20th Congress of EAHP

Vigilance of adverse events during drug development

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Disclaimer

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Nothing to disclose

Vigilance of adverse events during drug development

Question 1

A signal can not be identified by an adequately documented case with a medically significant ADR

- Yes (green)
- No (red)

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Vigilance of adverse events during drug development

Question 2

Should the investigator follow-up AEs/SAEs until recovery or stabilization of the condition?

- Yes (green)
- No (red)

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Vigilance of adverse events during drug development

Question 3

The Risk Management Plan describes, among the others, what is known (i.e. identified risks) and not known (i.e. potential risks) about the safety profile of the concerned medicinal product(s)

- Yes (green)
- No (red)

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Introduction

CTs are important part of medical research and should be performed with good conduct and intention

Each study should

- an appropriate scientific design
- based upon credible scientific data
- well conducted
- analysed by rigorous standards
- continually monitored
- protect the subject confidentiality and safety

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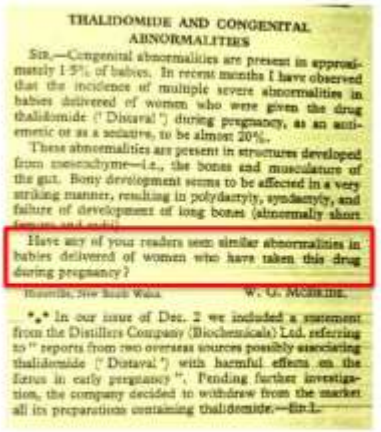
Lesson learned from Thalidomide disaster



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ("Distaval") during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femurs and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Roseville, New South Wales — W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ("Distaval") with harmful effects on the fetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—Ed. L.

Key pharmacovigilance principles

1. Patient exposed to a drug
2. Identification of a serious and unexpected event (signal)
3. Evaluation of causal relationship
4. Communication of that signal (not recognized during clinical trials)

- The need for adequately testing medicines prior to marketing
- Regulation of medicines
- Avoidance of unnecessary use of medicine in pregnancy
- Same risks can be successfully minimized

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At the time of authorisation

Information on the safety of a medicinal product is relatively limited as randomized CTs are primarily designed to provide reliable information on the efficacy of interventions

CTs, an 'ideal' world (?)

- Relatively small number of subjects
- Some categories of subjects often excluded from CTs
  - young, elderly
  - women of childbearing age
  - pregnant women
  - certain ethnic groups
  - with concomitant diseases
    - cardiac disease
    - renal disease
    - hepatic disease
    - multiple impairments
  - with concomitant medications

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At the time of authorisation

Increasing regulatory demands for additional information before approval have increased the average numbers of patients in applications, especially for new chemical entities; nevertheless, **the numbers remain far too small to detect uncommon or rare adverse drug reactions (ADRs), even if these are serious**

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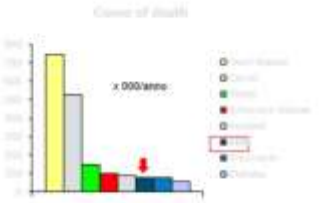
Post-marketing setting

It is estimated that 5% of all hospital admissions are due to an adverse drug reaction (ADR) and that **ADRs may rank from the 4th to 6th leading cause of death** (*)



Ref. Press release Memo/00/782; 10/12/2000
(*) J. Lazarou et al. Incidence of Adverse Drug Reactions in Hospitalized Patients – A Meta-analysis of Prospective Studies. JAMA 1998 (Apr 15); 279 (15): 1200–1205

It is also estimated that

- 197,000 deaths per year in the EU are caused by ADRs
- the social cost to society of ADRs in the EU is € 79 billion

A new pharmacovigilance legislation became effective in the EU (July 2012)

- **Regulation (EU) no. 1235/2010** amending Regulation (EC) No 726/2004
- **Directive 2010/84/EC** amending, as regards pharmacovigilance, Directive 2001/83/EC
- **Commission implementing regulation (EU) no. 520/2012** of 19 June, a legally binding act published by the European Commission in June 2012 that provides details on the operational aspects for the new legislation
- **Guideline on good pharmacovigilance practices (GVP)**, practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation

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CT legislation. Where are we?

