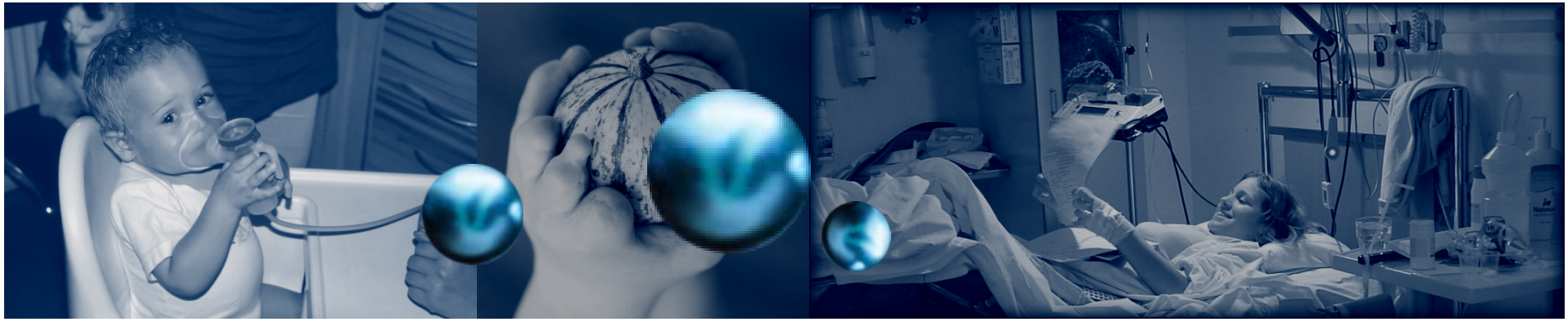
Patients and pharmacovigilant!



François Houÿez

Director of Treatment Information & Access

ENRDHL, Paris, 24 May 2013

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Rare Diseases Europe

EURORDIS Drug Information Transparency and Access 'DITA' task force members

- Claudie Baleydier, Friedreich Ataxia, FRA
- Greetje Goossens, European Myeloma Patients, BEL
- Juan Fuertes, Primary Pulmonary Hypertension, SPA
- Ellen van Veldhuizen, Addison Disease Org., NLD
- Rainald von Gizycki, Pro Retina, GER
- Danijela Szili, Rett synd., HUN
- François Houÿez, Anne-Mary Bodin, EURORDIS, Paris
- Rob Camp, EURORDIS, SPA
- Lise Murphy, Marfan syndrome, SWE
- Oliver Timmis, Alkaptonuria Society, GBR
- Christine Lavery, Muco-polysaccharidosis Society, GBR
- Philip Bloom, European Myeloma Patients, FRA
- Dragomir Slavev, Thalassemia org., BLG
- Richard West, Behcet Society, GBR

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For your organisation, you will learn:

- To access regulatory data, agendas, minutes
- To make your own research on drug safety
- To participate in the decision making
- How safety information is generated
- Where to find more facts on benefit/risk
- How to be involved in risk communication

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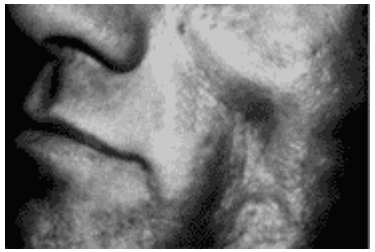
A patient reported

- 24 July 1997, weird side effects
  - I've made reference here to my "Crix Belly." My belly is slightly enlarged, but it's solid. In fact, you can see the muscle lines across my stomach (if I stand in a really good light), so it doesn't feel like fat. It's hard. The other strange thing is that my belly button went from an "inny" to an "outy." We have been assuming a hernia.
  - Well, yesterday someone from my online Crix group said something about their belly button doing the exact same thing. Could be a coincidence, but if anyone reading this has had a similar reaction, I'd like to hear about it. The other side effect I'm having is sore muscles, leg cramps, etc.

