EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Overview of comments received on recommendations in report on lessons learnt from presence of *N*-nitrosamine impurities in sartan medicines

Commenting stakeholder organisations
Association of the European Self-Care Industry (AESGP)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
European Heart Network (EHN)
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
European Organisation for Rare Diseases (EURORDIS)
Medicines for Europe (MfE)
Pharmaceutical Group of European Union (PGEU)

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Stakeholder	Recommendation[1]	Comment
AESGP	1	Aligned with EFPIA comment.
AESGP	2	We note the recommendation but we wonder how this would work with the CEP process. We fear that if API suppliers have to provide information both to EDQM for the CEP and to the MAH this defeats the purpose of the CEP process. We indeed support the role of the EDQM in evaluating the API Manufacturers proprietary information and strengthening the use of the CEP to identify risks that should be considered in the finished product.
AESGP	3	We believe this is not an issue of awareness as MAH is already well aware of the responsibility he bears for the medicinal product. However, in line with the underlying principle of these processes, for the API manufactured with ASMF or CEP, the MAH needs to be able to rely fully on the API supplier.
AESGP	4	We support the proposal but we believe this is not easily transposable in reality. As reported in our earlier response to the GMDP survey on audits, auditing is not a simple process. It can happen that due to the continuous audit burden in terms of time (reluctance to allow a minimum 2-day audit), risks and costs, API manufacturers try to restrict the onsite audit support for auditors, typically by restricting frequency (sometimes difficult to respect the 3-year cycle), audit time (this is often experienced in European API sites), limited access to documents or parts of the facility, difficulties in signing the confidentiality agreement, obliging company to carry out a joint onsite audit with several other companies being present at the same time, refusal of audit (based on low volume/quantity of material purchased). Audit fees may be applied to individual auditors (e.g. £ 5,000 to be allowed on a site). Other restrictions such as limiting access to facilities, documents or personnel may also be experienced.

[1] Recommendation number 38 has been removed from the report on lessons learnt from presence of *N*-nitrosamine impurities in sartan medicines, as the issue raised had been addressed satisfactorily before finalisation.

		In our response to the survey, we also added a number of suggestions to make audits more effective.
AESGP	5	We are aligned with the EFPIA response.
AESGP	6	Agree with EFPIA's response.
AESGP	7	Penalties are indeed enshrined into the legislation and should be applied in case of faulty behaviour and clear breach of the legislation. We believe CEP-ASMF are strong tools which should be reinforced.
AESGP	8	We are aligned with EFPIA's comment.
AESGP	9	We are aligned with EFPIA's comment.
AESGP	10	We are aligned with EFPIA's comment.
AESGP	11	We are aligned with EFPIA's comment.
AESGP	12	We are aligned with EFPIA's comment.
AESGP	13	We are aligned with EFPIA's comment.
AESGP	14	We are aligned with EFPIA's comment.
AESGP	15	We are aligned with EFPIA's comment.
AESGP	16	We are aligned with EFPIA's comment.
AESGP	17	We are aligned with EFPIA's comment.
AESGP	18	We are aligned with EFPIA's comment.
AESGP	19	We are aligned with EFPIA's comment.
AESGP	20	We are aligned with EFPIA's comment.
AESGP	21	We are aligned with EFPIA's comment.

AESGP	22	We are aligned with EFPIA’s comment.
AESGP	23	We are aligned with EFPIA’s comment.
AESGP	24	We support this recommendation provided their CCI nature is dully respected and enforced by all regulators receiving this information by existing confidentiality agreements between the authorities sharing such information.
AESGP	25	We support provided the exchange of sensitive information is done between authorities having confidentiality agreements in place.
AESGP	26	We are aligned with EFPIA’s comment.
AESGP	27	We are aligned with EFPIA’s comment.
AESGP	28	Information on supply chain is commercially sensitive. We support with the understanding that access to information on the database is possible by the authorities only. Companies would have access only to entry they provide.
AESGP	29	What is meant by ‘tool ‘ here ? Is that a database? In the current pandemic, we already see that sharing data on needs of which market is complicated and therefore we would be cautious on the feasibility of such tool. To be efficient such tool would need to contain very detailed data on the quality part of the dossier which would make it even more sensitive.
AESGP	30	We refer to our above comment and to the highly sensitive degree of those information; we refer to our comments on confidentiality agreements made earlier. We are also unclear as to what tool this could be.
AESGP	31	We are aligned with EFPIA’s comment.
AESGP	32	We are aligned with EFPIA’s comment.
AESGP	33	We are aligned with EFPIA’s comment.
AESGP	34	We are aligned with EFPIA’s comment.
AESGP	35	We are aligned with EFPIA’s comment.

