Safety Labeling, Safety Reporting, and Risk Minimization Activities

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Objectives

Interrelations between the safety labeling specifications and risk management activities

Agenda

- **Role of CCDS as a pharmacovigilance document**
- **Periodic Safety Update Reports (PSURs) and Periodic Adverse Drug Reactions Report (PADRs)**
- **Risk Management Plan (RMP) vs. Risk Evaluation and Mitigation Strategies (REMS)**
- **RMP and Labeling touchpoints**
- **REMS and Labeling touchpoints**
- **Roles and Responsibilities**

Origin of PSUR and Company Core Safety Information (CCSI)

- CIOMS made significant contribution in the area of safety requirements concerning drug development and use.
- CIOMS I – International reporting of ADRs
- CIOMS II – Standard for PSUR
- **CIOMS III/V – Proposed principles for CCSI (Company Core Safety Information) and Development Core Safety Information (DCSI) for drugs undergoing investigation**
- CIOMS IV&V – Risk management including new proposal for investigator brochure.
- CIOMS VI - Management of Safety Information from Clinical Trials
- CIOMS VII – DSURs
- CIOMS VIII – Practical Aspects of Signal Detection and Pharmacovigilance

CCDS and Local labeling as pharmacovigilance documents

- **Core safety and Core efficacy sections are clearly aimed at safety and pharmacovigilance.**
- **"Gold Standard" internally and externally to assess if safety issue is appropriately and clearly addressed.**
  - **Supports pharmacovigilance activities (RMP, REMS, PSURs) as well as marketing/promotional activities, clinical trial activities.**
  - **Reference document to respond to any customer queries (often these are safety-related).**
  - **Reference document for all product liability related activities.**

What is Company Core Safety Information?

PER ICH GUIDELINES: (ICH E2C)
Company Core Safety Information (CCSI) generally includes:
- **CONTRAINDICATIONS**
- **WARNINGS AND PRECAUTIONS**
- **SPECIAL POPULATIONS**
- **DRUG INTERACTIONS**
- **SIDE EFFECTS**
- **OVERDOSAGE**

WHAT ABOUT CORE EFFICACY SECTIONS?
- **INDICATIONS:** Supports efficacy and safety
    - Indications identifies the appropriate symptoms, disease, population, duration etc
    - Additional text for mitigation measures (restrictions, limitations) to prevent off-label use
- **DOSAGE AND ADMINISTRATION**: Supports efficacy and safety
    - Dosage regimen to achieve efficacy benefits and to avoid overdose
    - Specific instructions for special populations (geriatric, pediatric) and conditions (hepatic, renal) to mitigate untoward effects
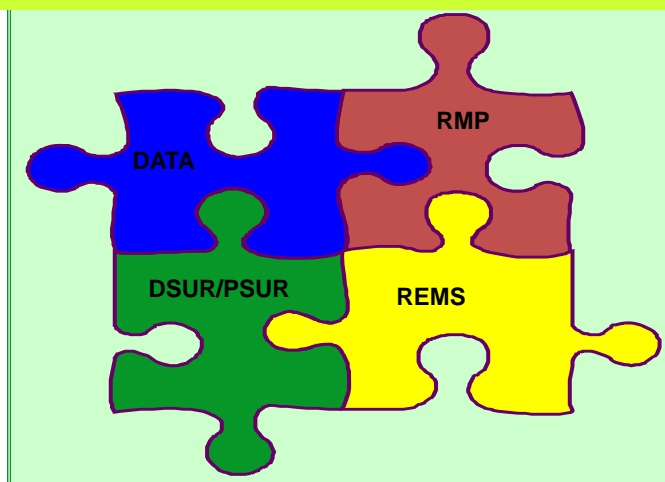
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CCSI = Finished puzzle with many pieces put together

CCSI = Data + RMP + REMS + DSUR/PSUR +Other

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What are PSURs and PADERs?

PSUR – **P**eriodic **S**afety **U**pdate **R**eport (Required in EU and a **few** other countries)

- Compilation and assessment of world-wide safety experience of a medicinal product at defined timelines post-approval.
- Establishes whether information recorded during the reporting period is in accordance with previously existing knowledge of the drug's safety and helps determine whether changes should be made to its labeling
- Timelines: Timelines are complex and are governed by local requirements. Generally every six months.

PADER – **P**eriodic **A**dverse **D**rug **E**xperiences **R**eport (Required by FDA)

- Purpose is same as PSUR.
- PADER timelines are different from PSUR timelines. PADER required quarterly during first 3 years after approval and yearly thereafter.
- PADER requirements are different from PSUR requirements.
- USPI is the reference document for labeling discussions.
- Summary of all safety-related labeling revisions made during the reporting period.

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PSUR/Labeling Touchpoints: CCDS

CCDS supports PSUR discussions regarding **"listedness"** of an adverse drug reaction. CCSI portion of the CCDS meets the requirements of PSUR. Therefore, not all sections of the CCDS are required to be included with the PSURs.

Versions of the CCDS:

- ***Version at the beginning of the reporting period***: The version of the company core data sheet (CCDS) with its company core safety information (CCSI) in effect at the beginning of the period covered by the report should be used as the reference.
- ***Versions during and at the end of the reporting period:*** Changes to the CCSI, already made during the period covered by the report, should be clearly described, with presentation of the modified sections.
- ***Pending changes not implemented***: Changes currently under consideration but not yet implemented in the CCDS. Sponsors should have a clear policy to handle the scenario.

