Introduction:
How are drugs approved and monitored?

Nicole Schröter
3 May 2015

Drug development and approval process (innovator product)

Idea

12+ years, 1bn+ EUR investment, ~ 2% success

1 Pre-clinical

New Drug Development
- New?
- More effective?
- Less side effects?

Animal testing
- Toxicity, Damage, other cancers?

→ Drug ready for testing in humans

2 Clinical

Phase I study
- „first in man“
- 20-80 healthy volunteers[1]

Phase II study
- 150-350 patients
- Toxicity, Safety

Phase III study
- 250-4000 patients
- Efficacy in comparison

→ Market-ready drug

3 Approval

Regulatory Approval
- Marketing Authorization (Application, Authorization)

Health Technology Assessment[2]
- Assessment of cost effectiveness

→ Drug ready to reach patients

4 Post-Marketing

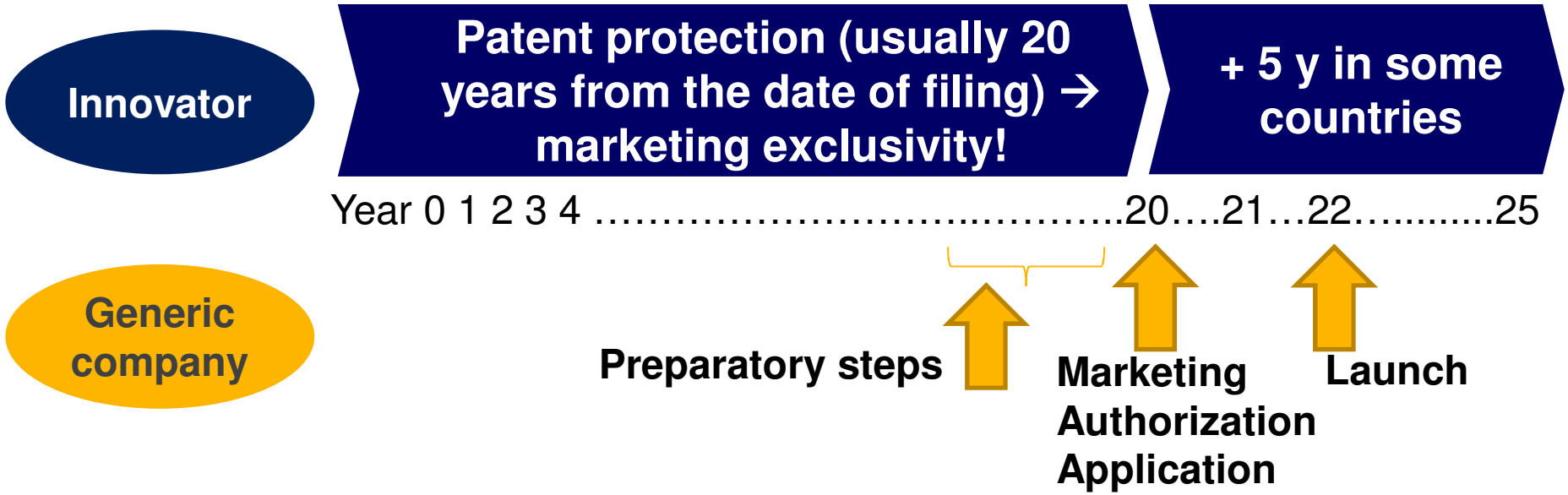
Product launch

Post marketing surveillance:
- Phase IV studies
- Observational studies
- Adverse event monitoring
- Patient Registries
- …

→ Improve quality of health care

[1]) Exception for cancer therapy: Late stage tumor patients included; [2]) Selected countries only

When & how do generics come into play?



- → **Generics can be launched at a significantly lower price**
  - → **Little development costs (no research)**
  - → **No clinical trials required**
  - → **Less marketing campaigns, as originator drug is known to doctors**
  - → **Increased competition**

Simplified process in case of generic drugs

1 Pre-clinical

New Drug Development
- Novel?
- More effective?
- Less side effects?

Animal testing
- Toxicity, Damage, other cancers?

2 Clinical

Phase I study
- „first in man“
- 20-80 healthy volunteers[1]

Phase II study
- 150-300 patients
- Toxicity, Safety

Phase III study
- 250-3000 patients
- Efficacy in comparison

3 Approval

Regulatory Approval
- Marketing Authorization (Application, Authorization)

Health Technology Assessment[2]
- Assessment of cost effectiveness

4 Post-Marketing

Product launch

Post marketing surveillance:
- Phase IV studies
- Observational studies
- Adverse event monitoring
- Patient Registries
- …

→ Drug candidate for testing in humans

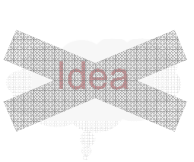
→ Marketable drug

→ Drug ready to reach patients

→ Improve quality of health care

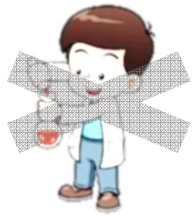
[1]) Exception for Cancer therapy: Late stage tumor patients included; [2]) Selected countries only

Let´s go into detail…



Idea

12+ years, 1bn+ EUR investment, ~ 2% success



1 Pre-clinical	2 Clinical	3 Approval	4 Post-Marketing
New Drug Development New? More effective? Less side effects?	Phase I study „first in man“ 20-80 healthy volunteers	**Regulatory Approval** – **Marketing Authorization (Application, Authorization)**	**Product launch**
Animal testing Toxicity, Damage, other cancers?	Phase II study 150-300 patients Toxicity, Safety	Health Technology Assessment[2] – Assessment of cost effectiveness	**Post marketing surveillance:** – Phase IV studies – **Observational studies** – **Adverse event monitoring** – **Patient Registries** – **…**
	Phase III study 250-4000 patients Efficacy in comparison		
→ Drug ready for testing in humans	→ Market-ready drug	→ **Drug ready to reach patients**	→ **Improve quality of health care**

[1]) Exception for Cancer therapy: Late stage tumor patients included; [2]) Selected countries only

Approval of drugs takes around 2 years in usually 6 steps

Compilation of registration dossier

1

Review Meeting[1]

2

Filing of Application

3

Regulatory Approval Process

4

Application Review

5

Facility Inspection

6

Drug Approval

[1]) Selected countries only, eg. USA

"The standards for quality are the same for brand name and generic products."[1]

In tightly regulated markets like EU or US, generic drugs are required to have:

- Same active ingredient, amount of active ingredient, purity
- Same pharmacokinetic & pharmacodynamic properties
- Same stability
- Same mechanism of action, safety & efficacy
- Same therapeutic indication & route of administration

What is allowed are…

- Different salts
- Different excipients
- Different manufacturing process
- Different product name & packaging

Unless they differ significantly in their safety and/or efficacy properties → in this case, the generic manufacturer has to submit further proof of efficacy and safety.

