"The Utility of the Periodic Safety Update Report as a Useful Source of Medical Information"

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Topics

• Purpose and Origin of the PSUR
• Format and Content
• Strengths and Weaknesses
• Utility for Providing Important Medical Information
Purpose and Origin of the PSUR
Periodic Safety Report for Marketed Drugs = PSUR
Purpose of the PSUR

• A stand alone global-standardized document that can be used “worldwide” for:
  – Identification of new safety signals
  – Identification of changes to benefit-risk profile of medical product
    • Change in product label
    • Change in product name/package/promotional material
    • “Dear Doctor” Letter
    • Need for risk management initiatives
    • Withdrawal from the market
  – Monitoring effectiveness of risk management initiatives
Periodic Reports

• For marketed products
• Quarterly for first three years, annually thereafter (US) - current
• PSUR - every 6 months for first 2 years, annual for 3 years, then every 5 years
• US “Traditional” Adverse Drug Reaction Periodic Report very different than PSUR
• PSUR currently used in European Union, Japan, other countries
Origin of PSUR

• 1992 - “International Reporting of Periodic Drug-Safety Update Summaries” (Council for International Organizations of Medical Sciences [CIOMS] II)
• 1996 - “Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs”
Origin of PSUR

• 2001 - “Current Challenges in Pharmacovigilance: Pragmatic Approaches” (CIOMS V)
• 2002 – “Draft Consensus Guideline – Addendum to ICH E2C Clinical Safety Data Management Periodic Safety Update Reports for Marketed Drugs”
Proposed US Safety Regulations – “The TOME”

• Change periodic report to PSUR format (ICH E2C)

• Periodicity
  – Every six months for the first 2 years
  – Annually for the next 3 years
  – Every 5 years thereafter

• Interim Periodic Safety Report (IPSR)
  – At 7.5 years and 12.5 years after U.S. approval
  – Same information as PSUR excluding summary tabulations
Format and Content
Key PSUR Definitions

• Company core data sheet (CCDS)
• Company core safety information (CCSI)
  – Safety information in CCDS
• Listed/Unlisted
  – Based on CCSI (expected/unexpected – based on country-specific product information)
Key PSUR Definitions

• International Birth Date (IBD)
  – First approval in the world

• Data Lock Point (DLP)
  – Cut-off date for data to be included in report
Table of Contents of PSUR

• Introduction
• Worldwide market authorization
• Update of regulatory authority or MAH actions taken for safety reasons
• Changes in reference safety information
• Patient exposure
• Presentation of individual case histories
Table of Contents of PSUR

- Studies
- Other information
- Overall safety evaluation
- Conclusion
- Appendix
  - Company Core Data Sheet
  - Consumer Reports (US)
Table of Contents of PSUR

• Introduction
  – Brief summary of the drug’s characteristics
  – When the data lock date was, and what period of time the report covers
  – What number the report represents, e.g., this is the first periodic report, this is the 6th periodic report
Table of Contents of PSUR

• Worldwide market authorization
  – Typically a table summarizing:
    • Countries where the drug has been approved
    • Countries where there was a lack of approval, etc.
Table of Contents of PSUR

• Update of regulatory authority or MAH actions taken for safety reasons - for example:
  • Failure to obtain marketing re-authorization
  • Withdrawal from the market
  • Suspension of clinical trials, etc.
Table of Contents of PSUR

• Changes in reference safety information
  – Summarizes what changes to CCSII have or will be made from current one
Table of Contents of PSUR

• Patient exposure
  – Estimate of exposure and methodology used:
    • Number of tablets sold
    • Number of bottles of medication distributed
    • Number of prescriptions written
Table of Contents of PSUR

- Presentation of individual case histories
  - Listings – “Capsule view” of all the AEs reported by a patient with the most serious listed first
    - All serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
    - All serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient (“compassionate”) use;
    - All serious reactions, and non-serious unlisted reactions, from the literature;
    - All serious reactions from regulatory authorities
  - Tabulation of AEs including a tabulation for non-serious, listed reactions
  - Analysis of individual case histories
Table of Contents of PSUR

• Studies
  – Completed studies with new safety information
Table of Contents of PSUR

• Other information
  – New relevant efficacy information
  – Late breaking news
Table of Contents of PSUR

• Overall safety evaluation - A concise analysis of the data presented, taking into account any late-breaking information, and followed by the MAH’s assessment of the significance indicating a change in the benefit-risk profile of the drug
  – In addition:
    • Specifically looks at certain populations, e.g., elderly, pediatric, pregnancy
    • Drug interactions
    • Overdose
    • Long-term effects
    • Etc
Table of Contents of PSUR

• Conclusion
  – Should indicate the safety findings that are different than that found in the current reference safety information
  – Indicate what actions were or will be taken
    • Change in CCSI
    • Risk management initiatives, etc.
Table of Contents of PSUR

- Appendix
  - Company Core Data Sheet
  - Consumer Reports (US)
Strengths and Weaknesses
Strengths

• Aggregate data – to better identify new safety signals especially rare adverse events
• Worldwide data – safety signal strengthened if seen in more than one country
• Multiple sources of information - also strengthens the safety signal
  – Spontaneous reports
  – Healthcare professionals, Consumers (US)
  – Literature
  – Studies
  – Animal Findings
Weaknesses

- Resource intensive
- Quality dependent – “Garbage in garbage out”
- No set numerator or denominator to calculate accurate incidences
- Retrospective, potentially biased
- Safety signal identification (not verification)
- Label change required before information can be used “officially”
Utility for Providing Important Medical Information
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• Hypothesis generating – need for new study(ies) – results ultimately affect medical information
• Change in label – new medical information
• “Dear Doctor” Letter – new medical information
• Metrics – determines “effectiveness” of content of/mechanism of providing, medical information
“Knowledge is Power!”