EUROPEAN SURVEILLANCE NETWORK TO MONITOR THE LONG TERM EFFECTIVENESS AND SAFETY OF SYSTEMIC AGENTS IN THE TREATMENT OF PSORIASIS

Bergamo, April 19-20, 2007

PSONET

To establish a network of independent European population registries, in order to perform coordinated post-marketing surveillance studies aimed at monitoring the effectiveness and safety of systemic agents, including biologicals (i.e. Tumor Necrosis Factor *alpha*, TNF-*alpha,* and T cell targeted molecules), in the treatment of psoriasis.

Aims

- Investigation of the ***clinical effectiveness*** of systemic treatments for psoriasis, in a ***population context***;
- Identification of ***prognostic factors*** that can help in predicting the response to systemic treatments;
- ***Monitoring of adverse effects*** of systemic treatments, with particular attention to ***long-term and rare adverse events***, including infections, lymphomas and other cancers.

Phase 4 post-marketing programmes for biological agents

(examples from Stern, 2005)

- **Efalizumab** - due 3/31/2014

  Multicenter (500 sites) prospective

  5–year surveillance study of patients who have received at least one dose of the drug
- **Alefacept** - due 7/31/2010

  5000-person study

  After 2 years (March 2005), 657 enrolled
- **Etanercept** – due 9/30/2013

  2500 patients, not previously treated with etanercept

  All malignancies and infection

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

APRIL 19, 2007

The FDA and the Case of Ketek

David B. Ross, M.D., Ph.D.

Three years ago, the Food and Drug Administration (FDA) approved the drug Ketek (telithromycin), lauding it as the first of a new class of antimicrobial agents that circumvent antibiotic

study. Known as study 3014, it was an unblinded, randomized, controlled trial comparing the incidence rates of hepatic, cardiac, and visual adverse events in patients receiving Ketek and those

Drug Safety Reform at the FDA — Pendulum Swing or Systematic Improvement?

Mark McClellan, M.D., Ph.D.

Every 5 or 10 years, Congress enacts major legislation addressing pressing issues at the Food and Drug Administration (FDA). This year, the biggest reforms since at least 1997 are expected. A decade ago, reform was motivated by the perception that the agency wasn't getting new medicines to patients as efficiently as possible. Today, a leading concern is that it isn't protecting the public from drugs' risks as effectively as it might.

A key incident in raising such concern was the 2004 withdrawal by Merck of rofecoxib (Vioxx) because of an apparent increased risk of serious cardiovascular events. The withdrawal came amid questions about the FDA's handling of a possible association between selective serotonin-reuptake inhibitors and suicidal ideation in adolescents. Further concerns were raised about the agency's handling of staff disagreements about these and other drugs. In this context, the FDA sought a review from the Institute of Medicine (IOM).

The IOM's September 2006 report included a broad range of recommendations.[1] Legislators have introduced various proposals reflecting these and other ideas, and the FDA has issued an action plan.[2] Major legislation on drug safety is almost certain to be enacted before fall, as Congress reauthorizes the Prescription Drug User Fee Act (PDUFA), which provides fees from drug manufacturers to cover part of the cost of regulation. This legislation will influence the way safety issues are evaluated and addressed, with important implications for the available information about drugs' risks and benefits and for physician prescribing.

It represents an opportunity to implement a more systematic approach to improving drug safety and effective use, if some challenges can be overcome. Steps intended to enhance safety could also increase costs and reduce access. Agency critics believe such steps would strengthen the FDA's enforcement authority; although the agency can remove drugs from the market for noncompliance with marketing or labeling recommendations, it rarely takes this extreme step. But others counter that the liability and adverse publicity facing companies that fail to act on FDA drug-safety findings already compel compliance. Some also argue that increased reliance on special, drug-by-drug regulatory steps would be burdensome and confusing to physicians and patients, leading to access problems, the substitution of less safe or effective treatments, and medical errors.

