Risk Management

YOUR presenter

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psst pharma scientific services team

CEO & Founder
drug development + regulatory consultancy

What we will discuss

(in the next 30 min)

- **Risk Management in General**
- Principles of risk management
- Essential areas of the Risk Management Plan (RMP)
- How to prepare a good Risk Management Plan
- Impact of new legislation

Pharmacovigilance & Risk

"The dose makes the poison."

"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous"

Paracelsus (1493-1541)

To undergo treatment you have to be very healthy, because apart from your sickness you have to withstand the medicine.

Molière (french comedian)

NO Drug is without Risk

Viagra blindness alert

Britons 'lost sight after taking impotence drug'

Revealed: the danger of taking Prozac

Drug maker knew 20 years ago of possible link to suicide

Newsweek

Ritalin

Merck recalls Vioxx

Heart risk found in arthritis drug

PAINFUL

Merck's stock plunged after the pharmaceutical company said it was taking its arthritis drug Vioxx off the market.

Suicides blamed on acne drug

Remicade (Infliximab)

Side Effects Lawsuits

Tuberculosis, Multiple Sclerosis, Lupus, and Serious Infections

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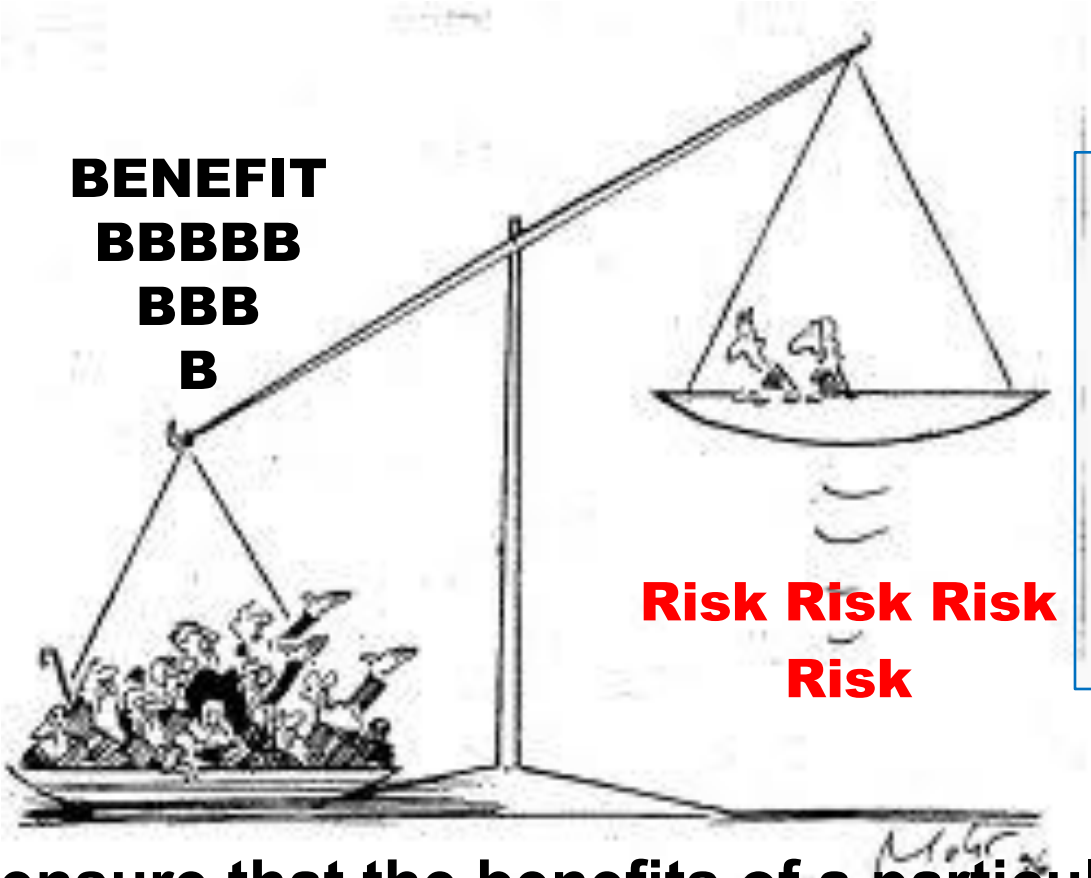
Overall Objectives of Risk Management Planning



Optimization of the Benefit – Risk ratio

"To ensure that the benefits of a particular medicine exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole"

