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Inefficiencies in pharmacovigilance: what can we do now and what could be done in the future

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EU QPPV Helsinn Birex

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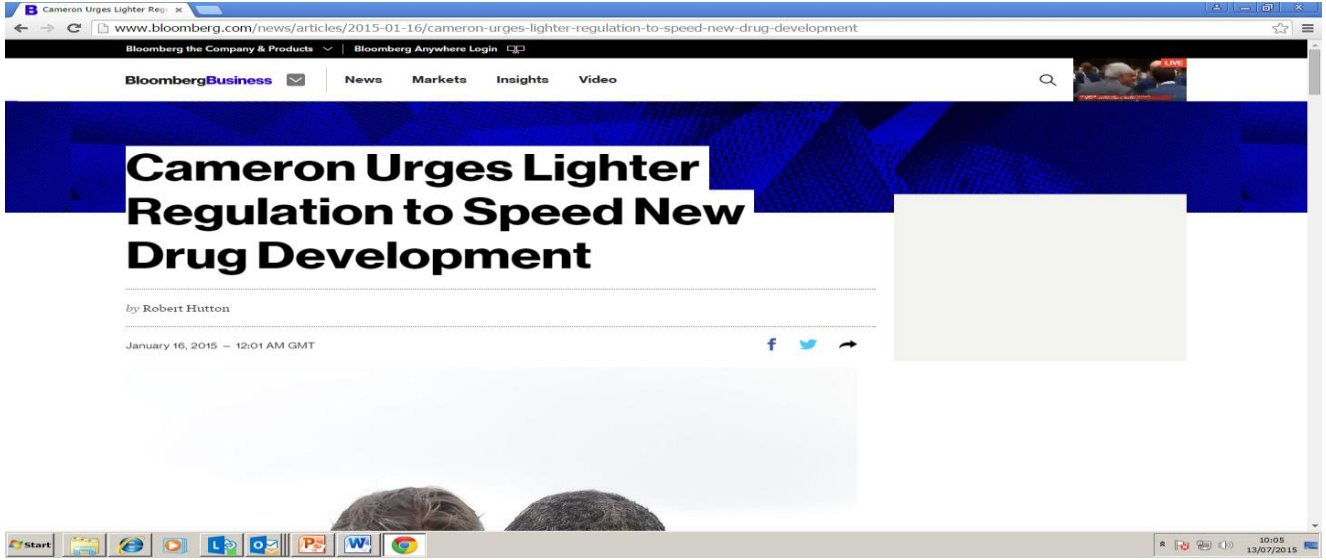
What are we going to discuss ?

Do the pharmacovigilance regulations achieve their aim of protecting patient safety ?

Have they become cumbersome and complex ?

Do we have too many regulations, resulting in too much redundant effort that has forced us in Drug Safety to spend more time doing busy work than actually monitoring, evaluating, and analyzing safety information so to take adequate risk minimization measures ?

Did ICH achieve the aim of harmonizing regulations?



U.K. Prime Minister David Cameron will push for lighter regulations on the pharmaceutical industry in order to speed the path of new medicines to the market.

Cameron, who is in Washington to meet with President Barack Obama, sees the current process of developing and licensing new drugs as “abhorrently expensive and time consuming,” according to a statement from his office

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Chinese regulations

PSURs are prepared in the old ICH format (R1).

Periodicity: every year since obtaining registration until renewal. Then every five years

Data collection period

Data collection for the Periodic Safety Update Report commence as of the day when the drug approval documents are obtained, and collected data shall be reported within 60 days after the data deadline. It is permitted to submit the Periodic Safety Update Report with the data's international generation date as the collection commencement date, provided that, if the data deadline of the aforesaid report is earlier than that required in China, the data collected after the deadline of the report till the required deadline shall be supplemented and analyzed

Chinese ICSRs regulations

ICSRs originating in China

All adverse reactions occurred within 5 years from the date of authorization

Any new and/or serious adverse drug reactions occurred after 5-year period

Timelines:

Any new and/or serious adverse drug reaction within 15 days from first awareness

Death cases shall be reported immediately, other ADRs in 30 days

Follow-up information shall be timely

Death cases: investigation report in 15 days

All serious adverse reaction from outside China in 30 days

Appendix 1

Adverse Drug Reaction / Event Report Form

First report□ Follow-up report□ Code: _____

Type of report: new□ serious□ general□ Classifications of report units: medical institution□ operational enterprise□ manufacturer□ individual□ other□ _____