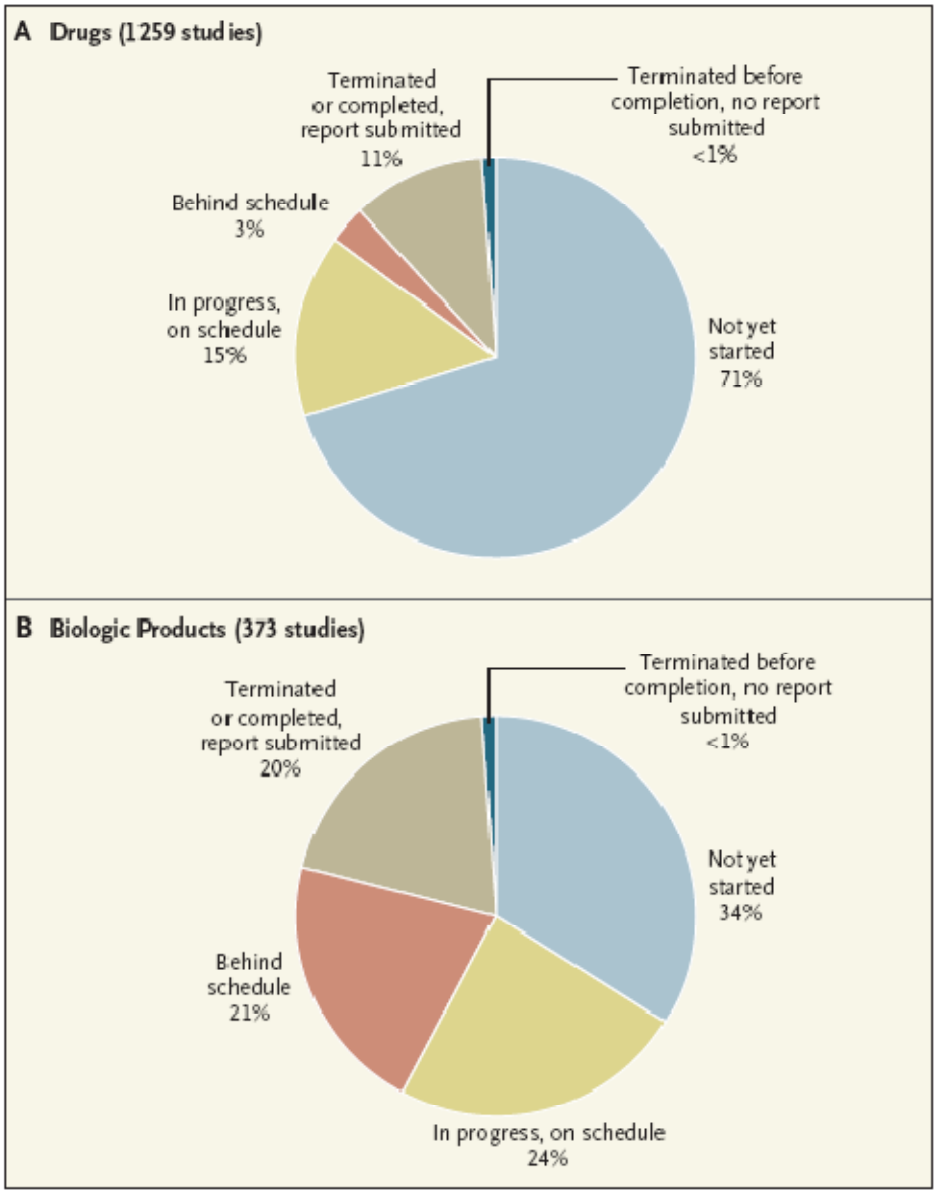
A third aspect of reform could help avoid increased costs and reduced access from new drug-by-drug regulation: implementing a fundamentally better system for postmarketing surveillance, with developers to clarify approval standards and for research on predicting safety problems and patients' responses to drugs. It would also expand the resources for postmarketing surveillance to $29.3 million, permitting the hiring of additional personnel and the enhancement of postmarketing capabilities. For fiscal year 2008, total user fees would be nearly $400 million, accounting for more than 40% of FDA resources for drug regulation.