Definition

The Risk Management System

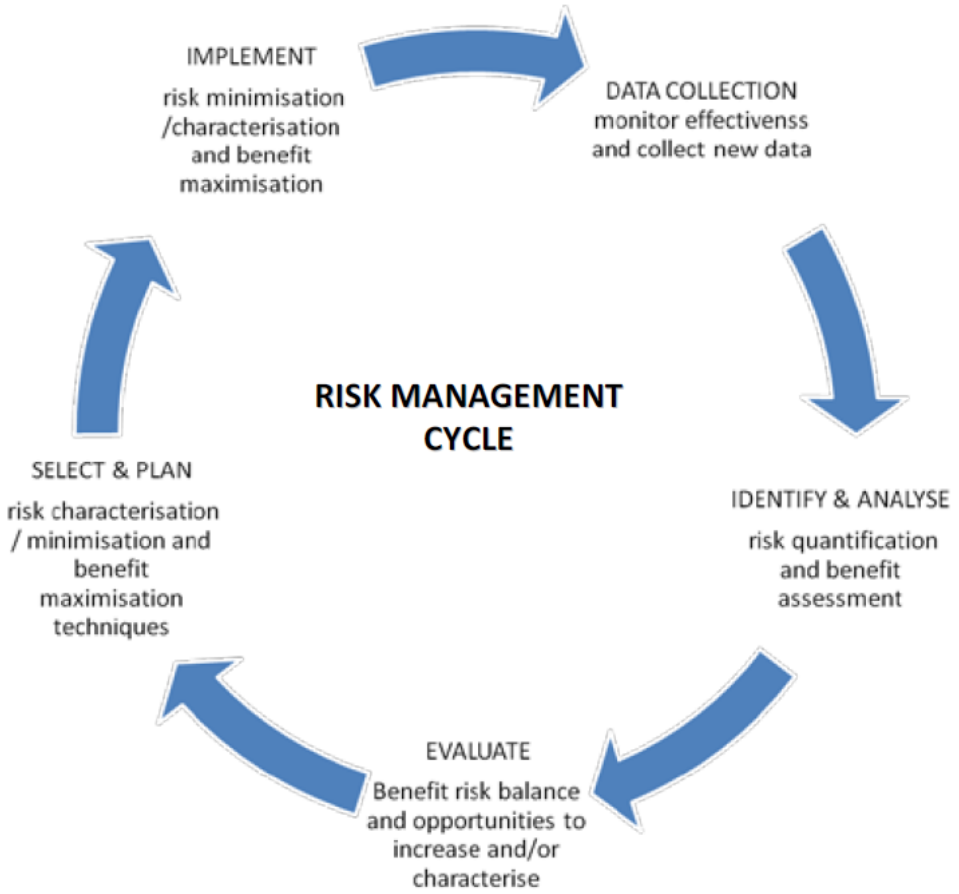
A set of pharmacovigilance activities and interventions designed to

- identify,
- characterise,
- prevent or minimise

RISKs relating to medicinal products, including the assessment of the effectiveness of those interventions

- **Carried out by Applicant/MAA**
- **Evaluated by the Authorities**

The risk management cycle



http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

What DRUG Risk Management is Not !!!??

"And now at this point in the meeting I'd like to shift the blame away from me and onto someone else."

Generally, Risk Management is the process …… the strategies employed include transferring the risk to another party, avoiding the risk, reducing the negative effect of the risk, and accepting some or all of the consequences of a particular risk. *From Wikipedia, the free encyclopedia.*

Common Assumptions

What says EU legislation?

EUDRA Lex	(European Union Drug Regulatory Authorities Legislation)
Vol. 1	Legislation MPs human
Vol. 2	Notice to applicants (nta) and reg. Guidance human
Vol. 3	Scientific guidance human
Vol. 4	GMP guidance human + vet
Vol. 5	Legislation MPs vet
Vol. 6	Nta and reg. Guidance vet
Vol. 7	Scientific guidance vet
Vol. 8	MRL (vet)
Vol. 9	**Pharmacovigilance guidance (human and vet)**
Vol. 10	Clinical trial guidance
Medicinal products for **paediatric use, orphan, herbal medicinal products and advanced therapies** are governed by specific rules	