What 20 to 40% patients were experiencing

Fat loss



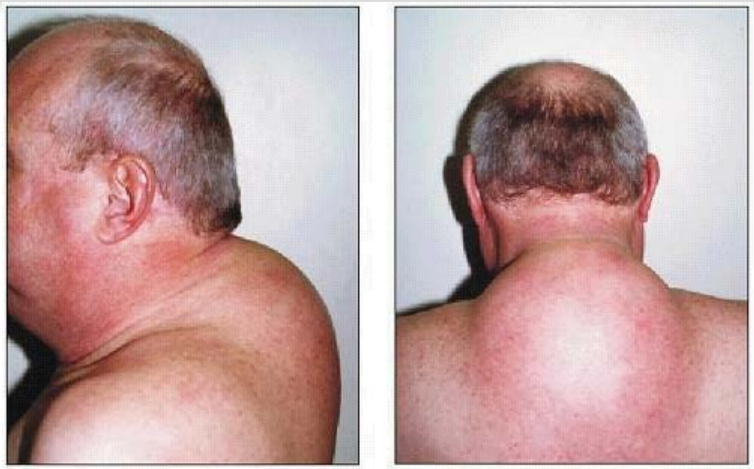
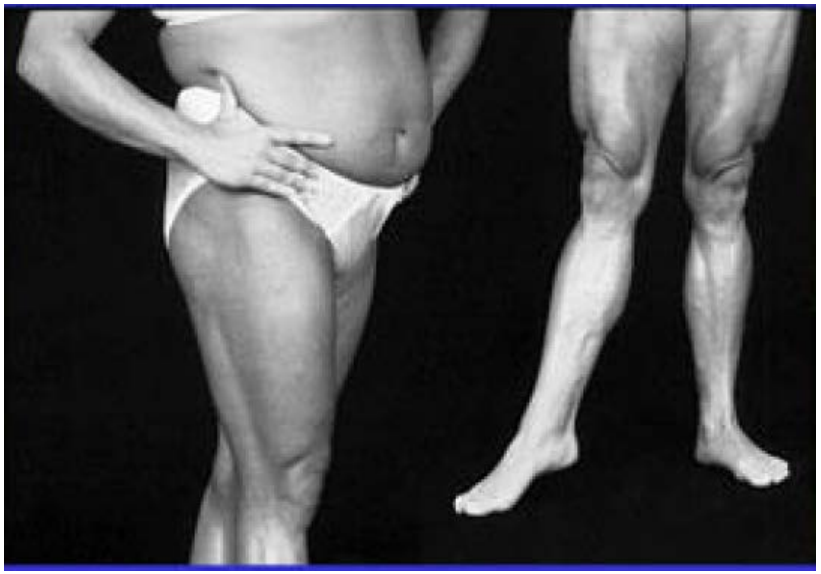
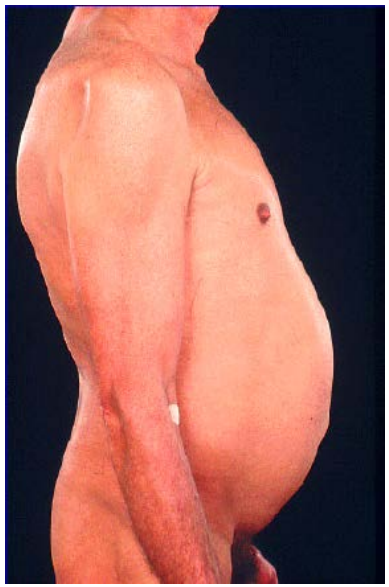


Figure 1) Left and right *A 52-year-old human immunodeficiency virus (HIV)-1-infected man presented with a football-sized mass in the dorsal cervical area ('buffalo hump'). It had existed as a minor area of fullness for several years, but had dramatically increased in size over the preceding year, after the protease inhibitor indinavir was added to his antiviral regimen*

Buffalo neck

Fat loss, prominent veins





Belly

Not in clinical trials, but during treatment with authorised combination therapies, and never seen before

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From the Eurordis survey on off-label use 2012

"My father had an injection of Avastin® for macular degeneration on 20 Feb 2012 and the drug was contaminated.

