15 May 2018

Submission of comments on 'Public consultation concerning the European Union template for good manufacturing practice (GMP) non-compliance statement’ – EMA/189939/2018

Comments from:

| Name of organisation or individual |
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| EFPIA |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | EFPIA welcomes this initiative to update the EU template for GMP non-compliance statement in order to integrate the key principles of ICH Q9 on Quality Risk Management and to improve situations that might lead to shortages of critical medicinal products. |  |
|  | The requirements could benefit from specifying timelines for responses from both industry and regulators to name e.g., 30 calendar days rather than 20 working days as there are different bank holidays in the EU member states. |  |
|  | This document talks in different parts about ‘affected’ Marketing Authorization Holders. We recommend to clarify if this is the country of origin and/or the importing country. |  |

1. Specific comments on text

| Statement, part I 2nd paragraph | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 1. Introduction Par. 3, bullet 3 |  | **… avoiding generation of conditioned GMP certificates..** Proposed change: Avoiding conditioned GMP certificates along with non-compliance statements is appropriate from a general perspective. However, when it comes to critical (essential) medicines, the possibility of a restricted GMP certificate should be maintained to ensure if required continuity of supply via maintaining necessary activities (manufacturing and/or testing). |  |
| 1. Introduction Par. 3, bullet 4 |  | **… providing specific guidance for Qualified Persons to facilitate release batches of critical drug products…**  Proposed change: We understand there will be a concept paper and the opportunity for industry to comment, if this part is revised. |  |
| 2. Consultation procedure |  | **… effective and harmonised risk-based approach for dealing with the supply of critical medicines in case of serious GMP non-compliance…**  Proposed change: There is the opportunity to also mention and consider supplementary measures from EMA and MS HA to facilitate / speed-up the risk / situation of shortage (e.g. fast track variation for registering a new API manufacturer). |  |
| Statement, part I; 2nd paragraph |  | Comment: It is important to clarify the nature of the risk assessment required. We recommend to add a reference to the risk question ‘manufacturing process’. However medical risk Assessment may also be included, as appropriate.  Proposed change:  ***‘****A documented risk assessment* ***(e.g. manufacturing process risk and/or medical risk as appropriate)*** *has been performed by, …’* |  |
| Statement, part I 2nd paragraph |  | Comment: The “Statement of Non-Compliance with GMP” is a mechanism for the exchange of information between National Competent Authorities of the EEA. With complex global supply chains there may be impact on the supply of critical medicines from the manufacturer to non-EEA countries.  Proposed change: To avoid interruption of supply of critical medicines, add a second note.  *Note to issuing authorities: If the statement is shared with non-EEA authorities, the Manufacturing Authorisation Holder should be informed to facilitate a conversation regarding impact and critical supply in non-EEA markets.* |  |
| Statement, part I 2nd paragraph |  | Comment: The receiving authorities shall contact the issuing authority within ‘**20 working days’** in case there are critical medicinal products potentially affected by this statement. Proposed change: We recommend to change to **30 calendar days** as working days are different per member state due to various bank holidays. |  |
| Statement, part I 4th paragraph |  | Comment:  Companies could have a QP structure and not only one QP, and therefore it is important to be more precise.  Proposed change: In exceptional circumstances there may be no objection to the Qualified Person **in the scope of the non-compliance statement** certifying affected batches thereby allowing their release provided all of the following conditions are fulfilled. |  |
| Statement, part I 4th paragraph ff |  | Comment: Since the conditions, for the Qualified Person to be able to release batches in exceptional circumstances, are critical for the correct behaviour, it is suggested to make a visual end-to-end representation (e.g. flow chart) of the required conditions and steps to be followed. It is believed that such a representation will increase understand ability.  Proposed process to add a short flow chart:  QP for scope of non-compliance statement Risk assessment (conditions 1-3) ->  National competent authorities (condition 4) ->  Supervisory authority (condition 5) ->  Affected marketing authorisation (condition 6) ->  Further conditions and conclusions (condition 7) ->  Feedback form to the manufacturer (condition 8) |  |