Seeing the agency as overly dependent on industry funding, some observers propose eliminating user fees. However, the fees are based on the resources required for reviewing drugs and overseeing their use; they are not tied to FDA decisions. The rate at which drugs have been withdrawn from the market has not increased since PDUFA was implemented, and the increase in resources has resulted in important public health benefits, including a reduction in drug review time estimated to have saved 180,000 to 310,000 lives.[3] Furthermore, specific proposals to reduce dependence on user fees only authorize additional spending — Congress has no plans to actually appropriate the funds for the FDA.

One reason drugs may be used for years before risks become evident is that we have no active drug-surveillance system.

The second category of proposed reform is new authority for the FDA. A bill sponsored by Senators Edward Kennedy (D-MA) and Mike Enzi (R-WY) would formally authorize the agency to use a range of regulatory tools to help assure drug safety. The new authority includes the ability to require special medication guides for patients, restrict which physicians can prescribe a drug, and impose special requirements for prescribers (e.g., documentation of laboratory testing through FDA-approved monitoring procedures). Because of the burdens on providers and patients, including the potential for restricting access, the FDA has in the past used such tools only rarely, for drugs that have important benefits but also clearly cause serious side effects (e.g., thalidomide).

This authority would be exercised through a required "risk evaluation and mitigation strategy," which might include measures such as prescribing restrictions, limits on direct-to-consumer marketing, and requirements for postmarketing studies. The risk-management strategy would be monitored and updated over time, and the FDA could impose monetary penalties for noncompliance.



Status of Open Commitments for Postmarketing Studies Requested by the FDA, as of September 30, 2006.

Data are from the Federal Register.

Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies. **JAMA** 2006;295:2275-85.

The need for collaboration

Disentangling *the effects due to ongoing treatment from those due to psoriasis risk factors and/or natural history, or the effects of prior therapies* ***is complex*** *and only carefully designed studies, with large numbers of patients and entailing the collaboration of several experts from various disciplines can provide useful information on the safety profile of biological agents.*

Even a ***national registry might not be able to provide meaningful information*** *on rare adverse events* ***in a reasonable time***

PSONET programme

- **Survey of national registries** of systemic treatments for psoriasis in Europe and establishment of an international collaboration;
- **Implementation of study procedures to merge selected national data** into an international database to be regularly updated;
- **Conduct of analyses to assess specific safety and effectiveness issues**

International Coordinating Committee

This will include representatives of national registries and, in some instances, national pharmacovigilance centres

Participants in the Rome meeting, December 16, 2006

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Advancement of the project

First meeting of registry representatives held in **Rome on December 16, 2006**

The following countries have already established a registry (or are in the process of establishing one in the near future) and have agreed in principle to collaborate: **France, Israel, Italy, Spain, Sweden, United Kingdom**.

Circulation of signals on potential safety issues originated by individual registries was considered to be a priority area.

Collaboration with rheumatologic registries was considered as particularly useful since it makes it possible to compare the rate of events associated with prescriptions for different indications.

It was agreed that the property of the data rested on the individual centres and that, according to the country, individual patient data or only summary data could be merged

	Registry already established?	Coverage of the registry	Systemic treatment considered	Modality of data collection	Support
UK	Yes	Nationwide	Biologicals and Conventional treatments including PUVA	Electronic form	Via professional body BAD Pharmaceutical companies sponsorship
The Netherlands	Work in progress	Local	Biologicals	Electronic form	?
Sweden	Yes	Nationwide	Biologicals and Conventional treatments including PUVA	Electronic form	Governmental grant
Spain	Yes (rheumatology) Work in progress (dermatology)	Local (rheumatology) Nationwide (dermatology)	Biologicals (rheumatology) Biologicals and Conventional treatments (dermatology)	Electronic form	Governmental grant pharmaceutical companies sponsorship (rheumatology)
Portugal	Working in progress	?	?	?	?
Israel	Core registry established	Nationwide?	?	?	?
Italy	Yes	Nationwide	Biologicals and Conventional treatments including PUVA	Electronic form	Governmental grant
France	Work in progress	Nationwide?	?	?	?

