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EU - Risk Management Plan

Angela van der Salm, Director PV

Disclaimer

The views and opinions expressed in the following Power Point slides are those of the individual presenter.

A number of the slides have been graciously shared by Dr. Lambert Creuwels, H. Lundbeck A/S

Topics

- Background
- When is an RMP required?
- How to prepare an RMP
- Special situations
- Take home messages

Risk Management Background

- ICH:

Pharmacovigilance planning E2E (ICH Harmonised Tripartite Guideline (18 nov 2004)

- Europe: (previously Volume 9A)

Guideline on Good Pharmacovigilance practices (GVPs):

  - Module V – Risk Management Systems, rev 1 (EMEA/838713/2011)
  - Module XVI – Risk Minimisation measures: selection of tools and effectiveness indicators, rev 1 (EMEA/204715/2012)
  - Guidance on format of the risk management plan (RMP) in the EU – in integrated format (EMA/718034/2012)
- FDA (March 2005):
  - Guidance for Industry: Development and Use of Risk Minimization Action Plans
  - Guidance for Industry: Good Pharmacovigilance Practices and Pharmaco-epidemiologic Assessment
  - Guidance for Industry: Premarketing Risk Assessment
- CIOMS:
  - CIOMS IV (1998) – Benefit Risk balance for marketed drugs
  - CIOMS IX (2014) – Risk Minimisation Measures

Despite the required investigations, studies etc …

- Risks become apparent after approval of the drug:
  - clinical studies are limited in size and duration (efficacy)
  - subgroups at risk are not studied (age, ethnicity, co-morbidity)
  - better detection systems, awareness what to look at

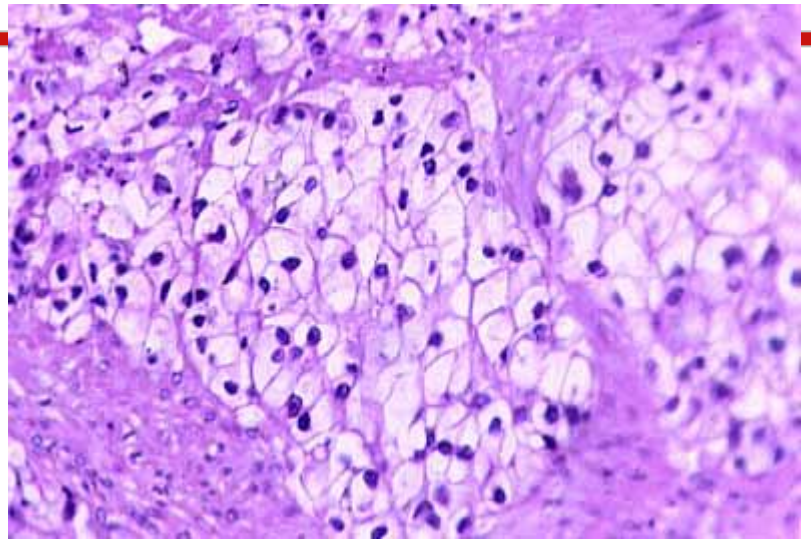
➔ initiation of a risk management system

Chance that a very rare side effect (0.01%) will NOT be observed	
# of patients treated	Chance of missing (%)
500	95.1
1000	90.5
5000	60.7
10000	36.8
20000	13.5
30000	5.0

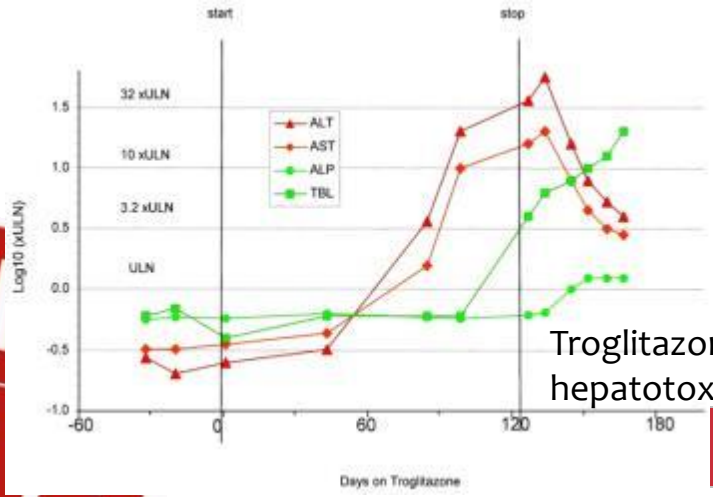
Amery: Pharmacoepidemiology and Drug Safety 1999, 8:61-64

