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Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

From signal to regulatory action

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UMC Training Course
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www.lareb.nl

From signal to regulatory action

- Sources of information
- Stakeholders
- Examples
- Concluding remarks

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Evidence

- Signal generating or descriptive
  - Spontaneous reporting
  - Intensive monitoring
- Signal confirmation or analytical
  - Case control studies
  - Cohort studies
  - RCTs

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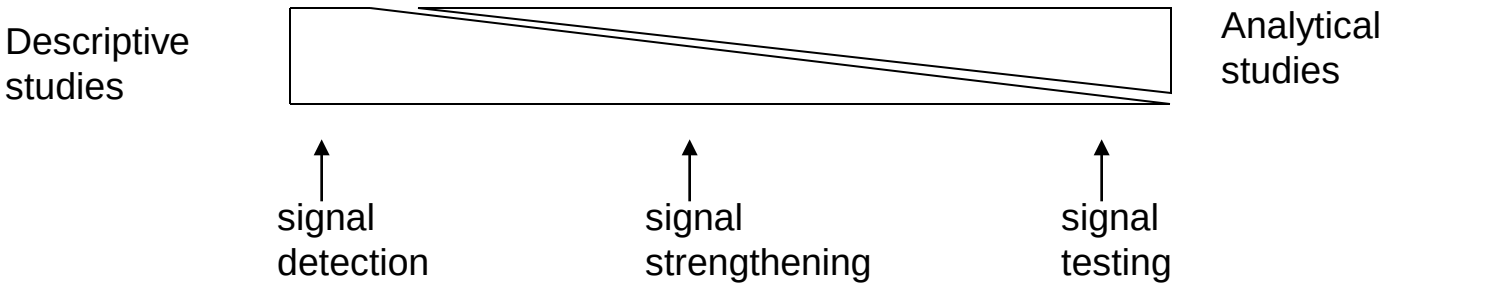
Signals



Statistical evidence

Clinical & pharmacological information

Evidence?

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Table 1 Drug safety issues and their evidence in Europe since 1995

Drug	Safety concern	Key evidence	Regulatory action
Trovofloxacin	Hepatoxicity	Spontaneous ADRs	Withdrawn
Tolcapone	Hepatoxicity	Spontaneous ADRs	Suspended
Cisapride	QT prolongation cardiac arrhythmias	Spontaneous ADRs	Patient registration licences subsequently cancelled
Bupropion	Seizures Drug interaction	Spontaneous ADRs	Posology change Warnings
Cerivastatin	Rhabdomyolysis	Spontaneous ADRs	Withdrawn
Hormone replace therapy	CVS risk and cancer long term	Epidemiological studies	Warnings and restriction of indication
SSRIs	Suicidal behaviour in children	Clinical trials	Warnings accompanied by clinical guidance
COX IIs	CVS risk	Clinical trials	Warnings and clinical guidance
Topical macrolide immunosuppressant	Risk of cancer	Spontaneous reports	Restriction of use Risk management plan

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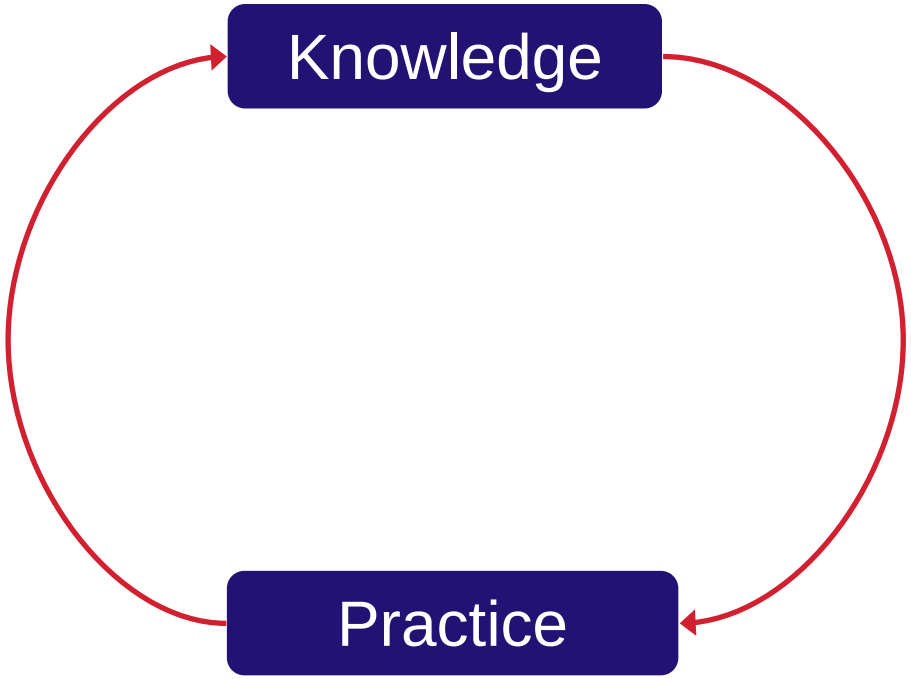
Circle of knowledge and practice