- **Directive 2001/20/EC** of the European Parliament on the approximation of the laws, regulations and the administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (April 2001)
- **Guidance CT 3 -** Detailed guidance on the collection, verification and presentation of adverse events/reactions reports arising from clinical trials on medicinal products for human use (June 2011)
- **ICH guideline E2F -** Note for guidance on Development Safety Update Reports (September 2011);
- **ICH guideline E2A -** Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (October 1994)

Regulation EU 536/2014

of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (April 2014)

- aims to create an environment favourable for conducting CTs, with the highest standards of patient safety, for all EU Member States
- it will apply no earlier than 28 May 2016

Until that date, CTs performed in the EU are required to be conducted in accordance with the Directive 2001/20/EC, which will be repealed on the day of entry into application of the CT Regulation

It will however still apply three years from that day to:
- CTs applications submitted before the entry into application (no earlier than 28 May 2016)
- CTs applications submitted within one year after the entry into application if the sponsor opted for old system

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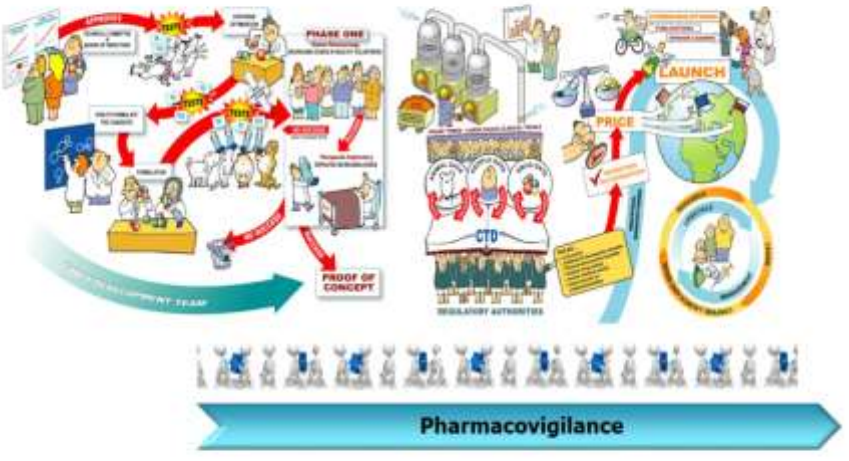
When is PV involved in the drug development?



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On going safety evaluation

Study related activities

- Case-Handling process
  - identification, collection, evaluation and submission of AEs and SAEs
- Provision of a safety reporting rules in the protocol
- Informed Consent Form
- Case Report Form & guidelines
- Appropriate training to investigators
- Data Safety Monitoring Board
- Clinical Data Review
- Clinical Study Report
- PV Agreements with the concerned Contract Research Organisations (CROs)

Product related activities

- Investigator Brochure
- Development Safety Update Reports (DSURs)
- Risk Management Plan (RMP)
- CTD / e-CTD documents

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Clinical protocol: safety sections

Schedule of events

	Pre-screening	Screening	Treatment Period			
Visits	V 0	V 1	V 2*	V 3	V 4	VP / ETV
Time (Weeks)	Within 1 Wk of V1	Wk -2	Wk 0 (+3 days)	Wk 4 (+3 days)	Wk 12 (+3 days)	Wk 24 (+3 days)
Informed consent procedures	✓					
Demographic data	✓					
Instructions for the screening visit	✓					
Patient card	✓					
Inclusion/Exclusion criteria		✓				
Eligibility confirmation for randomization			✓			
Medical history/Previous medications		✓				
Concomitant medications		✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓
Weight and height		✓	✓	✓	✓	✓
Smoking status		✓	✓	✓	✓	✓
Vital signs (BP) at pre-dose and 10 min post-		✓	✓	✓	✓	✓
12-lead ECG pre-dose and 10 min post-dose		✓	✓	✓	✓	✓
St. George's Respiratory Questionnaire			✓	✓	✓	✓
Daily diary dispensing		✓	✓	✓	✓	
Daily diary returning			✓	✓	✓	✓
Haematology – Blood chemistry		✓			✓	✓
Serum pregnancy test		✓				✓
Urinary pregnancy test			✓	✓	✓	
Drug dispensing		✓	✓		✓	
Drug returning			✓		✓	✓
Adverse events/Serious AEs		✓	✓	✓	✓	✓