Examples

Thalidomide: teratogenicity



Di-ethyl-stilbestrol (DES): clear cell adenocarcinoma



Troglitazone: hepatotoxicity

Rofecoxib (Vioxx): myocardial infarction

Watkins:Toxicol Pathol. 2005, vol 33, p1-5

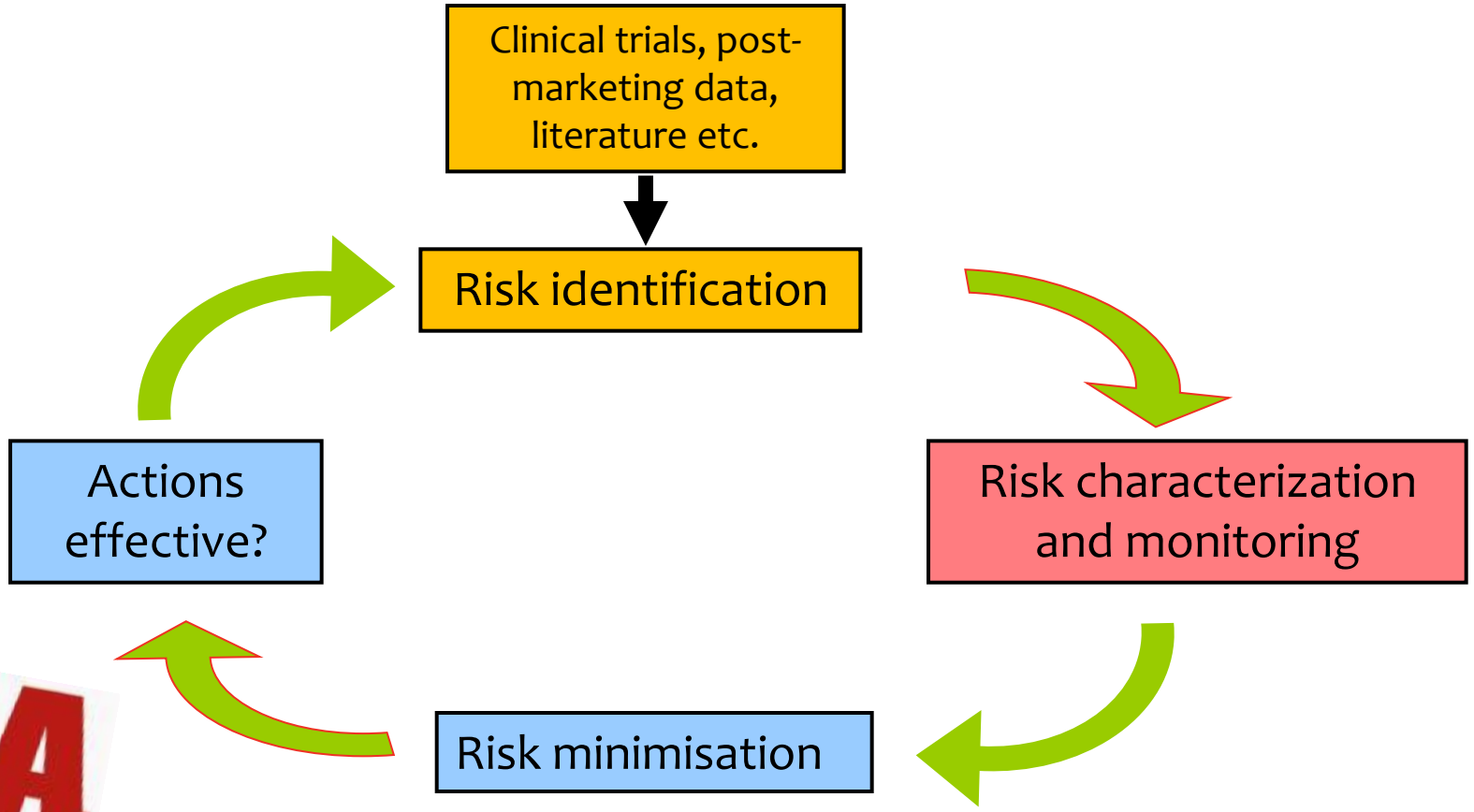
Risk Management Background

- Risk management system: a set of activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of effectiveness of those interventions

- Risk management is a continuing process throughout the lifetime of a medicinal product.

- Written down in an EU-RMP (EU-Risk Management Plan)

Risk management (visual)



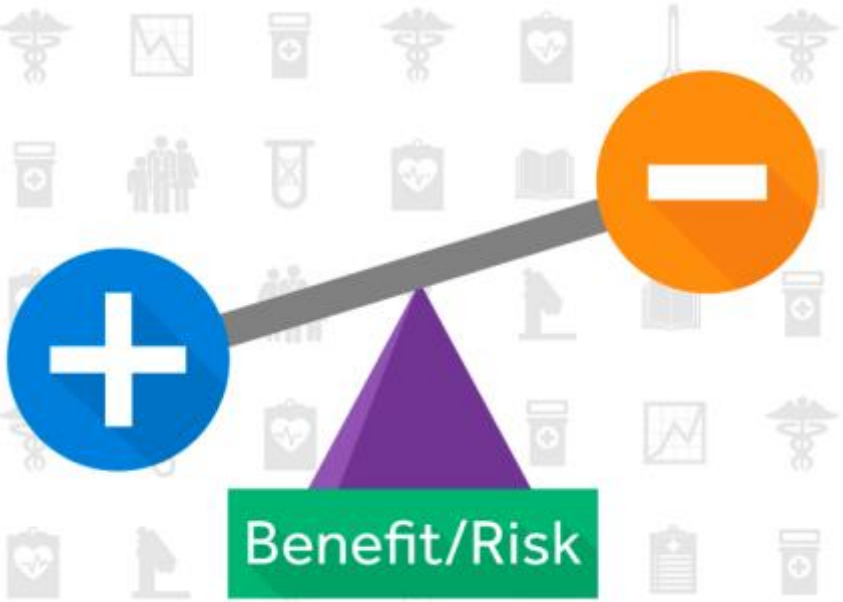
Purpose Risk Management

- … to ensure that the benefits for a particular drug exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole

- Note:
  - Risk Management Plan focuses on minimisation of risks (but this might also be done by increasing the benefits)
  - RM is relative and considered as a balance between risk(s) and benefit(s)
    - ‘benefit-risk management’

Risk Management Background

- Risk is **balanced** by Benefit and this balance should be **positive** at the time of granting of the MA.
  - The greater the benefit, the greater the risks?



When is an EU-RMP required?

- An EU-RMP may need to be submitted at any time of a product's life-cycle

  (i.e. during both the pre-authorisation and post-authorisation phases)

- In particular an EU-RMP should be submitted:

1. for **all new** marketing applications, an RMP including a summary thereof should be submitted:

   (e.g. any product containing a new active substance, a similar biological medicinal product, a generic/hybrid medicinal product*)

* certain sections of the RMP may be omitted

When is an EU-RMP required?

