Reference Safety Information and Pharmacovigilance

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• Importance of reference safety information.

• What are we looking for on inspection.
  – Changes since the new legislation.

• Common pitfalls and the key root causes.

• What can you do to avoid inspection findings in this area.
Types of reference safety information

• Summary of Product Characteristics (SPC)
• Patient Information Leaflet

• Company Core Data Sheet (CCDS)
• Company Core Safety Information (CCSI)

• Investigator’s Brochures
• Abbreviated prescribing information

Mandatory: Part of the Marketing Authorisation

Non-mandatory: MAHs may define core information to aid management of portfolios that span multiple territories
Why do we look at this on pharmacovigilance inspections?

- The SPCs / PILs are key documents in communicating safety information regarding medicines to HCPs and patients.
  - Promoting the safe use of medicines.
  - Providing information to allow HCPs and patients to make appropriate treatment choices.

Directive 2001/83 EC as amended, Article 23 (3)
“The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge…”
Why do we look at this during pharmacovigilance inspections (2)?

• Provision of reference safety information to healthcare professionals and patients is a legal requirement.

• Depending on the nature of inspection this may be covered during medical information interview session or the reference safety information session.
Why do we look at this during pharmacovigilance inspections (3)?

**Directive 2001/83 EC as amended, Article 56a**
The marketing authorisation holder shall ensure that the package information leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially-sighted.

- Meeting between RNIB, MHRA and ABPI in 2012 clarified the expectation with regards to the provision of alternative format PILs to patients:
- Detailed guidance on the MHRA website.
  - Alternative formats are not limited to Braille (audio, CD ROM, large print)
  - Timeframe to supply this information should be no longer than 5 working days. However this may not always be appropriate in instances where the treatment course is acute.
Why do we look at this during pharmacovigilance inspections (4)?

- Updates to safety sections of SPCs / PILs are often an output from pharmacovigilance activities.

- SPCs/CCDSs are used as a reference tool to inform certain pharmacovigilance activities:
  - Expectedness assessments.
  - Signal detection activities.

- Timeliness of MAH safety variation submission should be described in the PSMF.
What are we looking for on inspection?

• Required safety updates are promptly identified and all potential triggers determined:
  – Signal detection outcomes
  – PSUR recommendation by MAH
  – Updates to CCDS/CCSI
  – Comparison with brand leader product information
  – PSUR assessment report from NCA
  – NCA / EMA request

• Once the need to make a safety update has been identified, the MAH should have adequate processes in place to ensure timely variation preparation and submission.
What are we looking for on inspection (2)?

- How the MAH has recorded the “decision date” i.e. the date that the decision / notification was received by the MAH to update the product information.
  - This date is used as day zero for variation submission.
  - Determine whether the metrics monitored by the MAH are reflective of the timelines.

- Where timelines have not been imposed, expectation is a maximum of 6 months.
  - Exception to this would be updates that communicate urgent safety information.
What are we looking for on inspection (3)?

- Following variation approval, implementation of updated documents is completed in a timely manner:
  - PILs into product packs (where timelines have not been imposed expectation is that this occurs within 6 months of approval, with the exception of updates that communicate urgent safety information).
  - Internal dissemination of updated documents (medical information, pharmacovigilance, sale representatives, manufacturing sites, GMP QP. etc.)
  - External dissemination of updated documents (partners, upload onto public facing websites).
Has anything changed since the introduction of the new legislation?

- Expectations regarding the timely update of RSI remains.
- Inclusion of information on the timeliness of safety variation submission in the PSMF.
- Additional text regarding the monitoring of EU websites:

  Directive 2001/83 EC as amended, Article 23 (3)
  “The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web portal…”
Has anything changed since the introduction of the new legislation?

<table>
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<tr>
<th>Directive 2001/83 EC as amended, Articles 11 (SPC) and 59 (PIL)</th>
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<tr>
<td>• New requirements to include standard statements in mandatory reference safety information documents (SPCs/PILs).</td>
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<td>• For products subject to additional monitoring:</td>
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<tr>
<td>- Inclusion of a standard statement and display of the black triangle symbol.</td>
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<tr>
<td>- Implementation phase – latest date for existing products 31 December 2013.</td>
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Has anything changed since the introduction of the new legislation?

