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Lessons learnt from presence of *N*-nitrosamine impurities in sartan medicines

Implementation Plan

In June 2020, the European Medicines Regulatory Network published a report on lessons learnt from the presence of *N*-nitrosamines in sartan medicines (also known as angiotensin II receptor antagonists). The report sets out a number of recommendations for strengthening the regulatory framework in order to reduce the potential of *N*-nitrosamines and other impurities being present in human medicines in the future and to support the regulatory network's preparedness for managing similar cases of unexpected impurities should they occur in the future.

A summary of the recommendations with the assigned responsible party and indicative implementation timelines is provided below.

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LLE Report Recommendation	Corresponding actions from the LLE Report Technical Background	LEAD	Involved Parties	Timeline
1) Clarify responsibilities of MAHs, finished product manufacturers, API manufacturers ASMF Holders and API CEP holders throughout the life cycle of medicinal products, including responsibilities for quality, safety and efficacy. Areas of responsibilities to be clarified include quality management systems, personnel, documentation, supplier qualification, contract and technical agreements, and management of quality defects, complaints and product recalls.	Section 2.4 (page 42) Remind MAHs of their responsibilities.	QWP	QWP EDQM GMDP IWG	Medium (1-3 years)
	Section 2.4 (page 42) Review the way CEPs are used and consider how to better address the needs of marketing authorisation holders and regulators with a focus on increased transparency. This should include clarification of regulatory texts on responsibilities of the MAH in cases where API is covered by a CEP and those of CEP holders towards the MAHs regarding availability of dossier information. The information provided to the MAHs should not be less than the applicant's part of an ASMF on manufacturing process and impurities.	QWP/EDQM		Medium (1-3 years)
	Section 4.2.4 (page 61) Draft or amend existing guidelines (e.g., EU GMP guideline Part 1, Chapter 7) addressed to MAHs and holders of CEPs and ASMFs (i.e., API manufacturers) clarifying their respective responsibilities with regard to the medicinal product over its lifetime, including its safety, quality and efficacy, covering at least the following areas: quality management system, personnel, documentation, supplier qualification, contract and technical agreements, quality defects, complaints and product recalls. Consideration should be given to the possibility of including some of these aspects in the good manufacturing practice and marketing authorisation holders guidance currently being developed by the GMDP Inspectors Working Group.	GMDP IWG		Medium (1-3 years)

	Section 4.2.4 (page 60) Draft a questions-and-answers document for MAHs and manufacturers to emphasise regulatory authority expectations regarding the information and data provided to the medicinal product manufacturer or MAH by the holder of the CEP or ASMF. This document should ensure that MAHs can take responsibility for quality of the active substance and the medicinal product and cover areas such as: - clear and comprehensive confidentiality and quality agreements. - the conduct of investigations and risk assessments and provision of data and information to MAHs and regulatory authorities in case of quality issues. - the scope and depth of audits of API manufacturers by medicinal product manufacturers.	GMDP IWG		Medium (1-3 years)
2) Improve exchange of information between CEP or ASMF holders and marketing authorisation holders regarding impurity formation during the API manufacturing, the manufacturing process and materials used in manufacturing so that marketing authorisation holders can take full responsibility for the quality of their products, including APIs.	Section 2.4 (page 42) Review the way CEPs are used and consider how to better address the needs of marketing authorisation holders and regulators with a focus on increased transparency. This should include clarification of regulatory texts on responsibilities of the MAH in cases where API is covered by a CEP and those of CEP holders towards the MAHs regarding availability of dossier information. The information provided to the MAHs should not be less than the applicant's part of an ASMF on manufacturing process and impurities.	QWP/EDQM	QWP EDQM GMDP IWG EC	Medium (1-3 years)
	Section 2.4 (page 44) Consider amending the GMP guideline Part 1, chapter 7, to clarify how marketing authorisation holder can take full responsibility for the quality of their products including the API for marketing authorisations granted with reference to a CEP or ASMF.	GMDP IWG		Medium (1-3 years)
	Section 2.4 (page 42) Consider amending the guideline on the ASMF procedure to provide better transparency on impurities of the process to the MAH including knowledge on materials used in the manufacturing, when an ASMF is used.	QWP		Medium (1-3 years)
	Section 4.2.4 (page 61) Consider a change in the current legislation that would prescribe more information that active substance manufacturers need to disclose to manufacturing and importation authorisations holders and marketing authorisation holders (under confidentiality	EC		Long (3-5 years)