2. with an application involving a significant change to an existing marketing authorisation

   (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, pediatric indication, other significant change in indication)

3. at the request of the Competent Authority (both pre- and post-authorisation).

4. with a submission of final study results impacting the RMP or when a PSUR identifies (a change to) safety concerns for which the RMP should be updated

Templates: EU

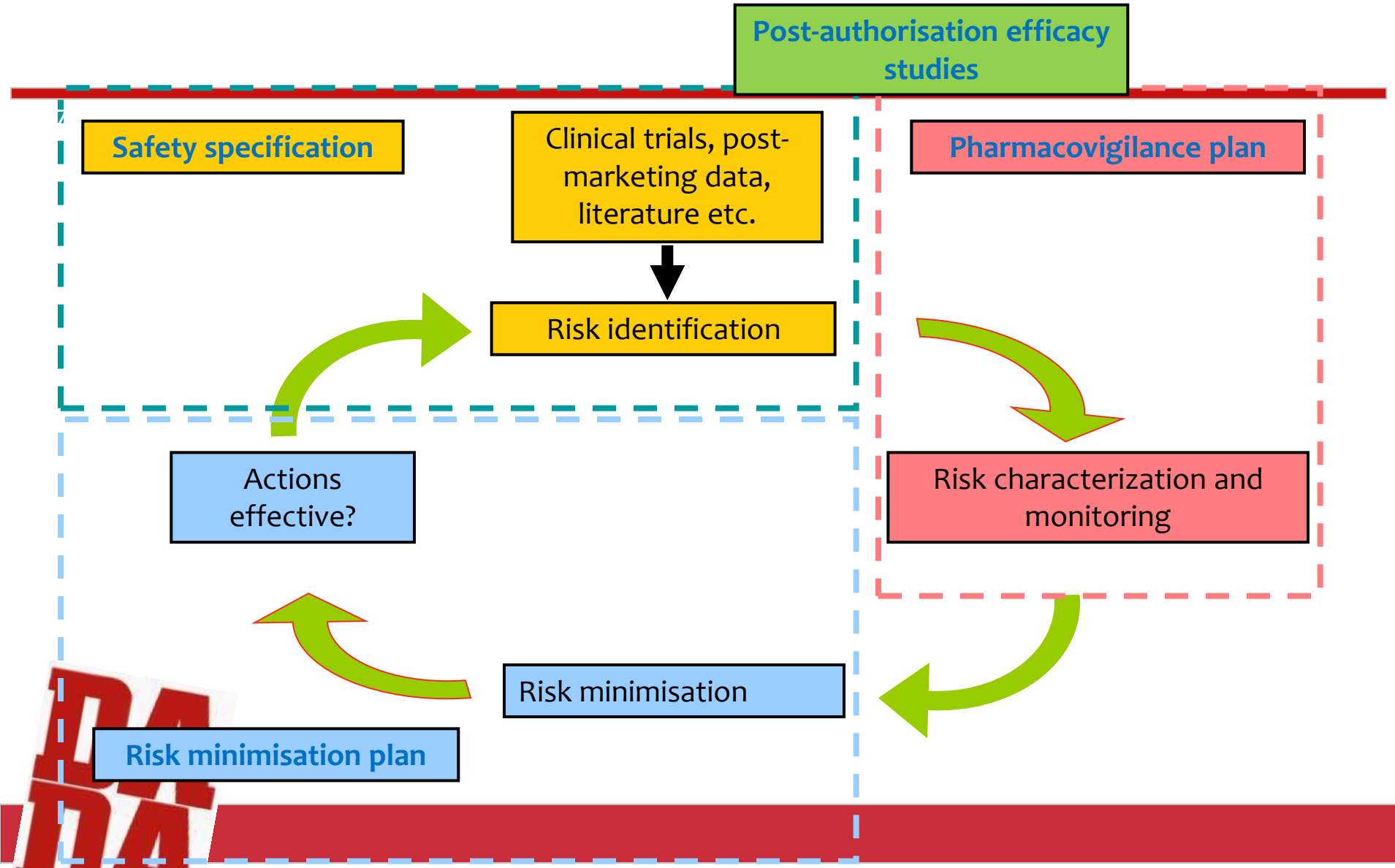
- MHRA: draft template for a RMP (2004)

- Template for EU Risk Management Plan (EU-RMP) (EMEA/192632/2006)
  (old template; still on website although it is obsolete)

- Guidance on format of the risk management plan (RMP) in the EU – in integrated format (EMA/465932/2013 Rev.1)

How to prepare an RMP

- To indicate what we do know, and what we do not know about our product ("the safety specification")
- To define actions to increase our knowledge about the safety of our product ("the pharmacovigilance plan")
- To define actions to minimize the known or potential risks of our product ("risk minimisation measures")


Post-authorisation efficacy studies
Safety specification
Clinical trials, post-marketing data, literature etc.
Pharmacovigilance plan
Risk identification
Actions effective?
Risk characterization and monitoring
Risk minimisation
Risk minimisation plan

EU-Risk Management Plan

As per Module V of the GVP: 14 modules

- Part I Product Overview
- Part II Safety Specifications (more detail: SI-SVIII)
- Part III Pharmacovigilance Plan
- Part IV Post-authorisation efficacy studies
- Part V Risk minimisation measures (including evaluation of effectiveness of these measures)
- Part VI Summary of RMP (public, in lay language)
- Part VII Annexes

Safety Specification

- A summary of the safety profile. This includes (module SI-SVI):
  - epidemiological data (on the indication)
  - non-clinical data
  - clinical trial exposure
  - populations not studied in clinical trials
  - post-authorisation experience
  - additional EU requirements (overdose, transmission infectious agents, misuse, medication errors, off-label use, etc)

- Identification of important adverse events that are (possibly) related to the drug ("the risks") (Module VII)
  - Identified risk
  - Potential risk

Safety concerns: definitions

- (Important) Identified risk:
  - An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest
- (Important) Potential risk:
  - An untoward occurrence for which there is some basis of suspicion of an association with the medicinal product of interest, but where this association has not been confirmed
- Missing information:
  - Information about the safety of a medicinal product which is not available at time of submission of the RMP and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace
- Safety concern: IIR + IPR + MI

Safety Specification: beware …

- Safety concern: event that could impact on the risk-benefit balance of the product or have implications for public health.

