EIPG Guidance on

"Safety Features Implementation and QP Responsibilities"

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Agenda

- ***The hystory of this guidance***
- ***The basic reasons***
- ***The changing environment***
- ***The focus of this guidance***
- ***Conclusive remarks***

History (1)

February 2016 *«Commission Delegated Regulation 2016/161»*

⇨ *EIPG started focusing on its implementation issues*

July 2016 ⇨ *EIPG issued a statement, recommending review of Annex 16 to better clarify the QP role in safety features implementation practice*

November 2016, *at the «Interested Parties meeting» (London)*

⇨ *EIPG presentation, highlighting the need of a guidance for QPs*

⇨ *EMA reply: no need of Annex 16 update («industry needs to sort it out»), though the issue could be handled via Q&A*

December 2017*, at the «Interested Parties meeting» (London)*

⇨ *EIPG raised the point about the additional challenge posed by the timelines for implementation of the Delegated Regulation in the same quarter as the UK withdrawal*

History (2)

***May 2018*, at the EIPG General Assembly (Casablanca)**

- ⇨ ***AESICA presentation on safety features technical issues***
- ⇨ ***Working Group discussion and decision on a guidance***

***January 2019*, at the EIPG Bureau Meeting (Milan)**

- ⇨ ***Presentation of a first draft guidance, which had been prepared and revised with the contribution of two colleagues from A.F.I.***

***January 2019*, at the «Interested Parties meeting» (via telecon)**

- ⇨ ***Discussion topic about QP responsibilities in the implementation of serialization (FMD)***
- ⇨ ***EIPG/EQPA joint statement on the introduction of an additional Q&A to clarify the position of QP about batch certification and data upload in repository system***

The Basic Reasons

❑ Directive 2011/62/EU

⇨ The Market Authorization Holder (MAH) - Art. 47a

- *To verify that the medicinal product concerned is authentic and that it has not been tampered with …*
- *To replace those safety features with safety features which are equivalent …*
- *To conduct the replacement of the safety features in accordance with applicable GMP …*

⇨ The Qualified Person (QP) - Art. 51(1)

- *The qualified person shall, in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging …*

The Basic Reasons

❑ Commission Delegated Regulation (EU) 2016/161

⇨ *"**The Manufacturer**"*

- *To place on the packaging a unique identifier … (Art. 4)*
- *To encode the unique identifier … (Art. 5, points 1 and 2)*
- *To print the barcode on the packaging … (Art. 5, points 3 to 6)*
- *To evaluate the quality of the printing … (Art. 6)*
- *To print data elements … (Art. 7)*
- *To verify the readability and correctness … (Art. 14)*
- *To keep records … (Art. 15)*
- *To verify the integrity and authenticity … (Art. 16)*
- *To ensure the equivalency of the unique identifier … (Art. 17)*
- *To not release the product … if tampered or non authentic … (Art. 18)*
- *To employ a proper method of safety feature verification (Art. 10 and 11)*

The Basic Reasons

❑ Commission Delegated Regulation (EU) 2016/161

⇨ “**The Market Authorization Holder**” – **Art. 33**

- *To ensure that the information is uploaded to the repositories system before the product is released for sale or distribution by the Manufacturer and to keep up to date thereafter*
- No mention about QP involvement

❑ EU GMP Annex 16 – Point 1.7.21 (*The Process of Batch Certification*)

- *In the case of medicinal products for human use intended to be placed on the market in the Union, the safety features referred to in Article 54(o) of Directive 2001/83/EC, as amended, have been affixed to the packaging, where appropriate*.

A Changing Environment

- ✓ *Introduction of additional GMP activities*
- ✓ *Extension of application of quality risk assessment*
- ✓ *Managing change control and setting up new SOPs*
- ✓ *Requiring team working (Manufacture, Regulatory, Quality, IT)*
- ✓ *Updating of the QMS*
- ✓ *Personnel training and motivation (leadership)*
- ✓ *Developing new communication tools among key actors (MAH, CMO, QP, GP)*
- ✓ *The inclusion of data uploading in the process flow of batch certification and release, requiring definition of organizational details*

A Changing Environment

Basic Activties	Case 1	Case 2	Case 3	Case 4	Case 5
Safety Features Affixing	**MAH = Manufacturer**	**MAH = Manufacturer**	**CMO**	**CMO**	**CMO**
Code Number Uploading	**MAH**	**MAH via a GP**	**MAH via a GP**	**MAH via a GP**	**CMO via a GP**
Batch Release	**QP (MAH)**	**QP (MAH)**	**QP (CMO)**	**QP (MAH)**	**QP (CMO)**
Quality Technical Agreements	**All internal activities**	**QTA: MAH and GP**	**QTA (1): MAH and CMO** **QTA (2): MAH and GP**	**QTA (1): MAH and CMO** **QTA (2): MAH and GP**	**QTA: MAH-CMO-GP**

The Guidance Focus

- ***Main reference to the requirements of DR 161/2016***
- ***Description of all operations, at a workshop floor level***
- ***Highlighting potential issues in implementation***
- ***Presenting control measures to be adopted***
- ***Determining the changes for QMS compliance***
- ***Identifying the QP responsibilities and determining the additional duties***