	agreements) as a basis for appropriate GMP audits as well as for robust risk assessment and quality investigations. In addition, consider legal obligations for active substance manufacturers and ASMF/CEP holders located outside the EU.			
	Section 4.2.4 (page 60) Draft a questions-and-answers document for MAHs and manufacturers to emphasise regulatory authority expectations regarding the information and data provided to the medicinal product manufacturer or MAH by the holder of the CEP or ASMF. This document should ensure that MAHs can take responsibility for quality of the active substance and the medicinal product and cover areas such as: - clear and comprehensive confidentiality and quality agreements. - the conduct of investigations and risk assessments and provision of data and information to MAHs and regulatory authorities in case of quality issues. - the scope and depth of audits of API manufacturers by medicinal product manufacturers.	GMDP IWG		Medium (1-3 years)
3) Raise awareness amongst manufacturing and importation authorisations holders, marketing authorisation holders, and CEP and ASMF holders of the importance of thorough development studies and of process and product knowledge in order to strengthen oversight of the entire supply chain.	Section 4.2.4 (page 61) Draft specific guidelines for industry in order to raise awareness amongst holders of MIAs, marketing authorisations, CEPs and ASMFs of the importance of thorough development studies and of process and product knowledge. These guidelines should also aim to increase awareness of the importance of strengthening oversight of the entire supply chain, including the development phases.	QWP	QWP EDQM GMDP IWG	Medium (1-3 years)
4) Strengthen quality agreements between marketing authorisation holders and API and intermediate manufacturers; require more effective audits of API manufacturers; improve the	Section 2.4 (page 42) Encourage improved quality agreements between MAHs and API manufacturers. These should be technical quality agreement rather than just purchasing agreements.	GMDP IWG	QWP EDQM GMDP IWG	Medium (1-3 years)
	Section 2.4 (page 42) Require better quality audits of API manufacturers by MAHs and improve the QP declaration system to ensure it is reliable.	GMDP IWG		Medium (1-3 years)

reliability of the qualified person declaration system so that marketing authorisation holders can exercise effective oversight of API and intermediate manufacturers; and improve supply chain traceability of API in finished products.	Section 4.2.4 (page 61) Consider a change in the current legislation that would prescribe more information that active substance manufacturers need to disclose to manufacturing and importation authorisations holders and marketing authorisation holders (under confidentiality agreements) as a basis for appropriate GMP audits as well as for robust risk assessment and quality investigations. In addition, consider legal obligations for active substance manufacturers and ASMF/CEP holders located outside the EU.	EC		Long (3-5 years)
5) Review requirements in the EU variations guideline for conditions/documentation for variations associated with adding or changing API manufacturers and manufacturing processes (including those documented in ASMFs and CEPs).	Section 2.4 (page 44) With regard to the EU variations guideline, the lessons learnt group recommends that the network convene a dedicated group to assess the need to update the classification guideline in terms of conditions/documentation for indents associated with adding or changing API manufacturers and manufacturing processes (including those documented in ASMFs and CEPs) to avoid misclassification or to better appraise impact of such changes in relation to the drug product quality. It is recommended to strengthen requirements for introducing a new source of API covered by a CEP to ensure the MAH has adequate knowledge of the quality of the active substance.	EC	EC Variation Working Group QWP EDQM	Medium (1-3 years)
6) Require marketing authorisation holders to include data on impurities and information from the API manufacturer in their dossier, irrespective of how the active substance documentation is submitted (e.g. via ASMFs or CEPs).	Section 2.4 (page 42) Consider requiring MAHs to generate and submit their own information on impurities rather than just relying on information provided by their API suppliers.	QWP	QWP EDQM GMDP IWG EC	Medium (1-3 years)
	Section 2.4 (page 43) Consider amending the guideline on the ASMF procedure to provide better transparency on impurities of the process to the MAH including knowledge on materials used in the manufacturing, when an ASMF is used.	QWP		Medium (1-3 years)
7) Ensure that marketing authorisation holders as well as manufacturing and importation authorisation holders are subject to effective, proportionate and dissuasive penalties (in accordance with Article 111 (8) of Directive 2001/83/EC) if product quality is not	Section 4.2.4 (page 62) Consider taking necessary measures to ensure that MAHs as well as manufacturing and importation authorisation holders are subject to effective, proportionate and dissuasive penalties (in accordance with Article 111 (8) of Directive 2001/83/EC) if product quality is not appropriately ensured.	EC	NCAs	Long (3-5 years)

