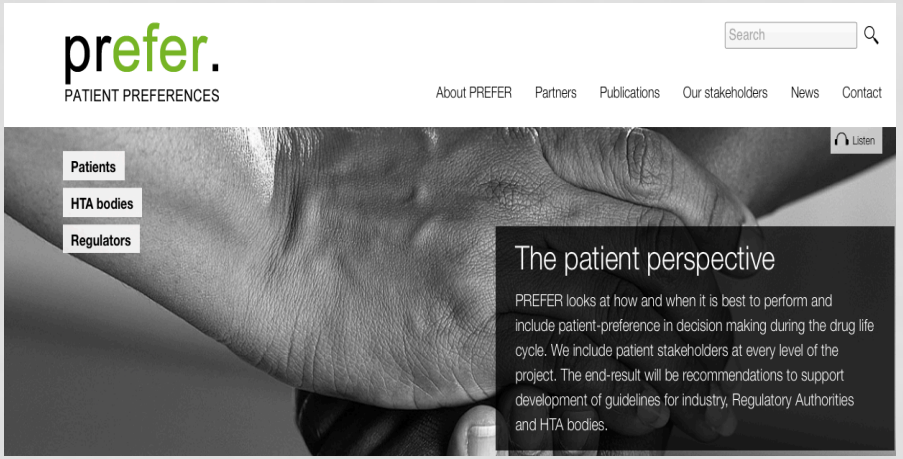
EU NETWORK PROJECTS

- **PREFER :** looks at how and when it is best to perform and include patient-preference in decision making during the drug life cycle. Inclusion of patient stakeholders at every level of the project. The end-result will be recommendations to support development of guidelines for industry, Regulatory Authorities and HTA bodies
  - Amongst several objectives : new approaches to benefit risk decision



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EU NETWORK PROJECTS ON PV

- **WEB-RADR : «** Recognising Adverse Drug Reactions »
  - Launched in September 2014
  - WEB-RADR is developing a mobile app for patients and healthcare professionals to report suspected adverse drug reactions to national EU regulators (UK, NL, Croatia...), and investigating the potential for publicly available social media data for identifying drug safety issues

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AGENDA

- Strengthening of the PV legal framework
- PV process improvements
- Engagement of patients
- Social media a new actor
- New challenges

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FRENCH EXAMPLE OF MIRENA®

- MIRENA 52 mg (20 microgrammes/24 heures), intra-uterine device– Levonorgestrel
  - Marketing authorisation date: 21.07.1995
- Spring 2017, creation of FaceBook groups "les victimes du stérilet" : reporting of many adverse events/ effects (AE): dizziness, anxiety disorders and arthritis…
- Dissemination to other social medias
- Reporting of many AE to the new official portal dedicated to health events reporting (launched in March 13th, 2017)
- Surprise and denial of the gynaecologists community

4 154:
4 503: subscribers

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FRENCH EXAMPLE OF MIRENA®

- Results of the ANSM survey: 99% of patient reports
  - 510 AE between1997 and 15.05.2017
  - 2714 AE between 16.05.2017 and 04.08.2017 (1789 reported as serious by patients)
- Patient initiatives in x countries, especially in Germany but highest peak of AE reporting in France in May 2017
- PRAC assessment: at this stage no association between MIRENA and "psychiatric disorders"

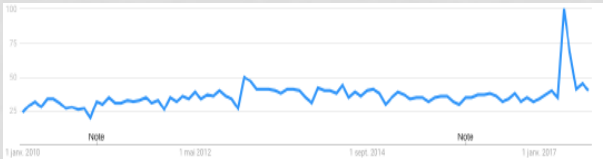

Figure 2. Tendance concernant le volume de requête mentionnant Mirena® en France depuis le 01/01/2010 – Données issues de Google Trends®

Figure 3. Tendance concernant le volume de requête mentionnant Mirena® dans le Monde depuis le 01/01/2010 – Données issues de Google Trends®

ANSM survey report 05.10.2017

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FRENCH EXAMPLE OF LEVOTHYROX® (LEVOTHYROXINE SODIQUE)