Entry criteria

All the subjects with **active psoriasis** who receive, **for the first time in their life**, at least one single dose of **a new systemic agent** for psoriasis (the collection may be limited to biological agents in some countries). Only patients recruited within the national registries will be considered for inclusion.

Common definitions for variables such as "disease severity" and "response to treatment" should be adopted. Uniform coding strategies should be better developed. Internal consistency checks will be also defined.

European Medicines Agency
Evaluation of Medicines for Human Use

London, 18 November 2004
CHMP/EWP/2454/02 corr

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PSORIASIS

- **Mild to moderate psoriasis** Good control of lesions with topical therapy alone. BSA involvement <10% or PASI <10. Category "mild to moderate" on PGA.

- **Moderate psoriasis:** Topical therapy still possible to control the disease. BSA involvement >10% or PASI 10 or more. Category "moderate" on PGA.

- **Moderate to severe psoriasis**: Topical therapies fail to control the disease. BSA involvement >10% or PASI 10 to 20. Very thick lesions located in "difficult to treat" regions (e.g. palmo-plantar) with BSA involvement <10% may also be considered. Category "moderate to severe" on PGA.

- **Severe psoriasis:** A justified need for systemic treatment to control the disease. BSA involvement > 20 % or PASI >20. Very important local signs with very thick lesions with BSA involvement >10% may also be considered. Category "severe" on PGA.

- **Treatment success**: patient clear or almost clear on a global scale, or >90% improvement in PASI from baseline. This is very stringent requirement and is not always a target possible to obtain in clinical practice.

- **Remission**: complete clearing of psoriasis. Residual post-inflammatory pigmentary alteration is not considered residual disease.

- **Relapse**: when the achieved maximal improvement from baseline is reduced by >50%. A more subjective definition would be a relapse of psoriasis necessitating the re-initiation of treatment.

- **Rebound**: may signify a severe deterioration of psoriasis that is significantly worse than before the treatment was initiated or a change in the character of the psoriasis, e.g., from plaque to pustular form, or both. **Rebound** is defined as worsening of psoriasis over baseline value (e.g. PASI>125%) or new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months of stopping therapy.

Follow up

Active follow up (at least one contact per year) with minimum loss to follow up (less than 20%) will be aimed for.

Updates every 6 months.

Minimum set of variables (basal time)

1. Patients' **socio-demographic characteristics** (age, gender), skin type*
2. **Personal habits:** smoking (yes/no/previous/unkwn), alcohol consumption (average n. drinks per week)*
3. **Anthropometric variables** (weight and height), waist circumference*
4. **Psoriasis characterization** date of first diagnosis, type of psoriasis, severity*, previous systemic treatments (yes/no/unkwn)
5. **Co-morbidities** ischemic heart disease, hypertension, dyslipidemia, diabetes, cerebrovascular disease, tuberculosis, HIV, chronic viral hepatitis, other infections requiring hospitalisation, cancer [type of cancer], kidney, liver disease
6. **Systemic treatment for psoriasis at entry** (drug and dosage)
7. **Gynecological information:** Pregnancy and its outcome*
8. **Systemic co-medication:** yes/no/unkwn for specific drug categories (immunosuppressive,lithium salt, calcium antagonists, ACE inhibitors, NSAIDs)

(*) Non mandatory information

Minimum set of variables (follow up)