- Definitions
- Expectdness
- Intensity of adverse events
- Causality assessment
- Action taken wtth study drug(s)
- Outcome
- Recording adverse events
- Reporting adverse events
- General notes

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Investigators responsibilities

Play the most important role in ensuring the rights and safety of subjects, and in collecting complete and accurate data.

- monitor and record all AEs in the CRF/e-CRF occurring from the signature of the informed consent until the end of patient's participation
- assess the causal relationship between the study drug and the event(s) by questioning if there is a reasonable possibility of relatedness to study drug (Yes/No)
- report to the Sponsor all SAEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluation within 24 hours of awareness
- follow-up AEs/SAEs as defined in the protocol until recovery or stabilization of the condition
- fulfill the safety reporting requirements in force in his/her country, as applicable

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Investigators responsibilities

Play the most important role in ensuring the rights and safety of subjects, and in collecting complete and accurate data.

- report to the sponsor **all pregnancy cases immediately within 24 hours of awareness**
  - the patient is immediately withdrawn from the study then followed-up with due diligence until delivery
  - if criteria for a SAE is met (e.g. abortion) the procedure for reporting SAE should be followed-up
  - all follow-up pregnancy information is to be reported promptly

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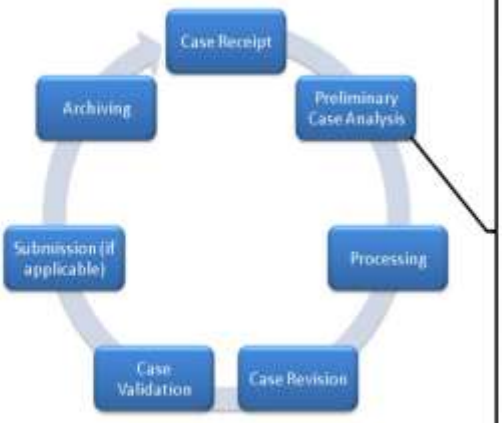
Case management



- Minimum Information
- Report Status
- Primary source
- Product Characteristics
- Seriousness
- AE/ADR term assessment
- Relatedness (only CT)
- Expectedness
- Unblinding Procedure
- Safety issues?
- Case priority

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Expedited reporting

What	When	To whom
SUSARs i.e. adverse reactions • Serious → usually assessed by the investigator • Unexpected → assessed by the Sponsor based on the Reference Safety Information • with a reasonable possibility of relatedness to study drug → usually assessed by the investigator. If the Sponsor disagree, both assessments should be provided with the report	• Fatal and life-threatening initial report asap but no later than 7 calendar days after awareness. The completed report to be submitted within additional 8 calendar days • Other SUSARs asap but no later than 15 calendar days • Significant new information on an already reported case as a follow-up report within 15 calendar days	• Competent Authorities/EMA (by Eudravigilance or by paper) • Ethic Committee (EC) issuing the single opinion if SUSAR occurred in the concerned study and in the concerned Member State • Investigators (by line-listing of SUSARs)

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Signal analysis

Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously

A signal may be identified if any of the following criteria are met:

- three or more reports of any similar events
- an adequately documented case with positive re-challenge
- an adequately documented case with a medically significant ADR (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome, anaphylaxis, torsade de pointes)
- a possible excess of an AE compared with placebo or active comparator;
- off-label use or product abuse/misuse resulting in ADRs
- ADRs resulting from medication errors
- if there is other suspicion of a new (unlisted) ADR or drug interaction
- if there is possible identification of a new risk factor for a listed ADR

In addition, a signal may be identified at any time during the medical review of single cases in the course of case processing

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Signal analysis

If the signal is considered "potential", an "extended evaluation" will be then carried out.