appropriately ensured.				
8) The network publishes detailed information about potential sources of N-nitrosamine impurities and other cohort-of-concern compounds.	Section 2.4 (page 42) The network may publish a detailed questions-and-answers document with information on potential sources of N-nitrosamine impurities and of other cohort-of-concern compounds (e.g. azoxy compounds), including the conditions under which they can form.	QWP	QWP	Short (<1 year)
9) The Ph.Eur. Commission pursue its ongoing revision of the general monograph on substances for pharmaceutical use with the intention to include new requirements in order to mitigate the risks of N-nitrosamines.	Section 2.4 (page 42) The group suggested that the European Pharmacopoeia Commission consider additional recommendations for all active substances to avoid the risk of deliberate or inadvertent introduction of cohort-of-concern compounds in general in substances used in medicinal products along with appropriate control strategies. The group noted that the European Pharmacopoeia Commission has already started the revision process for the general monograph Substances for Pharmaceutical Use (2034) with the intention of including new requirements to mitigate the risk of N-nitrosamines.	EDQM	EDQM	Medium (1-3 years)
10) The network reviews the EU guideline on the chemistry of active substances with a view to providing recommendations on preventing the generation of cohort-of-concern compounds and implementing adequate contamination risk mitigation measures. Companies could be required to submit a justification for proposed manufacturing processes and mitigation measures as part of regulatory submissions.	Section 2.4 (page 42) Consider revision of EU's Guideline on Chemistry of Active Substances to: - Refer to the above-mentioned questions-and-answers document. - Recommend under S.2.6. developing processes that do not generate CoC compounds or minimising the contamination by implementing adequate risk mitigation measures. - State that all the used materials (starting materials, solvents, reagents, catalysts, processing aids, gases and materials used for quenching and work-up) should be disclosed clearly in both sections S.2.2 and S.2.3 and attributed unequivocally to the corresponding step or sub-step, stating also the intended function. In section S.2.2, the molar quantities of the applied reagents, catalysts and depletion agents should be stated and expressed in molar equivalents by relating to each starting material in the respective manufacturing step. Use of such materials in excess should be justified adequately unless demonstrated to be standard practice, e.g., NaOH in alkaline ester hydrolysis. - Require companies to justify the selected manufacturing process by discussing the presence or potential for formation of potentially mutagenic impurities, particularly CoC compounds. If the use of nitrosating agents is unavoidable within the synthetic process,	QWP	QWP EDQM EC	Long (3-5 years)

	then combination with nitrosatable compounds under conditions amenable to N-nitrosamine formation should be avoided unless adequately justified. Justification could include nitrosatability testing (WHO NAP test) or Ames testing of any relevant N-nitroso impurities. - Recommend that recycled materials be used only in the same process and preferably in the same step and that they should be avoided in the final manufacturing step. - Provide guidance on the possible contamination of raw materials (e.g., reagents and solvents) with nitrosating agents (e.g., NaNO2) which may be carried over from steps used to prepare them. Adequate acceptance criteria are to be defined and justified by carry over studies. - Revise the section on impurities to clarify the new systematic approach suggested by ICH M7 on mutagenic impurities that consists of hazard assessment of all organic impurities (database and literature searches for carcinogenicity and bacterial mutagenicity data) to classify impurities as non-mutagenic or mutagenic and apply the corresponding relevant acceptance criteria. Currently, applicants use an outdated approach to identify the alert structures in many cases. - Provide guidance on the quality and specifications of starting materials of API and intermediates that may contain N-nitrosamine impurities. - Recommend further guidance for specific option controls regarding CoC compounds under section S.3.2. of the guideline.			

