HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY

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

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Overview and recommendations

Overview

In mid-2018, the European medicines regulatory network[1] became aware of the presence of *N*-nitrosamines in sartan[2] active pharmaceutical ingredients (APIs) and instituted regulatory actions across the EU, including recalls of some medicines from pharmacies and measures to prohibit the use of APIs from certain manufacturers.

A subsequent review of sartans by the European Medicines Agency (EMA) found that the risk from the *N*-nitrosamine impurities (which are classified as probable human carcinogens) was low.[3] In the vast majority of sartan medicines, *N*-nitrosamines were either not found or were present at very low levels. Given the greater risk to patients from stopping their treatments, regulators advised patients not to stop their sartan treatments without speaking with their healthcare professional.

As for the source of the impurities, EMA's review concluded that the use of the solvent dimethylformamide together with sodium nitrite in the presence of an acid led to the formation of *N*-nitrosamines during the manufacture of sartan APIs. There was also a potential for contamination from other sources, including solvents, reagents and manufacturing equipment already contaminated with *N*-nitrosamines. Taking these root causes into account, the review set out new requirements for marketing authorisation holders (MAHs) of sartan medicines, including the requirement to test their products for *N*-nitrosamines and make necessary changes to their API manufacturing processes.[4]

The sartans case and the subsequent review of sartans in the EU raised a number of important issues. First, it had become clear that the potential for *N*-nitrosamine formation had not been recognised during the development or evaluation of sartan medicines. Second, although the risk to patients was considered low, some API batches contained levels of impurities that necessitated regulatory actions, such as recalls. Third, the incident caused significant concern among patients and the general public with possible implications on adherence to treatments.

In May 2019, the network embarked on a lessons learnt exercise to consider ways to prevent unexpected impurities such as *N*-nitrosamines from being present in human medicines and to better manage such cases should they occur in the future. Drawing on the experience from the sartans incident, the lessons learnt group made recommendations covering prevention, incident management, market surveillance, communication and international cooperation.

[1] The network comprises the European Commission, the European Medicines Agency, national competent authorities in the European Economic Area and the European Directorate for the Quality of Medicines & HealthCare.

[2] Also known as angiotensin II receptor blockers.

[3] The review was carried out under Article 31 of Directive 2001/83/EC.

[4] See more details of the outcome of the review on EMA's website.

The recommendations from this exercise are those of regulators in the European regulatory network. Other stakeholders, such as the pharmaceutical industry, are encouraged to conduct their own exercises and consider what additional actions they should take.

Preventing N-nitrosamines from being present in medicines

The European network has several guidelines aimed at controlling impurities in APIs and finished products, many developed in conjunction with international partners under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In addition, the European Pharmacopeia sets out standards for the quality of medicines and their ingredients which are legally binding within the EU.

These guidelines provide detailed information on how companies should assess the risks of impurities being present in their products, how they should report such risks to authorities and measures they should take to mitigate them. One such guideline, ICH M7 (R1), which complements others such as ICH Q3A, ICH Q3B, ICH Q3C and ICH Q3D, provides information on *N*-nitrosamines which are considered part of a 'cohort of concern' because of their mutagenic potency.

Despite available guidance, the potential for *N*-nitrosamine impurities in sartans was not recognised during the development, manufacture and evaluation of medicines subsequently found to contain them. In addition, MAHs, who usually outsource API manufacturing, may not have had sufficient oversight of the manufacturing processes.

The lessons learnt group evaluated relevant guidelines and determined that certain amendments and clarifications would help both companies and regulators better assess the potential for impurities such as *N*-nitrosamines. In addition, the group proposed further training for regulatory assessors in the network to improve the chances of identifying potential impurities during the evaluation of marketing authorisation applications and certificates of suitability (CEPs).

Responding to the presence of unexpected impurities

The network reacted swiftly once the presence of *N*-nitrosamines became known, taking immediate measures to protect patients and the quality of medicines in the EU. These measures included coordinating recalls of medicines across the EU, prohibiting the use of affected APIs in EU medicines (via CEP suspensions or issuance of certificates of non-compliance with good manufacturing practice (GMP)), testing of medicines on the market, inspecting manufacturing sites and conducting an EU-wide review of sartans medicines.

The scale of the actions taken by regulators and the speed with which they were carried out demonstrated the network's ability to coordinate activities of its constituent parts effectively and take a leading role in the global response to major incidents. The Rapid Alert Network (RAN) and the Incident Review Network (IRN) served as important forums in this regard, allowing the network to take timely decisions to protect the quality of EU medicines.

The experience gained from the sartans case affords the network the opportunity to assess and improve the efficiency of its regulatory responses to such incidents. To this end, the lessons learnt group identified areas for improvement. These include the development and use of improved technology to obtain information and track activities within the network and the review of guidelines and procedures for sampling and testing of products on the market. With respect to sampling and testing, additional resources for official medicines control laboratories are required to enable the network to deal with unexpected impurities potentially affecting several medicines.

Communicating with patients and healthcare professionals

The presence of *N*-nitrosamines in sartans led to significant public interest. In the early stages, a major challenge faced by communication teams within the network was the dearth of information about the potential risk to patients and medicines that could be affected. Patients across EU (and the wider world) were understandably concerned about the safety of their medicines, and healthcare professionals needed adequate information to be able to advise them.

