
C B G
M E B

Challenges and opportunities to measuring the impact of regulatory actions

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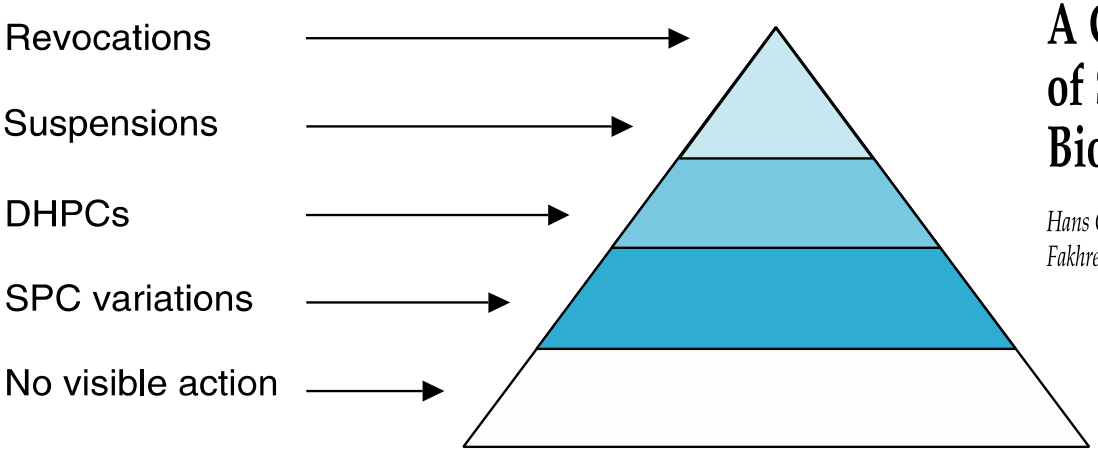
9.7.3 Outcomes of regulatory action

The strengths and weaknesses of the European PhV System regarding the outcomes of regulatory action can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
•	• The outcomes of regulatory action are only assessed in exceptional cases. • There is very little information about what prescribers do with label information and label changes. Moreover, when information is there, the results are not very encouraging. • The missing information on outcomes is partially attributed to far too few inspections of MAHs with a pharmacovigilance focus.

Generally, the outcomes of regulatory action cannot easily be evaluated, because even the agencies do normally not have such information. Actions are not evaluated pro-actively, and even if changes in the morbidity and mortality caused by ADRs were detected they could not causally be related to single regulatory acts.

Regulatory actions



A Cohort Study Exploring Determinants of Safety-Related Regulatory Actions for Biopharmaceuticals

Hans C. Ebbers,[1] Aukje K. Mantel-Teeuwisse,[1] Ellen H.M. Moors,[2] Fakhredin A. Sayed Tabatabaei,[3] Huub Schellekens[2,4] and Hubert G.M. Leufkens[1,3]

- PSUR
- Additional risk minimistation

Drug Saf 2012; 35 (5)

Safe Drugs and the Cost of Good Intentions

Hans-Georg Eichler, M.D., Eric Abadie, M.D., June M. Raine, M.D., and Tomas Salmonson, Ph.D.