- 2 medicines on the French market to treat 2.6 million patients with hypothyroidism, including one formulation of drops reserved for children and people who can not swallow
- Medicine with a narrow therapeutic margin
- Unstable product within and between batches
- Decision of the ANSM in 2013 to ask the firm to modify the formulation of the product
  - Change only of the lactose excipient replaced by mannitol and citric acid
- As of March 2nd, 2017, >400,000 letters sent to health professionals / Q&A document…
- March 27th, 2017: release of the new formulation and start of the official PV survey

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FRENCH EXAMPLE OF LEVOTHYROX® (LEVOTHYROXINE SODIQUE)

- From May 2017 but especially in August, large media coverage, patient testimonials on social medias and media communication of a famous actress
- Between March 27th and September 10th: 8952 cases of PV were recorded including 1150 cases suggestive of a dysthyroidism with probable amplifying effect of the reporting portal of the AEs : "signalement-sante.gouv.fr"
- 0.59% of patients reporting an AE
  - 1200 reports on one day 16.08.17
  - As of 15.09.17 number of reports was 14633 of which 5062 were registered in the National PV database
- Comparable safety profile between old and new formulation but much higher frequency of adverse events reporting with the new formulation

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FRENCH EXAMPLE OF LEVOTHYROX® (LEVTHYROXINE SODIQUE)

- October 2nd, 2017, temporary marketing of limited quantities of the old Levothyrox, gradual marketing of new generics
- Numerous reactions of pharmacists, creation of FB group, open letters to the Health minister
- Update of the PV survey from 15.09.17 to 30.11.17
  - 12 248 new cases (90% of patient reports), 0,75% of treated patients
  - Same conclusion to the first part of the PV survey
  - Pharmacoepidemiology study expected in the first quarter of 2018

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FRENCH EXAMPLE OF LEVOTHYROX® (LEVTHYROXINE SODIQUE)

- Amongst many ANSM and Ministry of Health reactions/decisions
  - Several press releases
  - Setting-up of **an information mission** to improve information on the medicies, co-chaired by a physician together health columnist for the media and a president of a patient association + 4 other members
    - A pharmacist
    - A general practitioner
    - A representative of a patient association
    - A sociologist

  Report expected for May 31st, 2018

Health crisis, media crisis or communication crisis?

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SOCIAL MEDIA AS FACILITATOR

- Tool to
  - motivate communities in patient support programmes…
  - facilitate recruitment of patients, healthcare professionnals in non-interventional studies
  - Support questionnaires in surveys…
  - Disseminate educational information, safety messages…

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EVALUATION OF THE IMPACT OF SOCIAL MEDIA IN DISSEMINATING SAFETY MESSAGE

JMIR PUBLIC HEALTH AND SURVEILLANCE Sinha et al

Original Paper

Social Media Impact of the Food and Drug Administration's Drug Safety Communication Messaging About Zolpidem: Mixed-Methods Analysis

Michael S Sinha[1], MD, JD, MPH; Clark C Freifeld[2], PhD; John S Brownstein[3], PhD; Macarius M Donneyong[4], MPH, PhD; Paula Rausch[5], PhD, RN; Brian M Lappin[5], MA; Esther H Zhou[5], MD, PhD; Gerald J Dal Pan[5], MD, MHS; Ajinkya M Pawar[1], PhD; Thomas J Hwang[1]; Jerry Avorn[1], MD; Aaron S Kesselheim[1], MD, JD, MPH

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EVALUATION OF THE IMPACT OF SOCIAL MEDIA IN DISSEMINATING SAFETY MESSAGE

- FB and Twitter posts, google trends analysis following safety communication by FDA on zolpidem risks using social media dissemination