He went blind within two hours.

I now know 14 patients who were affected by this batch".

Question to you: how many cases are needed to ring the alarm?

NB: Avastin is indicated for Renal Cell Carcinoma, Non-Small-Cell Lung Carcinoma, Breast Neoplasms, Colorectal Neoplasms, Ovarian Neoplasms

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Setting the scene: new European Union Pharmacovigilance legislation

November 2012

Presented by: Dr Peter Arlett
Head, Pharmacovigilance and Risk Management
European Medicines Agency

What is pharmacovigilance?

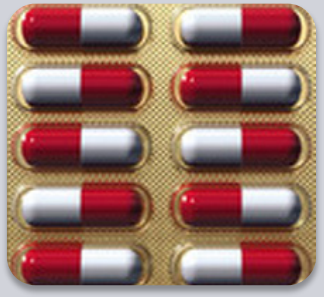
Pharmacovigilance is the science and processes of monitoring the benefits and risks of medicines on the market and taking action to maximise benefit and minimise risk

Dr Peter Arlett, Head, Pharmacovigilance and Risk Management,
European Medicines Agency

New legislation impact:

- For patients / consumers:
  - Patient reporting of suspected adverse reactions
  - More studies of safety + benefit risk balance of medicines
  - Patient access to data and better information
  - Participation in the assessment and decision-making:
    - Members of the committee (PRAC)
    - Public hearings for major safety issues
  - Major increase in transparency
  - Faster warnings, restrictions, improvements to product information
  - Optimised safe and effective use

The benefit-risk is a matter of



Constrains and ease of use

Frequency of side effects

Efficacy including quality of life

Severity of side effects

Uncertainty what is unknown as of today?

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Highlights on

PATIENTS' REPORTING OF SUSPECTED ADRs

Web-forms and ADR reporting by Patients/Consumers

- Administrative and patient details (contact details, age/age group, sex, weight, height)- Can report for oneself or on behalf of someone else e.g. your child.

- Side effect and medical info :
  - Side effect description
  - Outcome (e.g. side effect improved) and any action taken (e.g. side effect was treated by doctor)
  - Dates side effect occurred
  - Medical history free text

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A large experience already

1978	Kilen (S)	www.kilen.org	Consumer group
1993	FDA (USA)	www.fda.gov/medwatch	Goverment
2003	Medicines Agency (DK)	www.dkma.dk	Goverment
2003	Lareb (NL)	www.lareb.nl	Goverment
2003	Therapeutic good administration (AU)	www.tga.gov.au	Goverment
2003	Health Canada		Goverment
2004	Meldpunt Medicijnen (NL)	www.meldpuntmedicijnen.nl	Consumer group
2005	MHRA (UK)	www.mhra.gov.uk	Goverment
2006	Test Aankoop (BE) Test Achat	www.contactmedicaments.be www.meldpuntgeneesmiddelen.be	Consumer group
2008	Afssaps	www.afssaps.fr	Regulatory agency and patients' groups

