

Safety Webinar

Mastering Risk Management Plans (DRMPs) in Clinical Drug Development:

Comprehensive Overview of Requirements in China

Vjera Bilušić Vundać, PhD Pharm | Senior Director of Medical Writing

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With over 15 years of experience, PrimeVigilance is dedicated to delivering high quality, fully compliant global lifecycle management safety solutions.



Meet our Expert Speaker



Vjera Bilušić Vundać, PhD Pharm Senior Director of Medical Writing

Vjera has over 20 years of experience in scientific pharmaceutical research, pharmacovigilance, regulatory affairs, and quality and spent the last decade in managerial and directorial roles in both the pharma industry and pharma service providers. Her experience includes working with all range of medicinal products, from generics to originals, biosimilars, vaccines, and blood derivatives, covering both safety and regulatory aspects of medicinal product life-cycle.

Mastering Risk Management Plans (DRMPs) in Clinical Drug Development:

Comprehensive Overview of Requirements in China

Agenda

I.

Definition and Purpose of Risk Management Plans (RMPs) for Medicinal Products (MPs)

II.

Requirements for RMPs for MPs with Marketing Authorization and Developmental RMPs (DRMPs) for MPs in Clinical Development Stage

III.

Guidelines and Requirements for DRMPs in China

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I.

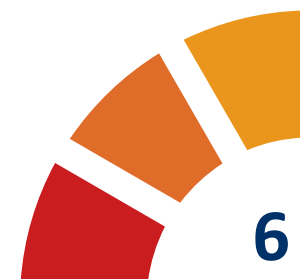
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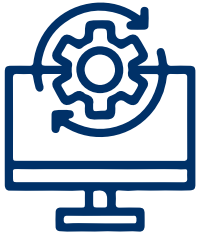
III.

Guidelines and Requirements for DRMPs in China



I.

Risk Management



Risk Management System

‘A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.’



Risk Management Plan

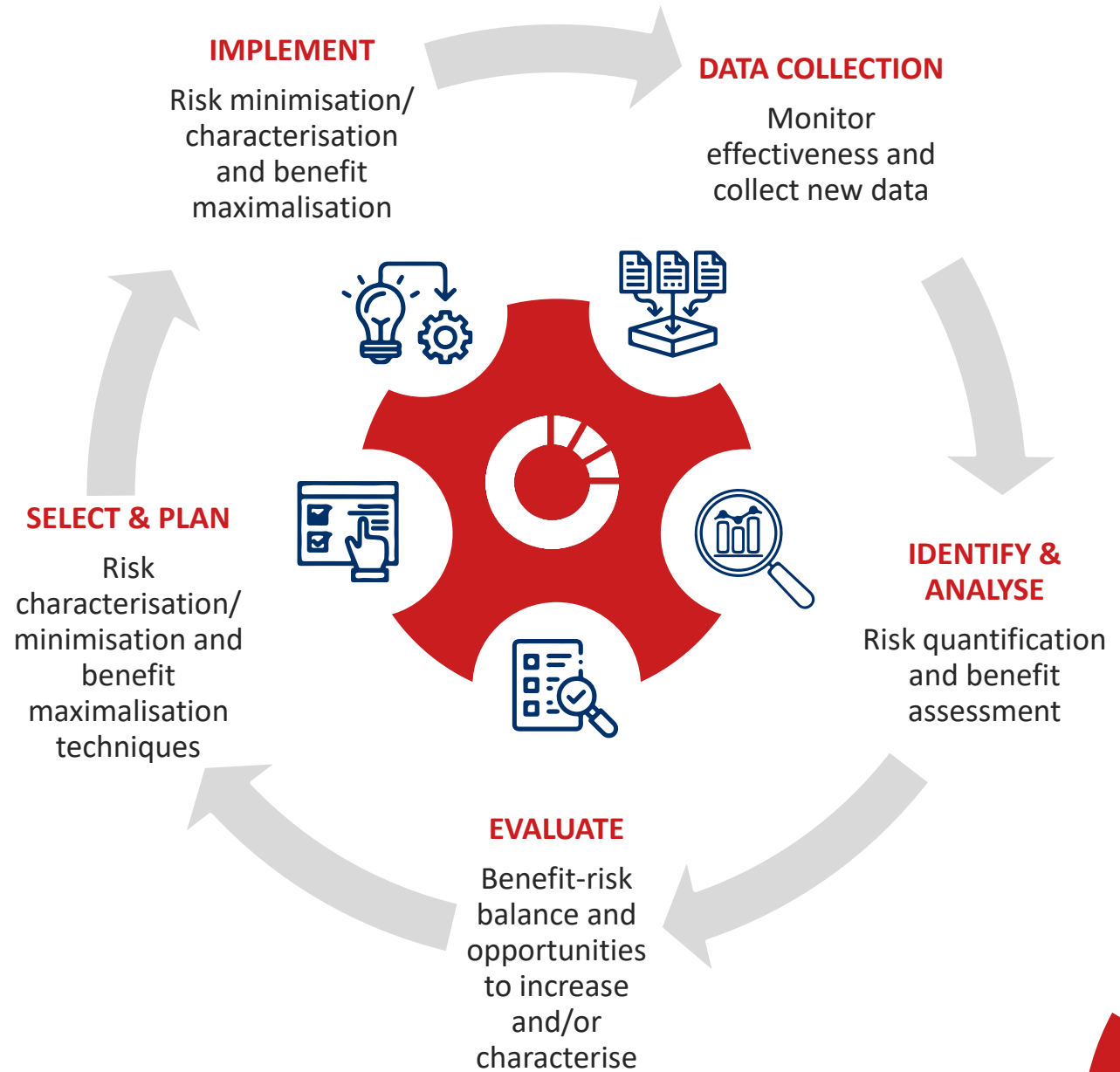
‘A detailed description of the risk management system.’

