2014 Scientific Symposium of EIPG
Sofia, April 11th

CURRENT LANDSCAPE FOR SAFETY REPORTING IN CLINICAL TRIALS

Borislav Borissov MD, PhD

Acknowledgment Prof. L. Martini


1960 Thalidomide – app. 10000 fetuses affected

1970 – DES /diethylstilbestrol - >160 000 children exposed – cancer, pregnancy disorders, morphological anomalies.

Drugs safety shake-up urged

FT 28.01.05

U watchdog calls for better monitoring ● Slower release times sought for products ● Comments set to spark transatlantic debate

How do we stop the Vioxx disaster happening again?

This question is exercising the minds of drug companies and scientists like. A report in this week's Lancet stimates there are 140,000 people with serious heart disease in the US aused by use of the painkiller Vioxx. The arthritis drug was withdrawn

taking Vioxx had a 34% higher chance of coronary heart disease than those on other painkillers.

British experts say up to half a million people in the UK may be affected.

"Signals of the problem were noted between 1999 and

Dr Graham agrees. "The US regulatory authority hasn't acted on behalf of public health, but corporate interests. It was aware of the scale of the problem in June 2000 but waited two years to

Drug firms warned to publish trial data after safety fears

ARE DRUG FIRMS AN UNHEALTHY INFLUENCE ON YOUR MEDICINE?

Arthritis pill heart attack warning to 600,000 users

PHARMACEUTICAL INDUSTRY

Ministers set rules for medicines regulators

Europe urged to keep eagle eye on drugs already in the market place

Andrew Jack hears the EU's top regulator call for more independent funding to do extra research on medicines already granted approval

Sharper teeth for medicines watchdog

A bitter pill for pharmaceuticals to swallow

...ffering from a bad case of distrust in the eyes of the public, writes David Firn

VIOXX®

STROKE ~ HEART ATTACK ~ DEATH
BLOOD CLOTS ~ PULMONARY EMBOLISM

Merck Pharmaceutical has recalled the popular pain and arthritis medication Vioxx® (rofecoxib) from the market after studies revealed that it may increase the risk of blood clots, stroke, heart attack and death. According to acting FDA commissioner Dr. Lester M. Crawford, "Overall, patients taking the drug chronically face twice the risk of heart attack compared to patients receiving a placebo."

YOU MAY BE ENTITLED TO MONEY DAMAGES

If you or a loved one have suffered a stroke, heart attack or deat
call attorney James Rolshouse toll free at 888-VIOXX-87 (8

James Rolshouse & Associates
Personal Injury Attorney

visit us online at

TOLL FREE 888


Market Repo
BY MICKEY
Glaxo shares under fire as $400m lawsuit loom

Remicade (Infliximab)
Side Effects Lawsuits

Tuberculosis, Multiple Sclerosis, Lupus, and Serious Infections

Click here to contact an experienced Risperdal Attorney.

The-Plavix-Lawyer.com
Ennis & Ennis, P.A.

1-800-856-6405
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- May 18, 2000. The New England Journal of Medicine, Vol. 342 **: Is Academic Medicine for Sale?;** автор Marcia Angell, MD

- May 22, 1999. The New York Times, Editorial: **Patients for Hire, Doctors for Sale**

"If you can't trust the studies, what happens to the profession and what happens to patients." John Wasson, M.D., Dartmouth, New York Times

Associated Press

THE TIMES

Letter to the Editor, 1996:

Sir, My wife has been prescribed pills. According to the accompanying leaflet, possible side-effects are: sickness, diarrhoea, indigestion, loss of appetite, belching, vertigo, abdominal cramps, dizziness, stomach ulcers, bleeding from intestine or blood diarrhoea, ulcerative colitis, sore mouth and tongue, constipation, back pains, inflammation of pancreas, mouth ulcers, skin rashes, hair loss, sensitivity to sunlight, drowsiness, tiredness, impaired hearing, difficulty with sleeping, seizures, irritability, anxiety, depression, mood changes, tremor, memory disturbances, disorientation, changes in vision, ringing in ears, bad dreams, taste alteration, allergic reactions, swelling due to water retention, palpitations, impotence or tightness of the chest.
Should she take them?
Yours faithfully,

EU Regulatory landscape:

New PhV legislation – Regulation 1235/2010 and Directive 2010/84 was adopted by European parliament and Counsel in December 2010.

This new legislation is *the biggest change in EU pharmaceutical regulation since 1995* and has significant implications for industry and regulatory agencies:

- To make roles and responsibilities clear,
- To minimize duplication efforts,
- To optimize resources by rationalizing and simplifying ADR and PSUR reporting,
- To establish a clear legal framework for post-authorization monitoring.

Why new rules:

In EU:

-5% of all hospital admissions are due to adverse drug reactions,

-5% of all hospital patients experience an adverse drug reaction,

-Adverse drug reactions are the 5th most common cause of hospital death,

-The legislation will /?/ save 5910 lives per year across the EU!

as well as:

Mixed responsibilities,

Too complex reporting rules, even more complex decision making process,

Differences at member state level, too soft penalties in some countries,

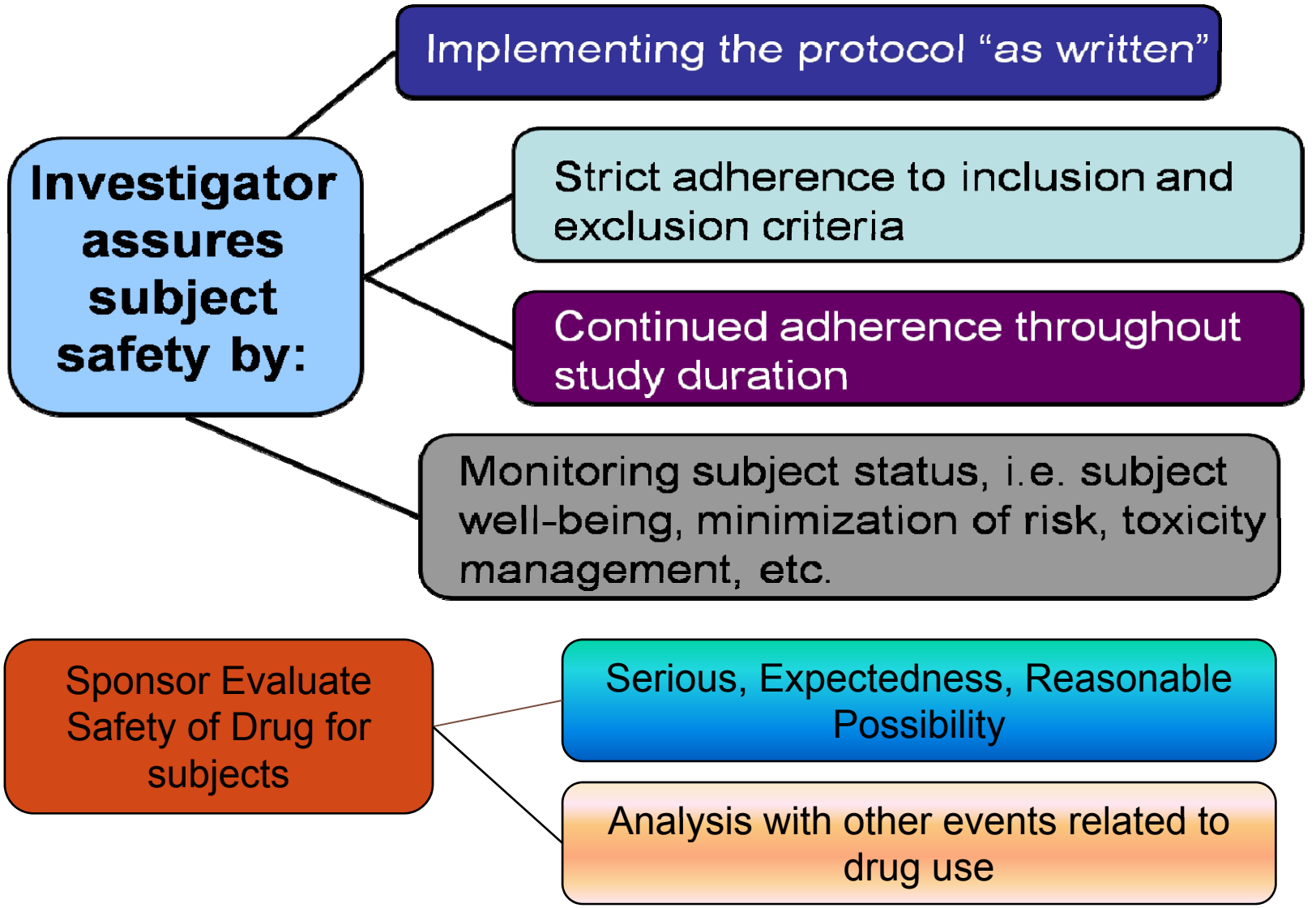
Lack of robust safety studies. . .

Why do we need to monitor safety post marketing?

REAL LIFE IS NOT LIKE A CLINICAL TRIAL

- Clinical trials only encompass a very small selected section of the population
- No pregnancy
- Concomitant medications are controlled
- Long term use
- Yellow card scheme

Safety Monitoring



1. New EU safety rules – impact on CTs:

SUSAR =

SUSPECTED

UNEXPECTED

SERIOUS

ADVERSE

REACTION

SUSAR =

SUSPECTED

UNEXPECTED

SERIOUS

ADVERSE

REACTION

Causality between event and IMP

«reasonable causal relationship»

SUSAR =

SUSPECTED

UNEXPECTED

SERIOUS

ADVERSE

REACTION

- it results in death
- it is life-threatening
- it requires hospitalisation or prolongation of existing hospitalisation
- it results in persistent or significant disability or incapacity
- it is a congenital anomaly or birth defect

An important medical event is also ‘serious’ if it jeopardises the clinical trial participant or requires an intervention to prevent a serious outcome

SUSAR =

SUSPECTED

UNEXPECTED

SERIOUS

ADVERSE

REACTION

Adverse reactions should be considered as unexpected if the nature OR severity of the reaction(s) is not consistent with the reference information for the IMP.

How to Handle - SUSARs

- Assess AE for
  - *seriousness*
  - *causality*
  - *expectedness*
- If serious, suspected causally related and NOT expected
  ➢SUSAR
- Expedited reporting to MHRA / MREC / Sponsor
  - ***fatal or life threatening*** = 7 days, follow-up in 8 days
  - ***other*** = 15 days
  - Report even if occurred outside the MS

SUSARs - What to report

Initial expedited reports must contain:

- A suspected investigational medicinal product
- An identifiable subject
  - initials, sex, age, date of birth, trial number
- An adverse event assessed as serious and unexpected and a reasonable suspected causal relationship
- An identifiable reporting source
  - Health care professional to report to regulatory authority
- Clinical trial identification
  - EudraCT number
  - Unique Sponsor's ID number
- Treatment assignment after unblinding and validation (or not) of the suspected causes

Data Elements for SUSAR Report

- Age
- Sex
- Medical History
- Daily dose of suspected medicinal product and regimen
- Start date
- End date
- Duration
- Indications for which suspect medicinal product was prescribed
- Starting date of onset of reactions (or time to onset)
- Dechallenge
- Rechallenge
- Causal relationship assessment
- Concomitant Drugs listed
- Concomitant Start date
- Concomitant End date

SUSAR Additional Information (Follow-up)

- If serious, criterion or criteria for regarding the case as serious
- Full description of reactions
- Patient outcome (at case level and when possible at event level)
- For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reactions
  - Any autopsy or post mortem findings
- Other relevant aetiological factors
- Stopping date and time or duration of treatment
- Specific tests and/or treatment required and their results

Special situations

- Pregnancy or impregnation
  - Follow up to birth
- Lack of efficacy
  - Not normally reported but can be discussed in periodic safety update report
- Overdose / abuse / Misuse
  - Pharma companies should provide guidance

FDA: Sept 2010

- Guidance for Industry And Investigators:
  - Safety Reporting Requirements for INDs and BA/BE Studies
- New Regulations
  - 21 CFR 312 IND Safety Reporting
  - 21 CFR 320 BA/BE Studies
- Refers to Drugs and Biologicals
- Closer alignment to ICH/EMA requirements

SUSARS

- For the first time FDA recognizes SUSARs
- Three criteria
  - Suspected adverse reaction
  - Serious
  - Unexpected
- Expedited IND safety report

2. New EU safety rules – impact on CTs:

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	EudraCT No.: 2005-001627-11

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
					60 year(s)	Male	88.00 kg	28	APR	2006	

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [LOWER LEVEL TERM] (Related symptoms if any separated by commas)
Cat scratch to thumb leading to infection [Infection]

Case Description: Sponsored Study ; Prot. ; Ctr. ; Pat.