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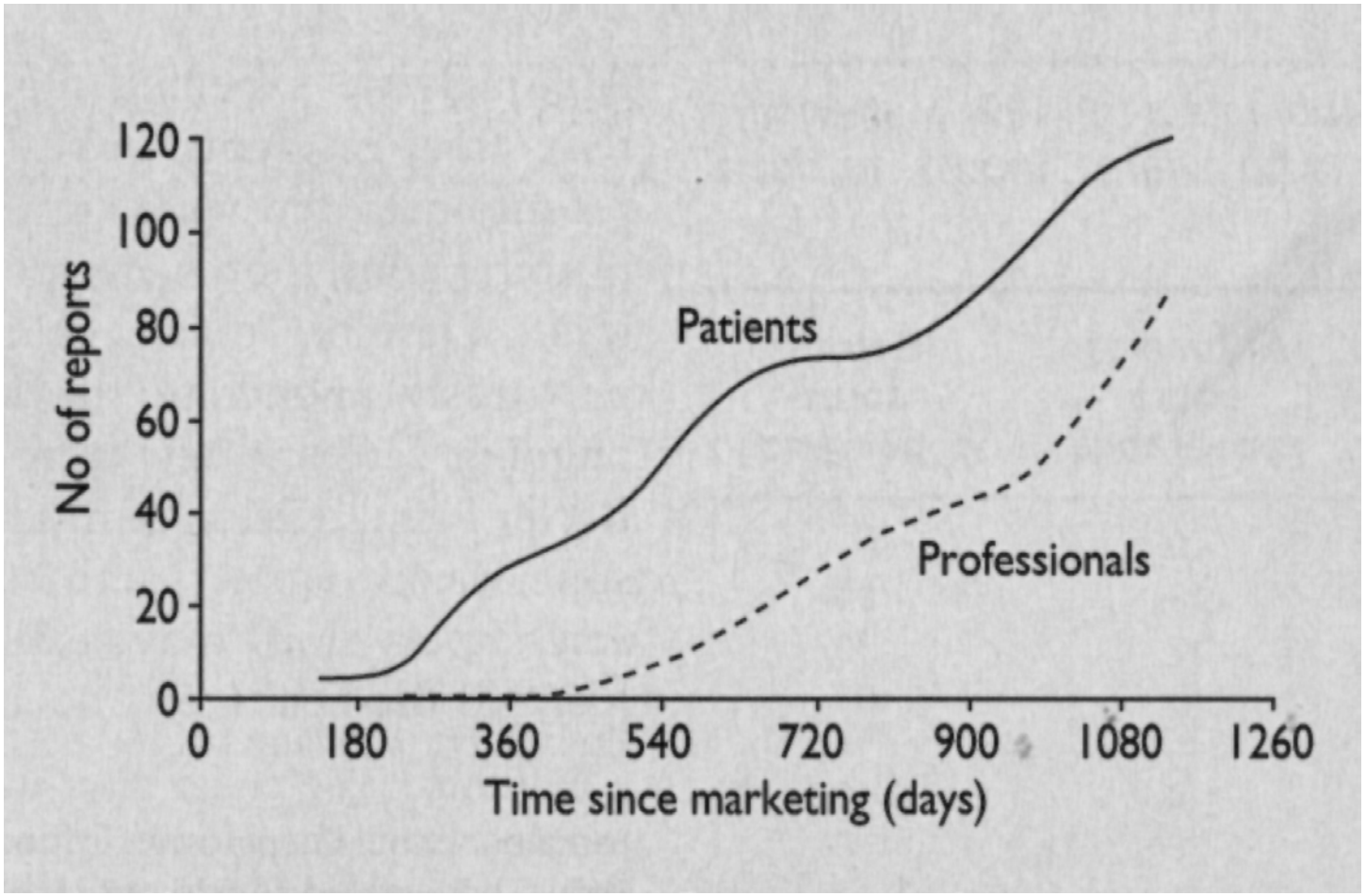
Paroxetine (antidepressant)
Time to first report of an unexpected AE

AE / ADR	Patients (days)	Physicians (days)	Difference
Rigours	390	578	188 days earlier
Bleeding	396	1025	629
Hypertension	432	1192	760
Mydriasis	597	660	63
Taste disturbance	635	827	192
Apathy	943	1124	181
Flushing	967	1100	133
Menstrual disorders	971	1162	191
Rash	1002	1125	123

Egberts TCG et al. BMJ 1996;313:530

Self reporting by patients



BMJ 1996;313:530-531

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Also for herbals, OTC

- Interviews with users of herbal remedies have indicated 69% of users would not consult their GP in the event of a serious suspected ADR to a herbal product
- 44% would not consult their GP with a serious reaction to an OTC medicine either.