Aim of the RMP

‘The aim of a risk management plan is to document the risk management system considered necessary to identify, characterize and minimize a medicinal product’s important risks.’

I.

Risk Management Cycle



Source: GVP Module V (Rev. 1)

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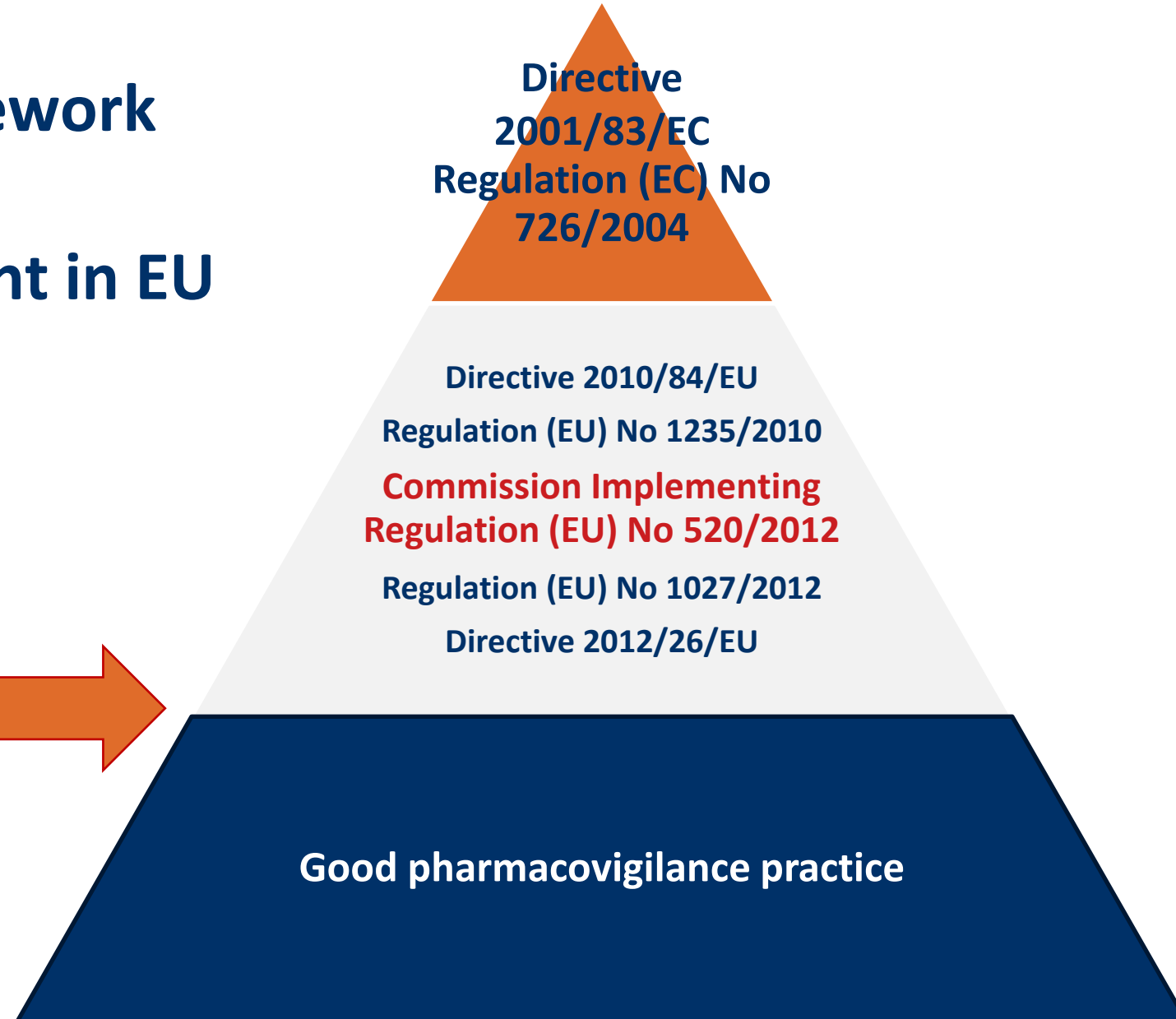
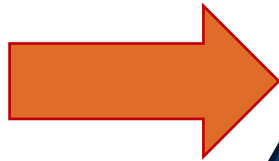
Guidelines and Requirements for DRMPs in China