11) ICH M7, to clarify how to control impurities, implement mitigation measures and set limits for cohort-of-concern compounds and to consider the retroactive application of the guideline to older products.	Section 2.4 (page 42) The network may consider amendment of the ICH M7 (R1) guideline to: - Clarify whether control options 2, 3, and 4 are applicable to cohort-of-concern compounds. The emphasis on process understanding, fate and purge is strongly supported. However, the lack of testing when there is a risk of such potent impurities being present is not supported. - Introduce recommendations from the Article 31 review of sartans in ICH M7 (R1), with the agreement of international partners, to take precautionary measures to mitigate the risk of the presence of N-nitrosamines during the manufacture and storage of all APIs and medicinal products. - Clarify the methodology that should be followed to calculate acceptable intake levels for CoC compounds. - Apply provisions of ICH M7 (R1) guidelines retroactively to all marketed products. - Consider expanding the list of CoC compounds to include additional compounds recognised by the European Food Safety Authority. - Clarify in section 5, that side reactions, including those unrelated to the active substance (e.g., between reagents and solvents) should also be considered when assessing potential impurities.	ICH	ICH SWP	Long (3-5 years)
12) ICH Q7, to include clarifications on the use of reagents or recovery processes that may be a source of cohort-of-concern impurities and on required mitigation measures.	Section 2.4 (page 43) Consider amending the ICH Q7 guideline on GMP for APIs to: - Include restrictions on the use of reagents or recovery processes that may be a source of CoC impurities. - Limit the use of recovered materials to the same process or even to the same step from which the material is recovered. Additional measures should be taken if they are used in final isolation steps. - Address the risk of contamination with highly toxic impurities when recovery is subcontracted to third parties, including listing such sub-contractors in the manufacturing section of the dossier. - Require process validation of recycling activities.	ICH	ICH GMDP IWG QWP	Long (3-5 years)

13) ICH Q9, to provide clarification and/or training material on what constitutes a risk assessment and how it should be performed.	Section 2.4 (page 44) Provide clarity in the ICH Q9 guideline on quality risk management as to how a risk assessment should be carried out. Due to uncertainties and gaps that became apparent during the implementation of the risk assessment for a high number of submissions, additional guidance on what constitutes a risk assessment and how it should be performed is considered necessary. It is envisaged that this would best be done by a questions-and-answers document and training materials.	ICH	ICH GMDP IWG QWP	Medium (1-3 years)
14) Clarify regulatory expectations for technology transfers and supplier qualifications.	Section 4.2.4 (page 61) Draft specific guidelines or a questions-and-answers document to clarify the regulatory expectations on GMP topics like technology transfer and supplier qualification.	GMDP IWG	GMDP IWG	Medium (1-3 years)
15) Clarify regulatory expectations for qualification and validation of facilities, equipment, utilities and processes for active substance manufacturing.	Section 4.2.4 (page 61) Make Annex 15 of the EU GMP guideline for medicinal products in relation to qualification and validation of facilities, equipment, utilities and processes also mandatory for active substance manufacturing.	GMDP IWG	GMDP IWG	Short (<1 year)
16) Ensure the retention and availability of samples of active substances and excipients used during the manufacture of a given medicinal product batch and consider the possibility of strengthening the legal basis for active substance sampling.	Section 4.1.4 (page 57) Review and amend legal provisions and guidelines, where necessary, to require that retained samples of active substances and excipients used during manufacture of a given medicinal product batch are available to GMP inspectors irrespective of whether or not the medicinal products or APIs are manufactured in the EEA.	GMDP IWG	GMDP IWG	Medium (1-3 years)
	Section 4.1.4 (page 57) Strengthen the legal basis for active substance sampling and elaborate a harmonised standard operating procedure for sampling of active substances during GMP inspections.	EC		Medium (1-3 years)
17) Ensure batch-specific supply chain traceability between API and finished products.	Section 3.3. (page 51) Provide additional guidance for marketing authorisation holders and medicinal product manufacturers on keeping records of batch specific supply chain traceability between the API and the finished products. For medicinal product manufacturers, this should be addressed either via a revision to the EC GMP Guide, or via a questions-and-answers publication in relation to the expected interpretation of the supply chain traceability requirements (as they apply to individual batches) of Chapter 1 (paragraph 1.10), Chapter 5 (paragraph 5.29) and Annex 16 (paragraph 1.7.2) of the EC GMP Guide.	GMDP IWG	GMDP IWG	Short (<1 year)