[1] Gary Buehler, Director of FDA's Office of Generic Drugs; applicable at least to US & EU

In the US & EU, approval of generics and innovator products is similar, except…

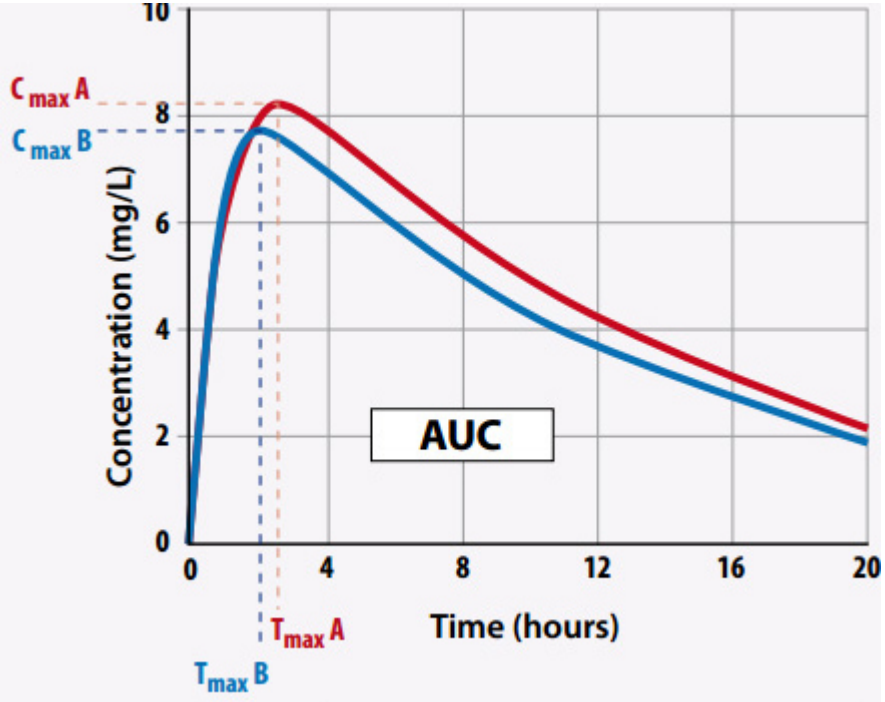
- Generics do not need to prove safety and effectiveness of the drug through animal testing, clinical trials in humans

  → **approval through referencing to originator product**

- BUT: Generic applicants must demonstrate that their product is **bioequivalent** to the innovator product

  → Most regulatory authorities require bioequivalence of the generic to be **80%-125%** of the innovator product (traditional bioequivalence limit)

Bioequivalence studies show that active ingredient in patients' bloodstream is the same in generic and innovator product



KEY: Innovator / Generic

C_{max} maximum plasma drug concentration

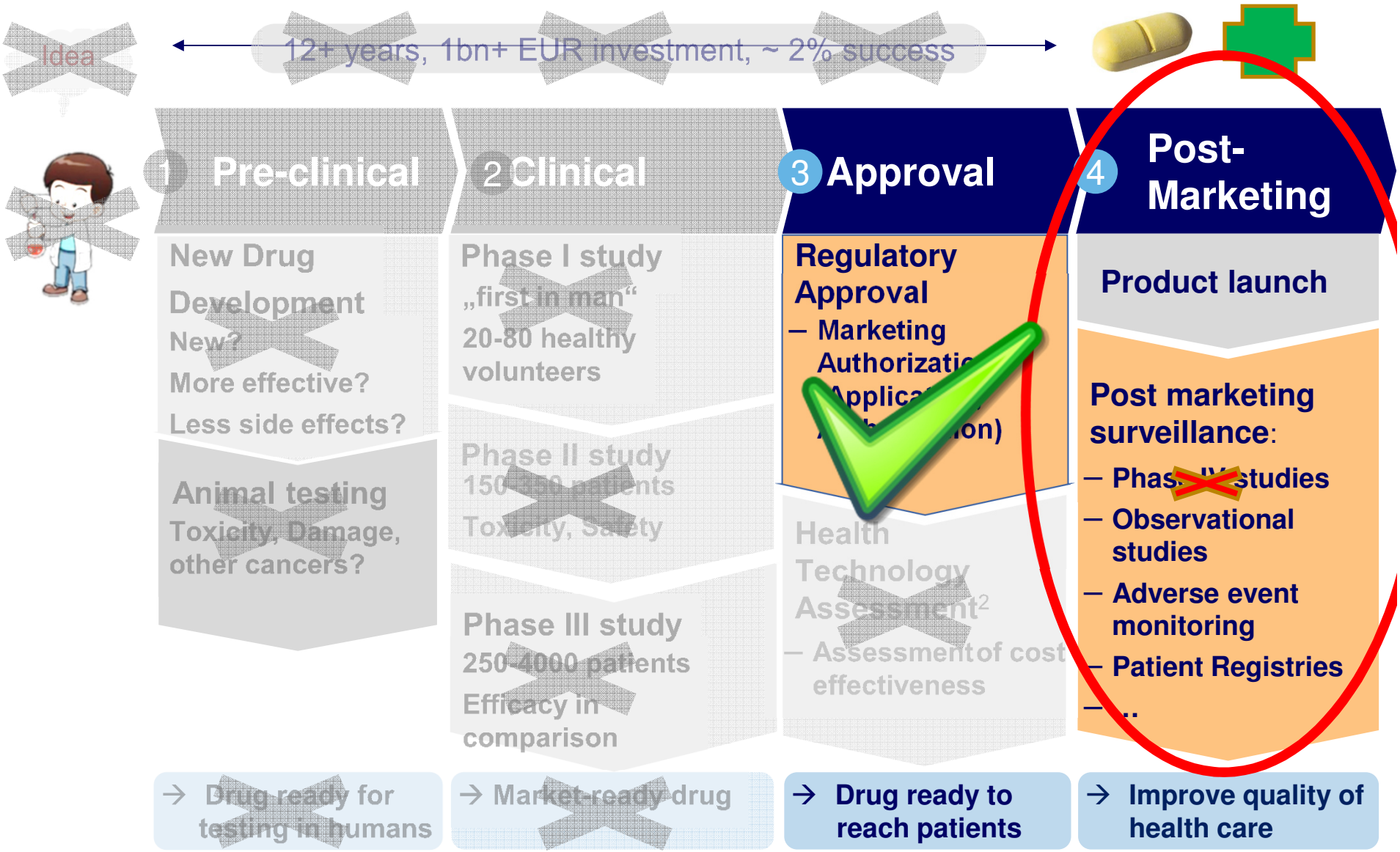
T_{max} time required to achieve a maximal concentration

