AIDE MEMOIRE FOR GMP INSPECTION OF MANUFACTURERS
COMPLIANCE WITH COMMISSION DELEGATED REGULATION (EU) 2016/161 FOR SAFETY FEATURES
20 June 2019

Area of operations / items	**Questions/Show me**	**References (where applicable)**
General	Are all prescriptions products manufactured at the site required to bear safety features? Are any products exempted under Annex I? Are any OTC products required to bear safety features under Annex II? Are there products with different requirements in different EU Member States (e.g. prescription in certain MS & OTC in another)? If so, how is this handled? Is there a procedure or authorised listing available specifying which products are within the scope of the DR and specific requirements in the different Member States (if applicable)? Review deviation/non-conformance listings for any exceptional release of batches without safety features, after the 9th February 2019. Check for notification/authorisation by NCAs in this regard. Seek clarification regarding any batches released prior to the 9th February 2019 bearing safety features. Has this data been uploaded? Are products imported from India and certified at the site? If so, has the company notified its CMO in India of the requirements of the Delegated Regulation and to request that the CMO seeks an exemption from the Indian Authorities in relation to the Indian traceability system, so that these Indian barcodes are no longer applied to packs exported to the EU?	Article 9 DR
Connection with the hub	Who is the On-Boarding Partner (OBP) and where is this entity located? Show me the agreement between the OBP and EMVO? Where the OBP is not the manufacturer, request to see the agreement/contract between the manufacturer and OBP outlining responsibilities of the parties. Are the responsibilities regarding the UI/ATD stipulated in an agreement/contract with the MAH?	EU GMP Guide, Part I, Chapter 7

	Do the contracts cover at a minimum responsibilities for the following: - Management of Product Master Data in the hub - The generation of SN's - The upload of data into the hub - Status changes to UIs to Recalled, Stolen, etc. - The immediate investigation and communication of a suspected falsified pack, based on an alert in the EMVS?	
Registration with the NMVOs	Where the manufacturer is also the MAH, has it registered with all relevant NMVOs?	
Data Flow	How does the batch data (serialisation numbers) get to the hub from the site of manufacture? Show me the system description, data flow and interfaces with other systems? Data-flow from: - where the SN's are generated - to where the UIs are printed on the packaging-line - to the hub where the UIs are uploaded Are all entities involved identified along the chain of flow of data? Who is the sites contracted serialisation partner? Show me the ISO 27001 Information Security Management System Certificate of Registration for this serialisation partner. Is the system a Cloud Based system and where are the servers located (e.g. US)? Has an audit been carried out to assess the quality of the serialisation partner's quality management system and hosted cloud environment? Is there a Gateway Provider involved? If yes, who is the gateway provider? Has this service provider been qualified? What knowledge do you have about the service provider's quality management system? Has a security audit/assessment been conducted? Show me the audit reports/assessment reports	EU GMP Guide, Part I, Annex 11, Principle & Paragraph 4; EU GMP Guide, Part I, Chapter 7 PIC/S Guide PI 011-3, Section 11 (IT Service supplier qualification) Q&A COM 7.19

	Are responsibilities defined in Quality/Technical Agreements/Contracts between all relevant parties involved in the chain of data flow? What additional software has been installed at the site for the purpose of serialisation and compliance with the DR? Where there are interfaces between the company's serialisation system and other systems (e.g. MES, ERP), do these other systems store or transfer the data (e.g. PC, SN)? Has the software been validated, including any inter-connections (e.g. no alteration to uploaded data: expiry date, capital letters vs. lower case etc.)? Is there a risk based audit trail review of the operations executed within the serialisation system?	
Generation of Serial Numbers (SNs)	Where/by whom are the SNs generated? Is there a Contract in place? Is it generated by a deterministic or a non-deterministic randomisation algorithm, in a way that the probability that the serial number can be guessed shall be negligible and in any case lower than one in ten thousand? Is the combination of the PC+SN unique until EXP+1Y or REL+5Y, whichever is the longer period? Is serialisation data received from other parties, e.g. CMO's? If yes, how (e.g. connection with the CMO's system)? Has the security of the connection been evaluated? Who manages/controls the Product Master Data in the hub (e.g. creation of a new product, changes to an existing product)? How is it ensured that only Product Master Data from legitimate marketed packs is uploaded? (*i.e. once a company passes EMVO's legitimacy check and gets access, how is that company prevented from creating non-existing products in the system and upload of SN's for this fake product, to enable distribution of falsified product*)	Articles 4b (ii), 4c DR Article 4d DR