Reports to SRS



Information Regulatory action

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Responsibility of National PhV Centre

- Maintaining system for ADR monitoring
- Evaluation and dissemination of possible signals

Responsibility of MAH

- Monitoring safety of own product on a continuous basis
  - Spontaneous reports
  - Evaluation of studies
  - Literature

Periodic Safety Update Reports

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Responsibility MAH

- Frequency
  - a PSUR every six months for the first two years after being placed on the market
  - during the following two years a PSUR every year
  - thereafter at three-yearly intervals
  - If needed more often….

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Responsibility of Regulatory authority

- Final risk/benefit assessment
  - Spontaneous reporting
  - Evaluation of PSURs
  - Pharmacoepidemiological studies/Clinical trials

Responsibility Regulatory authority

- Determine actions to be taken i.e. by
  - Amendment of SmPC
  - Dear Health Care Professional letter
  - Restriction of indication of use
  - Suspension or withdrawal of drugs

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Signal 1

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COX-2 inhibitors and CV safety

- Rofecoxib marketed in the Netherlands in April 2000
- June 2000: Lareb receives first report of possible myocardial infarction
- Autumn 2000: Case reports to Lareb indicating possible cardiovascular risks
- Nov 2000 VIGOR study: cardiovascular risk?

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Actions taken by Lareb

- Informed the regulatory authorities in December 2000
- Publication in national drug bulletin March 2001
- Discussion at NC meeting in October 2001

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Phase IV studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