18) Strengthen the role of the European Directorate for the Quality of Medicines & HealthCare in central management of the testing workload (coordination, prioritisation of testing and communication) for dealing with major incidents.	Section 4.1.4 (page 57) Strengthen EDQM's role in central management of the testing workload (coordination, prioritisation of testing and communication) so that more inspectorates/OMCLs can participate in the sampling and testing programme.	EDQM	EDQM OMCL Network EC HMA	Long (3-5 years)
19) Ensure that official medicines control laboratories have adequate resources for testing and are equipped with modern instrumentation for analysing mutagenic impurities at trace levels.	Section 4.1.4 (page 57) Ensure that OMCLs have adequate resources to deal with the requested workload and are equipped with modern instrumentation for analysing mutagenic impurities at trace levels (liquid chromatography–mass spectrometry and gas chromatography–mass spectrometry etc.).	EDQM	HMA OMCL Network	Medium (1-3 years)
20) Support central sourcing of reference materials by the European Directorate for the Quality of Medicines & HealthCare for dealing with major incidents and finance this activity through an emergency fund.	Section 4.1.4 (page 57) Support central sourcing and dispatch of reference material by EDQM and finance these activities through an emergency fund.	EDQM	EDQM EC	Medium (1-3 years)
21) Facilitate coordinated market surveillance for products at risk of containing N-nitrosamine impurities once corrective measures are implemented by the industry.	Section 4.1.4 (page 57) Carry out a coordinated market surveillance exercise at the European level once corrective measures are implemented by the industry.	EDQM	EDQM NCAs OMCL Network	Long (3-5 years)
22) Implement best practices in communication and employ more communication tools (e.g. social media) to improve the content, clarity, presentation, timing and dissemination of communication. Improvements could include,	Section 5.5 (page 73) Include adequate information for patients and healthcare professionals in communication as quickly as possible, including specifics such as batch numbers (e.g. following recalls), available alternatives, and lists of medicines affected particularly if a recall is performed at the level of the patients. (Authorities such as EMA, EDQM and the EC which do not conduct recalls should also add such information to their communication or provide clear easy-to-find guidance as to where the information can	EMA	EMA NCAs EC EDQM	Long (3-5 years)