| Statement, part I 4th paragraph ff |  | Comment: The form to sign contains a lot of details. We suggest to move the 4th paragraph included in the listing of the seven bullets of the ‘background’ part. This would make the form simpler.  Proposed change: e.g.,  *This GMP non-compliance statement would by default result in the suspension or revocation of the relevant Manufacturing Authorization, or in the case of importation into EU, in the ban of product importation, by the Supervisory Authority.*  *In exceptional circumstances, for critical medicinal products, the relevant Marketing Authorization Holder(s) and their QP(s) might apply for the maintenance of the Marketing Authorization that would allow the QP(s) to perform batch certification in order to maintain the supply of critical medicinal products only. Please refer to the relevant procedure in the CoCP for the conditions to fulfil.’* |  |
| Statement, part I 4th paragraph (2) |  | Comment: The template uses the term “critical medicinal product”. It can be clarified in which case a medicinal product can be considered as critical to support harmonisation among member states. However flexibility may be desirable. It may be preferable to require a decision by the Competent Authority from one relevant member state (e.g. for centralized products the state of the Marketing Authorization is grated).  Proposed change: add **A ‘critical medicinal product’ can be considered to be a medicinal product as an integral part of the treatment for a disease, which is life-threatening or irreversibly progressive, or without which the patient could be severely harmed or no alternatives are available (based on EMA/314762/2013, 3 September 2013).** |  |
| Statement, part I 4th paragraph (2) |  | Comment:  The implementation of repeated testing should not be considered as a relevant approach to mitigate the risks related to non-GMP compliance. The additional note proposal should be removed.  Proposed change (if any):  ~~Note: Repeated testing alone is not normally sufficient risk mitigation but, together with other actions, can form part of a strategy commensurate with the nature and the level of risk.~~ |  |
| Statement, part I 4th paragraph (3) |  | Comments: a) For clarity we recommend adding the nature of this risk assessment and link to patients.  b) We understand it can be helpful to e.g. 30 calendar days within which the authorities’ comments have to be sent to harmonise expectations from both industry and regulators.  c) Note: We understand the risk mitigation plan should be reviewed by the National Competent Authorities of the countries in which the product should be distributed only.  Proposed change:  d) It can be clarified that the report needs to be available prior to the QP certification and not necessary approved by the NCA prior to certification in order to continue uninterrupted supply. Proposed change: *A thorough* ***patient*** *risk benefit evaluation has been performed**and shared with the affected NCAs* ***prior to the QP certification****. Comments from those authorities****, usually received within* 30 calendar days,** *have to be taken into account. ….* |  |
| Statement, part I 4th paragraph (4) |  | Comment. There term ‘no objection’ seems to be very wide. We understand it can be specified.  Proposed change:  …and that there is no objection **based on the conclusions of the risk benefit evaluation’ to** distribution… |  |
| Statement, part I 4th paragraph (6) |  | *The affected Marketing Authorisations have not been revoked or suspended.*  Comment: We see the need for clarification on “affected Marketing Authorization” a) hold by the Marketing Authorization Holder (MAH) of the country of origin or  b) by the MAH of importing country or  c) both?  Proposed change: The affected Marketing Authorisations have not been revoked or suspended **in both, the country of origin and the importing country, as applicable** |  |
| Statement, part I 4th paragraph (8) |  | Comment  In cases where it has been concluded, that there are no objections to the Qualified Person certifying affected batches, it is advised to add an additional condition (8.), in order for the manufacturer to be able to provide documentation for the acceptance of the Qualified Person if requested.  Proposed addition:  **8. The manufacturer has received a statement from the issuing authority containing documentation of approval of release of batches by the Qualified Person for the scope of the non-compliance statement based on listed conditions.** |  |

Please add more rows if needed.