- *The Pharmaceutical Journal* 2009; **282:** 16–17.

Feedback from Netherlands

- Patients' reports contain **sufficient medical information** for pharmacovigilance purposes
- **Failure of HCPs to listen to complaints** about possible ADRs, or a lack of confidence that a report would be submitted were cited as key motivations for patients
- Outcomes of the ADR, such as **non-recovery**, were more likely to be reported by patients.
- Patients also focused on reactions that impacted on their **quality of life**, such as weight gain, decreased libido and fatigue, more than HCPs

- de Langen J, van Hunsel F, Passier A, *et al.* Adverse drug reaction reporting by patients in the Netherlands: three years of experience. *Drug Safety* 2008; **31**(6): 515–24.
- Layton D, Sinclair HK, Bond CM, *et al.* Pharmacovigilance of over-the-counter products based in community pharmacy: methodological issues from pilot work conducted in Hampshire and Grampian, UK. *Pharmacoepidemiol Dr S* 2002; **11**(6): 503–13.

United Kingdom, Yellow Card

Content analysis findings

- Patients more likely than HCPs to report:
  - Symptoms (93% vs 78%)
  - Impact of the ADR (47% vs 12%)
  - Temporal relationship between drug and suspected ADR
  - Extreme nature of the suspected ADR (47% vs 17%)
- Patient reports tended to be more elaborate in description of suspected ADRs

Professor Tony Avery, University of Nottingham, to PCWP Sept 2011
Evaluation of patient reporting to the Yellow Card System. 5180 patient reports and 20,949 from HCPs

Art. 102 of Directive 2010/84

- The Member States shall:
  - (a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected ADRs to the NCA; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate;
  - (b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

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Reporting tools as of 04/2013

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Where can we obtain information on

SPONTANEOUS REPORTS OF ADRs? www.adrreports.eu

Risk Management

Presented by: Dr Stella Blackburn
EMA Risk Management Development and Scientific Lead

An agency of the European Union

Highlights on

RISK MANAGEMENT PLANS

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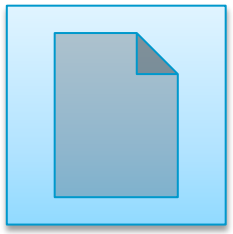

Highlights on

POST-AUTHORISATION SAFETY STUDIES

(E.G. BIPHOSPHONATES)

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How are drugs monitored throughout their life-cycle?

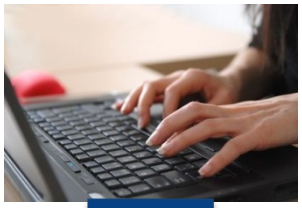
Periodic Safety Update Reports (PSURs)

Periodic Safety Update Reports (PSURs)

- To enhance patient safety and protect public health:
  - ➢ This new information should be assessed promptly (e.g. signal detection).
  - ➢ Periodic re-examination of the benefit-risk balance is needed to ensure that the balance remains positive.
  - This periodic re-examination is performed in a document called Periodic Safety Update Report (PSUR).
  - PSURs: *"Pharmacovigilance documents intended to provide an evaluation of the benefit-risk balance of a medicinal product for submission by pharmaceutical companies to the regulators at define time points during the post-authorisation phase".*

Benefit-Risk balance reassessment - PSURs

HCP



Patients

Studies

Literature

Pre-marketing → Initial Marketing Authorisation → e.g. 6 months → PSUR 1 → e.g. 6 months → PSUR 2

All available cumulative information

Rodrigo Postigo, Pharmacovigilance and Risk Management Sector EMA

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PSURs and the new Pharmacovigilance legislation

- PSURs content, scope and outcome have changed:
  - New format should include information about Benefits and not only Risks.
  - Should incorporate a critical analysis of the benefit-risk balance.
  - The outcome of the PSUR assessment is legally binding

Main content of the PSUR

Actions taken for safety reasons

- e.g. clinical trial suspension, communications to healthcare professionals

Significant findings

- Clinical trials, spontaneous adverse reactions reports, patient support programs, literature…