Patient's name:	Sex: male□female□	Birthday: YY/MM/DD or age:	Nationality:	Weight (kg):	Contact number:
Former disease:	Name of hospital: Disease document number/clinical number:		Former adverse drug reaction/event: Yes□_____No□ No idea□ Family adverse drug reaction/event Yes□_____No□ No idea□		

Important related information: cigarette□ alcohol□ pregnancy □ liver disease□ kidney disease□ hypersusceptibility□_____ other□_

Drug	Approval Number	Product name	General name (include dose pattern)	Manufacturer	Batch no. of production	Dosage (amount/time, access, times/day)	Starting and ending time of drug usage	Reason of drugs usage
Suspicious drug								
Co-used drugs								

Adverse drug reaction/event name: Adverse drug reaction/event time: Year Month Day

Description of Adverse drug reaction/event (include symptom, body feature, clinical test) and treatment measures (can be attached with pages):

Adverse drug reaction/event results: recovered□ better effect□ no effect□ no idea□ with aftereffect□ symptom: _____ death□ direct cause of death: _____ Death time: YY/MM/DD

After stop or reduce the drug, does the adverse drug reactions/events disappeared or eased? Yes□ No□ No idea□ didn't stop or reduce the drug□
I s there the same adverse drug reactions/events when take the drug again? Yes□ No□ No idea□ Never use again□

Influence to former disease: not obvious□ extending disease process□ worse disease□ case aftereffect□ cause death□

Relative evaluation	Evaluation on reporting person: affirmation□ highly possible□ possible□ maybe no relation□ waiting for evaluation□ can't evaluate□ signature: Evaluation on reporting unit: affirmation□ highly possible□ possible□ maybe no relation□ waiting for evaluation□ can't evaluate□ signature:			
Information of report person	Contact phone:	Career: doctor□ apothecary□ nurse□ other□_____		
	Email:		Signature:	
Information of reporting unit	Unit name:	Contact person:	Telephone:	Reporting date: YY/MM/DD

Appendix 3

Overseas Adverse Drug Reaction / Event Report Form

Product name：(Chinese: English:) General name：(Chinese: English:) Dose pattern：

Code	Name of the adverse drug reaction/event	Time of the adverse drug reaction/event	Results of the adverse drug reaction/event	Starting time of the drug usage	Ending time of the drug usage	Dosage	Reason of drug usage	Sex	Age	Original/following reports	Report source	Country of origin	Date of domestic handling	Note

Appendix 2

Group Adverse Drug Reaction / Event Basic Information Form

Area of occurrence:			Unit using the medicine:		Number of people using it:	
Number of people suffering adverse drug reaction:			Number of people suffering serious adverse drug reaction:		Death Number:	
Date of first usage: YY/MM/DD			Date of first incidence: YY/MM/DD			
Suspicious drugs	Product name	General name	Manufacturer	Drug specifications	Batch no. of production batch	Approval Number

Appliance	Product name	Manufacturer	Batch no. of production	Registration number
	Appliance in this column means the medical appliance used with the suspicious drugs related to the group adverse drug reaction, such as injectors and transfusion injector.			

Phenomenon of the adverse drug event:
Description of the process of group adverse drug event and handling (can be attached with pages):

Opinions of the reporting unit	

Agência Nacional de Vigilância Sanitária

PSUR cover letter requires:

- Main new safety information received in the reporting period
- Patient exposure
- Description of unlisted ADRs received during the reference period
- No of fatal cases
- Data on safety studies conducted during the reference period
- Routine pharmacovigilance activities/actions related to newly received safety information described in the latest RMP
- Minimization activities/actions related to new safety information described in the latest RMP
- Summary tabulation of ICSRs included in the PSUR

Latin America requirements for non serious cases

Argentina: pregnancy associated with ADR: 7 calendar days
pregnancy not associated with ADR: 15 calendar days

Costa Rica: 10 working days
Ecuador: every two months
Panama: 15 calendar days
Peru: 10 working day
Chile: monthly

There is the need to harmonize PV requirements world wide

Which should be the reference standard ?

ICH ? EU legislation?

Which are the pros and cons of these standards?