AUC total area under the plasma drug concentration-time curve

→ No significant difference between both products in terms of blood levels and time

Source: http://www.bpac.org.nz/magazine/2009/generics/docs/bpjse_generics_bio_pages_4-8.pdf

Let´s go into detail…

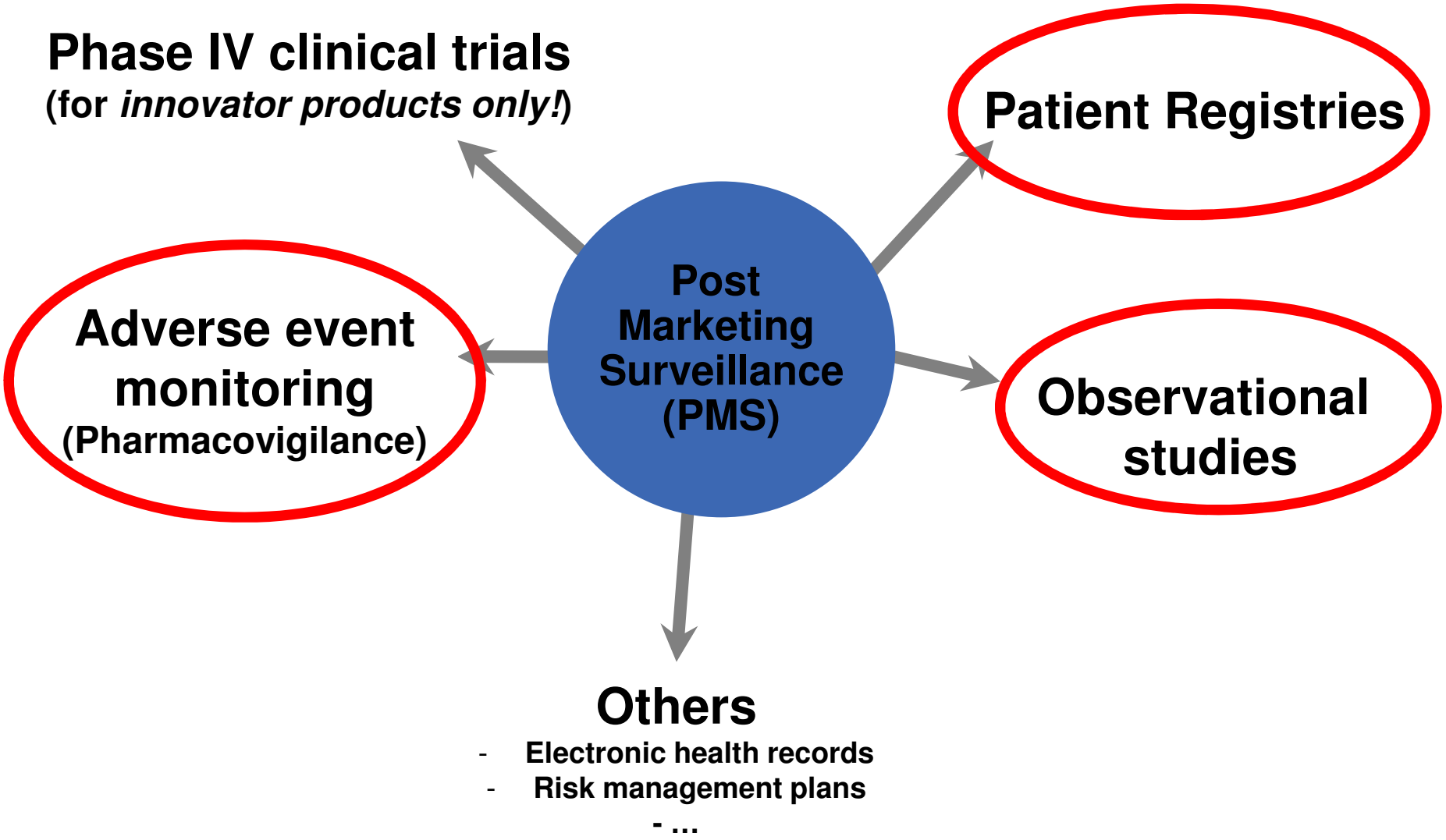


[1]) Exception for Cancer therapy: Late stage tumor patients included; [2]) Selected countries only

Post marketing surveillance: improving safety in use of medicines

- **“Post marketing surveillance”:**
  - Monitoring the safety of a drug after market authorization, and collecting further data
- **Objective: Evaluation in a real-world setting**
  - Explore long term effects
  - Real-world data in larger populations (more variety of patients, medical conditions, comorbidities)
  - Detect all (incl. rare) adverse drug reactions, drug interactions
  - Assess new uses and therapeutic areas
  - Understand the real benefit-risk relationship

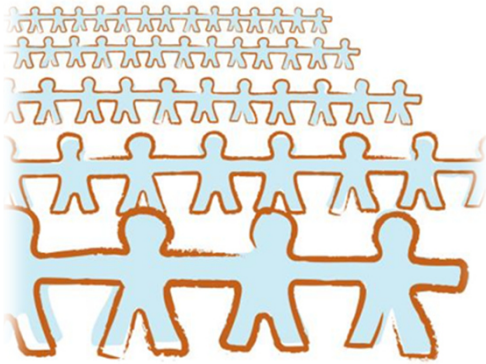
Post-marketing surveillance measures to monitor the safety of approved drugs



Observational studies provide information from a representative sample of 'real-life' patients

- **CHARACTERISTICS:**
  - Carried out in a routine clinical practice setting
  - Less rigorous and costly than randomized clinical trials, but lower level of evidence
- **OBJECTIVES:**
  - Monitor effect of a drug under routine conditions and for prolonged period of time
  - Provide additional details about the efficacy and safety of the drug
- **TYPICAL STUDY FIELDS:**
  - Different formulations, dosages, durations of treatment
  - New age groups, races, types of patient (e.g. pregnant women,…)
- **REASONS:**
  - Requested by Regulatory Authorities
  - Competitive reasons (e.g. finding new market for the drug)
  - Exploring and measuring ways to improve comfort and QoL,…

Patient Registries collect standardized information about patients that share the same condition or experience



- **OBJECTIVES:**
  - Recruiting patients for clinical trials[1]
  - Study best practices in treatment and care
  - Examine questions that are not being answered / looked at in clinical trials[1]
  - …
- **TYPES:**
  - Researcher-generated: established by research institutions, academic clinical institutions, or individual research teams
  - Patient-powered: established by patient advocacy organizations

[1] applies to innovator products only, not to generics!