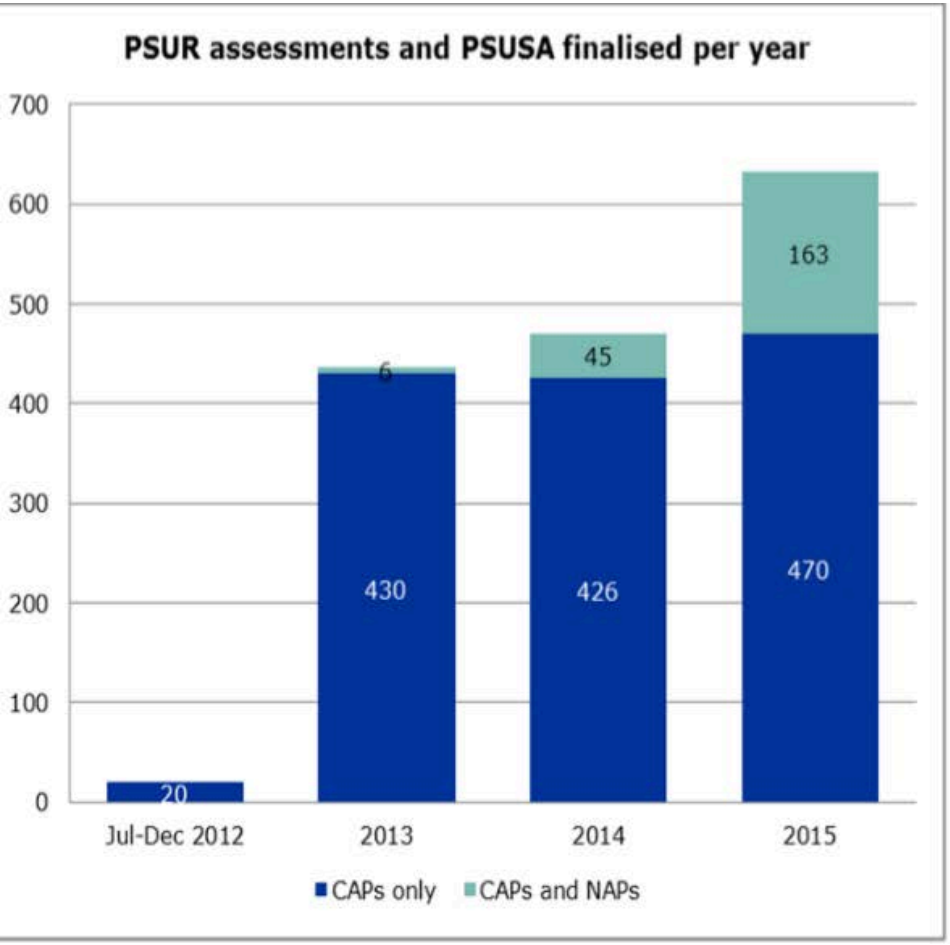
emerging pharmacovigilance tools and new legislative provisions, we should be able not only to refine benefit–risk assessments but also to maximize the public health benefit of new medical treatments.