REFERENCES:
IE-ASTELLAS-2006EU001586 (E2B Company Number)
Astellas paper report ID 2006EU001586 (E2B Report Duplicate)
Local ID 2006ECT001 (E2B Report Duplicate)
(continue)

☐ PATIENT DIED
☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION (Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)
#1 Tamsulosin OCR Tablet Blinded(Code not broken) (continue)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1 1 DF, UID/QD

16. ROUTE(S) OF ADMINISTRATION
#1 Unknown

17. INDICATION(S) FOR USE
#1 Benign prostatic hyperplasia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES (from/to)
#1 07-APR-2006 / Ongoing

19. THERAPY DURATION
#1 Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1 FLUCLOXACILLIN (FLUCLOXACILLIN) , ; 28-APR-2006 / 04-MAY-2006

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Indication	Benign prostatic hyperplasia

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Astellas Pharma Europe B.V.

Elisabethhof 19
Leiderdorp, 2353 EW NETHERLANDS

25. REMARKS

24b. MFR CONTROL NO.
2006EU001586

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
18-MAY-2006

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
23-MAY-2006

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

CIOMS form

age 2 of 2

Mfr. Control Number: 2006EU001586

ADDITIONAL INFORMATION

13. DESCRIBE REACTION(S) continued

:VENT INFORMATION #1>
ERBATIM TERM: Cat scratch to thumb leading to infection
T: Infection
: Infection
NSET DATE: 28-APR-2006
FFSET DATE:
TENSITY:
JTCOME: Recovering / Resolving
ERIOUSNESS CRITERIA: Hospitalized
AUSALITY (INV): Definitely Not
AUSALITY (MFR): Definitely Not

arrative: Study No. , Center , Patient . Randomisation date 06APR2006, medication no 761002.
randomized, double-blind, placebo-controlled study with two treatment arms (Tamsulosin OCAS 0.4 mg & placebo) to assess the ect of Tamsulosin OCAS 0.4 mg tablets, once daily on nocturia, compared to placebo, in patients with lower urinary tract symptoms sociated with benign prostatic hyperplasia. The study will comprise a 2-week single-blind placebo run-in followed by a 12-week uble-blind treatment period.
male 60 year old patient started double blind treatment from 07APR2006 following the placebo run in period. On 28APR2006 tient suffered from a cat scratch which led to thumb infection. Patient was seen by his GP who prescribed flucloxacillin until AY2006. The infection increased as seen by the GP on 8MAY2006 and patient was referred to hospital where he received ravenous antibiotics from 8MAY2006 to 12MAY2006. He was discharged from hospital on 13MAY2006, with treatment with oral tibiotics not otherwise specified. On the last visit 17MAY2006 the infection was improving. Treatment with antibiotics was continued 1 week.

aluator Comment:
incidental event, causality not related.

-19. SUSPECT DRUG(S) continued

SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Tamsulosin OCR Tablet Blinded(Code not oken)Orodispersable CR tablet, Unknown; gimen #1	1 DF, UID/QD; Unknown	Benign prostatic hyperplasia	07-APR-2006 / Ongoing; Unknown
Tamsulosin OCR Tablet Blinded(Code not oken)Orodispersable CR tablet, Unknown; gimen #2	0 mg, UID/QD; Unknown		Unknown; Unknown

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3. New EU safety rules – impact on CTs: DSUR reporting

Format

- Reference ICH E2F, DSUR (previous ASR)
- To be prepared after first authorization of a clinical trial in Europe

Reference Safety Information

- RSI applicable at the start of reporting periods and to be attached in appendix
- RSI serves as reference during reporting period

RSI changes/updates

- Substantial amendment to LEC and CA
- Alignment of DSUR, Investigator's Brochure and/or RSI update = alignment reporting period and reference documents.

DSUR reporting (2)

Content

- Listing all SUSARs (yearly basis) and Safety Summary
- To LEC and CA.

Start of DSUR submission to CA

- After first authorization by CA of a clinical trial with this IMP
  - Most recent DSUR to submit with initial CTA dossier, if study start in a MS is later than first authorization
  - Line listing unblinded SUSARs to fill possible gap?