Changes in EU pharmacovigilance legislation:

From Volume 9a (229 pages) to:

12 finalized GVPs + definitions, templates for RMP (60 pages) and PSUR, abbreviations, 3 GVPs still not final

9 «Other pharmacovigilance guidance» (final GVP annex III)

Guidance documents for submission of data to XEVMPD:

9 documents

Detailed guidance on the electronic submission of information on medicinal products for human use by marketing authorisation holders to the European Medicines Agency in accordance with Article 57(2), second subparagraph of Regulation (EC) No 726/2004

XEVPRM technical specifications, Chapter 3.I : 224 pages

References:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000336.jsp&mid=WC0b01ac05804d8b2b&jsenabled=true

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Changes in ICH guidelines

ICH E2B R3:

166 page implementation guide + 8 appendices - “old” E2B R2 was 29 pages

ICH E2C (new vs old version) grew from 10 to 19 chapters

Purpose of new EU legislation

Impact of the new legislation on marketing-authorisation holders

Marketing-authorisation applicants and holders are impacted by the legislation in a number of key areas. The legislation aims to:

- make roles and responsibilities clear;
- minimise duplication of effort;
- free up resources by rationalising and simplifying periodic safety update reports (PSURs) and adverse-drug-reaction (ADR) reporting;
- establish a clear legal framework for post-authorisation monitoring.

Redundancies are recognized

(EMA/CHMP/ICH/544553/1998)

		module with
1	Introduction	
2	Worldwide Marketing Approval Status	E2F
3	Actions Taken in the Reporting Interval for Safety Reasons	Parts may be common to E2E and E2F
4	Changes to Reference Safety Information	
5	Estimated Exposure and Use Patterns	
5.1	Cumulative Subject Exposure in Clinical Trials	E2E and E2F
5.2	Cumulative and Interval Patient Exposure from Marketing Experience	E2E and E2F (cumulative only)
6	Data in Summary Tabulations	
6.1	Reference Information	
6.2	Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials	E2F
6.3	Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources	
7	Summaries of Significant Findings from Clinical Trials during the Reporting Period	
7.1	Completed Clinical Trials	E2F
7.2	Ongoing Clinical Trials	E2F
7.3	Long-Term Follow-up	E2F
7.4	Other Therapeutic Use of Medicinal Product	E2F
7.5	New Safety Data Related to Combination Therapies	E2F
8	Findings from Non-Interventional Studies	E2F
9	Information from Other Clinical Trials and Sources	E2F
10	Non-Clinical Data	E2F
11	Literature	E2F
12	Other Periodic Reports	
13	Lack of Efficacy in Controlled Clinical Trials	E2F
14	Late-Breaking Information	E2F, if reports cover same period and submitted at

		Potential shared module with
		same time
15	Overview of Signals: New, Ongoing, or Closed	
16	Signal and Risk Evaluation	
16.1	Summary of Safety Concerns	
16.2	Signal Evaluation	
16.3	Evaluation of Risks and New Information	
16.4	Characterisation of Risks	
16.5	Effectiveness of Risk Minimisation (if applicable)	
17	Benefit Evaluation	
17.1	Important Baseline Efficacy/Effectiveness Information	
17.2	Newly Identified information on Efficacy/ Effectiveness	
17.3	Characterisation of Benefits	
18	Integrated Benefit-Risk Analysis for Approved Indications	
18.1	Benefit-Risk Context - Medical Need and Important Alternatives	
18.2	Benefit-Risk Analysis Evaluation	
19	Conclusions and Actions	E2F
20	Appendices to the PBRER	

Redundancies have not been resolved

16 out 40 sections in common between PBRER and DSUR; 3 with RMP

Periodicity is not the same:

- Annually for DSUR
- PBRER: Every 6 months after placing on the EU market for 2 years; once a year for 2 years; every 3 years. (depending on EU RD list)
- RMP: at the request of an authority; when important milestone is reached; new information can change the benefit-risk balance of the product

No modular approach is possible

- PADER: quarterly for first 2 years, then annually

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Redundancies

Renewals

- No PSUR is required, but addendum to clinical overview (in practice a PBRER in a different format with benefit evaluation and benefit-risk balance sections)