Rule of thumb:

- Identified risks all end up in 'Undesirable effects' (4.8; are not necessarily important)
- Potential risks end up in 'Warnings & Precautions' (4.5; only if important)

Safety Specification: beware …

- For ‘identified risk’ / ‘potential risk’ info is needed about:
  - seriousness
  - outcome
  - Severity and nature of risk
  - frequency with 95% CI
  - background incidence/prevalence
  - risk groups or risk factors
  - potential mechanisms
  - preventability
  - potential public health impact of safety concern
  - evidence source
  - regulatory action taken

Safety Specification: beware …

- For ‘Missing information’, info is needed about:
  - Populations not studied in the Pre-Approval Phase
    - children
    - elderly
    - pregnant or breast feeding women
    - patients with relevant co-morbidity such as hepatic or renal impairment (or cardiovascular, immuno-compromised, etc)
    - patients with disease severity different from that studied in clinical trials
    - sub-populations carrying known and relevant genetic polymorphisms
    - patients of different racial and/or ethnic origins

Safety Specification: beware …

Missing data: e.g.

- The CCDS mentions: "Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking." ➔ missing data
- "During clinical development no pregnancies were allowed." ➔ missing data
- "The clearance of <drug>may be decreased in patients with mild renal impairment (creatinine clearance <40 ml/min)." ➔ missing data (about moderate to severe renal impairment)

Pharmacovigilance Plan

Describes actions with the purpose to characterise and monitor each safety concern (+ to gain more knowledge)

Actions could be:

- Routine pharmacovigilance:

  Gathering information on AE's (incl. questionnaires) and reporting of individual cases, continuous monitoring of the safety profile, PSURs, signal detection, other requirements (local regulations)

- Additional pharmacovigilance:

  when routine pharmacovigilance is not deemed sufficient
  - Intensive monitoring (example: Using Addenda)
  - Comparative observational studies
  - Active surveillance programs
  - Registries

Post-authorisation efficacy study

- Are there gaps in the knowledge about efficacy in target population?
  - (e.g. 98% of all patients studied were caucasian)
  - Long term efficacy
  - Variability in benefits for sub-population?

- This should NOT include efficacy studies done to get an extra indication !

Risk Minimisation Measures

Describes actions: purpose to prevent or minimise risks

- Routine risk minimisation: legal status of medicine, product information (SmPC, PIL), pack size limitation
- Additional risk minimisation activities, such as:
  - Additional education:
    - Educational programs for physicians, pharmacists
    - Patient information leaflets, or brochures
  - Control of the conditions under which a drug may be made available to reduce risk of use or misuse: who may prescribe, dispense or receive the drug ?
    - Restricting prescribing and dispensing
    - Informed consent procedure
  - Controlled distribution
  - Other

Risk Minimisation Measures (1/2)

Pre-marketing:

- Revise inclusion / exclusion criteria
- Revise the Informed Consent form
- Conduct advisory board meetings
- Close PV monitoring
- Guidance documents

Risk Minimisation Measures (2/2)

Post-marketing:

- Label (change)
- (change) Dosage
- Increase monitoring frequency and increase awareness
- Registries
- Develop and distribute Dear Doctor Letter (DHPC)
- Informed consent procedure
- Supportive care medications
- Risk communication plan
- (change) Formulation (tablet to injections etc)
- Educational material
    - Direct to patient/doctor education program
    - Presentation slide kits/ printed materials
    - Advertising/promotion; increase Rx awareness
    - CME programs (CME= continuing medical education)
    - Field force training

Evaluation (part of risk minimisation)

- For each safety concern:
  - Describe the Routine RMM
  - If Additional RMMs are necessary: describe these
  - Describe the effectiveness of the RMM
    - Outcome indicators: measurement of overall level of risk control
    - Process indicators: provide insight into what extent the programme has been executed as planned

Summary of activities (1/2)

- Elements for summary tables in the EPAR
  - Summary table of safety concerns
  - Table of ongoing/planned PV studies/activities
  - Summary of post-authorisation efficacy development plan
  - Summary of risk minimisation measures
- Elements for a Public Summary

Summary of activities (2/2)

- Elements for a Public Summary (lay language!)
  - Overview of disease epidemiology
  - Summary of treatment benefits
  - Summary of unknowns relating to treatment benefit
  - Summary of safety concerns
  - Summary of risk minimisation measures
  - Planned post-authorisation development plan
  - Studies which are a condition of the marketing authorisation (if applicable)
  - Summary of changes to the RMP over time

Annexes

- Annex 1: Interface between RMP and Eudravigilance/EPITT (electronic only)
- Annex 2: Current (or proposed) local SmPC and package leaflet.
- Annex 3: worldwide marketing authorisation status by country
- Annex 4: Synopsis of on-going and completed clinical trial programme.
- Annex 5: Synopsis of on-going and completed pharmacoepidemiological study programme.
- Annex 6: Protocols for proposed and on-going studies in categories 1-3 in RMP part III.
- Annex 7: Specific adverse event follow-up forms.
- Annex 8: Protocols for proposed and on-going studies in RMP part IV.
- Annex 9: Synopsis of newly available study reports for RMP parts III-IV.
- Annex 10: Details of proposed additional risk minimisation activities (if applicable).
- Annex 11: Mock up examples of the material provided to HCPs and patients
- Annex 12: Other supporting data (including referenced material).