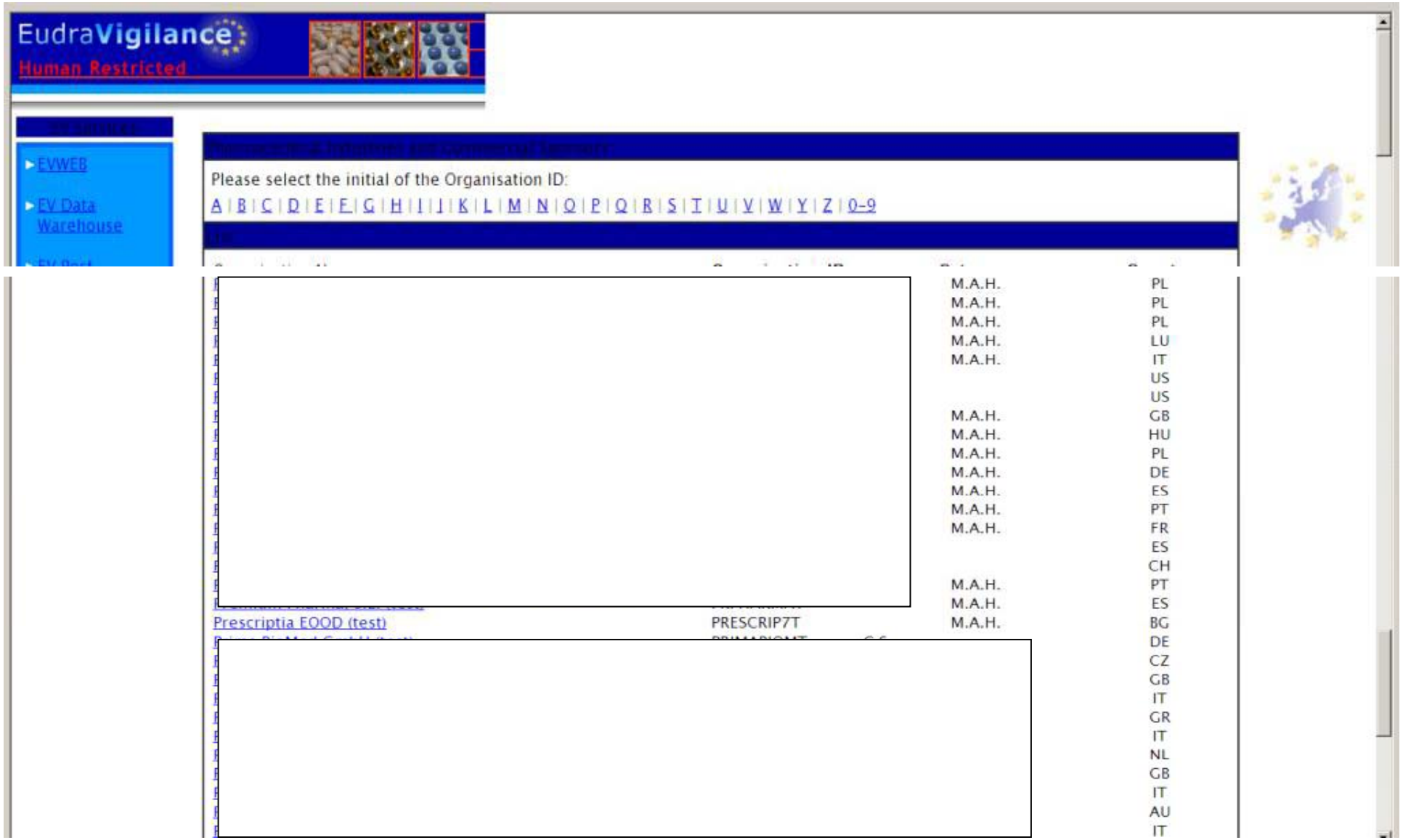
End of reporting

- Until LVLP in a MS = End of exposure
- Or until End of Trial criteria as specified in the protocol

DSUR reporting (3)

- **No DSUR required for trials < 1 year**
- **The Clinical Trial Report (CSR), as a part of the End of Trial notification, will serve as DSUR in this case**
  - CSR is not a part of the EOT notification
  - CSR issued max. 1 year later after worldwide EOT
  - No local EOT, only worldwide EOT
- **Recommended to submit DSUR if more short studies < 1 year with same IMP**
  - Recommendation or obligation ?

4. New EU safety rules – impact on CTs:


EudraVigilance
Human Restricted
EVWEB
EV Data Warehouse
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Prescriptia EOOD (test) PRESCRIP7T M.A.H. BG
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NL
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IT
AU
IT

From: evtraining [mailto:evtraining@ema.europa.eu]
Sent: Thursday, July 12, 2012 4:26 PM
To: Mariana Stoykova
Subject: Notification - Successful completion of the XEVMPD knowledge evaluation

Dear Mariana Stoykova,

This is a notification confirming your **successful completion** of the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) knowledge evaluation.

To register your Organisation with EudraVigilance for the electronic submission of information on medicines in accordance with Article 57(2), second subparagraph of Regulation (EC) No. 726/2004, **please attach this notification to the documents requested as part of the EudraVigilance registration process.**

The necessary registration documents can be accessed at: http://eudravigilance.ema.europa.eu/human/HowToRegister08.asp

For your information, please see below the feedback on your knowledge evaluation.

Yours sincerely,

European Medicines Agency

Part 1: Multiple-Choice Questionnaire
Pass
95%

Part 2: XEVMPD Product Message Report -
Pass
100%

Registration Date: 17/07/2012 Approval Date: 14/08/2012

Organisation Information

Category:	Marketing Authorisation Holder
Trademark:	Prescriptia
Organisation Identifier:	PRESCRIP7P
Organisation Name:	Prescriptia EOOD
Street:	28, Hristo Botev Blvd.
City:	Sofia
Postal Code:	1000
Area/State:	
Country:	Bulgaria
Functional Email:	office@prescriptia.com

Qualified Person Information

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Family Name:	Stoykova
Title:	Dr
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City:	Sofia
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Country:	Bulgaria
Telephone:	359-29434-773
Mobile:	359-888268686
Fax:	359-29434-225
Email:	mariana.stoykova@prescriptia.com

QPPV Alternative Contact Details

Name:	Adriana Vladimirova
Telephone Number:	359-29434773-

Transmission Mode

Send:	Direct
Via:	WebTrader

Sending Reports

Safety Reports:	NO
Product Reports:	YES

Third Party Information

Company Name:	
City:	
Street:	
Postal Code:	
Area/State:	
Country:	
Responsible:	
Telephone:	
Mobile:	
Fax:	
Email:	

Visibility

Affiliates Visibility:	No

MedDRA

Type of License:	Low Revenue MedDRA EudraVigilance Fee Waiver
Number:	EMA/SME/221/12