depending on the type of issue arising, giving more specific details (for example batch numbers of medicines affected if applicable), providing more context when explaining risks, and boosting cooperation among communication teams and other stakeholders.	be found.)			
	Section 5.5 (page 73) Take steps to ensure that patients can navigate websites and find appropriate information in a language and format suitable to them, for example, by keeping relevant information on homepages or specially set up dedicated pages during periods of intense public interest.	EMA		Long (3-5 years)
	Section 5.5 (page 73) Continue to implement best practices in communication and seek ways to improve the content, clarity and presentation of materials for target audiences.	EMA		Long (3-5 years)
	Section 5.5 (page 73) Build on coordination with international partners in the United States, Canada, Japan and Switzerland and consider expanding such coordination to other countries' regulators, such as regulators from Australia, China, India, Mexico, Russia and Brazil.	EMA		Long (3-5 years)
	Section 5.5 (page 73) Improve coordination of the timing of public communication, particularly when regulatory actions across the network are aligned.	EMA		Long (3-5 years)
	Section 5.5 (page 73) Increase cooperation between EDQM and NCAs, perhaps in the context of the HMA Working Group of Communication Professionals.	EMA		Long (3-5 years)
	Section 5.5 (page 74) Be better prepared to answer questions about the role of different parts of the EU regulatory system, for example, by preparing adequate briefing notes or publishing explanatory notes.	EMA		Long (3-5 years)
	Section 5.5 (page 74) Develop communication strategies for long-lasting communication challenges, for example, by adapting websites and webpages to ensure that they are suitable for dealing with evolving situations.	EMA		Long (3-5 years)
	Section 5.5 (page 74) Develop communication strategies for dealing with a lack of information (particularly in relation to media enquires) while investigations are underway. Such strategies may involve improving coordination to ensure that information available to one	EMA		Long (3-5 years)

	communication team is available to others.			
	Section 5.5 (page 74) Be active on social media and develop strategies to engage with users of different platforms.	EMA		Long (3-5 years)
	Section 5.5 (page 74) Consider establishing a hotline with dedicated staff might be useful in some cases.	EMA		Long (3-5 years)
23) Consider routinely creating a strategic group once a major incident comes to light (as was done in the sartans case).	Section 6.4 (page 77) Create a strategic group immediately following major incidents such as the detection of a genotoxic impurity in medicines and involve as many key impacted authorities as possible, including EDQM, OMCLs and regulators from main exporting countries. This would usually involve one authority volunteering to take on significant administrative tasks as was the case with the sartans incident when Health Canada took on responsibility for tasks such as setting up meetings and preparing agendas and minutes.	EMA	EMA	Short (<1 year)
	Section 6.4 (page 78) Update the procedure on global crisis management of ICMRA based on the outcome of this lessons learnt exercise. Main exporting countries such as China and India are members of ICMRA, which may serve as an important forum for dealing with quality incidents in future.	EMA		Short (<1 year)
24) Facilitate exchange of commercially confidential information between the network and other regulators.	Section 6.4 (page 77) Facilitate exchange of commercially confidential information between the network and other regulators on the basis that overriding public health interests should take precedence over confidentiality in situations where emerging health threats call for the urgent exchange of confidential information. Where no established confidentially arrangements exist, steps should be taken to create a time-limited arrangement for a specific incident. Consider concluding more confidentiality arrangements as appropriate, to reduce workload and also facilitate urgent exchanges of confidential information.	EMA	EMA NCAs EC	Long (3-5 years)
25) Exchange information, coordinate and share workload in relation to assessments, GMP inspections, sampling and testing,	Section 4.1.4 (page 57) Give OMCLs direct access to industry methods or standard operating procedures from international regulatory partners without requiring them to ask for extra permission. This should be considered in the overall incident management strategy.	EMA	EMA NCAs EC SWP	Long (3-5 years)

expert advice, regulatory decisions, communication and advice to patients.	Section 6.4 (page 77) Increase international cooperation on GMP to include more international agreements on exchange of information on GMP inspections with international partners and support EU NCA participation in collaborative inspection programmes of active substance manufacturers such as EDQM inspection programmes and the International Active Pharmaceutical Ingredient inspection programme.	EMA		Long (3-5 years)
	Section 6.4 (page 78) Exchange information, coordinate and share workload in relation to the root cause investigation of any incidents.	EMA		Long (3-5 years)
	Section 6.4 (page 78) Facilitate establishing validated methods for detecting and measuring impurities during an incident where an impurity is the cause of a quality defect. Relevant information (e.g. on methods) can be distributed among the network and international partners to improve efficiency. Batch testing tasks should be shared, and the work distributed to avoid duplication. This does require a common repository of data, with controlled access.	EMA		Long (3-5 years)
	Section 6.4 (page 78) Work together with international partners on the review of toxicological data and risk assessment to establish common acceptable limits for CoC impurities.	EMA		Long (3-5 years)
	Section 6.4 (page 78) Involve international partners in discussions at plenary meetings of EMA committees (such as the CHMP and the Pharmacovigilance Risk Assessment Committee) to share expertise during the handling of an incident.	EMA		Long (3-5 years)
26) Involve international partners systematically in relevant discussions at plenary meetings of EMA committees when major incidents occur requiring international cooperation (as was done during EMA's review of sartans).	Section 6.4 (page 78) Consider ways to improve coordination and, where possible, alignment in areas such as regulatory decisions, communication and advice to patients.	EMA	EMA	Short (<1 year)