Further data may include, but is not limited to:

- a search of the scientific and medical literature for other case reports of relevance to the possible signal including investigation of a possible class effect
- review of relevant data from clinical and pre-clinical studies and post-marketing setting (if the product is already marketed)

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Safety Committee

If, following the extended evaluation, the signal has not been refuted, it will be referred to the Safety Committee that will take appropriate decisions.

The signal will be referred together with an evaluation of the significance of the signal, its strength, impact on benefit-risk and a proposal for any further measures required

Possible measures may be include but are not limited to:

- keeping the safety issue under review
- obtaining independent expert advice
- instituting enhanced follow-up of future cases
- amending RMP to include the signal (i.e. risk)
- etc

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Development Update Safety Report (DSUR)

- A thoughtful, comprehensive annual review and evaluation of safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed
- A single DSUR including safety data from all CTs and covering all indications, all dosage forms, all intended populations, all strengths
- To be only submitted to the national Competent Authority and the Ethics Committee if the treatment of subjects is still ongoing in that Member state concerned
- Encourages risk-benefit evaluation and how any changes are communicated during the given period

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Risk Management

Risk Management System

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions

Risk Management Plan

The detailed description of the Risk Management System

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Risk Management Plan

- Identify and characterise **the safety profile** of the medicinal product(s) concerned
- Describe **what is known (i.e. identified risks) and not known (i.e. potential risks)** about the safety profile of the concerned medicinal product(s)
- Document measures to **prevent or minimise the risks** associated with the product, including an assessment of the effectiveness of those interventions
- Document **post-authorisation obligations**
- Indicate the level of certainty that efficacy shown in clinical trial populations will be seen in **every day medical practice** and document the need for studies on efficacy in the post-authorisation phase
- Plan how the **effectiveness** of risk minimisation measures will be assessed

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Risk Management Plan

Part I	Produc(s) overview
Part II	Safety Specification
Part III	Pharmacovigilance Plan
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures
Part VI	Summary of the RMP
Part VII	Annexes

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- Module SI: Epidemiology of the indication(s) and target population(s)
- Module SII: Non-clinical part of the Safety Specification
- Module SIII: Clinical trial exposure
- Module SIV: Population not studied in CTs
- Module SV: Post-Authorisation Experience
- Module SVI: Additional EU requirements for the Safety Specification
- Module SVII: Identified and potential risks
- Module SVIII: Summary of the Safety Concerns

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Risk Management Plan

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Discuss plans to identify and/or characterise the risks identified in the safety specification

Safety concerns

→ **Routine PV activities**

→ **Additional PV activities**

- Active surveillance
- Case control studies
- Cohort studies
- Registries
- Joint studies
- Drug utilisation studies
- Clinical trials
- Pre-clinical studies
- ....

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Risk Management Plan

Part I	Produc(s) overview
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Part IV	Plans for post-authorisation efficacy studies
Part V	**Risk minimisation measures**
Part VI	Summary of the RMP
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To provide details of the risk minimisation measures which are taken to reduce the risks associated with individual safety concerns

Safety concerns

→ **Routine Risk Minimisation measures**

- The SmPC
- The labelling
- The package leaflet
- The pack size(s)
- ....

→ **Additional Risk Minimisation measures**

- Controlled distribution
- Educational material
- Patient alert card
- Patient monitoring card
- Training programme
- ....

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developmental Risk Management Plan

- Risk management planning pre-authorisation now more commonly being defined in a **developmental risk management plan (dRMP**)
- It is a living document, re-evaluated upon completion of all pre-clinical or clinical studies, or significant interim safety findings
- Ensures the plan is already implemented and "road-tested" at the time of marketing authorization application
- Supports identification of known vs potential risks
- Development of safety specifications
- Enables studies to address such concerns
- Supports data with investigator's brochure
- Define the risk minimization strategies which may include the study under discussion

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Vigilance of adverse events during drug development

Question 1

A signal can not be identified by an adequately documented case with a medically significant ADR

- Yes (green)
- No (red)

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Vigilance of adverse events during drug development

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The Risk Management Plan describes, among the others, what is known (i.e. identified risks) and not known (i.e. potential risks) about the safety profile of the concerned medicinal product(s)

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