Specific content requirements

- Are depending on the type of new application:

Figure V.3. Requirements for new marketing applications

	Type of new application	Part I	Part II-Module SI	Part II-Module SII	Part II-Module SIII	Part II-Module SIV	Part II-Module SV	Part II-Module SVI	Part II-Module SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
8(3)	**New active substance**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10(4)	**Similar biological**	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10c	**Informed consent**[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
10(1)	**Generic medicine**	✓								✓	*	*	✓	*	✓
10(3)	**Hybrid medicinal products**	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10b	**Fixed combination**	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10a	**"Well established use"**	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
	"Same active substance"	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

How to prepare the RMP?

- Follow the SOP / procedure from your company …

… but use the EU RMP template

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&mid=WC0b01ac05800250b3)

How to prepare the RMP?

- What's changing? – draft GVP V soon open for consultation*:
- Replaced table with detailed description
- Expanded guidance regarding modified requirements for generic medicines (considering data on CMDh website http://www.hma.eu/464.html)
- Addressed all types if initial MAAs: informed consent, hybrids, fixed combinations, well established use, herbal products, new products with substances authorised for more than 10 years
- Detailed guidance on requirements for parts and modules: what is needed when?
  - Further guidance is included in the RMP template for the MAHs. i.e. when a section is required and when there is a limited scope or can be omitted
- Reshaped module SVII:
  1. Rationale for including safety concerns in the initial MAA RMP
  2. Update of the safety concerns
  3. Details of important identified potential risks and missing information

* Public consultation planned for autumn 2015: GVP V and RMP template (at the same time and in parallel

Emil Cochino (EMA), DIA EMA RMP information day dd 30-Jun-15

In practice:

- Come up with a team with relevant representation of departments
- Discuss within "the team" who will prepare and maintain the RMP
- Agree who will be the leader of "the team" (often for practical reasons PV)
- Discuss and agree within "the team" the safety concerns, and the actions to address the safety concerns
- Input needed from many departments
- Start well in advance

Who should be in the team? (1/2)

- Safety: safety profile, risks
- Regulatory: what regulatory procedure followed; submission
- Clinical: study info; clinical trial report; therapeutic area expertise (benefits)
- Biometrics; tables upon specified request
- Communications: to review text in lay language

Who should be in the team? (2/2)

- Toxicology: chapter non-clinical
- Marketing!!!: get sample of product including packaging, marketing strategy, marketing activities, non-study post-authorisation exposure and off-label use
- Medical writer
- Medical affairs: liability input, efficacy input
- Epidemiologist: many parts of the RMP
- 1 or 2 assistants: layout, subtopics, references, etc

More practical issues

- Align the documents: RMP should be aligned with
  - expectedness table / labeling
  - IB
  - CDP
  - Reference Safety Information
  - DSUR
  - (PSUR)

- Lay language section: look at PIL, use help of Communications, use help of proof-reading by a non-professional / patient.

RMP updates

- MAA/MAH may request advice on the need for development or content of an EU-RMP through the scientific advice procedure.

- Update of RMPs:

  There is no longer an automatic requirement to update RMPs on a fixed-time basis (e.g. 'annually until first renewal'). The Agency and the NCAs are now adopting a **risk-based approach** to RMP updates.

Versioning of RMP (1/2)

- Versioning is described in Module V (section 'Structure of the RMP'). Sections that cease to change -> 'locked'.

RMP version 4 may then hold (for example):

–Part 01 Product overview (version 4; since this is updated every time)
–Part 02 SI Epidemiology (version 2);
–Part 02 SII Non-clinical (version 1);
–Part 02 SIII Clinical (version 3);
–Etc ….
–Part 07 Annexes (version 4)

Versioning of RMP (2/2)

- EMA website: Q&A on pre-submission guidance #42: how to submit the EU RMP in eCTD?
  - Until further notice, companies have to send in all parts and modules of the RMP in one single PDF file so that a complete RMP is provided to the Agency. A cover letter stating which parts and modules of the RMP have actually been updated should be provided. Part I of the RMP also presents this information and should always be updated.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000024.jsp&mid=WC0b01ac0580022715

Local versions?

- After submission of the EU-RMP: you might receive requests to change the RMP.
- If you submit the EU-RMP to other countries, they also might want to change the content.
- Probably best solution is to have a core-RMP (with company position), plus local or regional versions
  - E.g. core-RMP plus Annex for Canada

Special situations

Often an RMP will ‘grow’ along with the development of the product.

=> However: a product might be already on the market before an RMP is needed (e.g. a significant change for a ‘vintage product’ and it was requested to write an RMP, etc).

RMP for post-marketing product

- Benefits can be found in section pharmacodynamic properties (study results). If there are no study results mentioned you might report as benefit the indication(s) for the drug

- Post-marketing RMP: align with the PSUR (section 16-18) !

So remember:

- The EU-RMP has a modular structure
  - Differing content for different application types!
  - Allowing overlap with PSUR, facilitating (?!) report writing
- It is required for each and every new MA application
- Routine Risk minimisation measures include label, packaging, pack size and legal status
- When additional Risk minimisation measures come in, measures of effectiveness should take place: define feasible criteria!
- The bigger the company, the more people involved.

Questions?