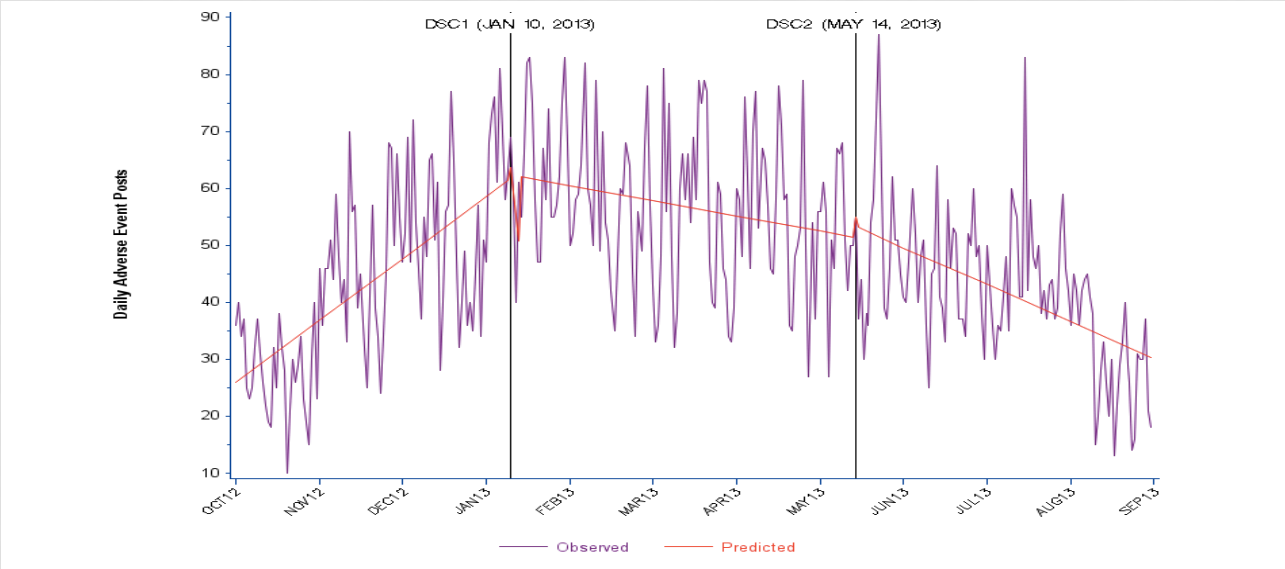

Figure 1: Daily Twitter adverse event posts about zolpidem from october 2012 to August 2013

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MAJOR QUESTION

- **Safety information / safety communication**

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ADEQUATE, TIMELY, FAIR, RELEVANT, OBJECTIVE AND QUALITY INFORMATION

Information

- When?
- Who?
- How?

Communication

- Communication of health authorities with health professionals
- Communication from health authorities with patients and the general public
- Communication of health professionals with patients and the general public
- Communication of health professionals among themselves
- Patient communication with each other

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MAIN PRINCIPLES OF THE SAFETY COMMUNICATION[1]

- Clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action
- Information on risks should be presented in the context of the benefits of the medicine
- Should address the uncertainties related to a safety concern
- Patients and healthcare professionals should, where possible, be consulted and messages pre- tested early in the preparation
- Should comply with relevant requirements relating to individual data protection and confidentiality
- The effectiveness of safety communication should be evaluated where appropriate and possible …