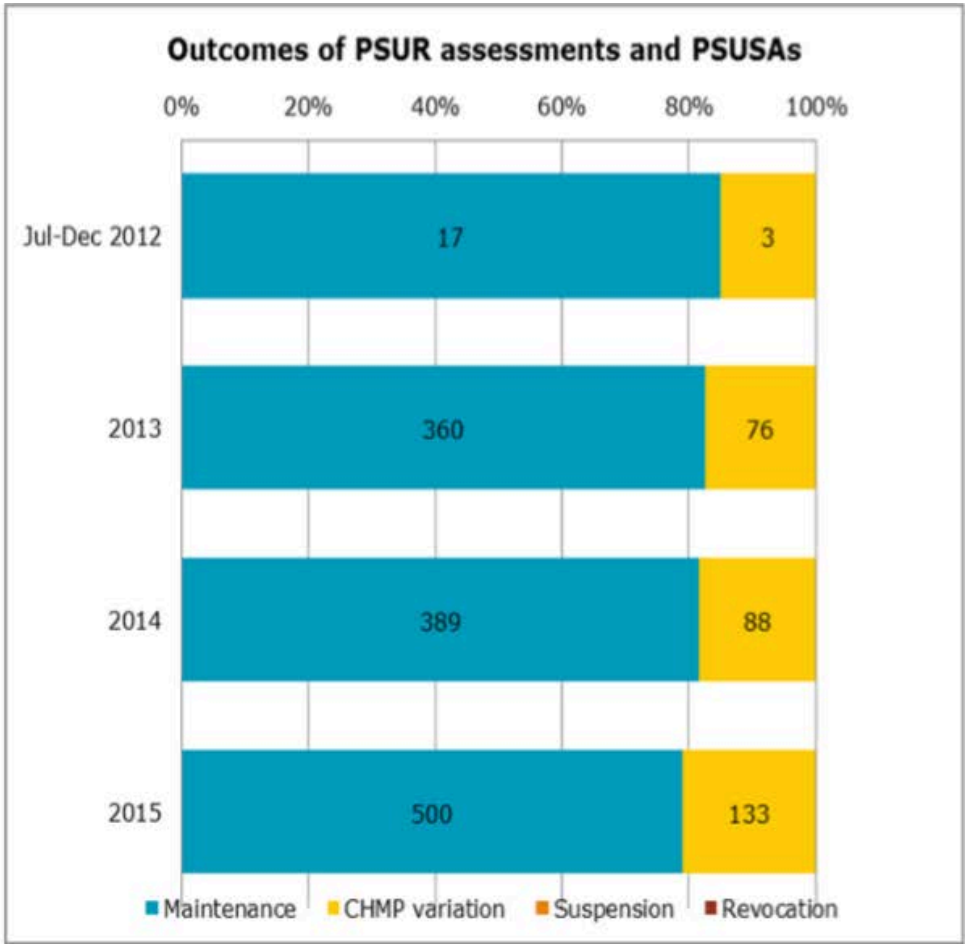
- ADR
- PSUR
- RMP
  - PASS
  - Questionnaires
  - Additional RMM
- Referral
- Additional monitoring list
- Safety communications
- .....