Risk minimisation Plan

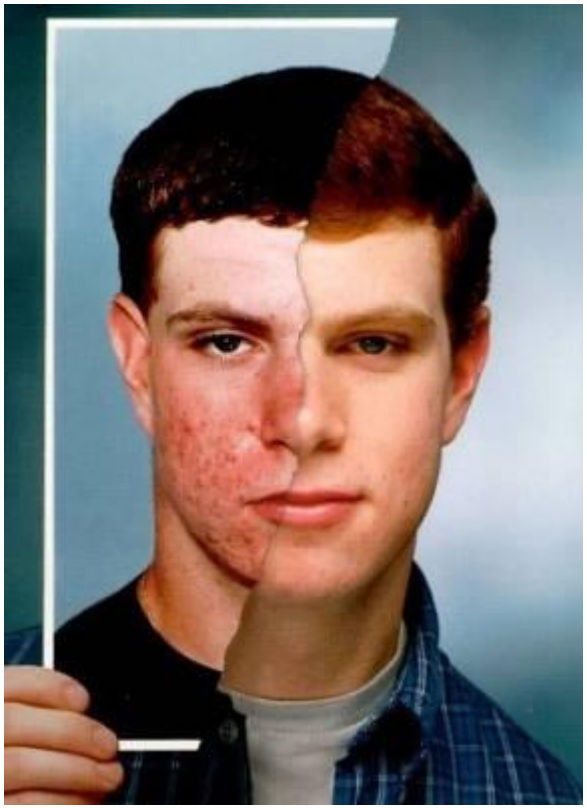
- Routine Risk Minimisation
  - SmPC: Summary of Product Characteristics
  - PIL (patient information leaflet)
  - Legal status of MP
- Additional Risk Minimisation
  - Educational material
  - Limited prescription, or limited box size
  - Restricted access
  - Registries
  - ….

Risk minimisation needed if…

- Serious adverse drug reactions
  - E.g. immune system disorders, teratogenicity
- New method of administration
  - E.g. new patch in neuropathic pain
- High potential for abuse / off-label use
  - E.g. risk for addiction

Isotretinoin (Roaccutane)

- The benefits:
- Highly effective in the treatment of cystic acne.
- Often the only effective treatment in severe cases



Isotretinoin

The risks:
Causes birth defects: 30% risk of congenital malformation

Major congenital malformations reported:
- hydrocephalus
- microcephalus
- cardiovascular abnormalities
- ear and eye abnormalities
- facial dysmorphia
- cerebellar abnormalities

Pharmacovigilance activities

- Possible activities to gain more information on isotretinoin and birth defects

  - Routine pharmacovigilance
  - Close monitoring of spontaneous reported cases (e.g. DCF procedure, use of questionnaires etc.)
  - Use of a registry:
    - **FDA iPledge program: Physicians, pharmacists and patient prescribing, dispensing or using isotretinoin have to register on the iPledge website**
    - **Information can be obtained via questions online**

Risk minimization activities (1/3)

- **To prevent birth defects is to prevent pregnancies while using isotretinoin**
- **Inform doctors and patients in the product labeling:**
  - Contraindication: Use in pregnancy
  - Warning against birth defects
  - Pregnancy test should be taken 2 weeks prior to start isotretinoin
  - Compulsory use of contraception from 1 month prior to start – 1 month after discontinuation of isotretinoin
  - Information in product labeling can be bold or boxed
- **Other methods to inform doctors and patient:**
  - iPledge website contains information and questions related to pregnancy tests, menstrual cycles etc.
  - Special brochures, information folders for patient, physician and pharmacist
  - "Dear doctor letters"

Risk minimization activities (2/3)

- **Restriction on prescribing and dispensing**
  - In many countries isotretinoin can only be prescribed by specialized health care professionals (e.g. consultant dermatologist)
  - In the US prescription can only be dispensed when dermatologist, pharmacist and patient have registered on iPledge
  - In certain countries: Physician may not prescribe more than 30 days supply. There is a 7 days window in which the prescription must be picked up from pharmacy.

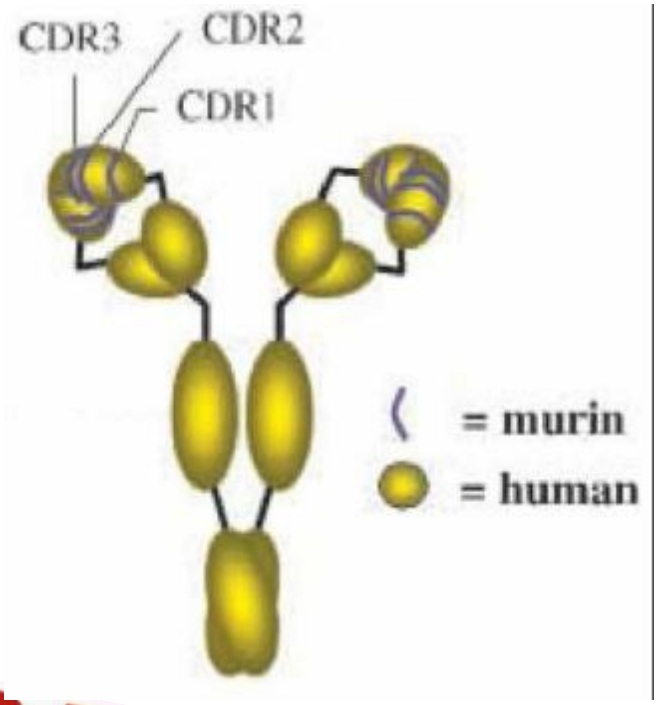
Risk minimization activities (3/3)

- **Informed consent**
  - In many countries informed consent for the use of isotretinoin
  - Patient is informed and consents to among others:
    - The possible occurrence of birth defects when pregnant
    - The use of at least 1 method of contraception
    - Starting method of contraception at least 1 month prior to starting isotretinoin
    - Confirmation of not being pregnant prior to the start of isotretinoin
  - Informed consent is signed by patient