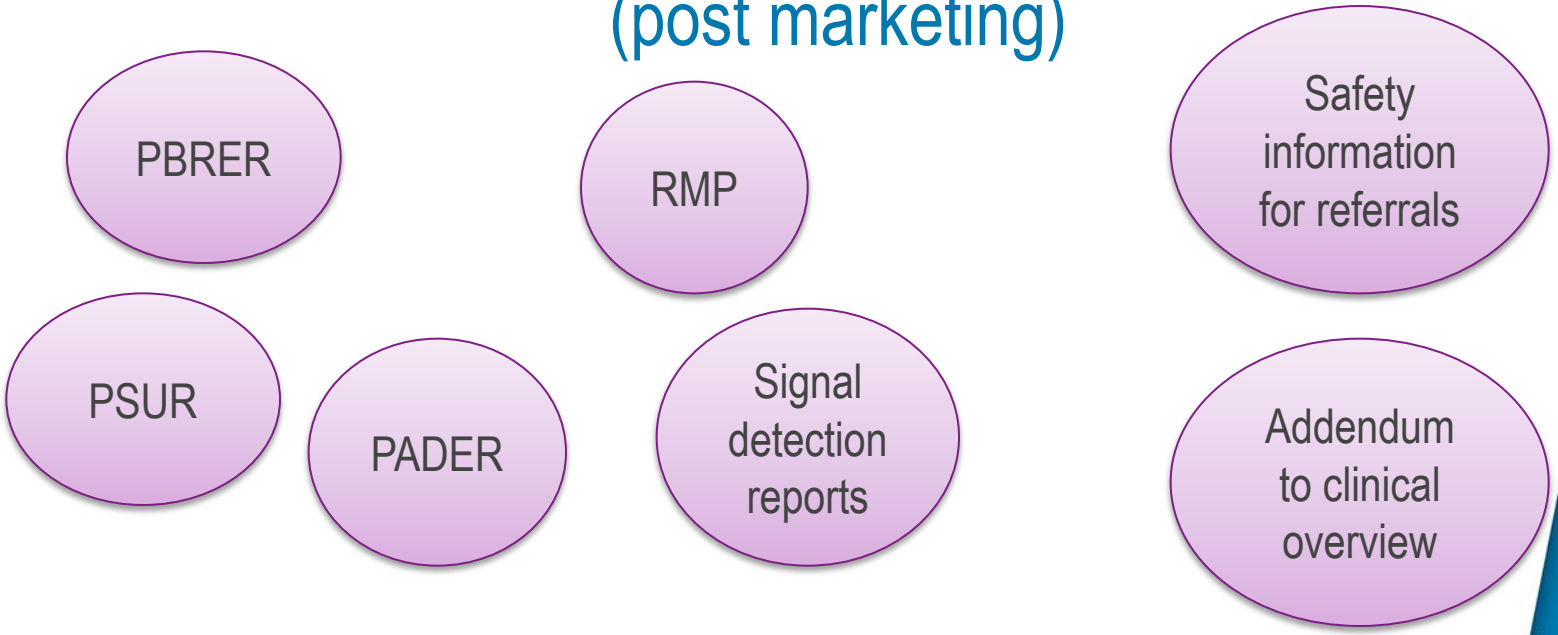
- Clinical Expert Statement (with confirmation that there are no new data that can change the benefit-risk balance)

Signal detection:

The marketing authorisation holder:
shall monitor the data in EudraVigilance to the extent of their accessibility. The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information

How many monthly signal detection reports for acetylsalicylic acid will be prepared ?

Documents addressing signals, risks, benefit-risk balance (post marketing)



More complicated overlapping documents = more time = additional costs

Clinical trials regulation 536/2014

Protocol (Annex I section d, 17)

The protocol shall at least include:

- A summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial
- A summary of the known and potential risks and benefits including an evaluation of the anticipated benefits and risks

Investigator's Brochure (Annex I section e, 27)

The information in the IB…..enables a clinician or investigator to understand it and make an unbiased benefit-risk assessment of the appropriateness of the clinical trial

Clinical trials regulation 536/2014

Investigational medicinal product dossier –IMPD- (Annex I, G)

SCOPE: The IMPD shall give information on the quality of any investigational medicinal product…and data from non-clinical studies and from its clinical use

- The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data (point 41)
- Overall risk and benefit assessment (point 48): This section shall provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the investigational medicinal product……unless the information is already provided in the protocol. In the latter case, it shall cross-reference to the relevant section of the protocol

DSUR (Art 43)

…as usual

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Redundancies from clinical trial regulations

Four documents with benefit-risk information for clinical trials:

IB is updated at least annually

DSUR is prepared annually

IMPD and protocol ? Will they need to be updated annually?