CIOMS VIII

The ultimate test for pharmacovigilance systems is the demonstration of public health benefit

Periodic Safety Update Reports





RMM effectiveness: what to measure?

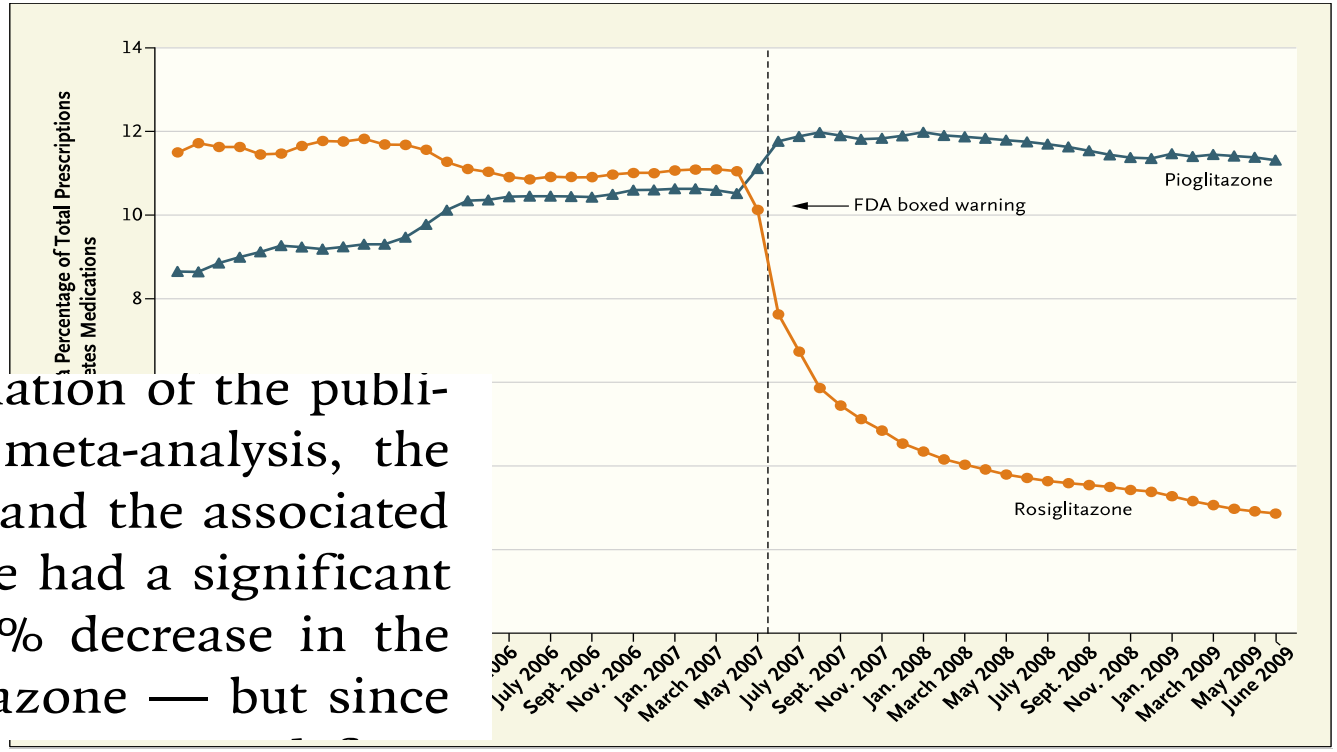
- **Process indicators**

evidence that the implementing steps of risk minimisation measures have been successful

- **Outcome indicators**

provide an overall measure of the level of risk control that has been achieved with a risk minimisation measure

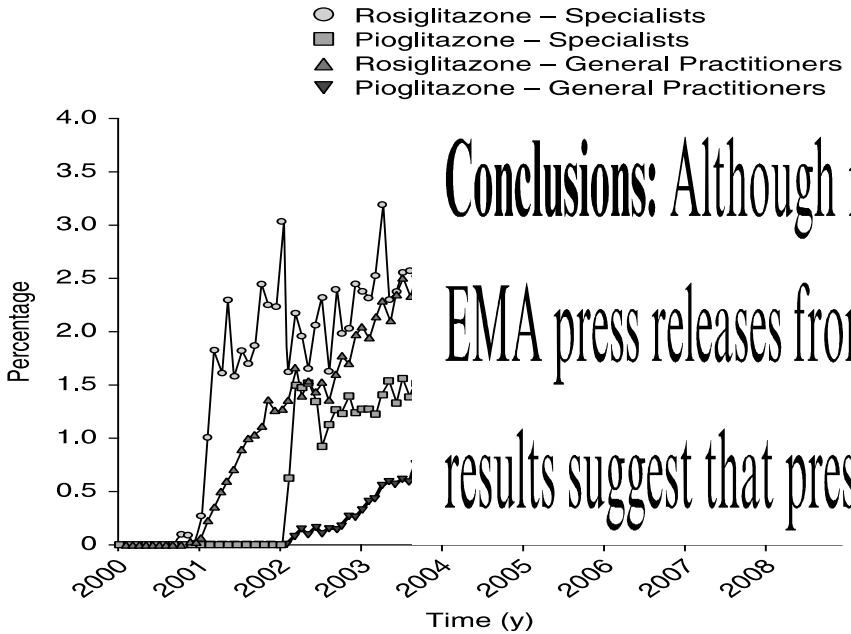
- ✓ performance of the overall program
- ✓ individual tool performance



The combination of the publication of the meta-analysis, the FDA warning, and the associated media coverage had a significant effect — a 70% decrease in the use of rosiglitazone — but since

Prescribing of Rosiglitazone and Pioglitazone Following Safety Signals

Analysis of Trends in Dispensing Patterns in the Netherlands from 1998 to 2008



Conclusions: Although it is difficult to disentangle the effect of DHPCs and EMA press releases from the effect of reports published in the literature, our results suggest that prescribers may react to such safety communications.