II.

Legal Framework for the Risk Management in EU

National
Legislation



II.

ICH Guidelines

ICH-E2E: Pharmacovigilance planning (2004)

Safety Specification summarizes important identified/potential risks and missing information of the medicinal product

Pharmacovigilance Plan

Ongoing safety issues – **Ongoing Safety Concerns**

No risk minimization measures!

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II.

Main Parts of the RMP

EU Regulations



Safety Specification (ICH-E2E)

Identification and characterization of the safety profile with emphasis on safety concerns, specifying which safety concerns need to be managed proactively or further studies



Pharmacovigilance Plan (ICH-E2E)

Planning of pharmacovigilance activities to characterize and quantify important risks, and to identify new adverse reactions



Risk Minimisation Plan (EU-RMP concept)

Planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these measures



II.

Risk Proportionality Approach and Legal Basis

EU Regulations

Set of minimum RMP requirements based on the legal basis of medicinal product

Product	Part	Part II								Part III	Part IV	Part V	Part VI
	I	SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
0. Full MA application 8(3)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
1. Generic product 10(1)	✓							‡	✓	✓	*	∫	✓
2. Informed consent product 10c	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Hybrid product 10(3)	✓	†		†				†	✓	✓	✓	∫	✓
4.a. Fixed combination product – new active substance 10b✓		‡	‡	‡	‡	‡	‡	✓	✓	✓	✓	✓	✓
4.b. Fixed combination product – no new active substance 10b			†	†				‡	✓	✓	*	∫	✓
5. Well established medicinal use product 10a	✓							✓	✓	✓	✓	✓	✓
6. Biosimilar product 10(4)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ = applicable/relevant

‡ = relevant only if “originator” product does not have an RMP and its safety profile is not published on CMDh website

* = relevant only when a PAES was imposed for the “originator” product

∫ = statement of alignment of safety information in PI is sufficient

† = requirements based on risk proportionality principle, addressing new data generated or differences with the “originator” product

‡ = focus on the new active substance

II.