1. **Updates on systemic treatments** for psoriasis during follow-up
2. **New diagnosis of conditions categorised as**: infections leading to hospitalization, cancer, any other new condition leading to hospitalisation or specialist consultation* (kind of condition categorised according to ICD-10 or other dictionaries)
3. **New systemic co-medications** taken for more than one month
4. **Any relevant suspected adverse event associated with treatment** (date of diagnosis, kind of event)
5. **Remissions and severe relapse** of disease during follow-up

Pooling of data from national registries

1. Individual patient data vs pooled data
2. Definition of intervals for data extraction in a standardized form
3. Establishment of a centralized database, under the control of the International Coordinating Committee, with appropriate insurance of data confidentiality
4. Consistency checks of data and regular updates

Control groups

1. Internal vs external comparisons
2. Internal comparisons will involve analyses of event occurrence in groups defined by different dosages/duration of treatment and/or different drugs.
3. External comparisons can be made by considering incidence rates in selected population samples. For rare events such as cancer incidence, only marked increases of incidence (i.e., twice or more) with respect to the general population could be detected by our system.

Analyses

In general, the analyses will be split into different steps.

A first phase will usually consist of descriptive analyses.

A further stage will consider simple univariate analyses.

Finally, in-depth analyses centered around specific questions and using more powerful analytical methods, e.g., multivariate models, can be adopted.

International Safety Review Board

Diagnoses will be reviewed by an International Safety Review Board. According to the clinical diagnosis, additional information may be required with retrieval of information from medical records, family doctors or directly from the patient.

International Safety Review Board

Professor Robert Stern (Department of Dermatology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston), *chair*

Professor Jean Claude Roujeau (Université Paris XII, Department of Dermatology, Hopital Henri Mondor, Creteil)

Professor Jean Jacques Grob (Université de la Mediterranee et Service de Dermatologie, Hopital Ste Marguerite, Marseille)

Professor Peter Elsener (Department of Dermatology, University of Jena, Germany)

Professor Carlo La Vecchia (Department of Biometrics and Biostatistics, University of Milan)

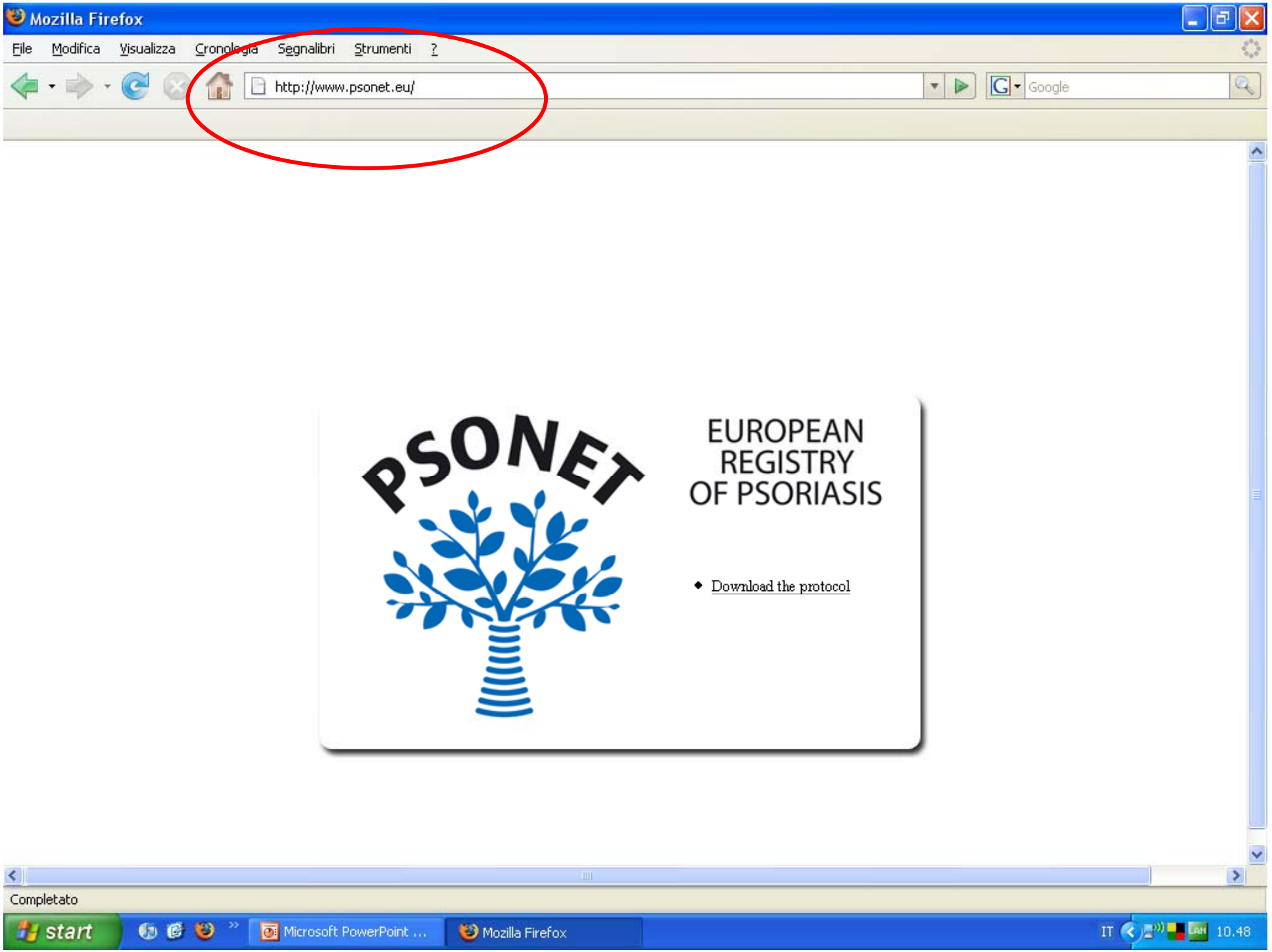
Criteria for signal generation in spontaneous surveillance systems