Security Information

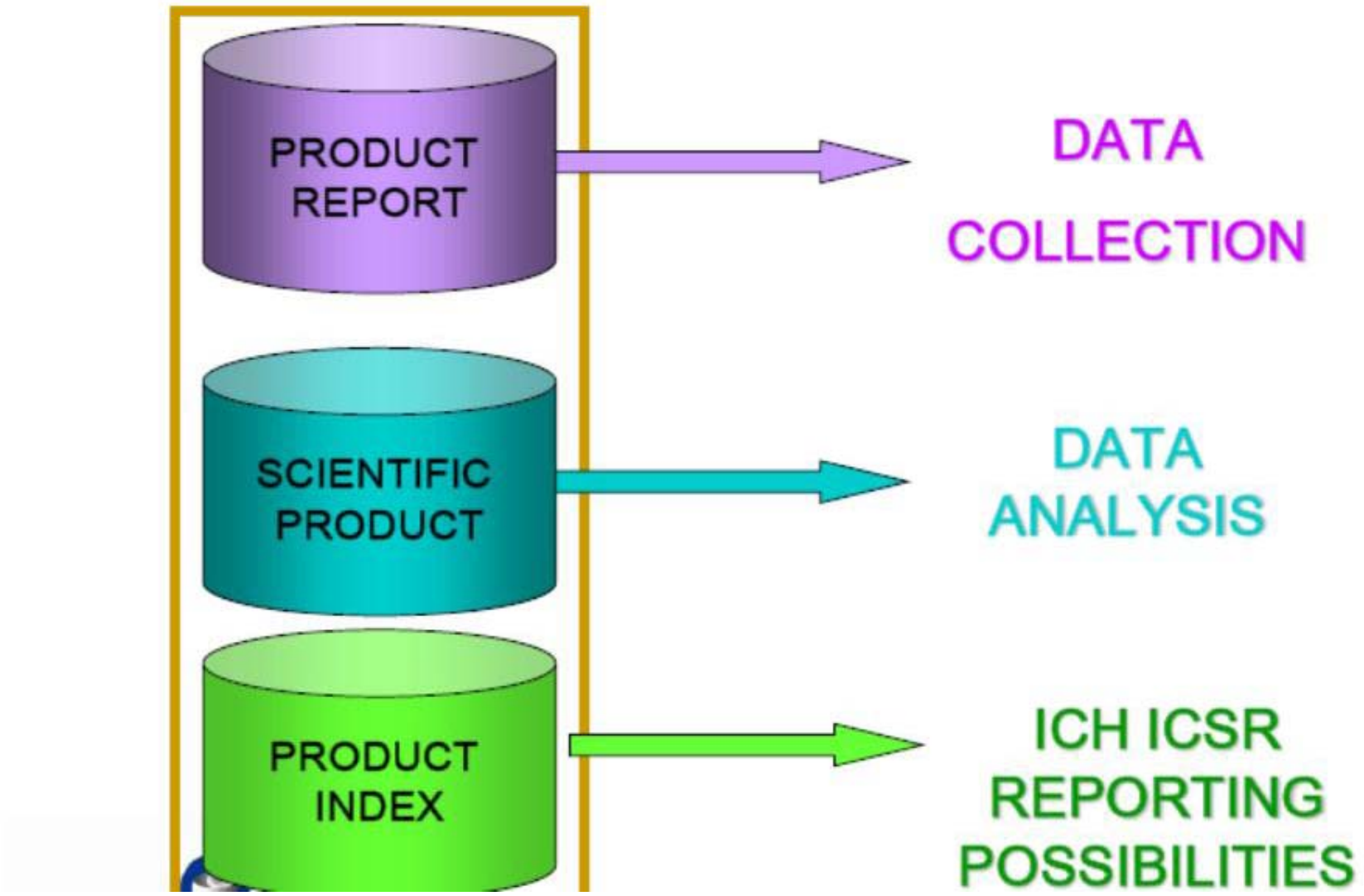
Grant Access to: All Computers

Users

Family Name	Date of Request	Approved

EudraVigilance

XEVMPD - Data Architecture



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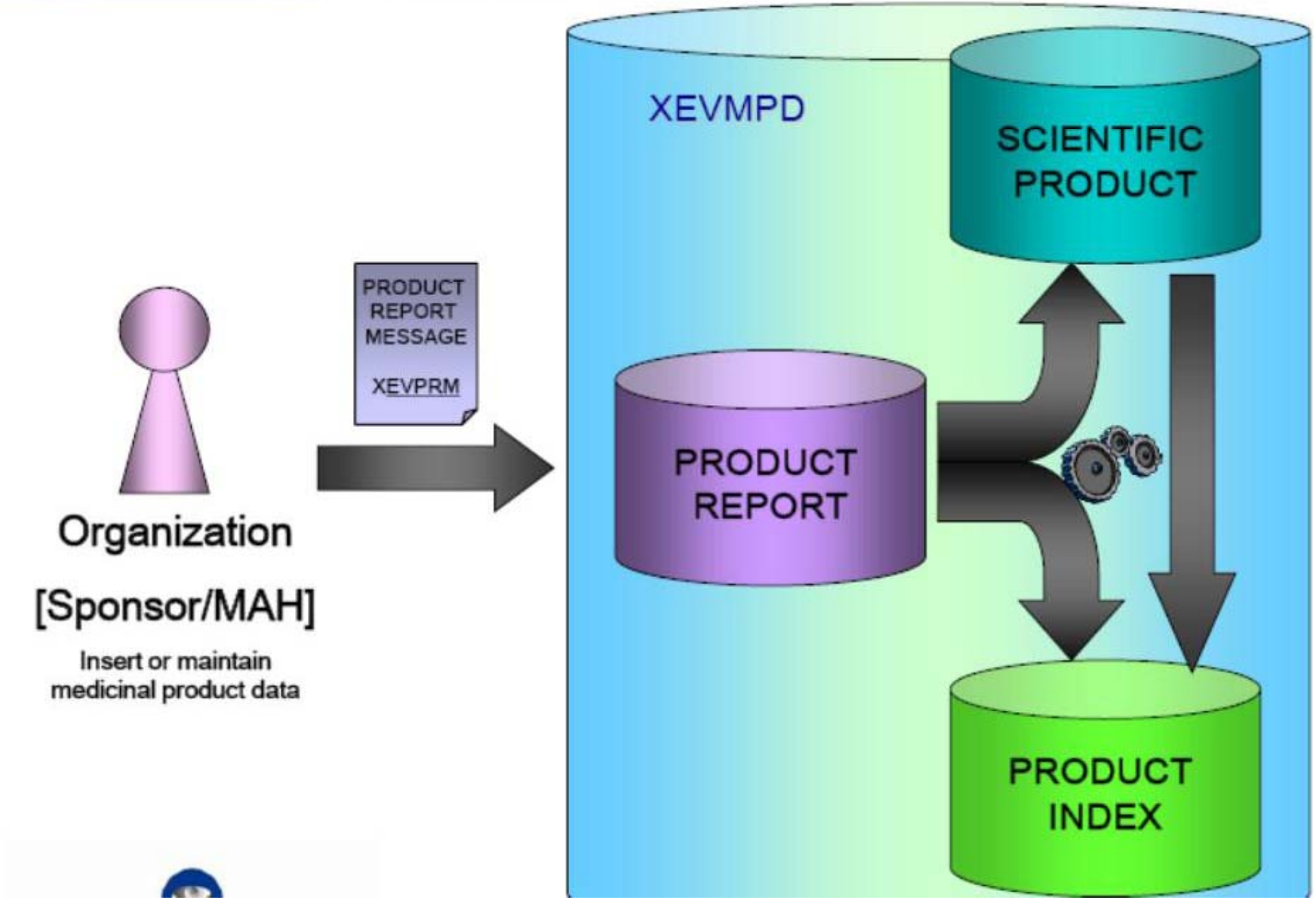