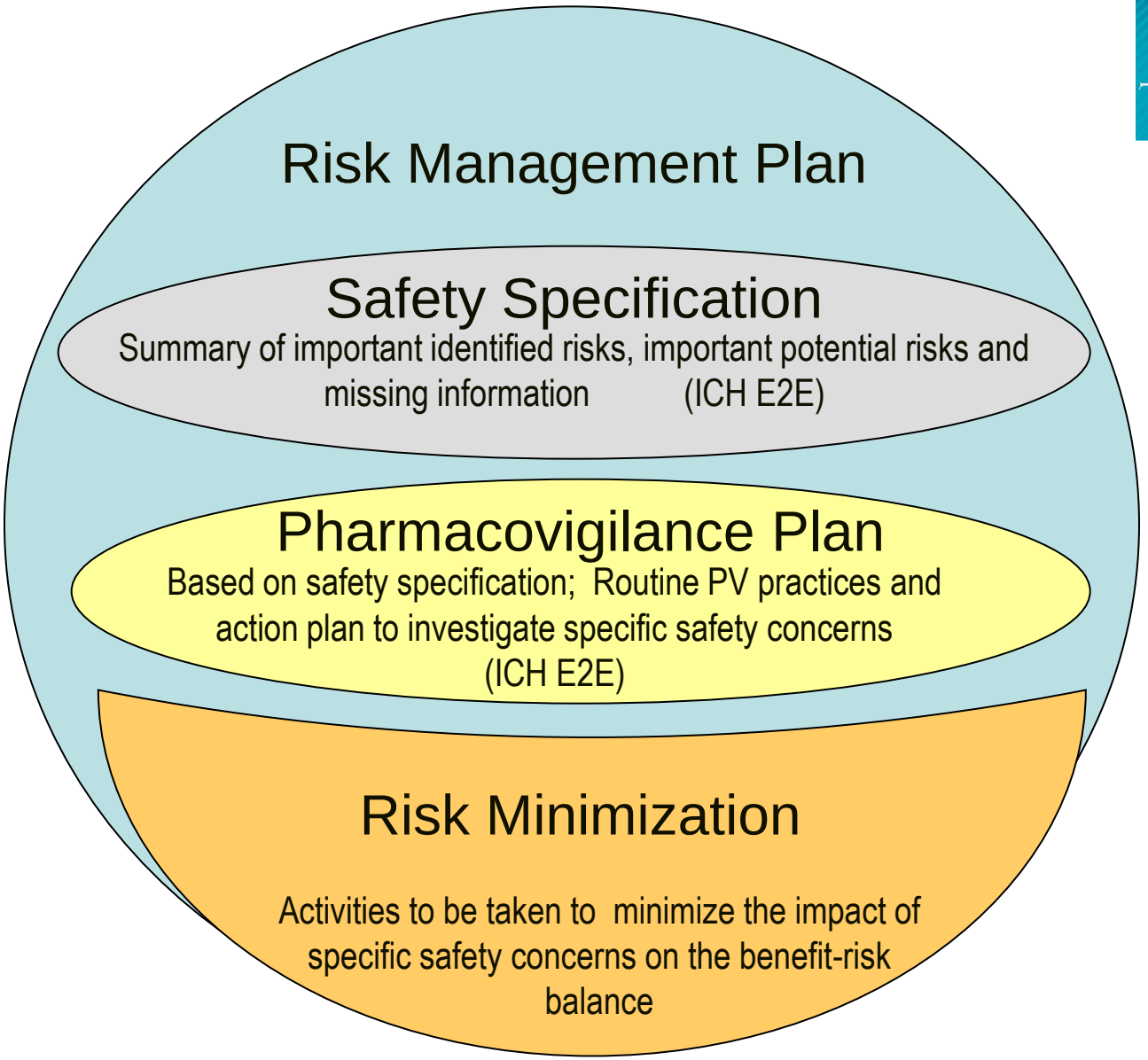
EudraLex Vol 9

- **Volume 9A** : pharmacovigilance guidance for human medicinal products
  - With the application of the new pharmacovigilance legislation as from **July 2012** Volume 9A is replaced by the **good pharmacovigilance practice guidelines(GVP)** released by the EMA. However, until the availability of the respective GVP modules Volume 9A remains the reference.
- **Vol 9 B**: Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use (Volume 9B - version October 2011)

GUIDANCE ON GOOD PHARMACOVIGILANCE PRACTICES (GVP)