• For products not subject to additional monitoring:
  - Inclusion of a standard statement to encourage the reporting of suspected adverse drug reactions to NCAs and MAHs.
  - Implementation phase – to use any upcoming regulatory procedure where the outcome will affect product information annexes (e.g. renewals, type Ib and type II variations, type IA_{IN}).
  - Deadline 30 June 2015.
What does this mean for you?  

• Process in place for the periodic checking of European medicines web portal:
  – Information included in PRAC meeting minutes
  • Published on a monthly basis.

• Process in place to ensure that your product information is in line with the innovator / brand leader (i.e. in line with current scientific knowledge)
  – Particularly important for generic authorisations in cases where not much safety data is received by the MAH.
What does this mean for you (2)?

- Planning of variation submissions to implement new mandatory language into SPCs and PILs:
  - Updates for additional monitoring language should now be complete.
  - Updates regarding ADR reporting language – ongoing.
What does this mean for you?  
PSMF inclusion

• Pharmacovigilance processes: To include a description of the implementation of safety variations to the SPC and PIL.

• Pharmacovigilance system performance (body text): To include an overview of the methods used to ensure the timeliness of safety variation submissions compared to internal and competent authority deadlines, including the tracking of required safety variations that have been identified but not yet submitted.

• Pharmacovigilance system performance (Annex): List of performance indicators (where applicable) and current results.
Common inspection findings

• Failure to identify and submit safety variations.

• Significant delays in submitting safety variations.

• Failure to implement updated RSI following variation approval.
Root cause 1

Poor communication between pharmacovigilance and regulatory affairs:

- Decision to update product information during signal detection activities not communicated to regulatory affairs.
- CCDS updates not communicated to regulatory affairs for consideration in SPCs and PILs.
- Regulatory affairs not informed of recommendations made during PSUR compilation.
Common inspection findings: Failure to identify and submit variations

Root cause 2

No mechanism to feedbackCompetent Authority SPC update requests made at a national level to review whether the same change should be applied to all regions.

- At a EU Competent Authority level.
- At a non-EU level.

Root cause 3

Failure to act upon recommendations made by PRAC.
Common inspection findings: Delays in submitting safety variations

Root cause 1
Delays in the completion of internal processes:
- Delays in fully evaluating safety signals.
- Delays in referral of the update to labelling committees etc.
- Delays in communicating the outcome to update the label to regulatory affairs.

Root cause 2
Incorrect calculation of day zero for the submission of safety variations.
Common inspection findings: Delays in submitting safety variations

Root cause 3

Inadequate quality management system to support the variation submission function:
• Inadequate resource resulting in backlogs.
• Inadequate/poor tracking systems.
• Inadequate central oversight of local functions and submissions.
Common inspection findings: Implementation of updated RSI

Dissemination of updated SPC/PILs:

Root cause
Lack of formalised procedures:
• No clearly defined allocation of responsibility.
• No clearly defined recipients.
• No defined timelines.
Common inspection findings: Implementation of updated RSI

Implementation of updated PILs into packs

Root cause
Lack of formalised procedures:
- Poor communication between regulatory affairs and manufacturing sites.
- Inadequate artwork controls.
- Poor feedback mechanisms from manufacturing to regulatory affairs.
Avoiding inspection findings

• Essential to have good working relationships between pharmacovigilance and regulatory affairs:
  – Communication of new updates:
    • Pharmacovigilance triggered (safety signals).
    • Regulatory affairs triggered (CA requests, innovator comparisons).
  – Feedback on ongoing submissions/approvals:
    • Timeliness of safety variation submission to be reported in the PSMF.
    • Dissemination of newly approved materials.
Avoiding inspection findings

- Clearly defined responsibilities.
  - Pharmacovigilance versus regulatory affairs versus medical affairs.

- Robust and comprehensive tracking systems:
  - Define the processes that you are including in the tracking system.
  - Clearly defined timelines.
  - Ensure that these systems are maintained and updated.
  - Escalation processes for when timelines are not met.
Conclusion

• There is a legal requirement to ensure that product information linked to a MA are up-to-date.

• Some additional measures have been introduced as part of the new legislation – key requirements remain the same.

• Deficiencies in the maintenance of reference safety information remain a key source of inspection findings.

• Ensuring a stable quality management system in this area will help avoid inspection findings.
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