The Guidance Focus

Operations and Controls

1. ***Line Equipment and Serialization Software***
2. ***Packaging Process and Control***
3. ***Artwork Design***
4. ***Online Printing and Verification***
5. ***Tamper Evident System Application***
6. ***Unique Identifier Application***
7. ***Batch Certification and Safety Features Information Uploading***

Line Equipment + Serialization Software

Operations

- *Equipment qualification, incluiding: online-printer, TE system, camera verification system, serialization software*
- *Data Matrix encoding, considering some risks:*
  - *loss or modification of data, when generated, before their use*
  - *correct transmission to the line and to printing device*
  - *secure data storing before uploading*

Potential Issues

- *Vendors reliability*
- *Software system (validation, data quality assurance, data integrity compliance)*
- *Expertise and partnership with key suppliers*

Line Equipment + Serialization Software

Actions

- ***to perform vendor qualification***
- ***to qualify the packaging equipment line***
- ***to define maintenance and calibration plans***
- ***to perform IT-validation (technical expertise essential)***

QP Responsibilities

Any deficiency or failure of the packaging line equipment, as well as the software system, would lead to data errors in the serialization process

⇨ ***QP to ensure that:***

- ***the QMS has been updated***
- ***all required actions have been assigned to competent people (suppliers)***
- ***all activities are documented and, when required, included in the batch record***

Packaging Process and Controls

Operations

- *Packaging "process validation"*
- *Training of all operators, making them aware of the safety features requirements and critical issues*

Potential Issues

- *packaging equipment line to be challenged, to identify critical issues*
- *re-validation process on an existing packaging line, when used for safety features implementation*
- *manual decommissioning activities, to be identified*

Packaging Process and Controls

Actions

- ***To rely on a validated packaging process procedure (information to MAH)***
- ***To plan a periodic re-assessment of the application of safety features***
- ***To implementation suitable IPCs, including those related to the official requirements***

QP Responsibilities

The use of a validated packaging procedure is essential for complying with both the QMS and the safety features application requirements, preventing the risk of batch recalls

⇨ QP involvement:

- ***approval of process validation documentation***
- ***approval of change controls and SOPs, as required for any new implementation***
- ***participation in operators and staff training***

Artwork Design

Operations

- *Artwork designs to be redefined and changed, in order to accommodate the printing and the tamper evident (TE) system*
- *Artwork solution taking into account the safety features requirements, the technical constraints (manufacturer) and the requests of the MAH*

Potential Issues

- *a wide range of tamper evident (TE) solutions*
- *the position of Data Matrix code and the human readable code*
- *the need of a mandatory unvarnished area on varnished boxes*
- *the serialization of bundled boxes*

Artwork Design

Actions

- ***To set up an internal artwork team (temporary basis) and to implement a workflow for artwork changes***
- ***To identify any impact on the modified artwork on packaging operations***
- ***To develop an updated "Packaging Master File"***

QP Responsibilities

⇨ QP involvement:

- ***approval of the artwork design re-definition, as part of QMS activities, and in agreement with the Manufacturer and MAH specific requirements***
- ***approval of the Packaging Master File, which will be issued or updated to record the new version of the artwork of each product***

On line Printing and Verification

Operations

- ***Printing and subsequent verification are critical***
- ***Application of database software with the serialization device in line***
- ***Application of the verification system for checking position and readability of variable data***

Potential Issues

- ***incorrect on-line printing, with automatic article elimination***
- ***verification system not appropriately set up for current article layout with no detection of incorrectly printed data***
- ***wrong type of ink used***

On line Printing and Verification

Actions

- ***To double check (visual) the verification system set-up and of the printed data***
- ***To introduce suitable IPCs (frequency, sampling procedure)***
- ***To implement SOPs for any manual operation (e.g. entering lot number and expiry date)***

QP Responsibilities

Any failure in printing and verification leads to non-conformant products. This deficiency could be limited to a single box, which would become not saleable at the end of the supply chain.

⇨ QP to ensure that:

- ***operations are under control, SOPs covering verification points and IPCs***
- ***all variable data and print quality Data Matrix code are part of batch certification***

Tamper Evident System Application

Operations

- *Correct application of the TE system chosen*
- *Qualification of the technical device used for application on the packaging line*
- *Adaptation of the packaging line according to the TE in use*

Potential Issues

- *Depending on the TE system, its application can show some issues:*
  - *“cold glue” taking time to set*
  - *labels not working on varnished areas*
  - *carton type and printed area can influence adhesive strength*
  - *perforation of labels damaged prior or during application*

Tamper Evident System Application

Actions

- ***To develop suitable SPOs for each TE system and its application***
- ***To double check the identified critical parameters (glue, adhesiveness)***
- ***To get stability data on the TE system performance***

QP Responsibilities

Any deficiency of an anti-tampering device would generate a non-conformity in the supply chain, with a possible rejection of the product, as suspected of counterfeiting.