27) a data tool for mutagenicity assessments for use by assessors at national competent authorities and EMA.	Section 2.4 (page 44) Establish an EU network-wide database for mutagenicity assessments for use by assessors at competent authorities. This would make alerting structures and proven mutagenic compounds visible to all assessors in the EU network.	EMA	EMA EC	Long (3-5 years)
28) existing databases for centrally and nationally authorised products with information on manufacturers of finished products and APIs in order to establish a link between API and finished product manufacturers and medicinal products across all EU markets, taking into account the potential use of ASMFs and CEPs.	Section 3.3 (page 51) Set up a database or improve current databases in order to establish a link between API and finished product manufacturers and medicinal products across all EU markets, taking into account the potential use of ASMFs and CEPs. This would enable the network to identify situations where a very large number of marketing authorisations across the EEA rely on an API from one API manufacturer. (The product management service module of the new 'SPOR' database that is currently under development may meet this requirement.)	EMA	EMA NCAs EC	Medium (1-3 years)
	Section 4.1.4 (page 56) Establish a central data repository linking active substance sources to individual products so that products or producers of potential concern can be quickly identified (e.g., using databases such as those for identification of medicinal products, Article 57 and EudraGMDP). Ideally, such a repository (for all European and national procedures) should also contain information on the ASMF or CEP version related to that active substance, where applicable.	EMA		Long (3-5 years)
29) a tool to capture and share information and decisions among EMA and NCAs when dealing with EU-wide quality incidents requiring a harmonised approach.	Section 3.3 (page 51) Develop an appropriate IT tool able to capture information updates and NCAs decisions in one centralised way as an incident evolves. Such a tool would have helped share key information and keep all relevant stakeholder groups updated in an efficient manner.	EMA	EMA EC	Long (3-5 years)
30) a tool for sharing information with international partners.	Section 6.4 (page 78) Exchange information, coordinate and share workload in relation to the root-cause investigation of any incidents.	EMA	EMA	Short (<1 year)