AESGP	36	We are aligned with EFPIA's comment. Such a guidance already exist in some NCAs (eg Germany) and therefore we would encourage sharing of best practice to inform such EU guidance document.
AESGP	37	We are aligned with EFPIA's comment.
AESGP	38	We are aligned with EFPIA's comment.
AESGP	39	We are aligned with EFPIA's comment.
AESGP	40	We are aligned with EFPIA's comment.
AESGP	41	We are aligned with EFPIA's comment.
EFPIA	General comment	The 'Lessons learnt' report provides information about the scientific root causes of nitrosamine potential formation in sartans. It will be useful if the Article 5(3) process has evaluated the apparent delay in identifying the issue in sartans (as noted in 'Main concerns from patients and the general public') to identify the root cause and appropriate preventive actions. EFPIA notes that ICH M7 was not in place at the time of the development or assessment of the sartans. As this document provides specific guidance on genotoxic/mutagenic impurities, the chronology of the changes leading to the presence of N-nitrosamines in some sartans in relation the implementation of M7, and other guidelines, is important to understand.
EFPIA	General comment	2. Communication to the public is addressed in the 'Lessons learnt' report and some improvements are identified in recommendation 22. EFPIA believes that it is also important to consider the effectiveness of communications to different industry sectors as the issue developed, beyond those MAHs and companies involved in sartans manufacture and supply. The subsequent decision to issue an industry-wide request to assess and confirm the safety of all approved, synthetically-derived medicinal products provided a critical opportunity for collaboration to determine the most expedient approaches to scientifically investigate, understand and effectively manage the potential sources of N-nitrosamine impurities. The request requires globally-aligned, consistent and concerted action across the pharmaceutical supply chain, and such a complex, resource-intensive activity benefits from strong industry - regulatory engagement.

EFPIA	General comment	3. The recommendations concerning guideline revision include several that necessitate revisions to ICH guidelines. The sartans issue related to global supply chains with regulatory oversight by multiple competent authorities, and therefore EFPIA considers it is important that improvements are agreed and adopted globally. Similarly, European regulatory guidelines and processes (including, for example, ASMF requirements, CEP process, and MAH responsibilities) need to be understood by industry and regulators in Third countries. Scientific understanding of the risk factors for the presence of nitrosamines in medicinal products continues to develop, and it is important that this knowledge is gathered from all stakeholders to ensure that regulatory requirements are driven by the science, focused and proportionate to the risks.
EFPIA	1	EFPIA support this proposal and note the related recommendations recent EMA Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders – EMA/457570/2019. Moreover, EFPIA believe many of these aspects are made clear in ICH Q7 and Q10, and hence highlight the need to enforce compliance with current expectations and recommend that this gap is addressed as part of the lessons learned. Any further clarifications should be globally-harmonised and take into account learnings from the current ongoing assessment of nitrosamine risks.
EFPIA	2	EFPIA support this proposal and note that controls and requirements in ICH guidelines (e.g. ICHQ7, Q9, Q11 and M7) if appropriately applied should identify and address risks from nitrosamines, as has been demonstrated in many scenarios. EFPIA believe that such proposals should therefore be developed with industry and recommend that they are included as part of the article 5(3) review.
EFPIA	3	EFPIA support this proposal and note that that controls and requirements in ICH guidelines (e.g. ICHQ7, Q9, Q11 and M7) if appropriately applied should identify and address risks from nitrosamines, as has been demonstrated in many scenarios. EFPIA believe that such proposals should therefore be developed with industry and recommend that they are included as part of the article 5(3) review.