Uploading of information in the repositories system	At what point in the batch release process is the data uploaded? Is the data sent to the serialisation partner's server first and held for a period or stored temporarily in the manufacturer's/MAH's cloud, prior to upload to the hub? How is the upload to the hub actually triggered? How is it ensured that only the data for 'good' packs (suitable for release) is uploaded to the hub? Is the system designed in a way that no upload of data goes undetected/that any upload of data requires approval (of the QP?) before actually sending it to the hub? What happens to the UIs which were generated but not used and UIs on packs ejected from the line at the eject stations during packaging? Is a verification of successful upload and distribution required to be obtained? Is it verified whether the quantity of serial numbers successfully received by the NMVS, corresponds to the quantity of serial numbers that was initially intended to be uploaded (reconciliation of the number of SN's)? Who receives this and what action is required in the event of a failed upload? Does the (successful) upload occur before or after batch certification by the QP? Does the (successful) upload happen before or after release to the market or for export? Are there procedures which describe these processes? (Note: The information laid down in Article 33(2) of Commission Delegated Regulation (EU) 2016/161 needs to be present in the system at the time the batch is released for sale and distribution)	Article 33 DR COM Q&A 8.6 COM Q&A 7.16

Packaging Lines	Was serialisation for EU implemented at the site under change control? Did this change control process include identification of QMS documentation which required update to incorporate safety features? (e.g. procedures for recall, quality defects, batch disposition, shipment, distribution etc.; batch records, job descriptions for key personnel/QP, technical/quality agreements) Are both the 2D barcode and the ATD applied? In the case of the ATD, get the company to demonstrate that if removed or broken, this is evident visually from the pack. Is stability data available? (Tamper evident nature should be proven throughout the shelf life of the pack) Which packaging lines have capability for serialisation? Was new equipment installed and was it qualified? (e.g. printers, cameras, reject stations etc.). Review change control, qualification documentation etc. Is the UI printed on the packs online or are labels/stickers applied to packs separately? Is there 100% verification of the readability of the 2D barcode? How is this done (e.g. on-line camera)? Is there an on-line sensor to detect the presence of ATDs and is it challenged? Is aggregation implemented? Explain how (e.g. UI's in 1 data-file. What happens with the data-file. How is this protected/transferred in a secure way)?	EU GMP Guide, Part I, Annex 15 Article 5.3 DR COM Q&A 2.21 Article 14 DR
Composition of the UI	Does it consist of the required data elements? - Product code (max 50 letters or numbers), allowing the ID of the name & common name of the product, pharmaceutical form, strength, pack size, pack type, optional: info regarding reimbursement <u>Should be printed on the pack, preceded by the letters **PC**</u>	Article 4 DR QRD Templates Appendix IIIA Section 18

	- Serial n° (max 20 letters or numbers) Should be printed on the pack preceded by the letters **SN** - Expiry date Should be printed on the pack by **EXP** (Note: The word "EXP" is not in use in all Member States. Country specific words may be used) - Batch number Should be printed on the pack by **LOT** (Note: The word "LOT" is not in use in all Member States. Country specific words may be used) How is the PC managed in the quality system? Who is responsible for its generation/management? What is its format (e.g. GTIN/NTIN)?	
Human-readable format	Are the following data elements on the packaging in human-readable format: (a) the product code (b) the serial number (c) the national reimbursement number, if required The batch number and expiry date should also be on the packaging in human readable format.	Article 7 DR
Quality of the printing of the 2D barcode	Has the manufacturer evaluated the quality of the printing by assessing the following parameters: (a) the contrast between the light and dark parts (b) the uniformity of the reflectance of the light and dark parts (c) the axial non-uniformity (d) the grid non-uniformity (e) the unused error correction (f) the fixed pattern damage (g) the capacity of the reference decode algorithm to decode the Data Matrix. How was this performed? If a dedicated equipment is installed for this purpose, is it qualified, is it included on the calibration/maintenance master plan etc.?	Article 6 DR
	Is the minimum quality of printing identified that ensures the reading of the Data Matrix for EXP-date +1Y, or REL-date +5Y, whichever is the longer period? (*Not required when it is demonstrated that the Quality of Printing is at least 1,5 if in accordance with ISO15415:2011*)	
Reversing the status of a decommissioned UI	Is there a procedure in place for the reversal of the status of UI?	Article 13 DR