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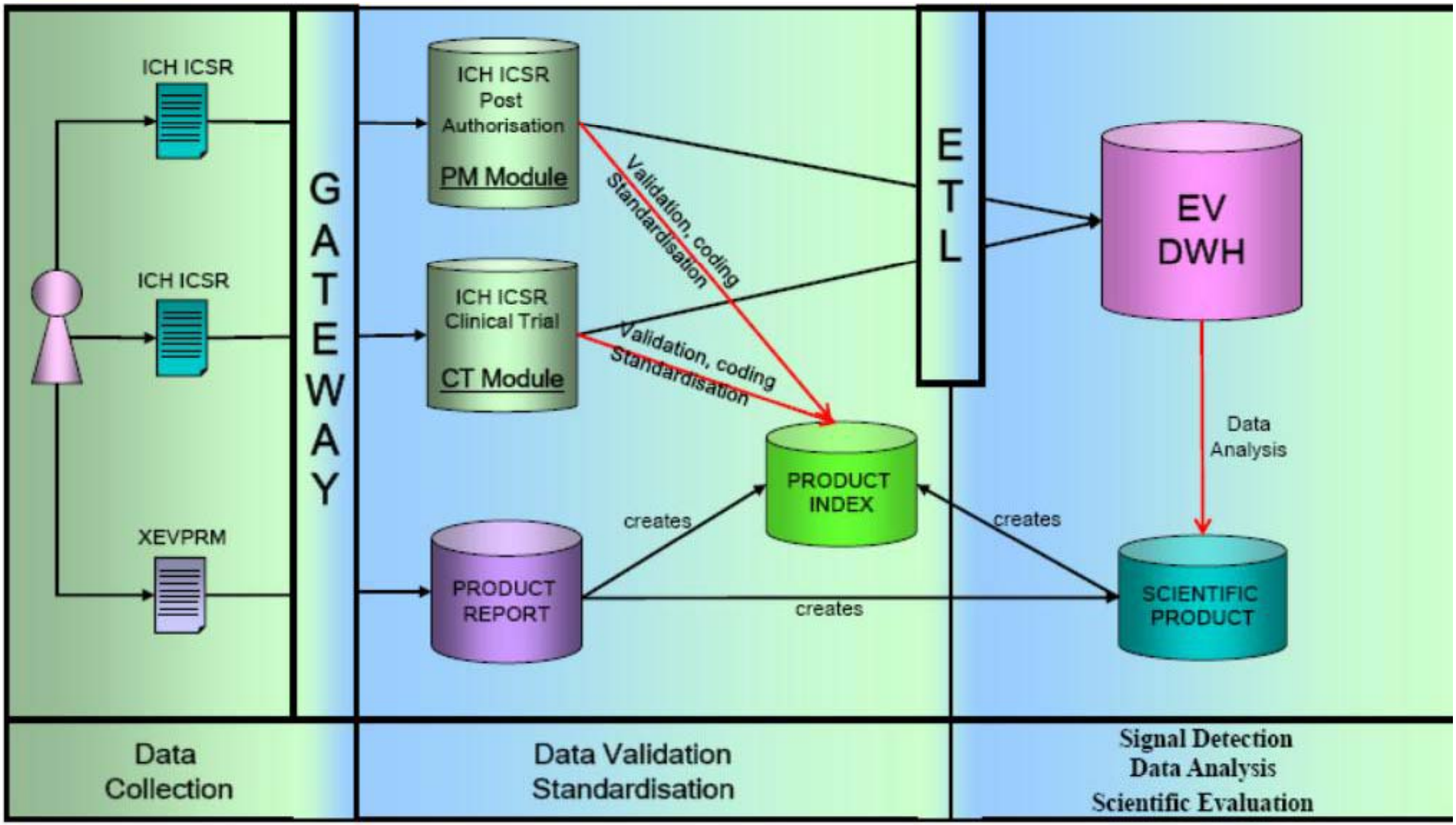