EFPIA	4	EFPIA support this proposal and note the related recommendations recent EMA Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders – EMA/457570/2019. EFPIA also note that controls and requirements in ICH guidelines (e.g. ICHQ7, Q9, Q11 and M7) if appropriately applied should identify and address risks from nitrosamines, as has been demonstrated in many scenarios. Hence, an additional learning should consider which elements of regulatory inspections of API manufacturers and MAH should be strengthened as a result of the Sartans issues discovered by MAHs and regulators.
EFPIA	5	EFPIA support a review of the EU variations guideline EFPIA note that any future changes to the variations guidelines should be aligned with the science and risk based approaches described in ICH Q9, Q10, Q11, Q12 and M7. EFPIA also note there could be further consideration of change management particularly with respect to the CEP procedure.
EFPIA	6	EFPIA believe the current CEP process is essential for medicines supply. It is important that the CEP process, supported by appropriate supplier quality oversight, remains a strong and robust element of the future EU regulatory system.
EFPIA	7	EFPIA support this proposal.
EFPIA	8	EFPIA support this proposal. EFPIA also note that the full understanding of where and how nitrosamines may form, their stability and purge, will be significantly increased once the ongoing risk assessment is complete. In addition, significant information on the true hazards of nitrosamines more structurally complex than the simple molecules cited in the report is needed. Such information on nitrosamines and other cohort-of-concern compounds should inform risk assessments and, ultimately, ICH M7 guidance on nitrosamines. For example EFPIA refer to the paper on azoxy compounds, published in 2013: Potentially mutagenic impurities: Analysis of structural classes and carcinogenic potencies of chemical intermediates in pharmaceutical syntheses supports alternative methods to the default TTC for calculating safe levels of impurities)

		Regul Toxicol Pharmacol.2013 66 (3), 326 (https://doi.org/10.1016/j.yrtph.2013.05.005)
EFPIA	9	EFPIA does not support this proposal – risks from nitrosamines are specific to individual drug products and any control strategy should be assessed based on process understanding in line with ICH principles. See EFPIA's separate and detailed response to EDQM provided regarding this proposed general monograph revision.
EFPIA	10	EFPIA support this proposal, and consider the following as key points that could be clarified: • Control of nitrosamine synthetic impurities is not a new phenomenon, and there are many examples of applicants appropriately identifying the risk and discharging through control strategies (e.g based on control through purging and appropriate controls aligned with Q7, Q10, Q11 and M7 principles). • Key chemistry that can form nitrosamines can be suitably utilised, provided the risk is properly considered and controlled. Hence, prevention of specific chemistry is not considered appropriate, nor aligned with ICH principles. Overall, the EU guideline on the chemistry of active substances should align with the principles of ICHQ11, which emphasises the need to evaluate potential impurities, identify which are critical quality attributes of the active substance and to establish an holistic control strategy (including through the design of the manufacturing process). EFPIA encourages the EMA to consider the principles of ICHQ11 and M7 as key to further updates.
EFPIA	11	EFPIA are supportive of the proposal to further clarify the guidance in ICH M7 related to nitrosamine control etc. EFPIA believe that the current ICH M7 guidance expectations for application to older products were carefully considered and should be revised only if seen as necessary by the ICH M7 EWG. The 'problem' with the sartans incident was not, we believe, driven by a failing of the ICH M7 guideline but by a manufacturer not being aware of the risk of potential presence of a nitrosamine. The principles of ICH M7, if appropriately applied, would have prevented the sartan problem arising from the process chemistry that was being utilised. Given that ICH M7 currently states that the guidance is applicable to established products where there is cause for concern (e.g. an impurity that where the structure is in the cohort of concern such as an N-nitrosamine)