Risks

- New risks identified and new information about already known risks

Benefit- Risk analysis

- Reassessment of the benefit-risk balance

Patient exposure

- Volume of prescriptions
- Actual use including use outside the authorised conditions

Signals

- New signals analysed

Benefits

- New benefits identified and new information about already known benefits

Conclusions and actions

- e.g. update of the product information with the new identified risk and risk communication as appropriate

The chef d’orchestre

THE PHARMACOVIGILANCE AND RISK ASSESSMENT COMMITTEE (PRAC)

Main characteristics (1)

- Composed of:
  - a chair and a vice chair, elected by serving PRAC members;
  - one member and an alternate nominated by each of the 27 Member States;
  - one member and an alternate nominated by Iceland and by Norway;
  - six independent scientific experts nominated by the European Commission;
  - one member and an alternate nominated by the EC after consultation of the EP to represent healthcare professionals;
  - one member and one alternate nominated by the EC after consultation of the EP to represent patients organisations.

Involving patients in the PRAC

- The work represents 70 to 80 days of volunteer work per year
- Support by EMA secretariat
- Training on pharmacovigilance highly recommended
- Should work in coordination with other patients' representatives (to be organised)
- And respect confidentiality

Main characteristics (2)

- Coordinates the monitoring of safety of medicines approved at the European or national level
- All agendas and minutes are public
  - See here
- Urgent referrals
  - Tetrazepam here
- Can organise public hearings

Profound increase in transparency

- Public:
  - Names and qualifications and declared interests of the committee members
  - All agendas and minutes of the committees
  - Summaries of all risk management plans
  - List of medicinal products
  - Locations of the company Pharmacovigilance systems and contacts points
  - Reporting information
  - PSUR submission dates
  - Protocols and results of post-authorisation studies
  - Announcement of referrals and public hearings
  - All conclusions of assessments, recommendations, opinions, approvals and decisions

Working with

YOUR NATIONAL COMPETENT AUTHORITIES

The ANSM and POs

- Working relations with POs
  - Already in 1992 (Agence du Médicament)
- Working group with patients' organisations since 2004
- Accredited POs can report suspected ADRs since 2010
- Patients to be members of the Management Board and scientific committees
- POs can request an opinion for a R.T.U (off-label use)
- 2012: call for projects to POs

ANSM Call for projects 2012

- Information for patients and / or carers: 5 projects, 145 000 €
- Practical difficulties with treatments: 2 projects, 40 000 €
- Support reporting of ADRs by patients: 2 projects, 75 000 €

Of 38 proposals submitted

- Information for patients and / or carers
  - "Explain to me ... Biotherapies", François Aupetit Association (AFA)
  - "Kit for Workshops on medicines", French Antirheumatic Association (AFLAR)
  - "Promoting the proper use of opioid substitution", Self-Support Group of Drug Users (ASUD)
  - "BLOOD Digital Help Service" for anticoagulant control AVK
  - "Addressing treatment interruptions and dose reductions by patients using corticosteroids," Pemphigus Pemphigus France

Of 38 proposals submitted

- Practical difficulties associated with a drug or other health product
  - Identification and evaluation of practical difficulties related to the treatment of patients with Dravet syndrome
  - Survey of behavioral disorders in Parkinson's disease
- Self-reporting of adverse reactions by patients (drugs & medical devices)
  - Self-reported adverse events related to Gylénia (fingolimod)
  - Self-reported adverse effects linked to the exposure to diethylstilbestrol (DES) to assess the risk of breast cancer in women exposed to DES in utero in France (2nd generation) and to point out other risks over 3 generations: cancer, malformations, effects on reproduction

http://ansm.sante.fr/S-informer/Presse-Communiques-Points-presse/Resultats-du-premier-appel-a-projets-associations-de-l-ANSM-Communique

Also of interest

- Medicines under evaluation
  - CHMP activity here