Record keeping	Are records kept of the operations that are performed with or on the UI until EXP+1Y, or REL+5Y, whichever is the longer period? Are these records available to the NCA? Are these records reviewed and approved? By whom?	Article 15 DR
Removing or replacing safety features	Are repackaging activities carried out? If yes: are the SF's verified before the repackaging activity? Is the status of the "old" UI decommissioned? To what status? Can you demonstrate the equivalence between the old and the new ATD? Do you have SOP's that describe this?	Articles 16 & 17 DR
Returns	Is the UI verified for returns of medicinal products? Is this requirement included in a procedure? Are records maintained?	Articles 19, 20 (a)
Decommissioning of unique identifiers	Are UIs verified and decommissioned for the following: (a) products distributed outside the EU (b) returns which cannot be returned to saleable stock (c) products intended for destruction (d) products requested as samples by NCAs (e) products distributed to persons or institutions referred to in Article 23, where required by national legislation Are the above requirements included in a procedure? Are stock management/distribution systems configured to meet these requirements for the Article 23 entities? Has the process been qualified?	Articles 22, 23 DR
	For holders of a compounding manufacturer's authorisation (these authorisation-holders may use commercially available product for unit-dosing or for compounding patient/prescription specific medicines for an individual patient) are the responsibilities for decommissioning defined?	
UI status change	What status changes can the manufacturer perform on a pack/on a batch/on the product (e.g. Recalled, Withdrawn, Intended for Destruction, Stolen, Requested as a Sample by NCA)? When the status of a UI is changed to for e.g. Stolen, Recalled, Withdrawn or Locked by the MAH, does the	Articles 36b, 36m DR

	manufacturer receive a message of this through the IT-system?	
	Does the manufacturer get information on the status of a UI (e.g. Decommissioned, Recalled, Withdrawn, Intended for Destruction, Stolen, Requested as a Sample by NCA, Indicated as Free Sample by the MAH) when he verifies the authenticity of the UI?	Article 36m DR
	Can a combination of a PC + SN of an old pack be removed from the EMVS, in order to upload a PC + SN of a new pack?	Article 42 DR
Actions to be taken in case of tampering or suspected falsification	Show me the procedures describing actions to be taken in cases of tampering or suspected falsification. Do procedures state that the manufacturer shall not release the product for sale or distribution and shall immediately inform the relevant competent authorities in the case of a confirmed falsification event, when technical/procedural root causes have been ruled out?	Articles 18, 24 37d DR
Alert Management	Are alerts of potential falsification, generated by the EMVS on products manufactured at the site, notified to the site? How does this happen in practice? Is there an SOP on the handling and investigation of such an alert, to determine whether the root cause is a technical or procedural issue?	Article 37d DR
Operations specific to Parallel Importers & Distributors	Has the equivalence of the new ATD & UI placed on the packs with the original UI/ATD been assessed? How was this conducted? Show me an example of how equivalence has been demonstrated. Is the authenticity of the safety features on the sourced pack verified before unpacking? Is the parallel repackaging functionality in the EU-Hub used when repackaging? Explain how you deal with the following situations: - Sourcing packs from a country where the product is in scope of the DR, but not in scope in the target market? - Sourcing packs from a country where the product is not in scope of the DR, but is in scope of the DR in the target market?	Article 17 DR Q&A COM 1.22 2001/83/EC Art 47a (1)a

	If the patient information leaflet is replaced, are the packs re-boxed (i.e. new cartons) or are the original cartons resealed (e.g. by applying a new ATD on top of the old, broken ATD)? If the original cartons are resealed, has this been notified to the NCA in the destination Member State for assessment?	Q&A COM 1.20