		the sartans manufacturing process risk would have been covered by ICH M7 expectations.
EFPIA	12	EFPIA is supportive of this proposed action for more clarification and learning on sources of CoC impurities, based on sound risk assessment and updated by a process which maintains global alignment and global stakeholder understanding. However, such clarification should stop short of defining specific actions for mitigation, as these would likely be case and chemistry dependent.
EFPIA	13	EFPIA understand that the ICH Q9 guidance will be considered for further amendment / clarification and are supportive of this action being taken through ICH. Nonetheless, EFPIA also note that the M7 risk assessment process has already been beneficial. The development of sartans predated ICH M7 and Q9 guidance and the principles of those guidance would have significantly addressed some of the issues 'learned' from the incident.
EFPIA	14	EFPIA note that these are two distinct topics that would best be considered separately. EFPIA note that technology transfer inside the auspices of a company may have significantly different lifecycle considerations to address than technology transfer to an external partner. MAHs use a variety of tools and information to perform supplier qualification (e.g. due diligence, licence reviews, inspection history, and quality audit). The flow of information from external suppliers to MAHs could be improved. EFPIA would welcome a regulatory mechanism to require the CEP holder to provide additional information to the MAH. ICH Q10 provides a good overview of how technology transfer forms an important part of a Pharmaceutical Quality System and 'WHO guidelines on transfer of technology in pharmaceutical manufacturing' provide good details in section 5 that relate to manufacturing of starting materials (section 5.5), active pharmaceutical ingredients (section 5.6), and excipients (section 5.7). Analytical method transfer also seems well covered by section 6 of the WHO document as well chapter 6 of the EU GMP guidelines. EFPIA understand why EMA may want to clarify some specific regulatory expectations for technology transfer. We recognise there may be opportunities for improvement especially where it may help to improve transparency between third parties and industry partners as technology transfer to or from an external partner may have an additional level of complexity.

EFPIA	15	EFPIA have no objections to such considerations being undertaken but note that many regulatory inspections of API manufacturing have been conducted against existing expectations as set out in ICH Q7 without significant concern being expressed about such fundamental matters. Hopefully such considerations will be focussed on those aspects identified as root causes of concerns from this report and not lead to root and branch 'new expectations' but rather to a reinforcement of current cGMP expectations.
EFPIA	16	EFPIA believe that annex 19 of the current EU GMPs provides sufficient details concerning reference and retention samples of both active substances and excipients held at the MAH. It is important that any specific changes to the current requirements such as increases to sample size, storage requirements, and retention times, remain in line with generally accepted international requirements.
EFPIA	17	EFPIA consider this to be a current expectation. EFPIA believe that MAHs should sufficiently document their supply chains for active substances and excipient suppliers in accordance with EU GMP annex 16. EFPIA have no concerns with this being reinforced as an expectation. EFPIA do not think GMP expectations require significant change.
EFPIA	18	EFPIA support this proposal, provided this is adequately resourced. EFPIA believe that EDQM CEP process optimisation for these learnings is a fundamental matter of higher short-term priority.
EFPIA	19	EFPIA support that the network should have such capability in place within the network, and a very clear role and remit. Collaboration with industry, who have experience of running and validating such methods, could optimally support rapid establishment of methodology and also understanding of potential issues.
EFPIA	20	EFPIA support this proposal.
EFPIA	21	EFPIA support this proposal, and note this should be after the establishment of the 'improved' guidances as discussed above. Further clarity is needed on what these surveillance exercises are intended to be to provide significant comment. Such coordinated market surveillance needs to be on a globally coordinated basis.

EFPIA	22	EFPIA agree that improved stakeholder communication would be a useful action. This should involve some 'two way' mechanisms for communication and sharing understanding (including with industry, beyond the 'affected MAHs'). Optimal communication is when a message is provided that is timely, transparent and balanced in its consideration of risk.
EFPIA	23	EFPIA support this proposal. A role for ICMRA and involvement of industry are strongly recommended.
EFPIA	24	EFPIA support this proposal.
EFPIA	25	EFPIA support this proposal. This was a positive aspect of the sartans issue management, and should be strengthened (e.g. the development of different analytical methods by different regulatory bodies).
EFPIA	26	EFPIA support this proposal
EFPIA	27	EFPIA support this proposal provided the database is fully accessible to all stakeholders and is built from established globally recognised 'good practice' systems. Any such data tool be transparent and be developed collaboratively with involvement of academic and industry expertise. Industry Associations would appreciate the opportunity to contribute to development of a data tool for mutagenicity assessments for use by assessors at national competent authorities and EMA. This could be, for example, via data sharing initiatives concerning N-nitrosamines coordinated by independent organizations and companies, and efforts to continue to refine and improve the predictivity of existing QSAR approaches and develop sub groups of class specific N-nitrosamine thresholds. Industry Associations would support the continued refinement of publicly available databases (e.g. Lhasa Carcinogenicity Database or the Original Carcinogenic Potency Database) that would support mutagenicity assessments, rodent carcinogenicity assessments (i.e. derivation of TD50, BMD10 values) but also definition of acceptable intakes for N-Nitrosamine impurities (based on consistent read across approaches) that should be transparently shared with the companies and in the public domain.