- Number of case reports
- Presence of a characteristic feature or pattern
- Site, timing, dosage-response relationship, reversibility
- Rechallenge
- Biological plausibility
- Laboratory findings (e.g., drug-dependent antibodies)
- Previous experience with related drugs

Dissemination of results

Results made available to the scientific community and, according to pre-defined criteria, to the general public. Dissemination means may include:

- scientific publications
- presentation of data in a project's website
- collaboration with pharmacovigilance units in different countries and EMEA (PhVWP)
- collaboration with patients' organizations.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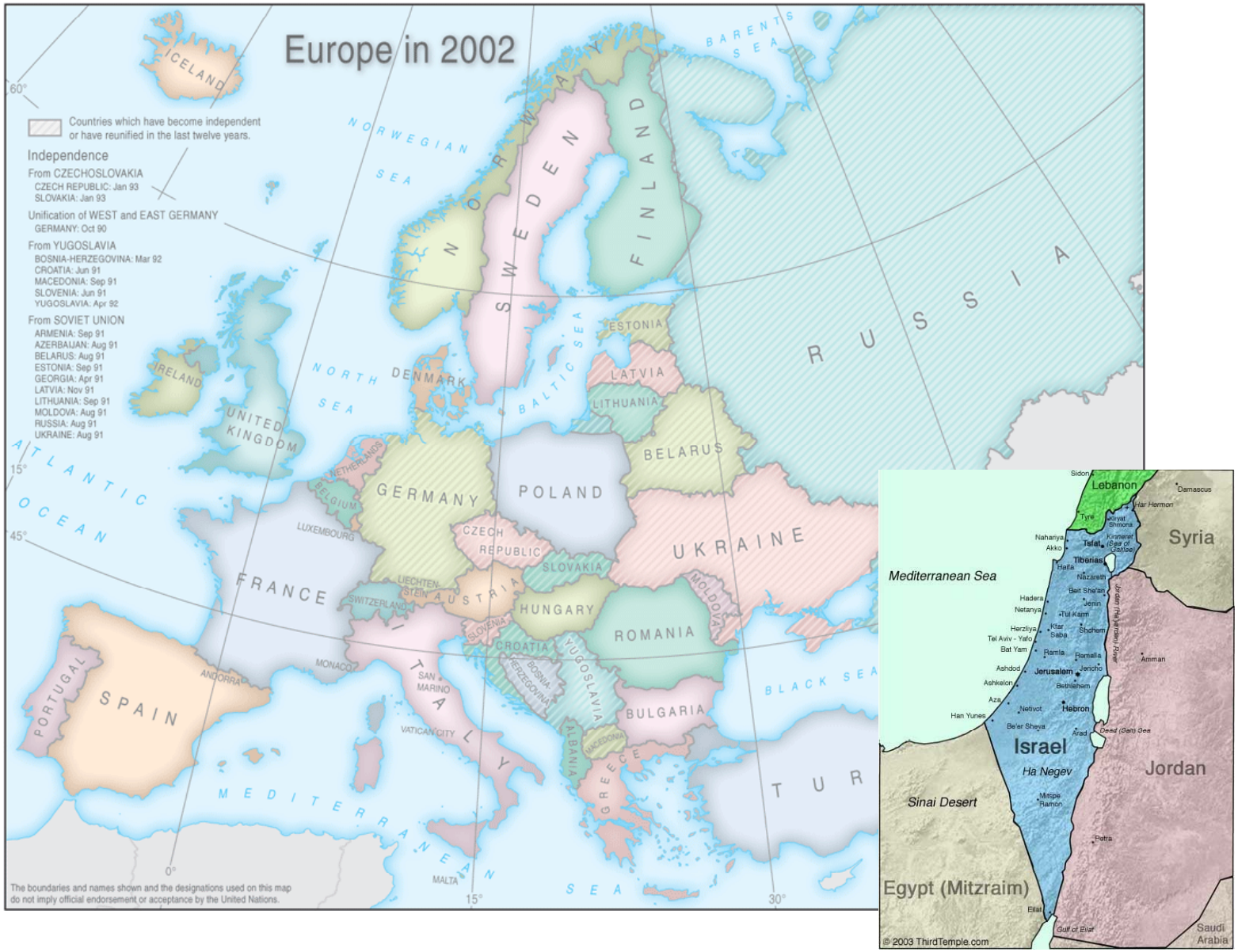
Europe in 2002
Countries which have become independent or have reunified in the last twelve years.
Independence
From CZECHOSLOVAKIA
CZECH REPUBLIC: Jan 93
SLOVAKIA: Jan 93
Unification of WEST and EAST GERMANY
GERMANY: Oct 90
From YUGOSLAVIA
BOSNIA-HERZEGOVINA: Mar 92
CROATIA: Jun 91
MACEDONIA: Sep 91
SLOVENIA: Jun 91
YUGOSLAVIA: Apr 92
From SOVIET UNION
ARMENIA: Sep 91
AZERBAIJAN: Aug 91
BELARUS: Aug 91
ESTONIA: Sep 91
GEORGIA: Apr 91
LATVIA: Nov 91
LITHUANIA: Sep 91
MOLDOVA: Aug 91
RUSSIA: Aug 91