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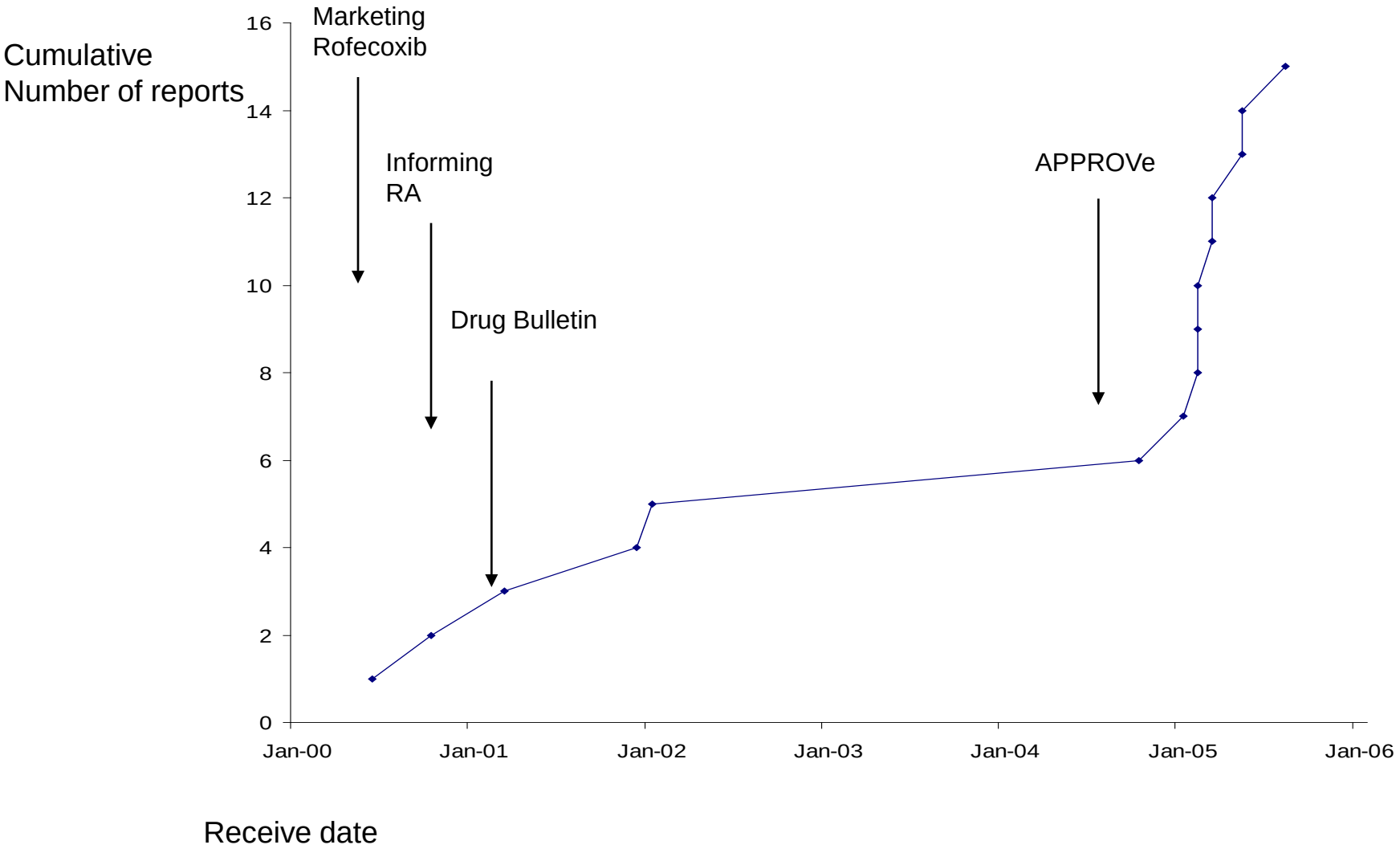
CONCLUSIONS

Among patients with a history of colorectal adenomas, the use of rofecoxib was associated with an increased cardiovascular risk.

Angina pectoris and myocardial infarction associated with rofecoxib



Immediate withdrawal of rofecoxib (Vioxx/Vioxxacutate)

30 September 2004

The Committee on Safety of Medicines has today been informed of the immediate voluntary worldwide withdrawal of the 'COX-2 selective NSAID 'rofecoxib (Vioxx/VioxxAcute) by the manufacturer. This follows new clinical trial results showing an increased risk of confirmed serious thrombotic events (including myocardial infarction and stroke) compared to placebo, following long-term use.

www.mhra.gov.uk

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Signal 2

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Pergolide

- Ergoline-based dopamine receptor agonist
- Used in the tretment of Parkinson’s disease

MHRA 2002

- 49 reports of fibrotic reactions with pergolide
- Pulmonary and pleural fibrosis, pleural effusion, retroperitoneal fibrosis and constrictive pericarditis
- The reported cases of fibrosis were discovered at an advanced stage, and 3 patients died

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MHRA 2004/2005

- Restricted use of of pergolide to patients who had failed therapy with other (non-ergot) medicines for Parkinson's disease
- Monitoring requirements for regular echocardiograms
- MAH to monitor the effectiveness of the risk minimisation measures

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ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

René Schade, M.D., Frank Andersohn, M.D., Samy Suissa, Ph.D., Wilhelm Haverkamp, M.D., Ph.D., and Edeltraut Garbe, M.D., Ph.D.

ORIGINAL ARTICLE

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease

Renzo Zanettini, M.D., Angelo Antonini, M.D., Gemma Gatto, M.D., Rosa Gentile, M.D., Silvana Tesei, M.D., and Gianni Pezzoli, M.D.