Electronic Common Technical Document

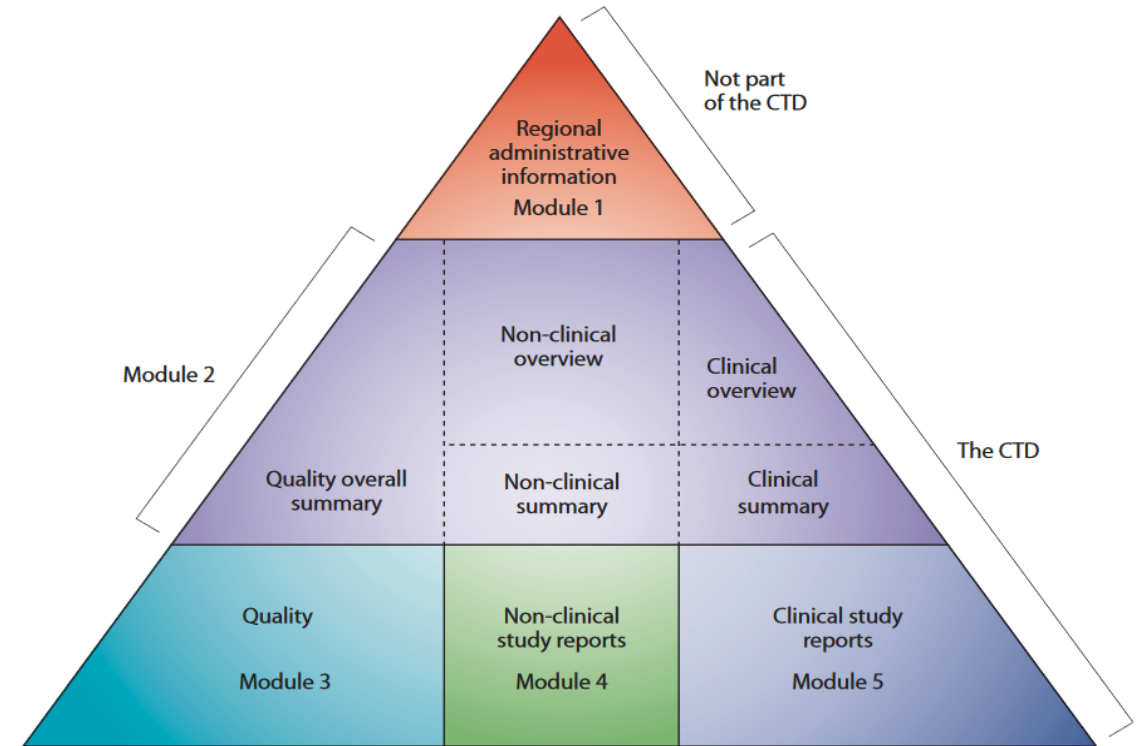
eCTD: internationally agreed format for the preparation of application dossier

Five modules:

- **Module 1** – regional
- **Module 2** – CTD overviews and summaries
- **Module 3** – Quality
- **Module 4** – Non-clinical study reports
- **Module 5** – Clinical study reports

Module 1.8.2 – EU-RMP

CTD Triangle



II.

Development RMP (DRMP)

Per ICH:

- **DRMP** is a plan to conduct activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects of medicines during clinical trials.
- **DRMP** should be initiated early and modified as necessary throughout the development process for a new drug or drug-use.
- Should be aligned with the DSUR (consistency of the information contained in the two documents).
- Involving document – changes during clinical development
- Not obligatory

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III.

DRMP (CRMP) in China



DRMP is referred to as
Clinical RMP (CRMP)

- **Regulatory framework:**
 - ICH E2E Guidelines
 - Technical Guidelines for Redaction of Clinical RMP, National Medicinal Products Administration (Dec 2021)
- Template for China available – in Chinese
- Developed in clinical stage, can be utilized for post-marketing when preparing PV Plan on RMP



III.

DRMP (CRMP) in China

Aim of the CRMP

‘The aim of a CRMP is to identify and describe important identified risks, important potential risks and important missing information of MP and propose PV plan and RMM that match the risks to ensure that the benefits outweigh the risks in medication process of the applicable population after the drug is marketed’

Three main elements (aligned with EU RMP approach):

- ✓ **Safety Specification**
- ✓ **Pharmacovigilance Plan (PV Plan)**
- ✓ **Risk Minimization Measures (RMMs)**



III.

Safety Specification

Part II:

Target indication epidemiology:

- summary of epidemiological data and characteristics of population
- characteristics of history of disease
- important co-morbidity and concomitant drugs in population
- currently available treatments
- **differences between China population and the population in other countries/regions**

**IMPORTANT
IDENTIFIED RISKS,
IMPORTANT
POTENTIAL RISKS,
IMPORTANT MISSING
INFORMATION**



III.