Adverse event monitoring *(Pharmacovigilance)* - the core of post marketing surveillance

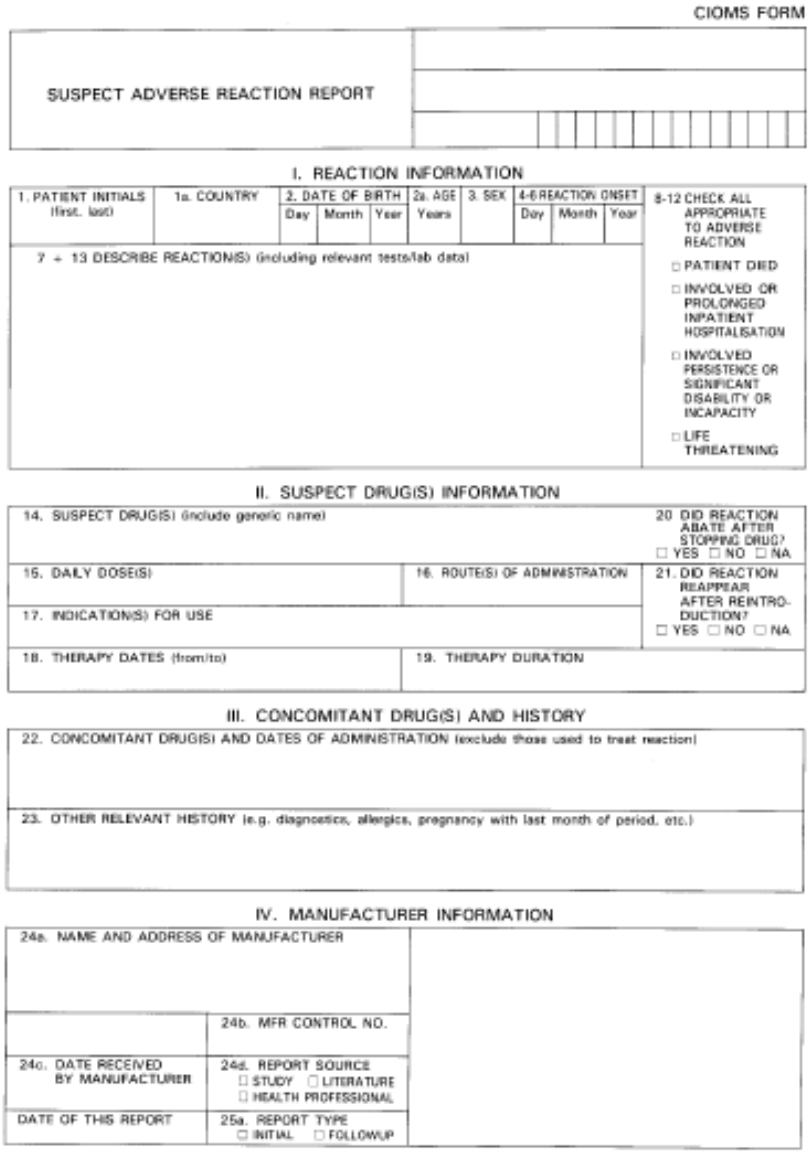
- **Etymology & definition:**
  - ***pharmakon*** **(greek) = drug**
    + *vigilare* (Latin) = to monitor
  - **“the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. “ (WHO)**

- **Why is pharmacovigilance (PV) so important?**
  - **5% of all hospital admissions in the EU are for side effects**
  - **Side effects are the 5th most common cause of hospital deaths**
  - **Nearly 200.000 deaths per year in the EU from side effects**

The provision of good quality, safe and effective drugs is responsibility of national governments

- **PV implementing measures[1]**
  - **Requirements applying to pharmaceutical companies** (extensive reporting systems, regular audits, employment of “qualified pharmacovigilance person”, etc.)
  - **Individual Case Safety Reports (ICSR) by companies and healthcare professionals**
  - **Direct consumer reporting systems**

[1] equally applicable to innovator drugs & generics



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

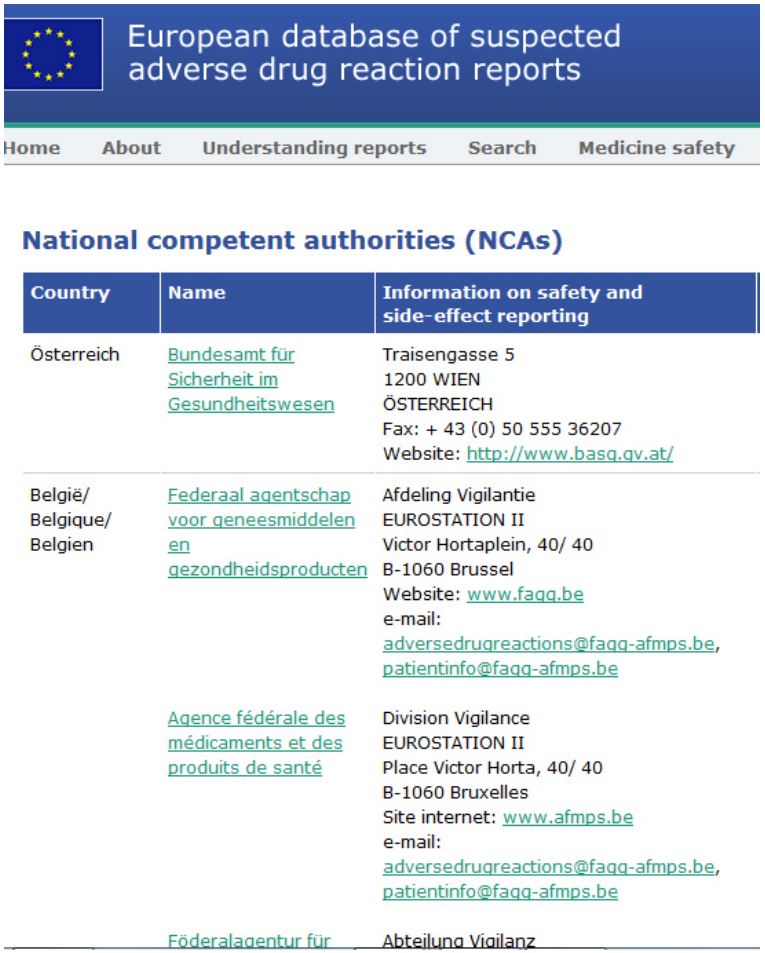
24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOW-UP	