31) Provide training for quality assessors on the identification and chemistry of mutagenic impurities (particularly cohort-of-concern compounds), control strategies and non-clinical aspects.	Section 2.4 (page 44) Providing training via the EU Network Training Centre to network quality assessors on the identification and chemistry of mutagenic impurities, CoC compounds, control strategies and non-clinical aspects. Such training should make use of expertise of assessment teams including experienced quality assessors with a sound background in organic chemistry synthesis accounting for of the increasing complexity of active substance manufacturing processes.	EMA	EMA NCAs	Medium (1-3 years)
32) Provide training on the functioning and roles of the RAN and the IRN and ensure a common understanding of the management of cases that are considered a 'crisis'.	Section 3.3 (page 51) Provide clarity on respective roles of the RAN and the IRN so that they are clearly understood by both parties and in order to avoid duplication of effort.	EMA	EMA	Short (<1 year)
	Section 3.3 (page 51) Ensure that there is clarity and understanding across the network of exactly when an issue is to be formally considered a 'crisis'.	EMA		Short (<1 year)
33) Provide training to assessors to ensure that future guidelines on controlling impurities, particularly N-nitrosamines impurities, are taken into consideration when assessing pending authorisation or variation applications for older products.	Section 2.4 (page 44) Re-assess older API dossiers in pending authorization/relevant variation applications to align with current EMA/ICH guidelines and lessons learnt with nitrosamines.	EMA	EMA NCAs	Short (<1 year)
34) Develop a risk-based model for triggering pre-approval inspections of API manufacturers.	Section 4.2.4 (page 61) Develop a risk-based model for triggering pre-approval inspections of API manufacturers during the assessment of marketing authorisation applications, CEPs and ASMFs.	GMDP IWG	GMDP IWG	Medium (1-3 years)
35) Develop a harmonised operating procedure for the sampling of active substances during GMP inspections.	Section 4.1.4 (page 57) Strengthen the legal basis for active substance sampling and elaborate a harmonised standard operating procedure for sampling of active substances during GMP inspections.	GMDP IWG	GMDP IWG	Medium (1-3 years)
36) Prepare guidance for GMP inspectors to verify during inspections of API manufacturers the measures taken to reduce the risk of presence of unexpected impurities.	Section 4.2.4 (page 60) Draft an aide-mémoire for GMP inspectors to verify during inspections of API manufacturers that a site has a clear control over activities to reduce the risk of presence of unexpected impurities. The aide-mémoire should cover areas such as: - Cross-linking between non-GMP activities (e.g., research and process development and	GMDP IWG	GMDP IWG	Medium (1-3 years)

	process transfer) and the operations performed under GMP (e.g., manufacturing process and analytical methods validation, and the routine manufacturing). - Company oversight over impurity profiles for the API as well as any changes to this profile as a result of modifications of the manufacturing process over time as well as compliance with regulatory registration. - Companies' awareness of ICH Q11 and ICH M7 with regard to assessment and control of impurities/mutagenic impurities. - A robust change control management oversight in case of introduction of new molecules or process changes related to products already manufactured at the site. - Validation of the recovery of solvents and control of raw material. - Companies' approach to investigations of unknown peaks during quality control testing. - Sampling APIs according to a common procedure when there are grounds for suspecting non-compliance with GMPs (see recommendations under section 5.2). - Compliance of manufacturing operations with the relevant regulatory files. - Outsourcing of critical GMP activities, such as solvents recovery and manufacture of intermediates. In the case of contract manufacturing organisations, these aspects should be appropriately covered in quality agreements with the contract givers, in the context of outsourced activities review.			
37) Develop a better strategy for identifying parallel imported/distributed products when dealing with quality defects.	Section 3.3 (page 51) Review and improve strategy for identifying parallel imported/distributed products, particularly due to the fact that some products were labelled with originator's brand names despite the fact that the source packs of the parallel imported products were generic versions of the branded products.	GMDP IWG	GMDP IWG	Medium (1-3 years)
38) Revise existing procedures in order to establish a procedure for the RAN and inspectors to share feedback when inspections are required during the management of critical quality defect cases.	Section 3.3 (page 51) Revise existing procedures in order to establish a procedure for feedback between RAN and inspectors during critical defect cases conducting related GMP inspections when needed.	GMDP IWG	GMDP IWG	Medium (1-3 years)

39) Ensure that there is an agreed and harmonised definition for the term 'quality defect' across the network.	Section 3.3 (page 52) Ensure that there is an agreed and harmonised definition for the term 'quality defect' across the network and ensure that this is reflected in the relevant Compilation of Community procedures.	GMDP IWG	GMDP IWG	Medium (1-3 years)
40) Improve the system for maintaining a single contact list for the various groups within the European network involved in managing incidents.	Section 3.3 (page 51) Convert the European Common Directory contact list into a Eudranet mailbox in order to ensure that all relevant contacts are always copied in key correspondence.	EMA	EMA	Short (<1 year)
	Section 4.1.4 (page 57) Establish and maintain a contact list (primary and deputy contact points) for the various groups involved in managing incidents (such as the IRN and RAN). Establish new IT tools to share documents with restricted safe access and define responsibilities for creating and updating discussions inside the tool.	EMA		Short (<1 year)