⇨ ***QP to ensure that:***

- ***in the batch certification, to evaluate the finished product based not only on the complete documentation, but also in the examination of samples taken from the manufacturing process, being representative of the batch, so including the tamper evident which has been applied.***

Unique Identifier Application

Operations

- *generation of the Serial Numbers (SN) by using a validated software*
- *implementation of authentication user levels, to allows audit trails*
- *alignment of SN, when manual decommissioning is performed*

Potential Issues

- *operators not well trained about manual actions to be performed*
- *user administration setup not updated (hired or newly line-dedicated operators and dismissed staff)*
- *mismatch of SN status in database and physical commissioned products at packaging site and during supply chain*

Unique Identifier Application

Actions

- ***To issue a SOP describing all steps and the access levels and responsibilities***
- ***To employ trained operators and to perform regular checks of user authentication level set up***
- ***To generate serialization reports, to be attached to batch record documentation***

QP Responsibilities

Any failure in serial number presence or mismatch leads to batch non–conformity or may cause batch recalls

⇨QP to ensure that:

- ***adequate SOPs have been developed and implemented (QMS updating)***
- ***a quality risk assessment has been performed, including data integrity requirements in managing all data***

Batch Certification and Information Uploading

❑ ***Batch Certification***

⇨ *According to Annex 16 (EU-GMP) - General Principles:*

*The process of **batch release** comprises of:*

I. *The **checking** of manufacture and testing of the batch, to verify that defined release procedures have been followed*

II. *The **certification** of the finished product, to verify that the finished batch is in compliance with GMP and the requirements of its MA*

III. *The **transfer to saleable stock** of the finished batch, which should take into account the certification performed by the QP*

Batch Certification and Information Uploading

❑ ***Batch Certification***

⇨ *According to Annex 16 (EU-GMP) – The Process of Certification*

Point 1.6

*The **QP must personally ensure** that the following operational responsibilities are fulfilled prior to certification of a batch for release to market or for export:*

I. *Certification is permitted under the terms of the MIA*
II. *Any additional duties and requirements of national legislation are complied with*
III. *Certification is recorded in a register or equivalent document*

Point 1.7.21

*In the case of medicinal products for human use intended to be placed on the market in the Union, the **safety features** referred to in Article 54(o) of Directive 2001/83/EC, as amended, **have been affixed to the packaging**, where appropriate*

Batch Certification and Information Uploading

❑ ***Information Uploading***

⇨ According to art. 33 of DR 2016/161:

*Information about the safety features are requested to be uploaded to the repository systems before the product is released for sale or distribution and the **MAH is responsible for accomplishing this operation***

⇨ According to Q&A Document Version 14 (April 2019), Point 7.16:

*The information needs to be present in the system **at the time the batch is released** for sale or distribution…*

… upload taking place before the medicinal product is transferred to saleable stock

Batch Certification and Information Uploading

The QP position

- *To comply with Annex 16 requirements, ensuring that:*
  - *packaging/labelling processes have been performed according to the related written procedures and instructions*
  - *safety features have been consistently affixed on the packaging*
  - *all aspects taken into account prior to batch certification, relying on the Quality Management System in place*
- *The transfer into "saleable stock" is a dependent but separate step from the certification and quality release steps*
- *The QP has no responsibility, defined by regulation, on data quality, data handling, data upload and data cleaning*
- *Responsibility for all data handling and its upload lies with the MAH*

EQPA / EIPG Joint Proposal to EMA

Question:

"Does the QP have to be personally responsible for uploading the information to the repository system before the product is released for sale or distribution by the manufacturer?"

Answer:

No. The responsibilities of the QP are defined in Directive 2001/83/EC and interpreted in Annex 16 of the EU-GMP-Guide.

Certification by the QP has to ensure that the safety features have been affixed on the packaging.

Uploading the information into the repository system should follow procedures established by the MAH and be performed by sufficiently trained personnel responsible for this activity, which is not necessarily the QP.

However, any deviations originating from this upload process may need to be brought to the attention of the QP to initiate the appropriate steps in accordance with GMP and the established pharmaceutical quality system.

Conclusive Remarks (1)

- ***The implementation of safety features requirements has a substantial impact on the manufacture and control operations***
- ***A directed involvement of the QP is requested in many operation steps***
- ***The QP has to give his/her contribution in terms of knowledge and competencies , which are to be developed according to the specific legislation requirements***
- ***The QP has to reinforce his/her accountability in terms of providing the appropriate supervision on all key operations, establishing good communication with the MAH and the other actors concerned with the serial number management***

Conclusive Remarks (2)

- ***It becomes more and more evident that QP has to count on appropriately trained personnel or third parties and to rely on a robust quality management system***

- ***The implementation of a good organization, with the presence of formal delegation of tasks to reliable personnel and with the allocation and distribution of responsibilities among different QPs should become a necessity for managing the additional duties***

- ***The professional level of the QP is further increased, becoming more evident the key role of this position in pharmaceutical manufacture***

- ***The QP is thus called upon to play a key role in the success of the implementation of the Delegated Regulation and the European Medicines Verification System, protecting patients from counterfeit medicines***

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- ✓ ***The EIPG/EQPA joint position paper on QP responsibilities in uploading***

Thank you
for your attention