EMA’s Defective Product Report incorporating MedDRA SOC Product Issues

MedDRA User Group Meeting - Glasgow, 28 March 2017

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Agenda

1. Types of notification
2. Revision of Defective Product Report (DPR) template
3. Defect classification
4. Next steps
5. Conclusion
1. Types of notification

- Quality defects
- Falsified medicinal products (including suspicious offer)/ theft
- Rapid alerts
- Statements of non compliance with GMP (SNC)
- Suspension/ withdrawal of Certification of Suitability (CEP)
- Warning letters and other alerts
1. Types of notification

Product authorisation type:

- **Centrally Authorised Products (EMA)**
- National Authorised product
- Mutual Recognition Procedure/Decentralised Procedure

Reported by:

- Marketing Authorisation Holders
- Wholesalers/Parallel Distributors
- National Competent Authorities
- International partner authorities
Quality defect reporting process

- Defective Product Report
- Investigation report
- Health Hazard Assessment report

- Rapporteur
- Co-Rapporteur
- Supervisory Authority
- Affected Member States

- Final assessment report with agreed actions
2. Revision of Defective Product Report (DPR) template

- Notifying suspected quality defects or product recalls

This content applies to human and veterinary medicines.

**Step 1.** Download the Defective Product Report Form.

**Step 2.** Complete the Defective Product Report Form ensuring that all of section 1 and as much as possible of section 2 are complete. Please do not complete the shaded areas.

**Step 3.** Send the form by email to qe@ema.europa.eu. If this is not possible you can fax the form to +44 (0)20 3660 5535.

**Step 4.** During normal working hours you should receive an acknowledgement within 48 hours. If you do not obtain an acknowledgement in this time, telephone the European Medicines Agency to confirm that the Defective Product Report Form has been received. The telephone numbers to use are:

- During office hours: +44 (0)20 3660 7474
- Outside office hours: +44 (0)788 5050597

**Step 5.** Continue to investigate the suspected quality defect (with the urgency indicated by the nature of the defect) and send a report to the European Medicines Agency, which includes at least the following information:

- a. Background information (e.g., information about the product, its manufacturing process and/or use);
- b. History of the incident with specific dates when it occurred and/or was observed;
- c. Potential root cause:
  - 1. If the problem is due to the presence of a foreign object, describe the foreign object's size and composition;
  - 2. If the problem is due to the presence of a contaminant (i.e. cleaning fluid, machine oil, paint vapours), the level of contamination should be given and the Material Safety Data Sheet for the contaminant should be provided;
- d. If the problem is due to failure of the product to meet product specifications, provide the specifications and report all test results.
Revision of Quality Defects terminology

- 2010-2015 registers:
  - Overlapping/subjective terminology
  - Incomplete terminology
  - Standardised vocabulary not used

- Data not easy to analyse
- No information on the quality of medicines present in the EU market

One pack of this batch contained 3 blisters with an expiry date of 07.2016 and another 3 blisters with expiry date of 07.2106

Incorrect variable data associated with the expiry date
What we wanted to develop

- **2014** (quality defect workshop) Member States identified the need of having some improvements in defects reporting:
  - Mandatory fields (e.g. manufacturer details)
  - Harmonisation of terminology used to describe the medicinal product (e.g. pharmaceutical form, route of administration)
  - Harmonisation of terminology used to describe the quality defect
  - Reminder in providing investigation report and health hazard assessment
  - Reminder to notify possible product market disruptions (shortages)
MedDRA SOC Product issues

- **2015** MSSO proposed to include a set of terminology related to product issues in MedDRA: Product quality; Devices; Manufacturing and quality systems; Supply and distribution; Counterfeit products.

- We became aware of this initiative at the end of 2015 and we volunteered to collaborate with our colleagues in pharmacovigilance, MSSO and FDA on the selection of a set of standardised terminology related to quality issues.

- **December 2015** (quality defect workshop) we informed Member States about our intention to include a selection of MedDRA SOC for product quality issues in a new version of the defective product report template. Good feedback was received.

- **Q2/Q3 2016**: we had several interactions with FDA and MSSO. We proposed our preferred high level terminology (HLT) and preferred terminology (PT) and we evaluated the terms suggested by FDA.
MedDRA SOC Product issues

- **August 2016**: the final list of HLT, PT and Lower level terminology (LLT) was agreed
  - MSSO considered both Agencies points of view.
  - EMA selected a restricted set of HLT and PT focussing on the description of the quality defect.
  - FDA preferred to adopt all the HLT, PT and LLT including terminology related more to root causes.

- **September 2016**: MedDRA version 19.1 was released.

- **November 2016** (quality defect workshop):
  - One common reporting template and one common defect categorisation throughout the network was promoted.
  - The list of the MedDRA terms selected by EMA was presented.
  - General agreement on the adoption of the proposed template was reached.
3. Defect classification

MedDRA terminology adopted by EMA for defect classification

Coded Defect Category: 5 HLTs (out of 13)
Coded Defect Descriptor: 29 PTs (out of 79)

- Quality issues terminology
- Restricted set of HLTs and PTs
- General definitions

→ Not all PTs have been adopted
→ Some specific PTs and LLTs have been grouped and used as guidance for the reporter

MedDRA terminology adopted by EMA for defect classification

- 5 HLT selected → DPR’s Defect Category

- **Product issues**
  - HLT Counterfeit, falsified and substandard products
  - HLT Manufacturing facilities and equipment issues
  - HLT Manufacturing issues NEC
  - HLT Manufacturing laboratory controls issues
  - HLT Manufacturing materials issues
  - HLT Manufacturing production issues
  - HLT Product contamination and sterility issues
  - HLT Product distribution and storage issues
  - HLT Product label issues
  - HLT Product packaging issues
  - HLT Product physical issues
  - HLT Product quality issues NEC
  - HLT Product supply and availability issues
MedDRA terminology adopted by EMA for defect classification