Isotretinoin risk minimisation activities in the Netherlands

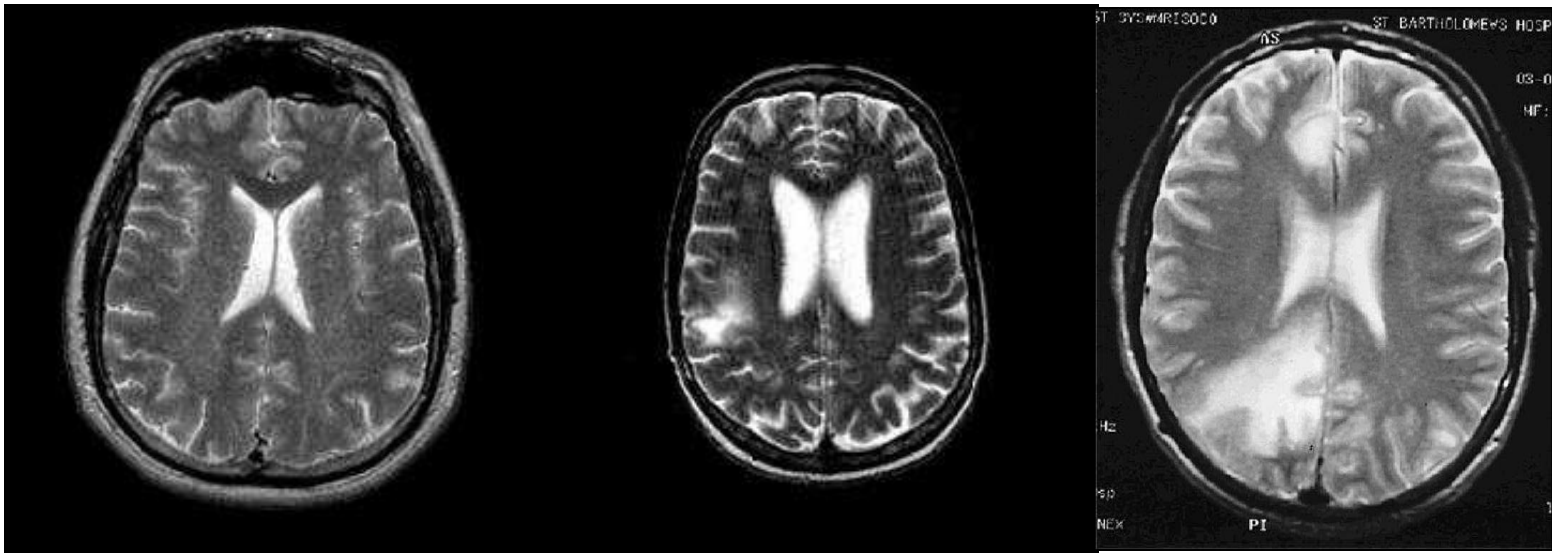
- Pharmaceutical companies producing isotretinoin have installed a "Pregnancy prevention programme" (mandated by the Dutch authorities)
  - Special manual for physician
  - Special manual for pharmacist
  - Special manual for patient
  - Informed consent form

Natalizumab (Tysabri)



- Natalizumab is a recombinant humanised IgG4 monoclonal antibody produced in murine myeloma cells
- Specific binding: a4-Integrin
- This binding reduces migration of activated inflammatory cells, including T-lymphocytes, from the vasculature into, for example, the brain parenchyma. This mechanism is thought that natalizumab manages to reduce plaque formation and relapse rates in patients with multiple sclerosis (MS).

Tysabri



serious adverse drug reactions:
Progressive Multifocal Leucencephalopathy (PML)
(rare disease, usually associated with severe immunosuppression (HIV, chemotherapy, transplantation))

N= 3 cases pre-marketing: marketing suspended; re-introduction in 2006 with comprehensive RiskMAP

Tysabri risk minimisation

- Clear-cut definition of the target population, i.e. restricted use only for patients with highly active disease without reasonable alternatives
- Requirement for established MS
- Escape rule for non-responders to avoid unnecessary exposure
- Administration only in specialised centres by experienced physicians
- Clear contraindications including a contraindication for combination with other immunomodulators
- Patient alert card
- Educational program for physicians including PML algorithm

Thalidomide

- After the withdrawal as anti-nausea drug, it stayed on the market. Indications were:
  - Lepra (1964)
  - Behçet's disease (1979)
  - Graft-versus-host reaction (1988)
  - HIV / aids complications (1989)
  - Angiogenesis inhibitor (cancer treatment) (1994)
  - Multiple myeloma (2008)

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  - Behçet's disease 1979
  - Graft-versus-host reaction (1988)
  - HIV / aids complications (1989)
  - Angiogenesis inhibitor (cancer treatment) (1994)
  - Multiple myeloma (2008) approved in EU

Use of the drug only under very strict restrictions !

=> Even for a drug like thalidomide there might be a need

Thalidomide

- Extensive additional risk minimisation programme:
  - production, dispensing and prescription is strictly controled;
  - women should use two forms of birth control;
  - submit to regular pregnancy tests;
  - dispensing rights to authorised pharmacies;
  - thalidomide education to HCP;
  - education to patients;
  - limiting prescription;
  - registry

Thalidomide

Despite this: circa 100 cases of embryopathy in Brazil from 2005 to 2010.

Mainly in poor illiterate Brazilians, in areas with poor access to healthcare: misunderstanding of the warning symbol: they thought it was an abortion drug !

⇒ The use of extensive RMM might not be enough to safeguard the population

How many Risk Minimisation Actions?