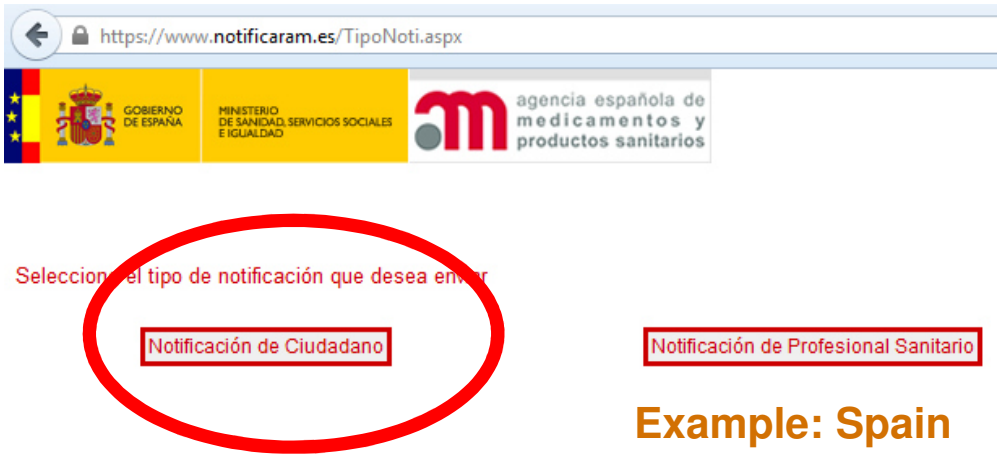
Direct consumer reporting
How to report a side effect?

- **EU:**
  - **Reporting of side effects** is normally carried out by **healthcare professionals**
  - **But:** increasingly, **patients** are able to report suspected side effects **directly**
    - through **online patient reporting forms** hosted by **national** medicines regulatory authorities → *see list of national medicines regulatory authorities*
    - by **telephone**.

"The European Medicines Agency cannot accept side-effect reports directly from patients or consumers!"

http://www.adrreports.eu/docs/ADR_reporting_FINAL_EN.pdf
http://www.adrreports.eu/en/index.html

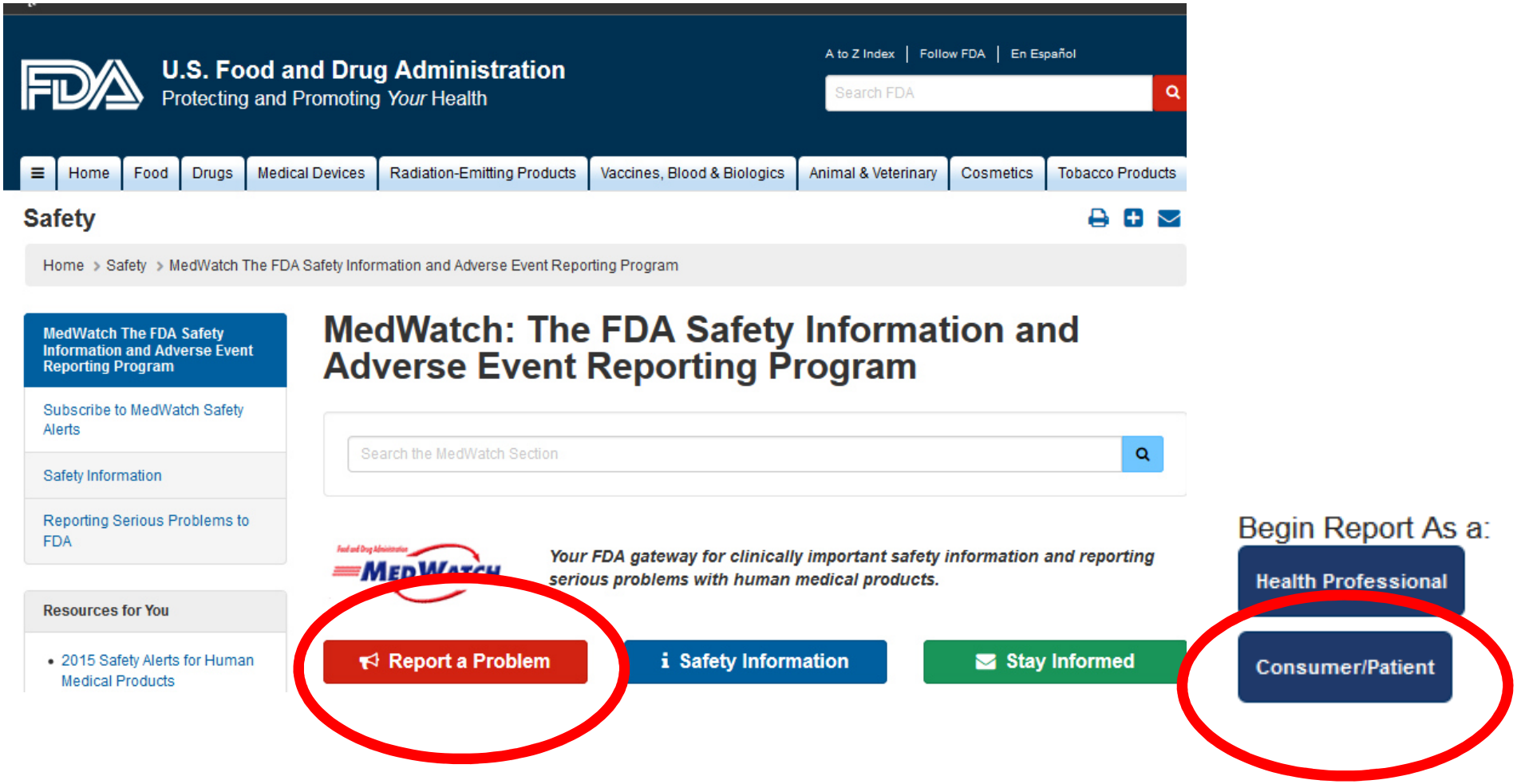




Example: Spain

Direct consumer reporting
How to report a side effect?

- **USA:**



http://www.fda.gov/Safety/MedWatch/default.htm

Pharmacovigilance interventions

- **In case important new risks are uncovered…**
  - **Manufacturers** are obliged to amend their labels / leaflets or add a boxed warning on their packaging
  - **Public** is informed through letters, public health advisories
  - In some cases **use** of the drugs is substantially **limited**
  - Every once in a while, drugs are **withdrawn from the market**

Can we fully trust generics?

→ There is no clear "yes" or "no" answer! It all depends…

- *"Doctors and patients can be confident that most generic drugs dispense in Western nations are of high quality"*[1]
- *"(…) but globally there are many generic drugs for which companies offer little or no support and monitoring, and regulators don't require generics to undergo phase IV post-marketing studies."*[1]
- *"(…)– developing countries face greater risks from lower standards (…)"*[1]

(Prof. Atholl Johnston, Professor of clinical pharmacology at Queen Mary, University of London)

→ The quality of a drug (innovator or generic) depends

1. **on the manufacturer AND**
2. **on a strong and vigilant Regulatory Authority!**

[1] Generic cancer drugs that we can trust (Beishon, Cancer World Jan-Feb 2015)

What is the situation in your country?