EFPIA	28	EFPIA support this proposal and note that provision of risk assessment information on API manufacturing is a useful component of the ongoing quality risk management.
EFPIA	29	EFPIA support this proposal and notes that it could be an internationalised tool, addressing existing concerns with different systems and expectations across the EU and globally.
EFPIA	30	EFPIA support this proposal
EFPIA	31	EFPIA support this proposal and note that alignment of such training with principles of ICH M7, Q9, Q11 etc and inclusion of the emerging knowledge gained from the ongoing risk assessment process will be essential.
EFPIA	32	EFPIA support this proposal
EFPIA	33	EFPIA support this proposal and note that alignment of such training with principles of ICH M7, Q9, Q11 etc and inclusion of the emerging knowledge gained from the ongoing risk assessment process will be important.
EFPIA	34	EFPIA support this proposal and the risk factors that will support such a proposal. EFPIA also request that such inspectional activities are aligned globally with mutually recognised international regulations.
EFPIA	35	EFPIA support this proposal.
EFPIA	36	EFPIA support this proposal. There should be clear expectations to enable consistent implementation, developed in line with mutually recognised international regulations.
EFPIA	37	EFPIA support this proposal.
EFPIA	38	EFPIA support this proposal. EFPIA note that development of guidance includes an important 'draft comment phase' which should will be important in this case.
EFPIA	39	EFPIA support this proposal.

EFPIA	40	EFPIA support this proposal and note such definitions should be globally aligned.
EFPIA	41	EFPIA support this proposal.
EHN	22	It should be mentioned somewhere that professionals such as physicians and pharmacists should be informed by their networks prior the media and therefore prior the patients. A situation where the patient has to go to the doctor and to the pharmacist back and forth and fight for the correct information/drug is unacceptable and must be avoided by all means. To my opinion it is also relevant to establish an information system that will kick in as soon as a situation that needs to be published has occurred. This includes international health care associations and societies, patient associations who again have to make sure that they are ready to immediately translate and pass on the information.
EHN	22	Include "and putting risk into context" into recommendation.
EUCOPE	1-7 14-17	Recommendations are focusing on API manufacturing & control. However, it is known, as part of the EMA risk evaluation, that the Finished Drug Product process (including packaging and cross contamination from other processes run on the same line) need to be considered. Recommendations on this latter would thus be expected. We were wondering whether EMA could include some instructions related to the Finished Drug Product under the headings "Guidelines on responsibilities of marketing authorisation holders and manufacturers" and/or "Guidelines on good manufacturing practice"?
EUCOPE	1-9 11-13	Lessons Learnt document makes proposals for updating several ICH guidances, including ICH M7 and ICH Q7, however, the current 'ICH Q3A' and 'EMA Chemistry of Active Substances' are written in a way that implies that only the drug substance synthetic route is the source of impurities. There is only a brief mention of side reactions between reagents or other chemical reactions that could occur that are unrelated to the synthesis, nor potential for inherent contamination of materials etc. (which was the case of the contamination for the sartans). Recommendations A 1-9 or 11-13 should thus be amended to discuss this.