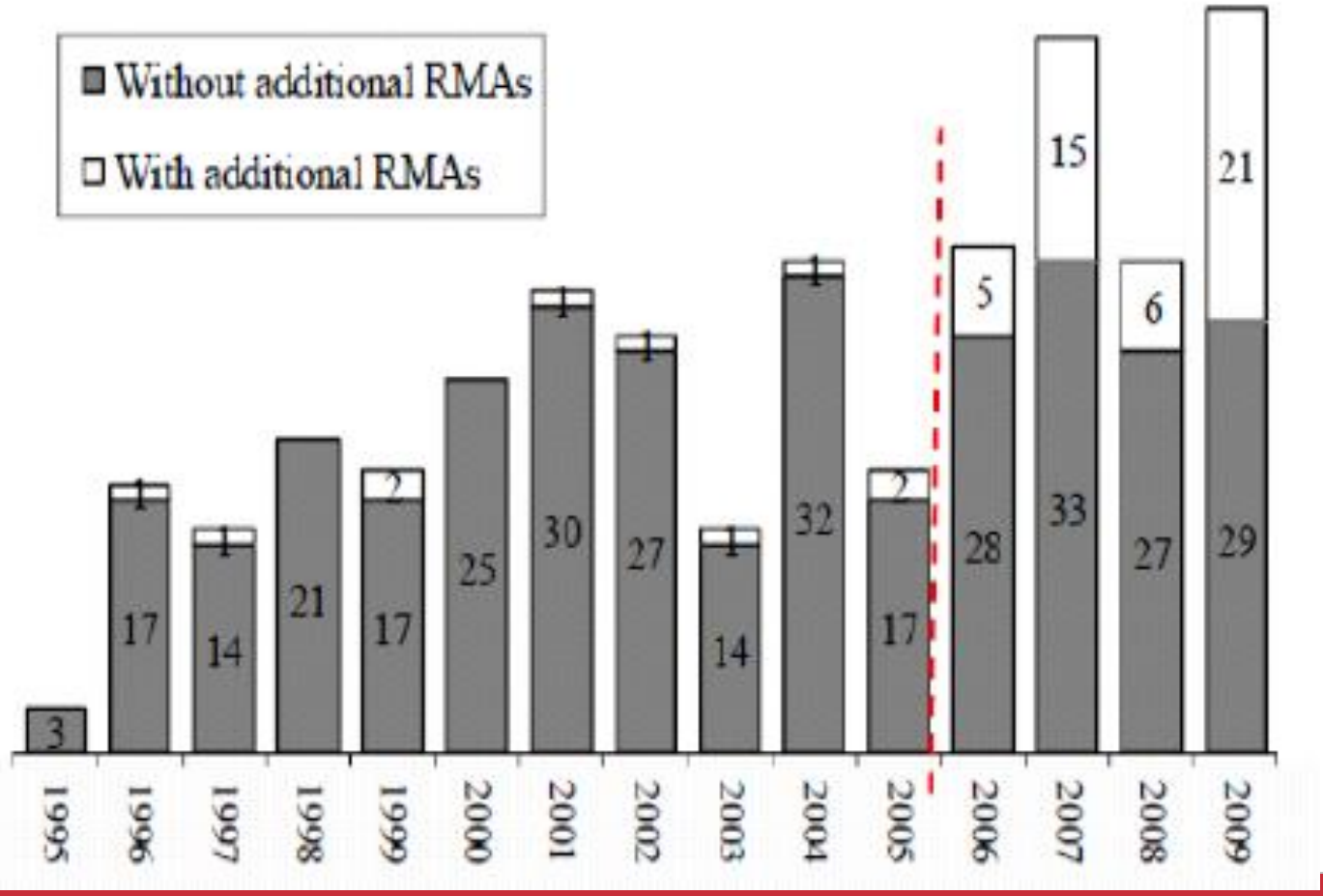
- Centrally authorised new active substances in the period January 1995 till January 2010: **391**
- Active substances with additional RM activities (of the 391): **57** **=> 14.6%**

(ref: M. Lagendijk, CBG-MEB: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/06/WC500107882.pdf)

- Per 27 May 2015: List of medicinal products under additional monitoring: 240

(ref: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142453.pdf)

Additional RMA



Additional RMA

Provision of educational material	57
- To health care provider	56
- To patient	31
Patient monitoring / screening	18
Controlled distribution	9
Pregnancy prevention activities	5
Special packaging / extra label	7
Others	6

I.M. Zomerdijk, Medicines Evaluation Board, Erasmus Univ. Rotterdam

How effective are RMM?

Haloperidol: QT assessment at baseline

- Example haloperidol: baseline ECG is recommended prior to treatment
- Proportion of ECG's:
  - when haloperidol was initiated
  - One year before (control)
- Results: 3420 patients were prescribed haloperidol. ECG at treatment initiation: 1.8% versus 0.8% (control).
- Patients with additional risk factors for QT prolongation: 1.9% versus 1.0% (control)

⇒ Compliance […] extremely low

Warnier, et al, Pharmacoepidemiuology and Derug Safety 2014; 23(S1): p228

How effective are RMM?

Glucose assessment in second-generation AP

- In 2003, the FDA issued warnings about hyperglycemia and diabetes with SGA's
- Since 2004, this risk in product labels. Guidelines have recommended baseline metabolic screening.
- Cohort: age 2 to 18 newly initiating SGA's 1/1/2006-31/12/2011: n=16 304.
- Results: 11% had glucose assessment in minus 90 to 3 days after treatment initiation (OLA > RIS, ARI, QUE)
- => Few children and adolescents starting SGA have baseline glucose assessed.

Raebel et al, Pediatrics 2014;134:e1308–e1314

How effective are RMM?

HHS report

- Approved REMS 2008-2011:
- FDA approved 199 REMS, 99 of which were still required in 2012. 49 REMS were reviewed.
- What was found: nearly half did not include all info requested; 10 were not submitted within timeframe. FDA has not identified reliable methods to assess the effectiveness of REMS; FDA assessment review times exceeded its goal of 60 days for all but one.

=> Findings raise concerns about the overall effectiveness of the REMS program

How effective are RMM?

- Added value of PASS / PAES
- Study: new active substances in 2007 approved = 47
- 22/47 had minimal 1 PASS (in total 31 PASS)

- 2014: 313 safety variations in SmPC (in 41 products)
- Source of deviations was investigated

⇒ 4% of all safety variations resulted from requested PASS

⇒ Costs !

Escher report, http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf

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