- **Is there a regulatory and safety monitoring system in place?**
- **Does your local authority require generic drug manufacturers to prove their drug exhibits bioequivalence to the innovator product?**
- **Do the same requirements apply for generic drugs as for innovator products?**
- **…**

GO AND FIND OUT!

Literature tip : http://www.isoponline.org - International Society of Pharmacovigilance

Thank you for your attention!

QUESTIONS

Backup slides

APPROVAL STAGE: Regulatory approval

1 Compilation of registration dossier

- **EU : Marketing Authorization Application (MAA)**
- **US : New Drug Application (NDA) or Abbreviated New Drug Application** *(in case of generics)*
- **Content and format are defined by competent authorities** (e.g. US/EU/Japan: CTD / eCTD[1])
- **Dossier usually includes:**
  - Extensive documentation on the drug & development (pre-clinical and clinical reports *(applies to innovator products only!)*, pharmacokinetics, product characteristics, risk-benefit analysis, stability data,…)
  - Administrative documents (Manufacturing Permit, GMP[2]-certificate,…)
- **Additionally, companies are required to submit:**
  - Samples of finished product, proposed labelling & leaflet
  - Reagents to perform analyzes

[1] (electronic) Common Technical Document
[2] Good Manufacturing Practice (GMP)

APPROVAL STAGE: Regulatory approval

2  Review Meeting

Meeting between pharma company and regulatory body prior to submission of dossier

3  Filing of Application

Independent regulatory body or Specialized department in the Ministry of Health (MoH)

4  Application Review

- **Review of dossier**
- **Review of drug labelling / content of leaflet** (is information communicated to health care professionals and consumers appropriate?)
- **Queries to the manufacturer and responses by staff of Regulatory Affairs Department**

APPROVAL STAGE: Regulatory approval

5

Facility Inspection

- **Essential part of drug quality assurance system**
- **Randomly and depending on the country**
- **Criticism by industry:** no collaborative global approach → various inspections by various regulatory bodies at one manufacturing site, while other sites are not covered by inspection

6

Drug Approval


МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ

РЕЄСТРАЦІЙНЕ ПОСВІДЧЕННЯ
НА ЛІКАРСЬКИЙ ЗАСІБ

- **Issuing of registration certificate / MA[2]**
- **Validity: usually 5 years (depending on the country)**
- **Renewal in due time**
- **Withdrawal if**
  - **MA holder does not fulfil obligations to maintain product on the market (e.g. reporting variations)**
  - **Product is not placed on market within defined period of time (depending on the country; EMA: "Sunset clause")**

[2] Marketing Authorization

APPROVAL STAGE: Regulatory approval

Procedure for obtaining Marketing Authorization

- **Most countries worldwide:** National procedure (national rules and requirements)
- **EU:**

Procedure	Centralized	Decentralized	Mutual recognition	National
Validity of MA	EU + EEA	CMSs of choice	CMSs of choice	Country of choice
Applicable to drugs…	…for which **centralized procedure is compulsory** (e.g. orphan drugs, cancer/ HIV-drugs,…)	…that have **not been registered in any member state** before	…that have previously received **MA in any member state**	…intended for **one country only** + **centralized proced. not compulsory**
MAA to file with…	EMA	Competent authorities of each CMS in which product shall be launched; one state acts as RMS		Competent authority of resp. CMS

CMS = Concerned Member State
RMS = Reference Member State

MA = Marketing Authorization
MAA = Marketing Authorization Application

What about comparative effectiveness: Health Technology Assessment*

- **Health Technology Assessment (HTA)**
  - Marketing authorization proves **safety as well as effectiveness** against a disease
  - HTA **compares effectiveness to other existing drugs**,
  - In some countries, HTA assesses whether **costs reflect value, or whether drug is cost effective**

  → **Support health care decisions and policy making**

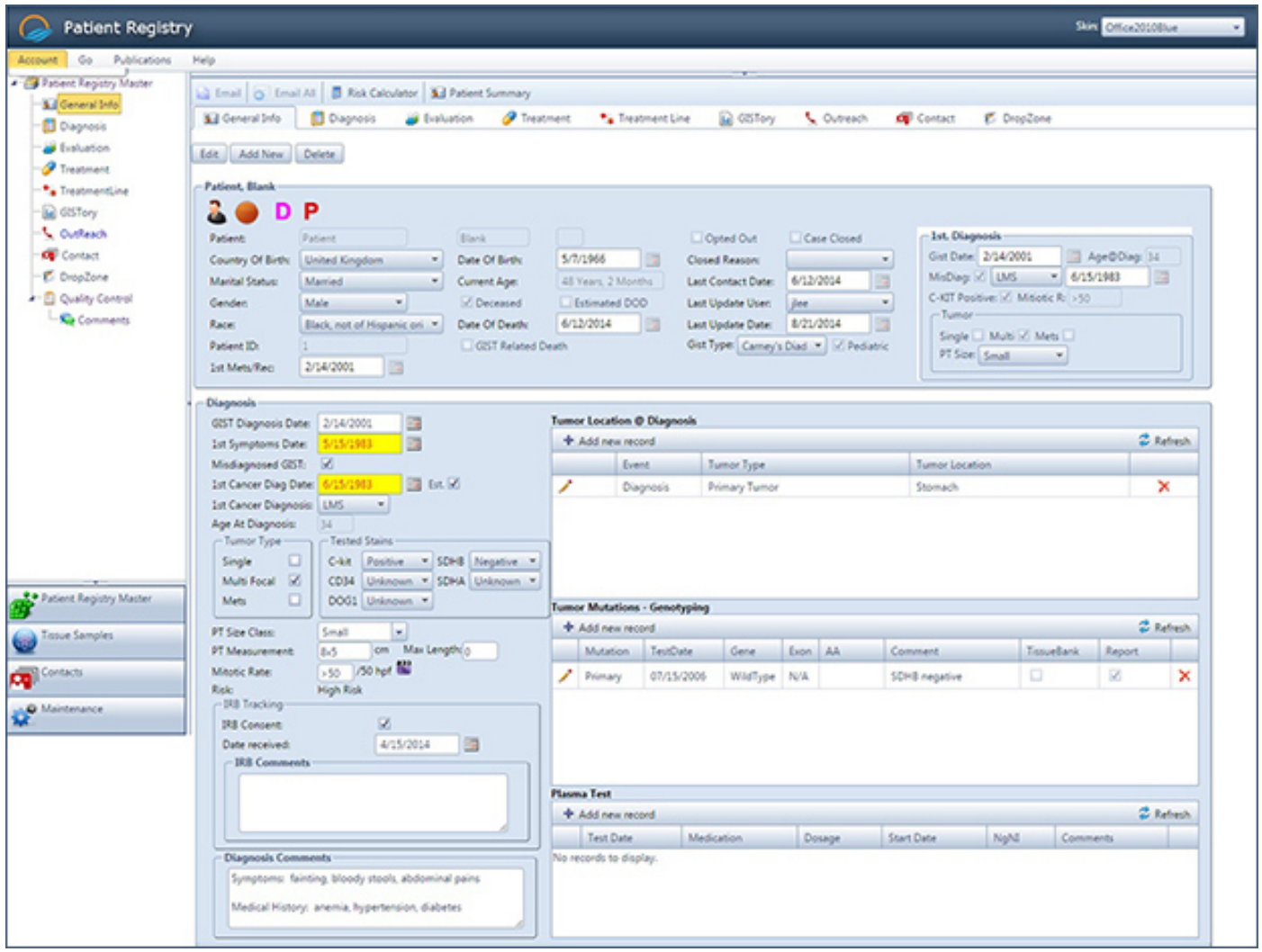
  → **Give government and insurance companies a basis for reimbursement decisions**