EURORDIS	General comment	Page 1. Unclear if this was due to a recent change, or to the manufacturing process since the very beginning of the production of sartans. Later in the document it is explained, but maybe to indicate here that these impurities might have been present since the beginning of the production of sartans, although undetected.
EURORDIS	22	There were some reports of discrepancies between products to be recalled or not, in pharmacies or on national authorities websites.
EURORDIS	General comment	Technical Background p73. Maybe to add some advice to developers of medical apps (e.g. Web-RADR) where patients can sign in products they're using and receive regulatory information, i.e. two-way communication. This could facilitate the recall of relevant packs.
MfE	General comment	We would like to bring to the attention the details of the Joint Industry Letter related to the Article 5 review on nitrosamines as forwarded the EMA on 21 May 2020. The content of this letter is highly applicable to the overall lessons learnt on nitrosamines in general.
MfE	General comment	In addition to training for quality assessors, improved inspection programs and centrally managed testing, HAs should continue towards strengthening their oversight over the quality of drugs and APIs, as a necessary supplement to MAH's oversight and responsibility for the quality of drugs. Further detailed guidance on the exchange of data between MAHs and APIMs should be provided, and guidance on contamination and quality assurance related issues should be strengthen within GMP related guidelines, rather than (solely) within the guidelines for registration documentation content. This to strengthen the understanding of the ultimate responsibilities by MAHs and the contribution and readiness of the API manufacturer to provide and update the relevant scientific information.
MfE	2	We propose that HAs would provide detailed guidance, to clearly define which information /the level of data that should be exchanged between CEP or ASMF holders and MAHs regarding impurity, manufacturing process and materials used in manufacturing so that MAHs can take full responsibility for the quality of their products, including APIs. General recommendation may not be sufficient to ensure harmonized understanding on the level of data that should be exchanged and consequently sufficient level of data being exchanged.
MfE	4	Within the supply chain process the audits and effective oversight of intermediates' manufacturers are typically API manufacturer's responsibility and contractual obligations.

MfE	6	While inclusion of API related data within FDF registration dossiers may facilitate MAH's oversight over API impurities, this measure should not hamper submission of changes during the lifecycle of the product. More specifically, we believe including API related information to the MAH dossier is not necessary. API manufacturer should share the data with MAH, however including detailed API data in the FDF dossier might cause additional regulatory burden and contradict the principle of DMF confidentiality. Especially in the case of CEP, this approach would actually oppose the CEP being a stand-alone API application that assures confidentiality of information and facilitates submissions.
MfE	10	Requirements and guidance on implementation of adequate contamination risk mitigation measures should be part of GMP related guidelines (e.g ICH Q7, ICH Q11) rather than the guideline for ASMF content (guideline on the chemistry of active substances). Cross-contamination related risks should be controlled with adequately established quality and GMP systems and checked properly by audits and inspections, rather than as a part of regulatory submission.
MfE	11	It is considered that ICH M7 guideline already provide clear guidance on acceptable control option for (potentially) mutagenic impurities, including cohort of concern impurities. Furthermore, ICH M7 clearly states that retrospective application of the M7 Guideline is not intended for marketed products unless there are changes made to the synthesis. Those substances and products are well established and considered as qualified by use, and efforts of the industry and HAs should be focused on establishment of adequate control of new, unknown (unapproved) products. The retroactive application of limits for older products that are currently on the market should not be so strict as for the ones applying for new molecules. Safety profile of older products should be taken into consideration in order to avoid an overkill approach
MfE	33	We propose to publish the training material on the EMA / CMDh website to get the best use of it by the industry as well.

PGEU	22	In particular, we welcome the recommendation to implement best practices in communication to the public (including healthcare professionals) and to employ more communication tools (e.g. social media) to improve the content, clarity, presentation, timing and dissemination of communication. Here we would like to emphasize the vital importance of communicating to healthcare professionals well in advance of communicating to the general public so that the negative impact on supply and potential panic outbreak with patients can be reduced and managed in the best possible way. In addition, as suggested in the recommendations, improvements could include giving more specific details (for example batch numbers of medicines affected if applicable) to pharmacists and prescribers and boosting cooperation among communication teams and other stakeholders. This information would be very useful for healthcare professionals to reduce the impact on patients as much as possible and be able to address their concerns. PGEU and its member organisations are eager to work closely with the communication teams of national and European competent authorities to ensure effective and rapid dissemination of the communications to individual pharmacists across Europe.