Impact of Safety-Related Regulatory Action on Drug Use in Ambulatory Care in the Netherlands

S Piening[1], KC Reber[2], JE Wieringa[2], SMJM Straus[3,4], PA de Graeff[1,3], FM Haaijer-Ruskamp[1] and PGM Mol[1,3]

Conclusion and recommendation

In conclusion, once safety issues for drugs are identified that warrant strong regulatory action, i.e., DHPCs, these result in substantial long-term reductions in use of only a third of issued DHPCs, independent of preexisting trends in use. The reason for less impact could be due to factors such as the type of adverse drug event, availability of alternative agents, and the type of prescriber. Further research is needed to determine the influence

Challenges for DHPC

- Safety issue is identified and requires urgent action
  - Actionable recommendations
  - Target groups
- Definition of succes/failure
  - What is succes
- Data
  - When
  - What
  - How

These data should be sufficient to dispel any serious concerns, but nearly 10 years after the labeling changes, the idea that the boxed warning had adverse consequences persists in the minds of many health professionals, in the media, and among the general public. Because thousands of data sources, geographic areas, time frames, and outcome measures can be examined, continued pursuit of this question will probably provide addi-

The FDA Warning on Antidepressants and Suicidality — Why the Controversy?

Marc B. Stone, M.D.

RMM effectiveness

- Process indicators
  - Implementation logistics/coverage/distribution
    - Distribution plan, target group, quality of the content
  - Awareness and clinical knowledge
    - % of HCP or patients with sufficient knowledge regarding the risk and ways to minimise it
  - Behavorial change/clinical action
    - Impact on daily practice, adherence to guidance, impact on patients

- Outcome indicators
  - Measure directly the health outcome goal
  - Surrogate endpoints if necessary

Additional risk minimisation: PPP

Pregnancy prevention programme (PPP)

- a set of interventions aiming to minimise the risk on drug exposure during pregnancy because of the drugs' potential teratogenic effects
  - Do not start treatment in pregnant women
  - Do not become pregnant during treatment (for a certain period of after stopping)

Isotretinoin PPP

- First version of the PPP in 1988
- In EU, in 2003 the PPP requirements for isotretinoine were harmonised throughout EU with a referral procedure
- All stakeholders are involved
  - Prescriber
  - Pharmacist
  - Patient
  - Payer

Measuring effectiveness of the PPP

- Decide on what to assess

- What is the objective of the PPP

  - No exposed pregnancies
  - No babies with birth defects
  - Full compliance to the recommended contraceptive use
  - Full understanding of the teratogenic risk

ORIGINAL REPORT

Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study

Hubertina J.M.J. Crijns[1,2*], Nienke van Rein[1], Christine C. Gispen-de Wied[2], Sabine M. Straus[2,3] and Lolkje T.W. de Jong-van den Berg[1]

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[2] Medicines Evaluation Board, The Hague, the Netherlands
[3] Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Nether

Isotretinoin Use and Compliance with the Dutch Pregnancy Prevention Programme

A Retrospective Cohort Study in Females of Reproductive Age Using Pharmacy Dispensing Data

Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy

Christof Schaefer · Reinhard Meister · Corinna Weber-Schoendorfer

Isotretinoin Exposure during Pregnancy

Assessment of Spontaneous Reports in France

Elisabeth Autret-Leca,[1,2] *Carmen Kreft-Jais,*[3] *Elisabeth Elefant,*[4] *Hawaré Cissoko,*[1] *François Darrouzain,*[1] *Lamiae Grimaldi-Bensouda,*[1,2] *Sarah Attia*[3] and *Annie Pierre Jonville-Béra*[1]

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Received: 2 April 2009 / Accepted: 23 April 2009

Additional risk minimisation: PPP

BMJ Open

Isotretinoin exposure during pregnancy: a population-based study in The Netherlands

Conclusions: Although a PPP was already implemented in 1988, we showed that isotretinoin exposed pregnancies and adverse fetal and neonatal events potentially related to the exposure still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

BMJ Open 2014, IM Zomerdijk et al

Challenges: datasources

- **Spontaneous adverse event data**

potentially biased outcome measure

systematic data collection or active surveillance of adverse events in populations with well-defined exposure

- **Active surveillance / data collection / sentinel sites**

costly, time consuming and may not detect rare events.

issues relating to response rates, representativeness, and reporting biases may limit the accuracy of survey results.