[1] **GVP Module XV Safety Communication**

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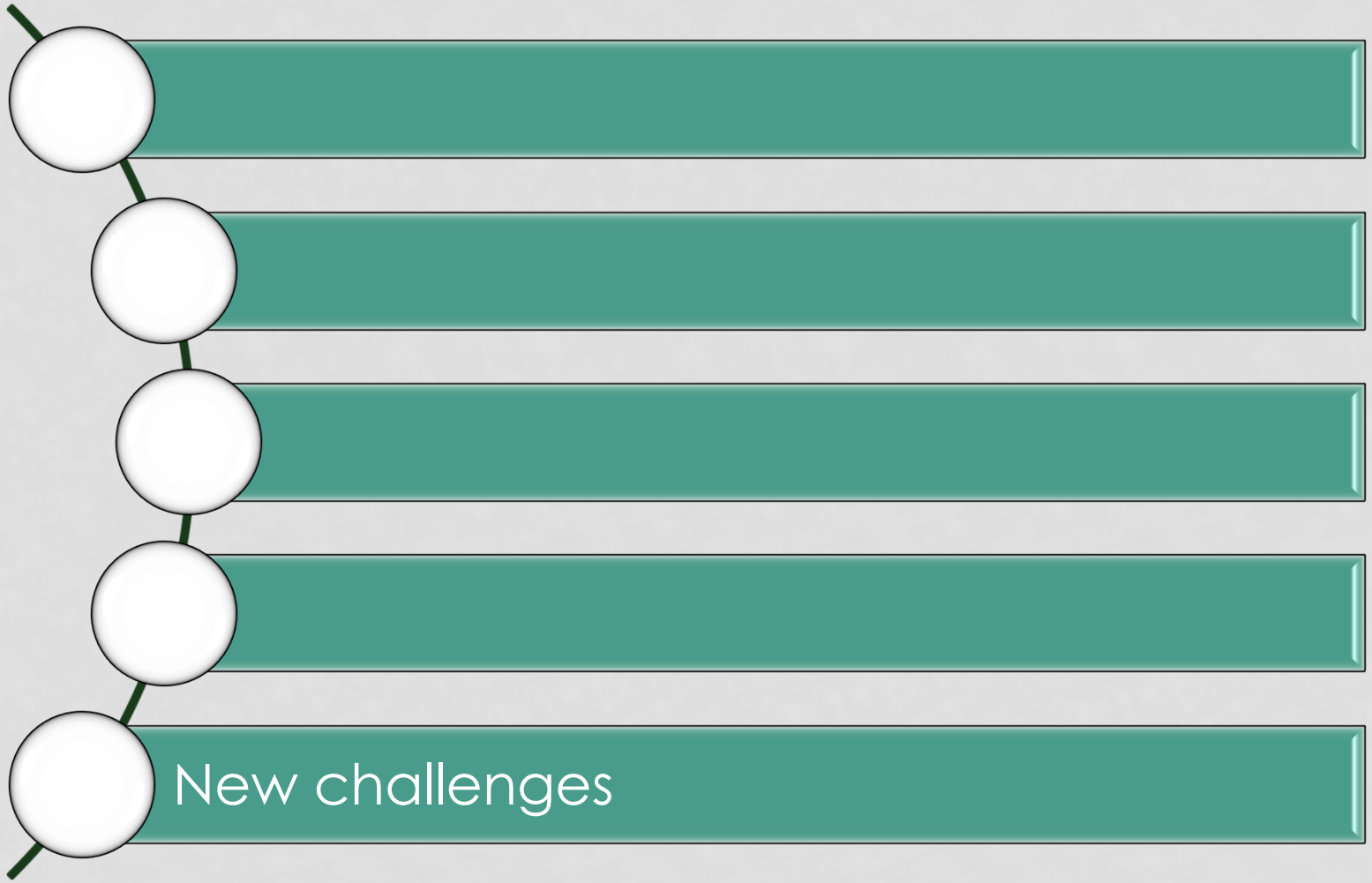
AGENDA



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NEW CHALLENGES

- At public and patient level
  - New medical encyclopaedia is Internet and social media
  - Lack of knowledge/understanding of national and European medicine agencies responsibilities
  - Lack of trust in industry based information
- At media level
  - Everything related to drugs is a potential scandal for media
  - Lack of knowledge/understanding of national and European medicine agencies responsibilities
  - Amplification and biased information in social media. Medias pushed to take quick positions without control

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NEW CHALLENGES

- At healthcare professionals level
  - Medical knowledge regularly questioned, but the information by the pharmacist is always sought by patients
  - Loss of trust in experts with suspicion of permanent conflicts of interest
  - Lack of knowledge/understanding of national and European medicine agencies responsibilities
  - Learn about the use of new applications and / or connected tools in safety area
  - Need to have time to understand and integrate new safety message into professional practice

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NEW CHALLENGES

- At health authorities level
  - Classical methods of PV are not always adapted to certain situations (look at social media analysis, google trends ...). Need to train safety professionals on new methods
  - Speed and amplification of non scientifically rigorous information in social media
  - Weight of poorly documented AE patient reports
  - The usual means of communication (letters, emails to health professionals ...) on the safety of medicines are necessary but not sufficient

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DIFFICULTIES AND OPPORTUNITIES

Social media as new source of data?

Big data analysis with sophisticated algorithms / connected devices

Engagement of patients and new behaviours of HCP

New data / innovative tools

Impact and results

New safety communication


OBRIGADO
PELA SUA
ATENÇÃO