INTRODUCTION	Legal Basis and Structure of Pharmacovigilance Guidance
MODULE I	**Pharmacovigilance Systems and their Quality Systems**
MODULE II	**Pharmacovigilance System Master File**
MODULE III	**Pharmacovigilance Inspections**
MODULE IV	**Pharmacovigilance Audits**
MODULE V	**Risk Management Systems**
MODULE VI	**Management and Reporting of Adverse Reactions to Medicinal Products**
MODULE VII	**Periodic Safety Update Report**
MODULE VIII	**Post-Authorisation Safety Studies**
MODULE IX	**Signal Management**
MODULE X	*Additional Monitoring*
MODULE XI	Public Participation in Pharmacovigilance
MODULE XII	Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication
MODULE XIII	For references to incident management, see Module XII
MODULE XIV	International Collaboration
MODULE XV	*Safety Communication*
MODULE XVI	Tools, Educational Materials and Effectiveness Measurement for Risk Minimisation

Basic Components of a Risk Management Plan



Overview of the parts and modules of the RMP

Part I Product(s) overview

Part II Safety specification

- **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** Populations not studied in clinical trials
- **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

Part III Pharmacovigilance plan

Part IV Plans for post-authorisation efficacy studies

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)

Part VI Summary of the risk management plan

Part VII Annexes

RMP Part I, Overview

Active substance information:

- active substance(s);
- ATC code / pharm-therapeutic group(s)
- name of MAH /applicant;
- date and country of first authorisation worldwide
- date and country of first launch worldwide
- number of medicinal product(s) to which this RMP refers.

Administrative information

- on the RMP:
- data lock point of the current RMP;
- date submitted and the version number;
- list of all parts and modules of the RMP with date and version of the RMP when the part/module was last (updated and) submitted.

RMP Part I, Overview

- authorisation **procedure** (CP; MRP, DCP, nat)
- **invented name** in EEA
- brief **description of DP**:
  - chemical class;
  - mode of action;
  - information re composition
- **indications:**
  - Current in the EEA;
  - Proposed in the EEA;
- **Dosage:**
  - Current in the EEA;
  - Proposed in the EEA;
- pharmaceutical **forms and strengths:**
  - Current in the EEA ;
  - Proposed in the EEA
- whether the product is **subject of additional monitoring** in the EU

Also very helpful : **Q & A**

3. Risk Management Plan (RMP)

3.1. Am I required to have a **risk management plan** for my **initial marketing authorisation applica**tion?

3.2. Do I have to **continue to operate** the RMP for my existing medicinal product?

3.3. For my risk management plan to be submitted shortly after 2 / 21 July 2012, what format should I use? (Update November 2012)

3.4. For my risk management plan to be submitted after 10 January 2013, what format should I use? (New November 2012)

3.5. Will a summary of my RMP be published?

3.6. Do I need to submit an RMP for my traditional herbal medicinal product?

3.7. Do I need to submit an RMP for my homeopathic medicinal product?

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127658.pdf

RMP part II "Safety specification"

a synopsis of the safety profile of MP(s):

- ❑ what is known ⇒ important identified risks
- ❑ what is **NOT** known ⇒ important potential risks

the safety specification will form the basis of the

- ✓ pharmacovigilance plan, and
- ✓ the risk minimisation plan.

8 RMP "Safety specification" modules

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	Populations not studied in clinical trials
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

correspond to safety specification headings in ICH-E2E. RMP module SVI includes additional elements required to be submitted in the EU.

Module S 6 (EU specific)

- Potential for harm from overdose
- Potential for transmission of infectious agents
- Potential for misuse for illegal purposes
- Potential for medication errors
- Potential for off-label use
- Specific paediatric issues

RMP Part III "Pharmacovigilance plan"

intended purpose : to discuss how MAH plans to identify / characterise the risks. It should be a structured plan for:

- the identification of the **new safety** concerns;
- further characterisation of **known safety** concerns including elucidation of risk factors;
- the investigation of **whether a potential safety concern is real or not;**
- how important **missing information** will be sought.

RMP Part III "Pharmacovigilance plan"

Pharmacovigilance activities can be divided into

- **routine** pharmacovigilance activities and
- **additional** pharmacovigilance activities.

For each safety concern, the planned PV activities should be listed. The proposed action should be proportionate to the risks of the product. If considered sufficient for post-authorisation safety monitoring, "routine pharmacovigilance" should be entered against the safety concern.

Routine PV activities

- the set of activities required to fulfil the legal requirements for Dir 2001/83/EC and Regulation (EC) No 726/2004.

Also:

- explain how the applicant will modify its routine pharmacovigilance activities to fulfil any special PRAC, CHMP or CMDh recommendations on routine pharmacovigilance.