- 29 PT selected → DPR’s Defect Descriptor

- Manufacturing laboratory controls issues
  - PT Manufacturing laboratory controls calibration issue
  - PT Manufacturing laboratory controls issue
  - PT Out of specification test results

- Product contamination and sterility issues
  - PT Exposure via contaminated device
  - PT Product cleaning inadequate
  - PT Product contamination
  - PT Product contamination chemical
  - PT Product contamination microbial
  - PT Product contamination physical
  - PT Product contamination with body fluid
  - PT Product sterility lacking
  - PT Suspected transmission of an infectious agent via product
  - PT Transmission of an infectious agent via product

- Product label issues
  - PT Physical product label issue
  - PT Product barcode issue
  - PT Product expiration date issue
  - PT Product identification number issue
  - PT Product label issue
  - PT Product label on wrong product
  - PT Product lot number issue
MedDRA terminology adopted by EMA for defect classification

**Product packaging issues**
- Failure of child resistant mechanism for pharmaceutical product
- Product blister packaging issue
- Product closure issue
- Product closure removal difficult
- Product commingling
- Product container issue
- Product container seal issue
- Product dropper issue
- Product outer packaging issue
- Product package associated injury
- Product packaging issue
- Product packaging quantity issue

**Product physical issues**
- Liquid product physical issue
- Product coating issue
- Product colour issue
- Product deposit
- Product dosage form issue
- Product friable
- Product gel formation
- Product leakage
- Product odour abnormal
- Product physical consistency issue
- Product physical issue
- Product reconstitution issue
- Product shape issue
- Product size issue
- Product solubility abnormal
- Product taste abnormal
MedDRA terminology adopted by EMA for guidance

- Other PT/LLT used for guidance:

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- HLT: Product quality issues NEC
  - PT: Product adherence issue
  - PT: Product compounding quality issue
  - PT: Product difficult to remove
  - PT: Product difficult to swallow
  - PT: Product formulation issue
  - PT: Product impurity
  - PT: Product measured potency issue
  - PT: Product origin unknown
  - PT: Product process control issue
  - PT: Product quality control issue
  - PT: Product quality issue
  - PT: Product substitution issue
  - PT: Product tampering

- HLT: Product label issues
  - PT: Physical product label issue
  - PT: Product barcode issue
    - LLT: Product barcode issue
    - LLT: Product barcode missing
    - LLT: Product barcode on wrong product
    - LLT: Product barcode readability issue

- PT: Product physical issue
  - LLT: Capsule extra shell
    - LLT: Capsule fill abnormal
    - LLT: Capsule issue
    - LLT: Capsule open
    - LLT: Capsule physical issue
    - LLT: Capsule separation
  - LLT: Product burst
  - LLT: Product physical issue
    - LLT: Scored tablet splitting issue
    - LLT: Tablet chipped
    - LLT: Tablet clumping
    - LLT: Tablet cracked
    - LLT: Tablet damaged
    - LLT: Tablet issue
    - LLT: Tablet physical issue
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MedDRA terminology not selected by EMA for quality issues

- Too specific
- Root cause description
**New Defective Product Report (DPR) template**

- Dynamic form adaptable to user requirements
- Presence of drop down menus enabling quick selection
- Presence of automatic and mandatory fields
- Presence of links to other reporting EMA webpages (withdrawn product notifications, pharmacovigilance reports)
- 2 levels of defect categorisation using MedDRA terminology
Retrospective classification of 2016 QDs using MedDRA terminology

128 Quality Defects received in 2016

- 1.0 Manufacturing laboratory controls issue
- 2.0 Product contamination and sterility issues
- 3.0 Product label issues
- 4.0 Product packaging issues
- 5.0 Product physical issues
Retrospective classification of 2016 QDs using MedDRA terminology

1.0 Manufacturing laboratory controls issues

- 1.1 Manufacturing laboratory controls issue (20)
- 1.2 Out of specification test results (33)

3.0 Product label issues

- 3.1 Physical product label issue (4)
- 3.2 Product barcode issue (25)
- 3.3 Product expiration date issue (3)
- 3.4 Product identification number issue (5)
- 3.5 Product label issue (6)
- 3.6 Product label on wrong product (4)
- 3.7 Product lot number issue (2)
Working plan

- Revision of EMA internal procedures
- Defective Product Report
- Assessment report template (for Rapporteur and Supervisory Authority)
- Rapid Alert report and procedures present in the compilation of community procedures
- Creation of a specific report for falsified medicinal product/theft
- Revision of external website (reporting page)

Promotion of the adoption of a single reporting template and of a single set of standardised terminology for quality defects affecting any type of product marketing authorisation present in the EU
4. Next steps

Pilot phase
- Templates
- User instructions
- Guidance

Q1/Q2

Publication for comments
- Feedback
- Revision

Q3/Q2

Training
- Use of templates
- Guideline
- EMA reporting process

Q4

Future:
- Update of HLT/PT if needed
- Root cause analysis
5. Conclusion

We are only at the start of this journey!

• The proposed DPR will facilitate defect reporting and categorisation.
• Defect categorisation with harmonised common terminology will facilitate the analysis of product issues and will provide information on the quality of medicinal products present on the EU market.
• Root cause classification and analysis is a future goal to achieve in order to have a full picture of medicinal products and manufacturing facilities quality and compliance.
Thank you for your attention

Further information

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