UKRAINE: Aug 91
ICELAND
NORWEGIAN SEA
BARENTS SEA
NORWAY
SWEDEN
FINLAND
RUSSIA
ESTONIA
LATVIA
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IRELAND
UNITED KINGDOM
NORTH SEA
DENMARK
BALTIC SEA
ATLANTIC OCEAN
NETHERLANDS
BELGIUM
GERMANY
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UKRAINE
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LIECHTEN-STEIN
SWITZERLAND
AUSTRIA
HUNGARY
MOLDOVA
ROMANIA
SLOVENIA
CROATIA
BOSNIA-HERZEGOVINA
YUGOSLAVIA
BLACK SEA
MONACO
ANDORRA
PORTUGAL
SPAIN
SAN MARINO
ITALY
VATICAN CITY
BULGARIA
ALBANIA
MACEDONIA
GREECE
TUR
MEDITERRANEAN SEA
MALTA
60°
15°
45°
0°
15°
30°
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Lebanon
Syria
Damascus
Har Hermon
Tyre
Qiryat Shmona
Nahariya
Akko
Tefat
Kinneret (Sea of Galilee)
Tiberias
Haifa
Nazareth
Mediterranean Sea
Beit She'an
Jordan (Ha Yarden) River
Hadera
Jenin
Netanya
Tul Karm
Herzliya
Kfar Saba
Shchem
Tel Aviv - Yafo
Bat Yam
Ramla
Ramalla
Amman
Ashdod
Jerusalem
Jericho
Ashkelon
Bethlehem
Aza
Netivot
Hebron
Han Yunes
Be'er Sheva
Arad
Dead (Sam) Sea
Israel
Ha Negev
Jordan
Sinai Desert
Mitspe Ramon
Petra
Egypt (Mitzraim)
Eilat
Gulf of Eilat
Saudi Arabia
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Items for the website