- **Surveys**

not be the most appropriate approach for the evaluation of behaviour

Well designed minimise potential biases and to optimise the generalizability

- **“The need for speed”**

existing databases, drug utilization studies

Challenges: datasources

Recycling existing data

- Limited recall bias
- Wide scope and coverage
- Longitudinal data
- Rapidly available data
- Low costs
- Limitations databases

Active data collection

- Very specific data can be collected
- Slow
- Low response rate
- Bias (non)response
- Cross-sectional
- Costly
- Self reported behaviour

Challenges: outcome definitions

- **Definitions of success / failure:**
  - What do we want to achieve, how should we measure eg PPP?

In pregnancy prevention programs :

- ✓ No pregnancies
- ✓ No children with congenital abnormalities
- ✓ 100% use of contraception in combination with teratogenic
- ✓ 100% awareness of the risks in HCP and users

Challenges: outcome definitions

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2013)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3494

ORIGINAL REPORT

Additional risk minimisation measures in the EU– are they eligible for assessment?†

Inge M. Zomerdijk[1,2]*, Gianluca Trifirò[1,3], Fakhredin A. Sayed-Tabatabaei[2], Miriam C. J. M. Sturkenboom[1] and Sabine M. J. M. Straus[1,2]

[1] *Departments of Medical Informatics, Erasmus University Medical Centre, Rotterdam, The Netherlands*
[2] *Dutch Medicines Evaluations Board, Utrecht, The Netherlands*
[3] *Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy*

- Currently, the majority of the aRMMs is however not considered suitable for evaluation in electronic healthcare databases, and it remains a challenge to analyse these aRMMs in an efficient and proper way.
- To facilitate the rapid evaluation of aRMMs and timely aRMM adjustment, it is essential that industry and regulatory authorities agree on well-defined aRMM key elements leading to unambiguous actions of the target group.

Challenges……..

- **Definitions of success / failure:**
  - What do we want to achieve , how should we measure eg PPP
- **Quality of the aRMM**
  - A RMM should have a clearly defined objective/actionable
- **Distinguishing between evaluation of goals and tools**
  achievement of goals and performance of tools may not be linked
- **Distinguishing between process and outcome**
  - a need for different remedies
- **Is more always better?**
  - Eg iPledge, is there an optimum?

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2013)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3481

ORIGINAL REPORT

Concomitant use of isotretinoin and contraceptives before and after iPledge in the United States†

Simone P. Pinheiro[1]*, Elizabeth M. Kang[1], Clara Y. Kim[2], Laura A. Governale[1], Esther H. Zhou[1] and Tarek A. Hammad[1]

A study conducted in The Netherlands,[11] where a less stringent risk management program has been in place, suggested higher, albeit still insufficient, concomitant contraception use with isotretinoin prescriptions. In the Dutch study, the proportion of women with total monthly overlap of isotretinoin and contraceptives ranged 38%–41% for systemic contraceptives and was approximately 12% for local contra-

Challenges: Need for speed

- **Definitions of success / failure**:
  - What do we want to achieve , how should we measure eg PPP
- **Quality of the aRMM**
  - A RMM should have a clearly defined objective
- **Distinguishing between evaluation of goals and** tools
  - achievement of goals and performance of tools may not be linked
- **Distinguishing between process and outcome**
  - If the RM does not perform need for different remedies
- **Is more always better?**
  - Eg iPledge, is there an optimum?
  - How to remedy if effectiveness seems to fail ?

- **How to ensure speedy amendments if needed, based on good quality data**

Summary of key issues

- Quality of (a)RMM
- Definitions of failure and success
- Readily available data versus customised data collection

Avoiding risks is impossible, managing them adequately is the key to success