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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DIA

THE ROLE OF PSURS IN PHARMACOVIGILANCE INSPECTIONS GETTING IT RIGHT AND PRACTICAL EXPERIENCE

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Menu……

1. **Basic principles**
2. General aspects of inspections
3. What we are/should looking/look for
4. PSURS and related aspects in PhV inspections
5. Conclusion and remarks

Basic principles……

PSURs/PBERs

– Focus on benefit-risk vs. line listings of adverse Reactions (no line listings systematically included anymore)

— Steps and timelines detailed in the legislation => no flexibility

– EU reference dates (EURD-list) for a harmonised frequency of reporting & single assessment (products authorised in more than one MS, and products containing the same active substance)

Basic principles……

- Waiver for generic, well-established use, traditional herbal and homeopathic medicinal products (unless requested)
- Timelines for submission: 70, 90 days
- Linked to Risk management system of the product

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Inspection general aspects……

Generation

Routine:

Inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections. A risk-based approach is implemented.

These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance.

Also, some particular concerns, e.g. raised by assessors, are included in the scope of this kind of inspections, in order to investigate the specific issues.

Inspection general aspects……

Triggered (for cause):

For cause pharmacovigilance inspections are undertaken when a trigger is recognised, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger.

Inspection general aspects……

Triggers :

- risk-benefit balance of the product
- assessment/validation
- reporting obligations (expedited and periodic)
- requests from competent authorities
- fulfilment of commitments
- inspections
- others

Inspection general aspects……

Inspection announcement

Letter

- According to CA Standard operating procedures
- Sent to the contact point on files/QPPV/Local responsible
- Typically includes inspectors, dates, duration, scope, documentation required *

* (Varies if a triggered inspection)

Inspection general aspects……

Inspection announcement

Agenda *

- Inspection plan outlining aspects to be covered,
- Opening and closing meeting
- Interviews and staff member to be present
- Closing meeting ideally the presence of any Manager or CEO who can take decisions on enhancement of the PhV system (investments in systems and personnel)

*(different if a triggered inspection)

Inspection general aspects……

Preparation phase (PSURs)

- Contact with assessors (fundamental)
- Read essentials of the PSUR/PSUSA ARs
- Check (last) PSUSA/PSUR/ WSP outcomes
- Previous PSURs/PBER (AR)
- Format and content aligned with Imp Reg (Art 35)
  - First page: PRAC Rapp, EMA PM, ideally PRAC assessor – contact information
  - Section 2 "Conclusions"– Information on quality/problems of PSUR
  - Section 3 "Recommendations"– decision if marketing autorisation should varied

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What we look at

* Recommended during preparation phase

PSURs

- Look for “understandable“ non-compliances
  - Signal detection process on first PSUR
  - No information on Section 16 “ Signal and risk evaluation “ zero risk?
  - Apendix 2.2 Cumulative and interval summary tabulation

What we look at

* Recommended during preparation phase

PSURs

- Content (inspectors check if the information on risks in the PSUR is consistent with that in the RMP (where applicable).
- Sections 5,6 and 7 have relevant information for the inspectors (cumulative subject exposure, reference information, number and findings on clinical trials)
- Section 8 and 9 Non interventional studies and other clinical trials

What we look at

* Recommended during preparation phase

PSURs

- Section 11 Literature cases
- Section 16
- Appendices

SmPC, CCDS, CCSI (Is the SmPC up to date)? Did the MAH implement variations?

Inspection general aspects……

Preparation phase (also)…..

- Review documentation provided
- Preparation of inspection plan (inspectors plan)
- Set up final logistics

Inspection general aspects……

Inspection conduct

- Based on agenda sessions and interview
- QPPV/ Local responsible always available
- Opening meeting and closed out meeting (last day)
- Presentation Overview of the PhV System

  (Sessions depending on the type of inspection)

- Clarifications and discussions on aspects inspected

(especially on those that are/can be observations)

Inspection general aspects……

Inspection conduct

- Interview with vendors, contractors or third parties (teleconference)
- Other departments /unit may be interviewed (IT)

Inspection general aspects……

Inspection conduct

Close out meeting:

- Verbal feedback of preliminary findings, observations or comments
- In Spain, a document named “Acta” with legal value is issued and signed off by the inspection team and inspectees . This lead to sufficient time to produce a draft of CAPA before the Inspection report is submitted

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PSURs and related aspects on inspections

- Contract/agreements
  - Signed before activities are delegated (responsibility can not be delegated)
  - PhV clause obviously detailed/GCP?
  - Clause allowing audits from client (MAH)
  - Pre selection audits (Ideal/SOP)

PSURs and related aspects on inspections

- QPPV oversight (awareness) on PhV system
  - Quality, correctness, completeness of PSURs
  - Ensuring compliance on timelines and implement corrective action if deviated- metrics on submission timelines (outsourced)
  - ARs conclusion PRAC recommendations, CMHP/CMDh positions and EC decisions
- Management of safety information/Procedures
  - Database (changes, migration of data high risk)
  - Solicited, unsolicited reports, other sources of information
  - Handling of safety cases
  - Signal detection and evaluation process

PSURs and related aspects on inspections

- Quality Management systems (SOPs, training, QC)
  - SOPs for relevant activities (PSUR writing, QC, submission)
  - Training on preparation, review submission and assessment
  - Quality check on documents produced for PhV (High risk when outsourced the process and also the QC)
  - Other electronic systems used (doc control, training)
- Quality Assurance
  - Vendor selection process, external and internal audits plans (QA on documents produced)
  - CAPAs

PSURs and related aspects on inspections

- Interaction with other department or units (Marketing,Regulatory, others)
  - Volumes of sales (exposure data)
  - Products information and control
  - Implemented measures safety aspects (variations from the organisation or requested by CHMP/CMDh/PRAC)

(implementing changes on reference information timelines)

Correspondence and meeting minutes kept !!!!

PSURs and related aspects on inspections

- Risk Management system
  - Identification, management and reporting of risk
  - RMP production
  - Effectiveness of risk minimisation
  - Consistency across documents (RMP and PSURs)
  - Business continuity process
- Validation of electronic systems (partial, complete)

  Changes on database,data migration!!
- Archiving, record retention

  Policies according Module I?

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Conclusion and remarks

- ✓ Cooperation and collaboration between assessors and inspectors is fundamental
- ✓ The “ideal” time for the first contact is during the inspection’s preparation phase
- ✓ PSUR/PBERs summarises plenty number of processes in Pharmacovigilance, thus these components are subject to inspection
- ✓ Interaction with the organisation during the inspection leads to a better understanding of our expectation to fulfill the legal framework requirement


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos

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