Version-control:

- Critical to have a tracking mechanism to track history of all changes to the CCDS.
- Typically, the labeling group provides information regarding current CCDS and all updates to the CCDS since the last PSUR.

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PSUR/Labeling Touchpoints: Local PIs

- **Local PI** supports PSUR discussions regarding **"labeledness"** of an adverse drug reaction as local PI can differ from CCDS.

- PSUR submission includes explanations of the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated.

  This explanation may be provided in the cover letter or as an appendix. For significant differences, a comparator chart of CCDS vs EU SmPC or Local SmPC/PI will be useful.

    For example:

    - For national products, a Core Safety Profile (CSP) is using nationally approved labeling. The CSP is compared to the CCSI.

    - For MRP and CP, safety sections of the EU SmPC are compared to the CCSI.

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What are RMP and REMS?

- **RMP** – **R**isk **M**anagement **P**lan required for all products in EU and Other countries

    Management of overall assessment and mitigation of risk during life of the product.

- **REMS** – **R**isk **E**valuation and **M**itigation **S**trategy (as required by FDA for some products)

    Management of risk minimization of specific identified risks during life of the product

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RMP vs. REMS
Similarities and Differences

RMP	REMS
REQUIRED for every product in EU	**REQUESTED/RECOMMENDED** AS NEEDED by FDA
Management of overall assessment of risk during life of the product. ***Safety specification and Pharmacovigilance Plan:*** Known safety information is evaluated in the context of whether the risk can be mitigated by routine pharmacovigilance plan and Labeling ***Risk minimization plan*** is submitted only when non-routine pharmacovigilance measures are needed for risks that can not be managed by routine pharmacovigilance and labeling.	Management of ***risk minimization of specific risks*** during life of the product: Interventions/risk mitigation strategies for these risks that can not be managed by routine pharmacovigilance and labeling
Risk minimization plan: ➢No additional labeling pieces other than EUSmPC and UPL (User Package Leaflet) ➢Educational ➢medication use control measures.	**Three categories of risk minimization activities**: ➢MedGuide (corresponding USPPI allowed) ➢Communication plan ➢Elements to assure safe use (ETASU)
RMP and Labeling concurrent development/review/approval!	REMS triggered and mandated by the Agency or may be submitted with the original application/or SNDA.

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RMP – Labeling Touchpoints

RMP generally includes discussions regarding:

- **Identified risks/potential risks and missing information and how this has been addressed within the context of labeling. Mitigating off-Label Use within the context of labeling**
- **Routine risk minimization activities which include labeling and routine pharmacovigilance activities.**
- **Non-routine risk minimization activities that are above and beyond labeling and routine pharmacovigilance. These include but not limited to: Educational materials or training programs and/or restricted access programs**

Example of an Assessment

Safety Concern	Routine Risk Minimization Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Exposure during pregnancy	Yes	Routine pharmacovigilance Labeling SmPC **Section 4.3 Contraindications** Contra-indicated in women….

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REMS - Labeling Touchpoints

- Management of risks that can not be managed by labeling and routine pharmacovigilance.
- Format/Content different from RMP.
    Format/Content of REMS:
    - Goals and Objectives specific to the safety concern
    - REMS Elements
        A. MedGuide
        B. Communication Plan
        C. Elements to Assure Safe Use (ETASUs)
        D. Implementation system
        E. Timetable for Submission of Assessments

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REMS-Elements

A. MedGuide

B. Communication Plan including:
   a) A Dear Healthcare Provider Letter (DHCPL)]
   b) Printed information or web-based information for health care providers
   c) Communication to professional societies

C. Elements to Assure Safe Use (ETASUs) including:
   a) Certification requirements for prescribers/patients/dispensers
   b) Registries to maintain certified prescribers/patients/dispensers
   c) Documentation of safe use conditions (e.g to become enrolled, each patient must review the Medication Guide and sign the Patient Enrollment Form with their prescriber)

D. Implementation system

E. Timetable for Submission of Assessments

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REMS Examples at WWW.fda.gov

- http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

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A Birds-eye view
Paths and triggers: Labels, PSUR, RMP, REMS – Pre-filing-Approval

APPROVED LOCAL LABELS PSUR, RMP, REMS

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Agency evaluations and Interactions and approval

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CCDS, USPI, EU SmPC, Product Monograph and other local labels

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DSUR   **REMS**   **RMP**

DATA AND ASSESSMENT

GOAL: PATIENT SAFETY

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A Birds-eye view
Paths and triggers: Labels, PSUR, RMP, REMS –
Post-marketing

Agency evaluations and triggers

RMP ↔ PSUR ↔ REMS

EU SmPC, Canadian PM, USPI

CCDS

RMP ↔ PSUR ↔ REMS

Company-triggered

Goal: Patient Safety

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**CCDS, Local PIs/PPIs/MedGuides –
Key Pharmacovigilance documents**

- Global Safety and Pharmacovigilance groups are generally responsible for PSUR, RMP, REMS.

- Members of labeling group are generally responsible for providing CCDS including version control and any implementation-related information.

- Labeling, Global Safety and Pharmacovigilance groups interact closely to align their respective documents.

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