- **HTA bodies (examples):**
  - UK's National Institute for Clinical Excellence (NICE)
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
  - German G-BA/IQWiG

*Applies to originator drugs only, no HTA in generics!

POST MARKETING STAGE
Post Marketing Surveillance

Example of a patient-powered Patient Registry



https://liferaftgroup.org/patient-registry/

- **Host:** LRG (Life Raft Group)
- **Classification:** GIST patients
- **Source of information:** patients and caregivers
- **Main purposes:**

✓ Look for treatment and response trends that can help our members reach tomorrow's cure.

✓ Reduce the lethal lag-time between discoveries of important data to communication.

POST MARKETING STAGE
Post Marketing Surveillance

Example of a research-generated Patient Registry

- **Title:** MotHER Pregnancy Registry
- **Classification:** Pregnancy
- **Description:** Prospective, observational cohort study in women who have taken selected drugs for breast cancer during pregnancy or within seven months of becoming pregnant.
- **Main purposes:** Learn about the health of these women and their babies.

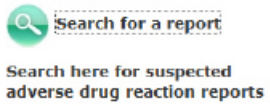
http://www.motherpregnancyregistry.com/
https://patientregistry.ahrq.gov/profile?freeText=cancer&rid=1447&cnt=5

POST MARKETING STAGE - Pharmacovigilance

Example: Europe

- **New EU Pharmacovigilance Legislation (effective since July 2012)**
  - **Reporting of Suspect Adverse Reaction by Healthcare Professionals and pharmaceutical companies**
  - **Direct consumer reporting:** online patient reporting forms hosted by national medicines regulatory authorities or by telephone.
  - EudraVigilance **Post-Authorization Module (EVPM)** for post-authorization Individual Case Safety Reports (ICSRs)
  - **Submission of Periodic Safety Update Reports (PSURs)** and **Risk Management Plans (RMPs) by pharmaceutical companies**
  - **Pharmacovigilance Audits**

http://www.adrreports.eu/en/index.html



- **Good Pharmacovigilance Practice (GVP):**
  - Set of measures to facilitate the performance of pharmacovigilance
  - Applies to MA-holders, EMA[1] and medicines regulatory authorities in EU Member States

→ **Full implementation of the new EU Legislation estimated to save 500-5.000 lives per year & savings to society of between 250 million and 2.5 billion euros per year in the EU**

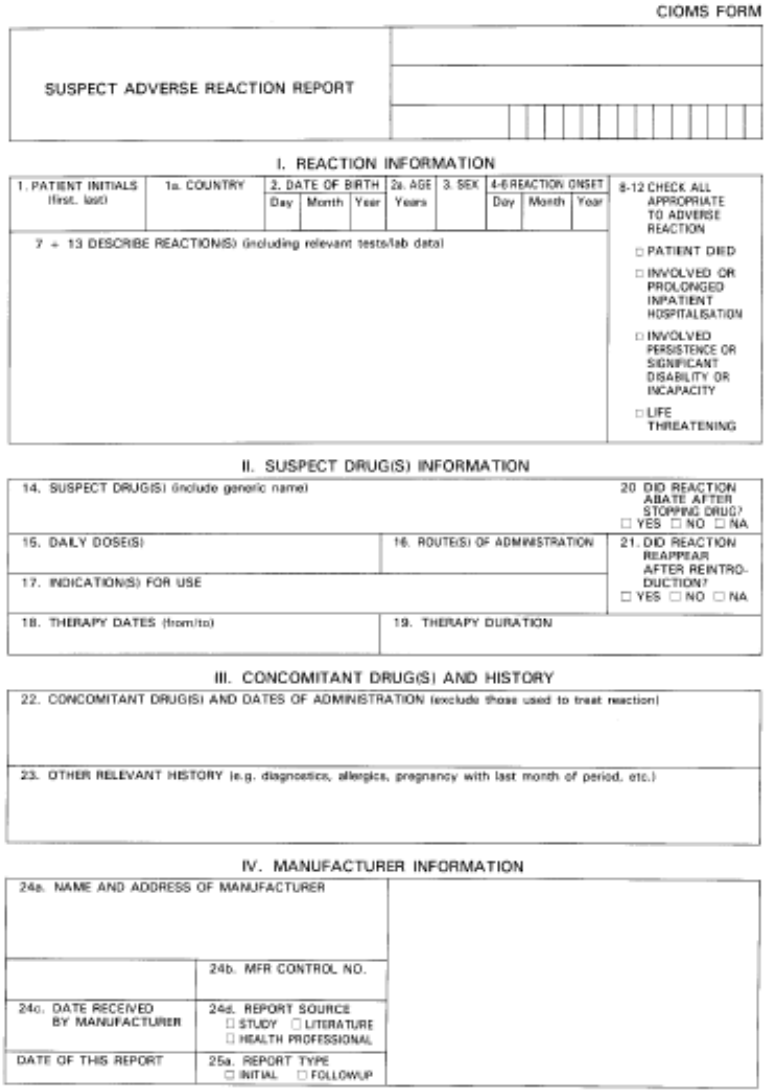
POST MARKETING STAGE - Pharmacovigilance

- **Example: USA**
  - **Periodic Safety Update Report (PSUR) must be submitted by pharmaceutical companies to FDA**
  - **MedWatch:** The FDA Safety Information and Adverse Event Reporting Program → direct reporting of adverse side effects by consumers and physicians. See:

POST MARKETING STAGE - Pharmacovigilance

- **Pharmacovigilance requirements applicable to license holders (pharmaceutical companies):**
  - Employing a QPPV (Qualified Person Responsible for PV)
  - Collection and evaluation of pharmacovigilance relevant cases
  - Individual Case Safety Report (ICSR) reporting
  - Systematic literature review and reporting
  - Periodic Safety Update Report (PSUR) submission
  - Risk Management Plan (RMP)
  - Pharmacovigilance System Master File (PSMF)
  - Standard operating procedures (SOP) on pharmacovigilance
  - Submission of variations
  - Pharmacovigilance Audits
  - …

POST MARKETING STAGE - Pharmacovigilance Suspect Adverse Reaction Report Form (CIOMS[1] Form I)[2] for Individual Case Safety Reports (ICSR)



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Healthcare professionals & companies <u>must</u> report:

- suspected adverse drug reactions including those related to quality complaints
- suspected interactions with other medicinal products and other forms of interaction
- experience during pregnancy and lactation
- data on use in children
- lack of efficacy
- overdose (symptomatic or not), abuse and misuse (symptomatic or not)
- medication errors

Minimum criteria:

- identifiable patient
- suspect drug/substance
- suspected adverse reaction
- identifiable reporter (primary source)

[1] CIOMS = Council for International Organizations of Medical Sciences (Associate Partner of UNESCO – in official relations with WHO

[2] Widely accepted standard for expedited adverse event reporting

POST MARKETING STAGE – Phase IV clinical trials[1] vs. observational studies

	Phase IV Clinical Trial	Observational study
Objectives	•Monitor drug's long-term effects •Provide additional details about efficacy and safety of the drug	
Design	•Randomized, controlled, blind •Narrow inclusion/exclusion criteria	•Routine clinic. practice setting •Less rigorous •Protocol driven
Study fields	•Different formulations, dosages, durations of treatment •New age groups, races, types of patient (e.g. pregnant women,…)	
Intervention	Interventional	Non-intervent. / observational
Reasons for conducting study	•Requested by Regulatory Authorities •Competitive reasons of manufacturer (e.g. finding new market for the drug) •Exploring and measuring ways to improve comfort and QoL,…	
Level of evidence	High	Lower
Cost	High	Low

[1] applicable to innovator products only!

Quality standards: The situation with generics

"The standards for quality are the same for brand name and generic products." Gary Buehler, Director of FDA's Office of Generic Drugs

(applies to all tightly regulated countries / areas such as US or EU)

Same FDA Requirements for Brand-Name and Generic Drugs

For reformulations of a brand-name drug or generic versions of a drug, FDA reviews data showing the drug is bioequivalent to the one used in the original safety and efficacy testing.	Brand Name Drug	Generic Drug
FDA evaluates the manufacturer's adherence to good manufacturing practices before the drug is marketed.	X	X
FDA reviews the active and inactive ingredients used in the formulation before the drug is marketed.	X	X
FDA reviews the actual drug product.	X	X
FDA reviews the drug's labeling.	X	X
Manufacturer must seek FDA approval before making major manufacturing changes or reformulating the drug.	X	X
Manufacturer must report adverse reactions and serious adverse health effects to the FDA.	X	X
FDA periodically inspects manufacturing plants.	X	X
FDA monitors drug quality after approval.	X	X

Source: U.S. Food and Drug Administration (FDA): http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm134444.htm (accessed 27.02.2015)

Myths and Facts about Generic Drugs

MYTH: Generics take longer to act in the body.
FACT: The firm seeking to sell a generic drug must show that its drug delivers the **same amount of active ingredient** in the **same timeframe** as the original product.

MYTH: Generics are not as potent as brand-name drugs.
FACT: FDA requires generics to have the **same quality, strength, purity, and stability** as brand-name drugs.

MYTH: Generics are not as safe as brand-name drugs.
FACT: FDA requires that all drugs be safe and effective and that their benefits outweigh their risks. Since generics use the same active ingredients and are shown to work the same way in the body, they have the **same risk-benefit profile** as their brand-name counterparts.

MYTH: Brand-name drugs are made in modern manufacturing facilities, and generics are often made in substandard facilities.
FACT: FDA won't permit drugs to be made in substandard facilities. FDA conducts about 3,500 inspections a year in all firms to ensure standards are met. Generic firms have **facilities comparable to those of brand-name firms**. In fact, brand-name firms account for an estimated 50 percent of generic drug production. They frequently make copies of their own or other brand-name drugs but sell them without the brand name.

MYTH: Generic drugs are likely to cause more side effects.
FACT: There is no evidence of this. FDA monitors reports of **adverse drug reactions** and has found **no difference in the rates** between generic and brand-name drugs.

Source: U.S. FDA: http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm134444.htm (accessed 27.02.15)

References

http://www.pharmainfo.net/reviews/new-drug-approval-process-regulatory-view
http://www.ifpma.org/quality/inspections.html
http://www.ema.europa.eu
http://www.adrreports.eu/docs/ADR_reporting_FINAL_EN.pdf
http://www.adrreports.eu/en/index.html
www.fda.gov
http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
http://cioms.ch/index.php/cioms-form-i
http://apps.who.int/medicinedocs/en/d/Js6164e/#Js6164e
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148611
http://www.sgs.com/~/media/Global/Documents/Technical%20Documents/SGS-Clinical-Marketing-Authorization-EN-09.pdf
http://www.cmladvocates.net/generics/glossary
www.cmladvocates.net
http://www.ncbi.nlm.nih.gov/books/NBK164514/
http://www.motherpregnancyregistry.com/
https://patientregistry.ahrq.gov/
http://www.virginia.edu/vpr/irb/HSR_docs/CLINICAL_TRIALS_Phases.pdf
http://www.mednetstudy.com/observational-studies-conducting-research-on-approved-treatments-in-real-world-settings/
http://www.encepp.eu/publications/documents/ENCePPinterpretationofnoninterventionalstudies.pdf
http://en.wikipedia.org/wiki/Marketing_authorization
http://en.wikipedia.org/wiki/Postmarketing_surveillance
http://en.wikipedia.org/wiki/Phases_of_clinical_research
http://en.wikipedia.org/wiki/Abbreviated_New_Drug_Application
http://en.wikipedia.org/wiki/Generic_drug
http://flexikon.doccheck.com/de/Anwendungsbeobachtung
http://www.ictsd.org/bridges-news/bridges/news/india-grants-first-compulsory-license-to-generic-drug-producer
http://www.i-mak.org/storage/Oxfam%20-%20Voluntary%20Licensing%20Research%20IMAK%20Website.pdf
European Patients' Academy Expert Training Course, Modul 1 & 2
http://www.cancerworld.org/Articles/Issues/65/March-April-2015/Systems--Services/708/Generic-cancer-drugs-that-we-can-trust.html