- (NOT the place to present the Pharmacovigilance System Master File, PSMF)

Additional PV activities

- eg. Long term follow-up of patients to identify/confirm certain risk
- eg. PASS, pharmacokinetic studies, other clinical trials or further pre-clinical work
- eg. Surveillance of specific target patient population
- Eg. Pharma-epidemiological studies

When any doubt exists about the need for additional PV activities, consultation with a competent authority should be considered

Additional PV activities

- Action plans for safety concerns with additional pharmacovigilance requirements
- Summary table of additional pharmacovigilance activities

- Annexes with study synopsis and other details should also be provided

RMP part IV "Plans for post-authorisation efficacy studies"

- products with a **concern about efficacy** which can only be resolved after the product has been marketed,
- applications
  - For a MA that include a paediatric indication
  - to include a paediatric indication in an existing MA
  - for a paediatric use marketing authorisation
  - for advanced therapy medicinal products.

May need long term follow-up of efficacy as part of post-authorisation surveillance

RMP Part V
"Risk minimisation measures"

On the basis of the safety specification, the MAH should assess what risk minimisation activities are needed for each safety concern.

- each safety concern needs to be considered on a case-by-case basis
- will depend upon
  - the severity of the risk,
  - the healthcare setting,
  - the indication,
  - the pharmaceutical form
  - the target population.

RMP Part V
"Risk minimisation measures"

Risk minimisation activities may consist of

- ❑ routine risk minimisation or
- ❑ additional risk minimisation activities

All risk minimisation activities should have **a clearly identifiable objective.**

(Risk minimisation measures and the assessment of their effectiveness is discussed in more detail in Module XVI)

RMP part V
"Routine risk minimisation"

Routine risk minimisation activities are those which happen with every medicinal product.

These relate to:

- the SPC (eg. warnings)
- the labelling (eg. exclude populations)
- the package leaflet (see SPC)
- the pack size(s) (eg. not more than 1 DD/per pack)
- the legal status of the product. (eg. Rx by special Physician)

RMP part V
"Additional risk minimisation activities"

should

- only be suggested when necessary for the safe / effective use of the MP
- be detailed and a justified
- be science based

Often based on **communication beyond the SmPC/PIL**

Additional risk minimisation activities will become, once agreed by the authority,

conditions of the marketing authorisation

"Additional risk minimisation activities"

Examples

- Boxed warnings
- Prescription only by specialised doctors
- Special training for prescribers / patients
- Educational material for patients
- Diagnostic follow up of each prescription

Format to present Risk Minimisation measures

- objective of proposed action(s)
- routine risk minimisation activities *
- additional risk minimisation activities (if any),
  - individual objectives and
  - justification of why needed
- how the effectiveness will be evaluated
- what is the target / criteria for judging success;
- milestones for evaluation and reporting.

monitoring the effectiveness of risk minimisation activities is included in Module XVI.

For routine risk minimisation activities, the proposed text in the SmPC should be provided along with details of any other routine risk minimisation activities proposed.

RMP part VI "Summary of activities in the risk management plan"

A summary of the RMP shall be made publically available

- must include key elements of the RMP
- safety specification should contain information
  - on potential and identified risks
  - and lack of knowledge
- specific focus on risk minimisation activities.
- should be written for the lay reader
- should present risks + benefits as a balanced picture
- will be included in the EPAR

RMP part VI "Summary of activities in the risk management plan"

based on RMP Ms SI, SVIII and RMP parts IV+V):

- overview of disease epidemiology
- summary of benefits/efficacy
- summary of safety concerns (in lay language)
- tables:
  - summary of risk minimisation activities by safety concern
  - planned post-authorisation development plan (safety and efficacy) including specific details that will become conditions of the marketing authorisation.

A template will be developped!

Annexes

1. Interface RMP/Eudravigilance/EPITT
2. SPC and PIL (current (or proposed)
3. Synopsis of clinical trials
4. Synopsis pharmaco-epidemiological studies
5. Protocols for proposed studies in RMP part III
6. Specific adverse event follow-up forms

Annexes

7. Protocols for proposed studies in RMP part IV
8. Newly available study reports
9. Details of proposed additional risk minimisation activities
10. Example(s) of actual material provided to HPs and patients
11. Other supporting data (incl. references)

Points to consider

Different types of application, different types of submission

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
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓								✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
"Well established use"	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
"Same active substance"	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] Application under Article 10(c) of Directive 2001/83/EC
^ May be omitted under certain circumstances
* Modified requirement

and other **points to consider** are discussed in the presentation of

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"Before I came here I was confused about this subject.
Having listened to your lecture I am still confused.
But on a higher level."

Enrico Fermi

Italian physicist, developed the first nuclear reactor

Danke für Ihre Aufmerk-samkeit

Any questions?

You may contact me directly:

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