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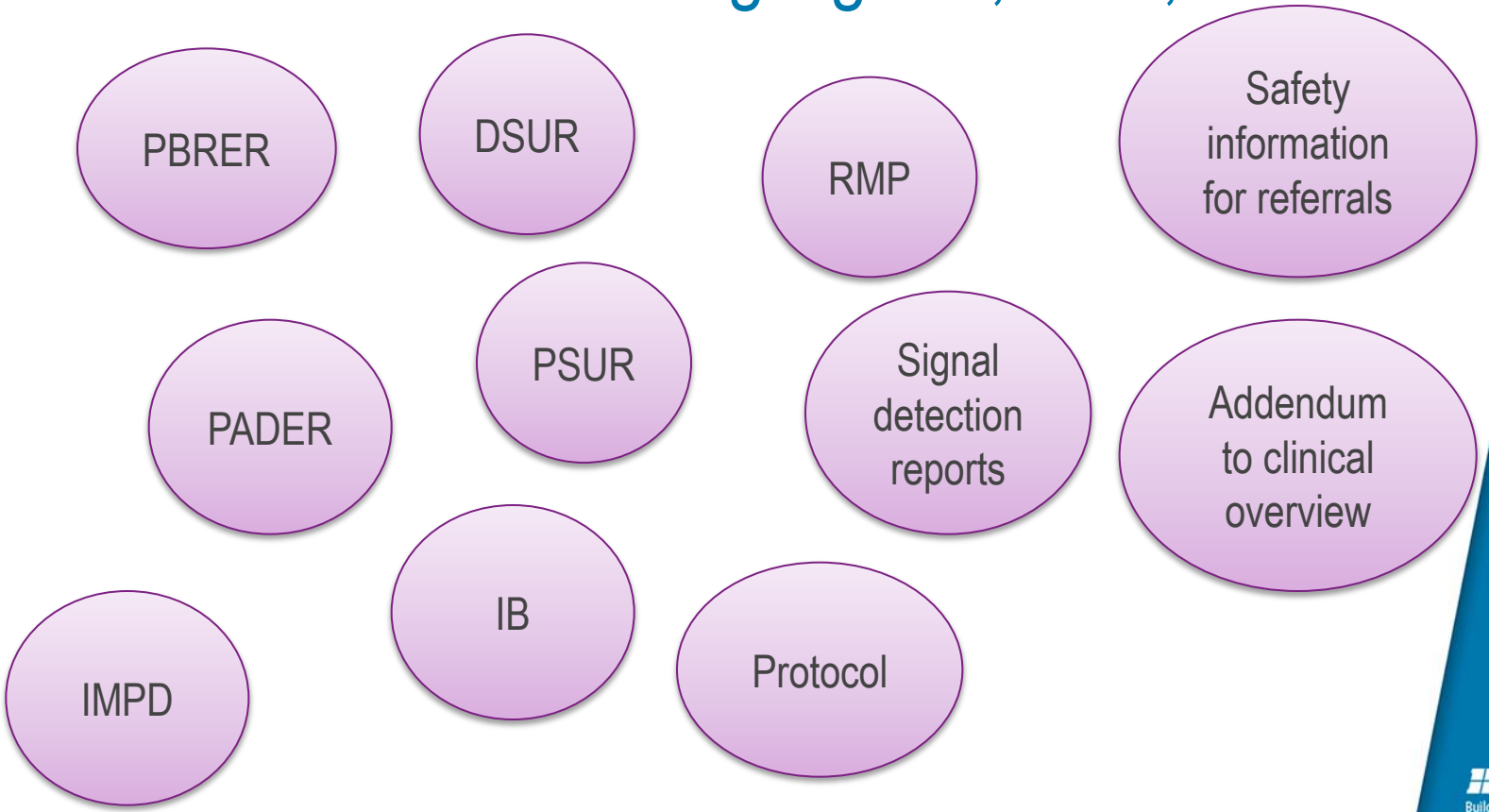
Documents addressing signals, risks, benefit-risk



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What is the impact of redundant regulatory requirements on the quality of the work ?

…and on the pharma sector in general?

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What happens when costs increase but revenues don't increase?