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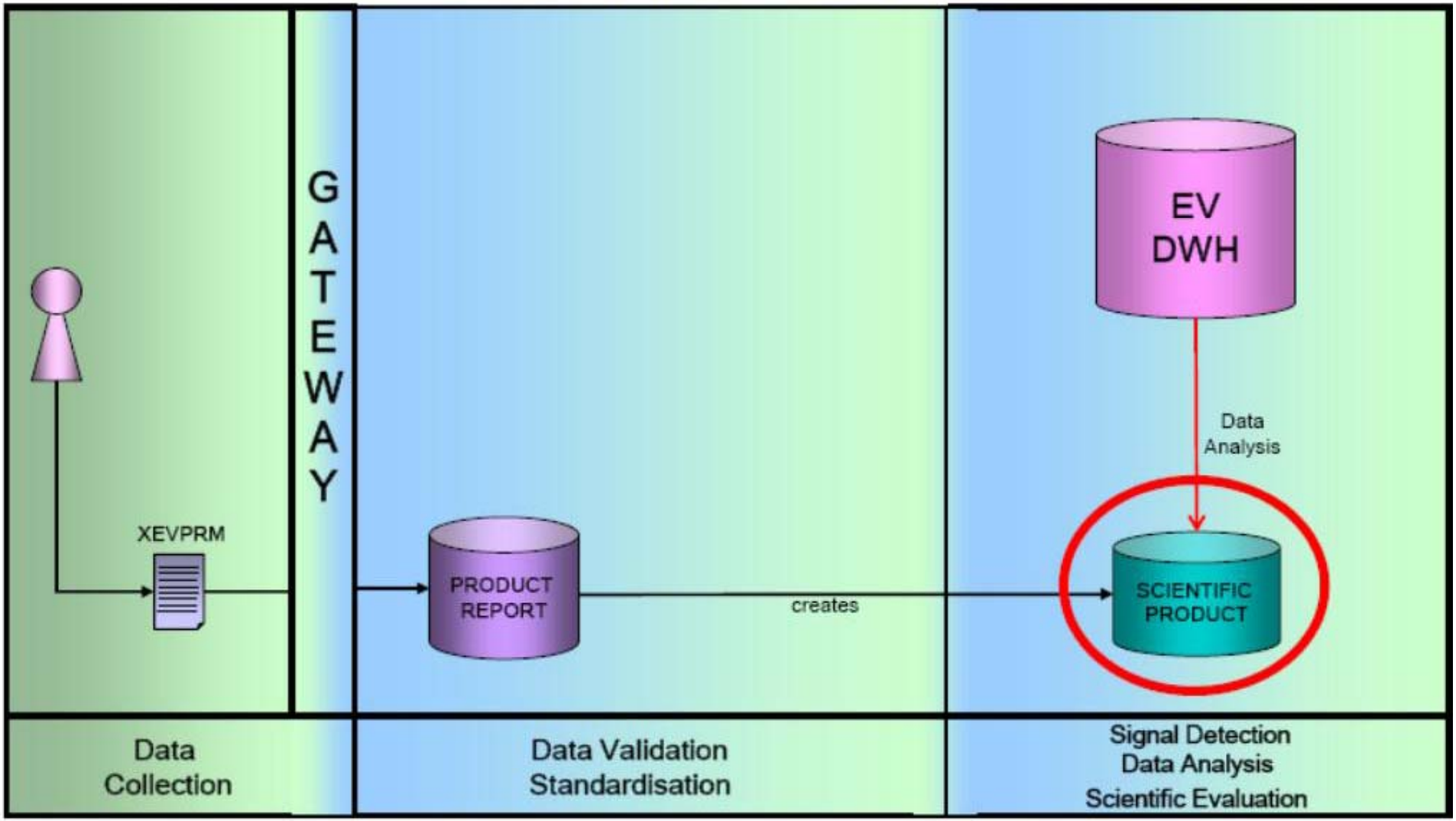
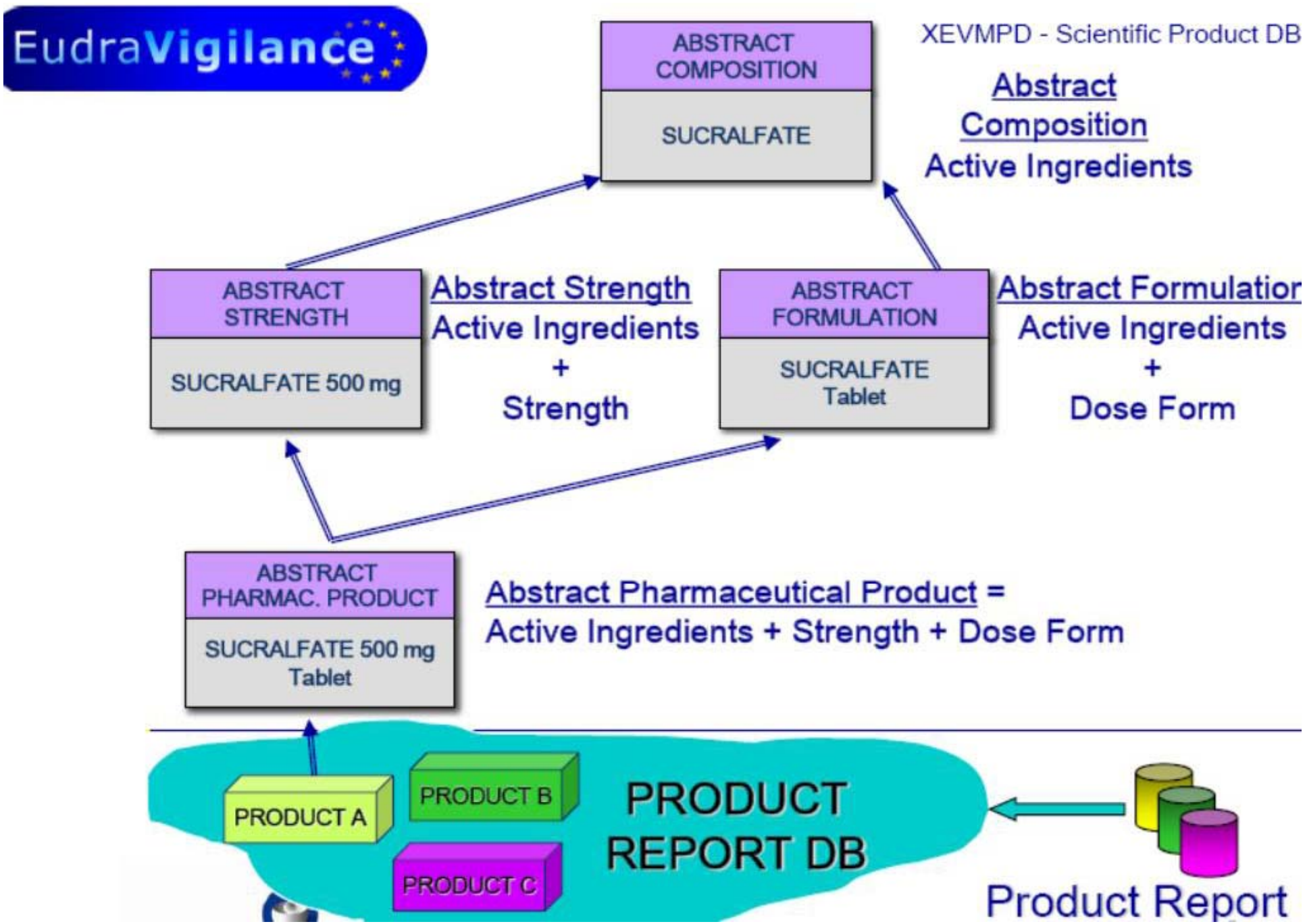
XEVMPD - Scientific Product DB