Safety Specification

RMP should focus on those risks that are relevant for the risk management activities (**GVP Module V**)

Determining factors whether risk is important in the **CRMP**:

- medical severity
- frequency, predictability, preventability and reversibility
- potential impact on public health

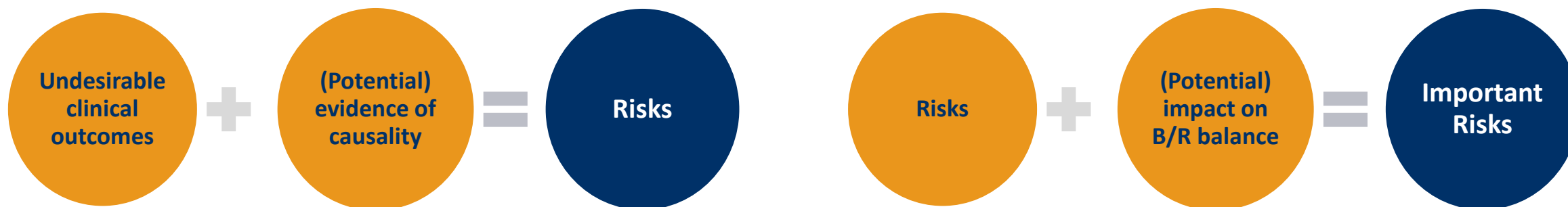
Important risk in **CRMP** (one or more requirements):

- serious consequences (e.g. death, disability, congenital anomaly etc)
- clinical intervention required
- major challenges to current clinical practice



III. Safety Concerns

IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, MISSING INFORMATION





III.

Safety Concerns

Identified Risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.
Potential Risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed .
Important Identified or Potential Risk	An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health .
Missing Information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.



III.

Presentation of Important Risks in CRMP

Risk name <MedDRA terms>

Reasons for identifying as important identified/potential risk

Risk mechanism <analysis of drug mechanism of action and/or pathophysiological basis>

Nonclinical data <high-level summary of important non-clinical safety data and it's clinical significance; toxicology, genotoxicity, pharmacological data ect. >

Clinical:

- **Background information on the corresponding risk of the target indication** <summary of relevant info such as epidemiology, analyses of possible difference in Chinese population>
- **Clinical data** <summary of exposure from CTs, estimated exposure in PM, , analyses of possible difference in Chinese population>
- **Identification and analyses of relevant risk factors** <target population and clinical data>

Preventability <identification of risk groups, early signs and diagnostic, treatment>

Impact on benefit risk balance/public health <available non-clinical and clinical data>



III.

Presentation of Important Missing Information in CRMP

Populations not studied or limited CT data:

- Children
- Elderly patients
- Pregnant or breastfeeding women
- Patients with relevant comorbidities
- Subgroup populations with known or associated genetic polymorphisms
- Patients of different ethnicities and/or races
- Other populations predicted to use MP 'off-label'



III.

Pharmacovigilance Plan

Part III:

Routine PV activities (ADR collection, safety update reports, signals, updates of instructions etc.)

Additional PV activities

- if required, if not required to be specified directly
- Applicant is obliged to:
 - propose and explain necessity of each additional PV activity
 - specify key points of implementation plan
 - define completion date
 - specify if additional PV activities are required by RA or proposed by applicant
 - list completed/terminated additional PV activities with date of completion, outcome of additional PV activity and adjustment of CRMP based on outcome



III.

Post-authorisation Safety Studies (PASS)

Part IV:

Carried out after a medicine has been authorized, in order to evaluate the safety and benefit-risk profile:

- identify, characterize or quantify a safety hazard;
- confirm the safety profile of a medicine, or;
- measure the effectiveness of risk-management measures.

PASSs can either be clinical trials or non-interventional studies.*

In CRMP PASS can be proposed – usually to be discussed in later stage of clinical development

*
Directive 2001/83/EC



III.

Risk Minimization Measures (RMMs)

Part V:

Routine RMMs (applicable to all MPs, PI, labelling etc)

Additional RMMs

- if required, when routine RMMs are not sufficient to reduce risk to acceptable level
- if not required to be specified directly

Applicant are to:

- propose and explain necessity of each aRMM
- specify timelines for implementation define completion date
- specify timeline for effectiveness evaluation

Usually, to be discussed in later stage of clinical development, consultations with RA advised beforehand

Summary

- RMP – obligatory regulatory document describing risk management system for MP
- submitted in approval stage of MA
- 'living document'
- CRMP/RMP - risk management during clinical trial
- usually obligatory, required by some RAs such as RA in China
- Chinese RA - published guidelines
- CRMP - developed by sponsor of clinical trial and submitted in Chinese

Thank You



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