In pharma industry we see:

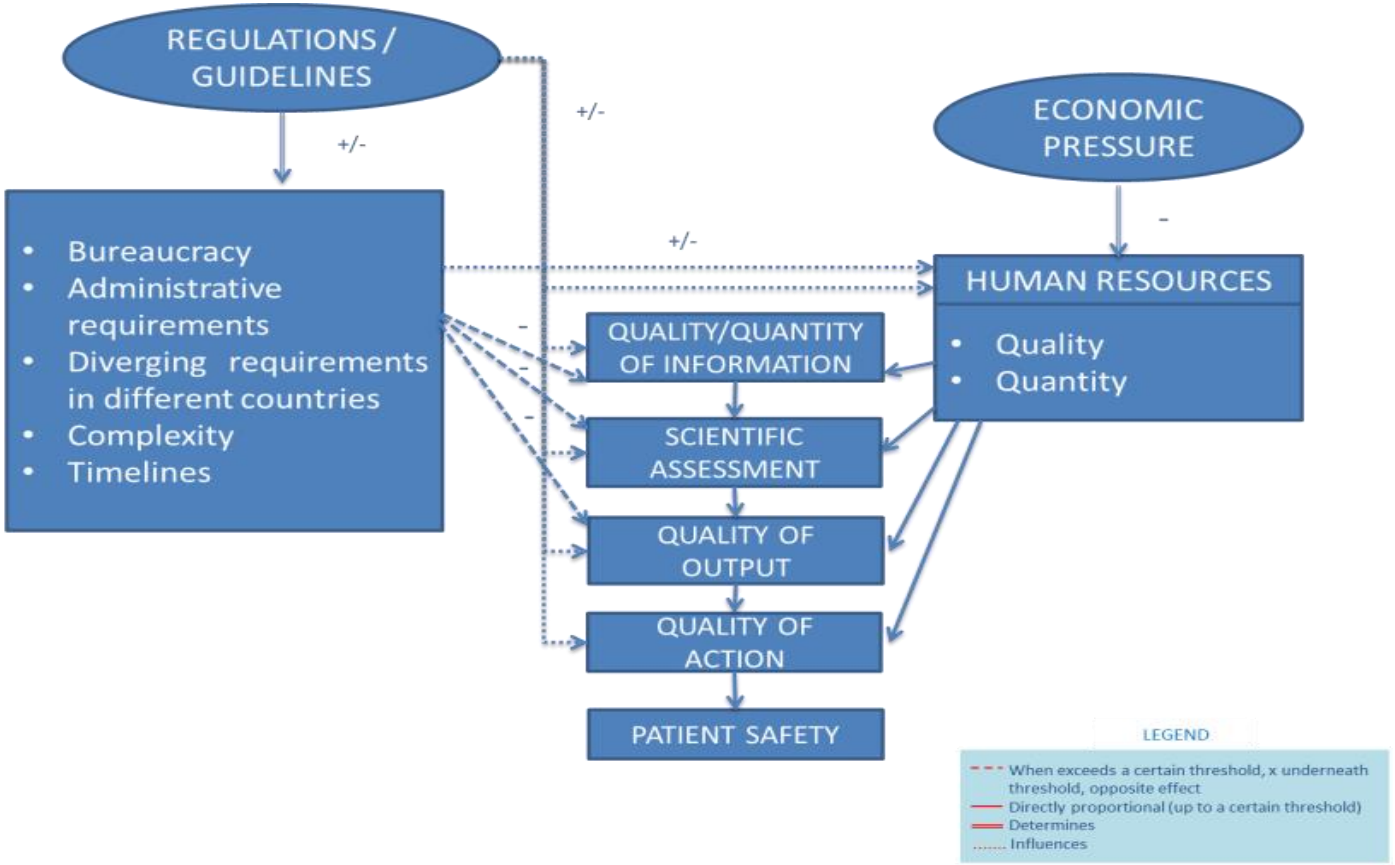
- No new antibiotics being developed
- Focus is on orphan drug development (costs less to develop), cancer, monoclonal antibodies (biogenerics are more difficult to register, innovator has longer market exclusivity)
- Drug shortages

In pharmacovigilance:

- Work outsourced at lowest possible cost (low cost = low quality ?)
- Work done by under qualified personnel
- Number of employees does not increase in a proportionate way to workload = work exceeds staff capacity
- Copy and paste exercises

Is this in the best interests of patient safety ?

Interactions between components playing a role in pharmacovigilance quality



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Any ideas on how simplify aggregate reports?

Do we need all of them?

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What are aggregate reports/pharmacovigilance about ?