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Active Ingredients
+
Strength
ABSTRACT FORMULATION
SUCRALFATE Tablet
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+
Dose Form
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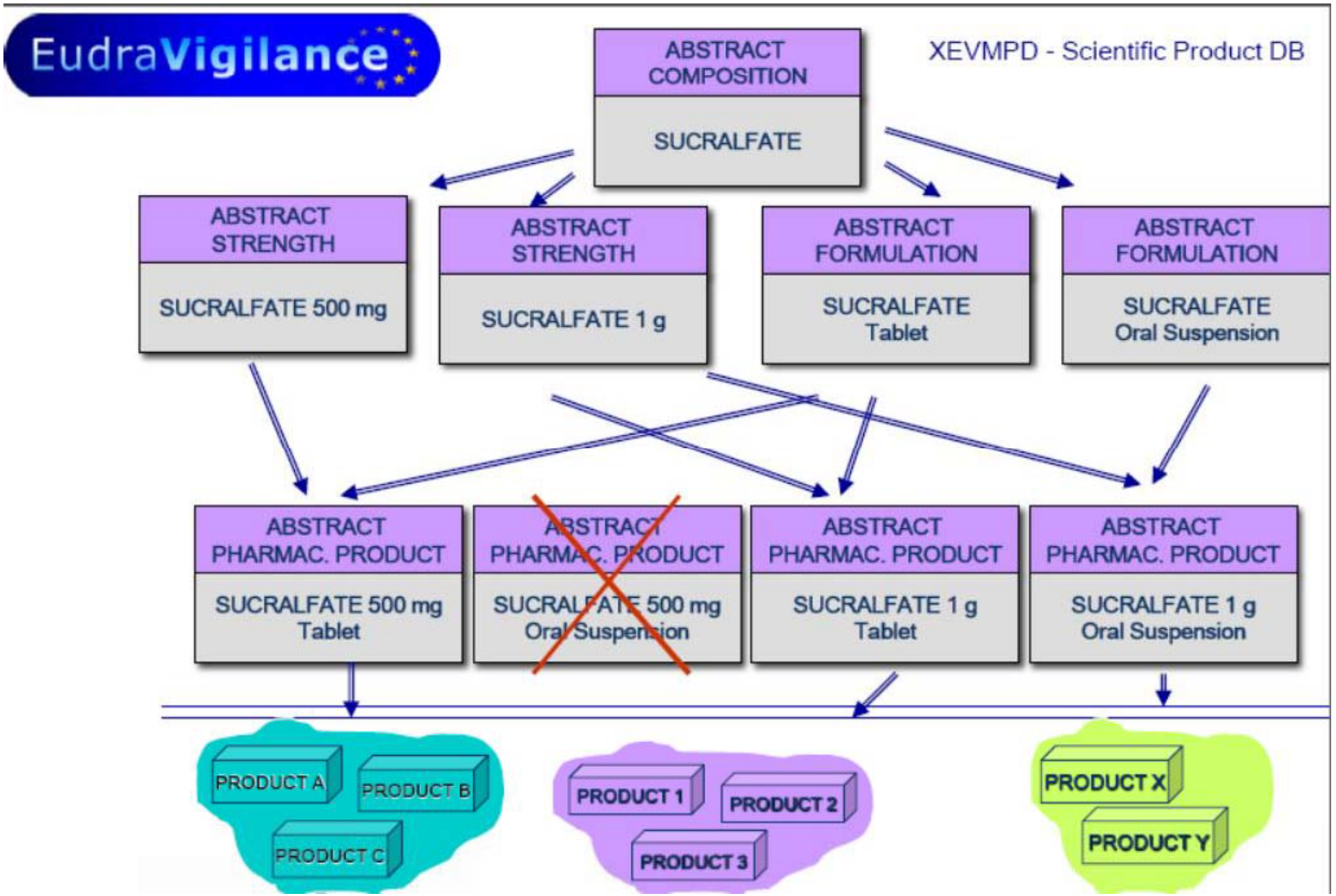
PRODUCT B
PRODUCT C
PRODUCT REPORT DB
Product Report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XEVMPD - Scientific Product DB
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ABSTRACT FORMULATION
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SUCRALFATE 1 g Tablet
ABSTRACT PHARMAC. PRODUCT
SUCRALFATE 1 g Oral Suspension
PRODUCT A
PRODUCT B
PRODUCT C
PRODUCT 1
PRODUCT 2
PRODUCT 3
PRODUCT X
PRODUCT Y

Conclusion

New focus in PhV – continuous Risk management,

Goal is to maximize benefits and minimize risks of the products,

Safety does not mean *Risk Free*

Safe = the predicted risk is reasonable given the expected benefits

"If you remember, I did mention possible side-effects."

There was something a little different about this one so it seemed better to be safe and sure. *Dr. Frances Oldham Kelsey on blocking Thalidomide s U.S. drug approval*

... [C]an we learn from this lesson; or can mankind educate itself only by disaster and tragedy? *Sen. Paul Douglas on Kefauver-Harris Amendments to the Food and Drug laws, Aug. 8, 1962*