- Aims, protocol and other materials
- Information on each national registry
- Update on ongoing collaboration
- News and links

CORDIS: FP7 Homepage - Mozilla Firefox

File Modifica Visualizza Cronologia Segnalibri Strumenti ?

http://cordis.europa.eu/fp7/home_en.html

Google

Seventh Research Framework Programme (FP7)

Important Legal Notice

CORDIS

2007 - 2013

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- Understand FP7
- Participate in FP7
- Find a call
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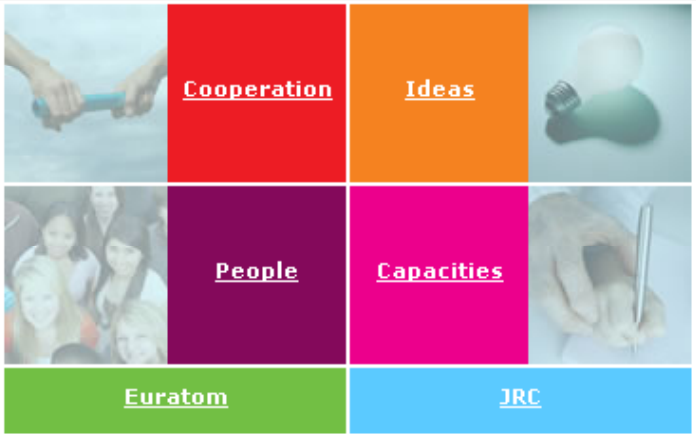
- Find project partners
- Find a document



What type of user are you?

The Seventh Framework Programme (FP7) is designed to support a wide range of participants... read more

- Private company
- Public organisation
- Individual researchers
- Outside the EU

In the spotlight

The Electronic Proposal Submission Service (EPSS) is now open for the following activities: Health, ICT, KBBE, NMP, Environment, Transport, Socio-Economic Sciences and the Humanities, Ideas, People, Research Infrastructures, SMEs, Research Potential

Latest News

Commission sets out plans to boost knowledge transfer

[Date: 2007-04-05]

Boosting knowledge transfer between research organisations and businesses is the focus of a new communication released by the European Commission on 4 April... read more

>> more news

Forthcoming Events

Highlights

- The EC has adopted the general model grant agreement applicable under the Specific Programmes of FP7
- A New Approach to International S&T Cooperation FP7 - the new brochure outlines how the international cooperation will work through the various

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Deadline 18 September 2007

- **HEALTH-2007-3.1-3: Patient Safety Research Network.** To establish a network of researchers in the field of patient safety to strengthen information and broker knowledge where the quality of health care systems on patient safety is concerned, focussing on leadership and patient safety culture in health care organisations taking into account the different national contexts in Europe and existing international cooperation. **Funding scheme:** Coordination and Support Action (Coordination action).

Next meeting?