1) What is known about a medicinal product (e.g. mechanism of action, patient exposure, action taken by regulatory authorities/MAH, which studies have been conducted, effect of products of the same class, metabolism)
2) What is not know about a product (e.g. in populations subgroups -safety/efficacy-)
3) Main risks (known and unknown)
4) Efficacy (known and unknown)
5) New safety information received during the reference period (risk characteristics, signals, benefits)
6) How are risks minimized
7) What has to be done to collect information on the unknowns
8) Benefit-risk evaluation

An “old” proposal

- 1 Introduction
- 2 World-wide Market Authorization Status
- 3 Inventory of Ongoing/Completed Safety Studies*
- 4 Changes to RSI*
- 5 Regulatory Actions Taken for Safety Reasons**
- 6.1 Patient Exposure**
- 6.2 Limitations of Human Safety Database
- 7 Drug Risks Currently Under Evaluation
  - 7.1 General Introduction (describe how the risk was identified and by whom)
  - 7.2 Sources of Evidence
    - 7.2.1 Spontaneous Reports
    - 7.2.2 Company Sponsored/Supported Interventional Studies
    - 7.2.3 Company Sponsored/Supported non-Interventional Studies
    - 7.2.4 Literature
    - 7.2.5.Other Sources
  - 7.3 Risk Characterization and Evaluation
    - 7.3.1 Risk Factors and sub-Populations at Risk
    - 7.3.2 Risk Severity/Seriousness and Frequency
    - 7.3.3 Biological Plausibility
    - 7.3.4 Clinical Plausibility (evidence strength and consistency)
    - 7.3.5 Risk Impact on Compliance and Benefit-Risk Balance
    - 7.3.6 Actions Taken and further actions that could be taken
- 8 Summary of resolved drug risks

* during the reference period
** cumulative and during the reference period

Reference: Drug Safety 2012; 35(8):615-622

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Drug Safety Master file: benefits

- No duplication
- No inconsistencies between documents
- One single assessment from authorities = no diverging assessments
- Harmonization between documents, internationally
- More resources for scientific assessment of safety data, collecting data, risk minimization activities

Is there anything the industry can do to simplify clinical and PV operations?

Why do we use separate clinical and PV databases?

Is there any benefit in having 2 separate databases?

Inefficiencies originating from separate clinical and safety databases

Clinical and safety run their operations independently and use separate databases with different data standards: CDASH (Clinical Data Acquisition Standards Harmonization) and E2B

- Duplicate data entry of SAEs and/or QC
- Different coding dictionaries or different versions of the same dictionary
- Reconciliation
- Maintenance and validation of two separate databases
- Drug safety does not immediately have access to all safety data originating from clinical trials (i.e. lab data/clinical exams, non-serious adverse events). More difficult to prepare:
    - IBs
    - DSURs
    - Signal detection reports

Inefficiencies originating from separate clinical and safety databases

- Duplicate queries to Investigators
- If EDC is implemented: drug safety may not be aware of SUSARs
- Less accurate signal validation and evaluation
- Increased costs (two data repositories, more time, more personnel)

Why two different standards ?

They have been developed independently

CDASH is an industry convention for accommodating SDTM FDA requirements , ICH is global

Clinical Data Interchange Standards Consortium (CDISC):

Mapped E2B (R2) with CDASH

Can operations be improved?

The differences between CDASH and E2B R2 are a matter of conventions, not driven by different scientific requirements.

Examples

- E2B is more granular than CDASH
- Dates for reporting information are not captured from the reporter (E2B – first awareness date) but extracted from the EDC (each entry has a date).
- CDASH employs letters for field labelling (e.g. AESDTH), while E2B alphanumeric with no relation to data type (A.1.5.2)