March 2007

- Contraindication in patients with a history of fibrotic disorders and/or anatomical evidence of heart valve disease
- Warnings
- Patient monitoring requirements
- Dear Health Care Professional letter

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Number of users

Year	2007	2008	2009	2010	2011
	1662	1181	832	596	456

www.gipdatabank.nl

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March 2007

FDA Announces Voluntary Withdrawal of Pergolide Products
Agency Working with Product Manufacturers

The U.S. Food and Drug Administration (FDA) today announced that manufacturers
remove these drugs from the market because of the risk of serious damage to pati

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Signal 3

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Rosiglitazone

- Thiazolinedione, approved for marketing in 1999-2000
- PPAR receptor agonist
- Decrease of insulin resistance

Cardiovascular safety

- In Europe worries about the cardiovascular safety of rosiglitazone, registered only as second line treatment
- Heart failure contraindication

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Cardiovascular safety

- EMA recommends phase 4 studies with cardiovascular safety as primary endpoint
- RECORD study

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

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hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

Review of safety

- RECORD trial
  - Rosiglitazone vs metformine or SU derivates
  - No difference in CV death
  - Statistically non-significant rise in myocardial infarction

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Press release

18/10/2007

European Medicines Agency confirms positive benefit-risk balance for rosiglitazone and pioglitazone

Finalising a review of the benefits and risks of the thiazolidinediones rosiglitazone (Avandia) and pioglitazone (Actos), the European Medicines Agency has concluded that the benefits of these antidiabetic medicines continue to outweigh their risks in the approved indications. However, the Agency recommended changing the product information for rosiglitazone and agreed further initiatives to increase scientific knowledge on the safety of both medicines.

Rosiglitazone

- March 2010 ‘risk-benefit’ balance still positive (EMA)

- New data
  - Retrospective observational study Graham
  - June 2010 Update meta-analysis Nissen 2007
  - RECORD study

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23 September 2010
EMA/585784/2010
Press Office

Press release

European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim

Anti-diabetes medication to be taken off the market

FDA significantly restricts access to the diabetes drug Avandia

Credit: Getty Images

[09-23-2010] The U.S. Food and Drug Administration announced that it will significantly restrict the use of the diabetes drug Avandia (rosiglitazone) to patients with Type 2 diabetes who cannot control their diabetes on other medications. These new restrictions are in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with Avandia.

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Concluding remarks

- Roubust evidence vs timely action

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Concluding remarks

- The decision has to be communicated effectively
- The decision has to be implemented in daily practice

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Individual risk assessment

The use of thalidomide as unapproved drug:

time trend and the impact of the clinical guideline in Japan

This study is partially supported by RHC USA Corporation.

Hikaru Watanabe[1], Eri Kawabe[1], Nobuhiro Ooba[1], Tsugumichi Sato[1], Yong Sa Lim[2], Kiyoshi Kubota[1].

1 Department of Pharmacoepidemiology, Faculty of Medicine, University of Tokyo : 2 RHC USA Corporation.

Background

Thalidomide

- is a teratogenic agent,
- is effective for multiple myeloma,
- is potentially effective for other malignancies as well, and
- is imported by Japanese doctors

JSCH guideline

- was published by the Japanese Society of Clinical Hematology in December 2004,
- requested doctors to register patients with multiple myeloma to

Objectives

- To examine time trend of thalidomide use since 2000 in Japan.

Thalidomide Use in the US

Experience with Pregnancy Testing in the S.T.E.P.S.® Programme

Kathleen Uhl,[1] *Edward Cox*,[1] *Rose Rogan*,[2] *Jerome B. Zeldis*,[2] *Dena Hixon*,[1] *Lesley-Anne Furlong*,[1] *Sarah Singer*,[1,3] *Tracy Holliman*,[2] *Joanne Beyer*[2] and *William Woolever*[2]

1 US Food & Drug Administration, Center for Drug Evaluation and Research, Rockville, Maryland, USA
2 Celgene Corporation, Summit, New Jersey, USA
3 National Institutes of Health, National Library of Medicine, Bethesda, Maryland, USA

Abstract

Introduction: In 1998, thalidomide (Thalomid®), a known human tera
approved by the US FDA for the treatment of erythema nodosum lep

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