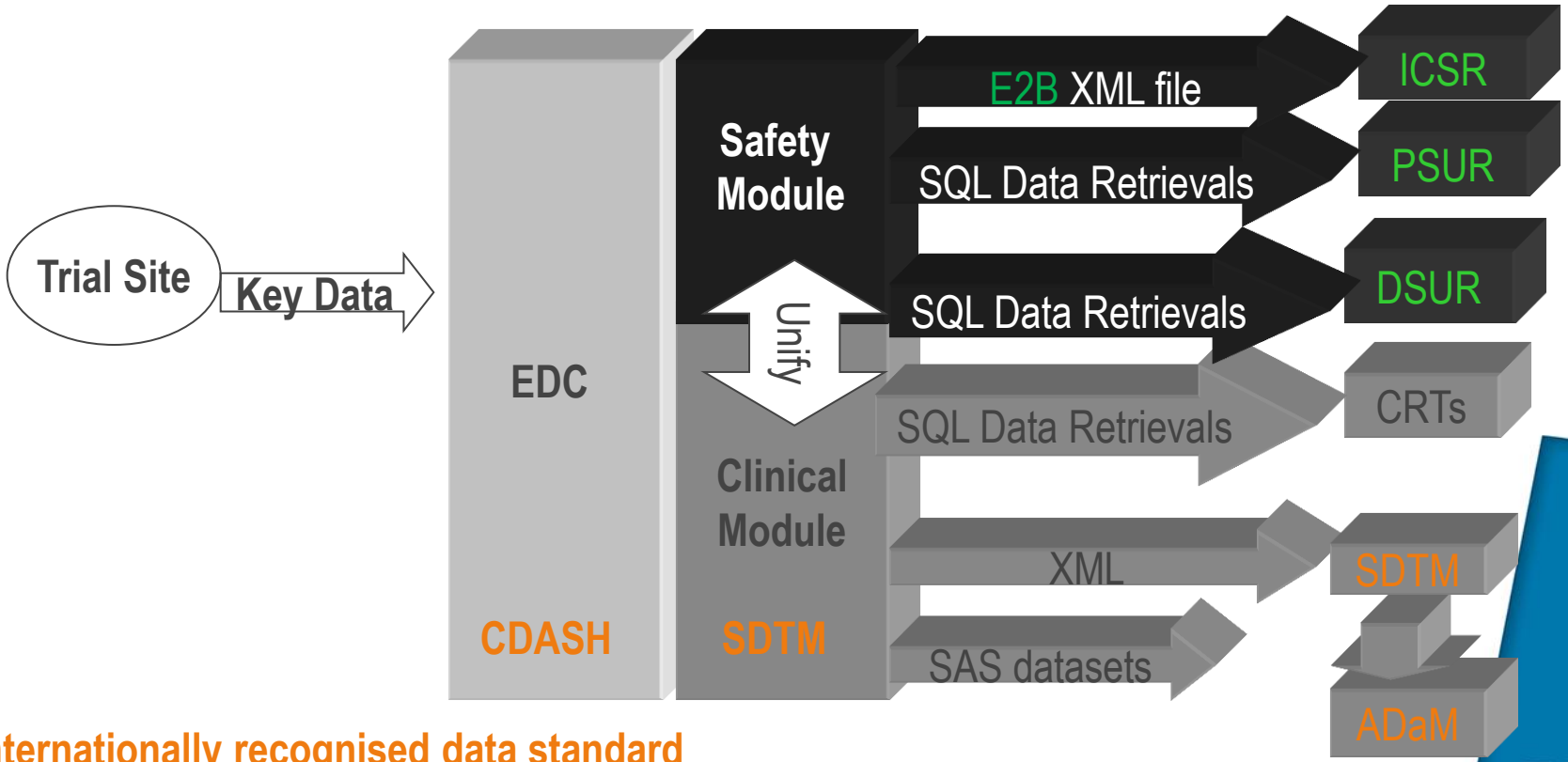
Reference: Current drug safety 2013, 8(1): 56-62

With release of new E2B R3 mapping needs to be re-done

HL7 needs to be accommodated

New standard to be developed

One data repository for all study data



Internationally recognised data standard

Internationally recognised safety report

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Potential benefits

- No duplicate data processing
- Same coding dictionary
- No reconciliation
- Reduced cost: one database instead of two, less time, less personnel
- Drug Safety has access to all clinical safety data:
  - ✓Easier preparation of aggregate reports
  - ✓Reduced time and cost for preparing aggregate reports
  - ✓Better signal validation and evaluation
- Safety and clinical become aware of SUSARs at the same time

Challenges

- Clinical and drug safety departments will need to be restructured
- Closer cooperation between departments
- Development of one single standard (unified database)
- For each study, define which database fields are relevant (for safety data)

Systems Approach

A system should not be the result of the development of its single components in isolation without taking into account the relationships among all socio-technical components

(i.e. the interactions between all stakeholders, components and factors – drug safety employees, environmental pressures, regulatory authorities, processes, etc.)

1994: US Army Blackhawk helicopter was shot down in north Iraq by friendly fire

System evaluation of the accident revealed multiple redundant layers of control

Many overlapping responsibilities and departments involved

Departments were using different communication codes and wave lengths

Complication, redundancy, overlap does not prevent failure

More is not better, it can be worse

Reference: Nancy G. Leveson. Engineering a Safety world. The MIT Press

ACRES (Alliance for Clinical Research Excellence and Safety)

A multi-sector alliance of like-minded people and organizations working collaboratively to build shared Global System for Clinical Research Excellence

Foster more effective and efficient ethical and regulatory oversight through standardization, innovation, collaboration and stakeholder engagement

Working on unified database project to make it reality

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Questions ?
Any ideas ?

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