The network reacted by communicating once recalls of medicines began. Using lines-to-take, the network delivered consistent messages to the public and media and developed more reassuring messages as additional information on the risk to patients became available. Among the important messages delivered by the network were that the risk to patients was very low, that most sartans tested had no detectable *N*-nitrosamines or had very low levels, and that patients should not stop taking their medicines without speaking to a healthcare professional.

The lessons learnt group concluded that public communication from regulators could be improved by including in their communication materials more specific details such as batch numbers (e.g., following recalls) and available alternatives. Other ways to improve the impact of public communication include working more closely within the network, using more tools such as social media, and taking extra measures to reach target audiences.

Cooperating with international partners

When the presence of *N*-nitrosamines in a sartan API came to light in late June 2018, it was clear that the findings would have far reaching and immediate global implications. The concerned APIs were used in medicinal products distributed in many regions and countries in the world, a situation that necessitated widespread recalls and coordinated regulatory actions.

In response, the European regulatory network enhanced its cooperation with international partners using both new and established tools. An ad hoc 'Angiotensin II Receptor Blockers (ARB) International Strategic Group' led by Health Canada was created to coordinate activities of the various authorities and to ensure that they were aware of each other's actions. The strategic group comprised Health Canada, the European Medicines Agency, US Food and Drug Administration, Japan's Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency, Australia's Therapeutic Goods Administration, Singapore's Health Science Authority, and Swissmedic. Areas of cooperation included the assessment of risks, testing methods and inspections, and public communication.

The setting up of this strategic group was instrumental in coordinating international efforts from sharing information to discussing and agreeing on scientific issues. The lessons learnt group concluded that this approach could serve as a model for dealing with future cases but noted that international efforts could benefit from increased cooperation with regulators from major API exporting countries such as China and India.

Recommendations

Taking into account lessons learnt from the presence of *N*-nitrosamines in sartan medicines, the lessons learnt group has made recommendations to reduce the potential of these and other impurities being present in human medicines. The recommendations will also help the European medicines regulatory network be better prepared to manage similar cases of unexpected impurities in the future.

The recommendations include several revisions or clarifications of guidelines as well as possible changes to legislation during implementation.

More details of aspects covered by the recommendations below are published separately in a 'technical background' document. The network can refer to the details in the 'technical background' when implementing the recommendations.

A. GUIDELINE REVISION

Guidelines on responsibilities of marketing authorisation holders and manufacturers

To ensure that MAHs and manufacturers fulfil their legal responsibilities with respect to the quality of their products, the lessons learnt group recommended that the European network take steps to update guidance in the area of quality, manufacturing and good manufacturing practice. The review of the guidance (and legislation where applicable) should:

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.

2) Improve exchange of information between CEP or ASMF holders and MAHs regarding impurity formation during API manufacturing, the manufacturing process and materials used in manufacturing so that MAHs can take full responsibility for the quality of their products, including APIs.

3) Raise awareness amongst manufacturing and importation authorisation holders, MAHs, 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.

4) Strengthen quality agreements between MAHs and API manufacturers; require more effective audits of API and intermediate manufacturers; improve the reliability of the qualified person declaration system so that MAHs can exercise effective oversight of API and intermediate manufacturers; and improve supply chain traceability of APIs in finished products.

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).

6) Require MAHs 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).

7) 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.

Guidelines for controlling impurities

With regard to guidelines and, where applicable, legislation for controlling impurities, the lessons learnt group recommended that:

8) The network publish detailed information about potential sources of *N*-nitrosamine impurities and other cohort-of-concern compounds.

9) The European Pharmacopoeia Commission pursue its ongoing revision of the general monograph on substances for pharmaceutical use with the intention of adding new requirements in order to mitigate the risks of *N*-nitrosamines.

10) The network review 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. MAHs could be required to submit a justification for proposed manufacturing processes and mitigation measures as part of regulatory submissions.

ICH guidelines

With respect to ICH guidelines, the lessons learnt group recommended that ICH consider the need for additional clarification of the following guidelines:

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.

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.

13) ICH Q9, to provide clarification and/or training material on what constitutes a risk assessment and how it should be performed.

Guidelines on good manufacturing practice

With respect to existing guidelines and, where applicable, legislation in the area of GMP and inspections, the lessons learnt group proposed that the network update or prepare additional guidance to:

14) Clarify regulatory expectations for technology transfers and supplier qualifications.

15) Clarify regulatory expectations for qualification and validation of facilities, equipment, utilities and processes for active substance manufacturing.

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.

17) Ensure batch-specific supply chain traceability between API and finished products.

Guidelines for sampling and testing

With respect to sampling and testing, the lessons learnt group recommended that the network review existing procedures, guidelines and, where applicable, legislation as well as available resources in order to:

18) Strengthen the role of the European Directorate for the Quality of Medicines & HealthCare in the central management of the testing workload (coordination, prioritisation of testing and communication) when dealing with major incidents.

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.

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.

21) Facilitate coordinated market surveillance for products at risk of containing *N*-nitrosamine impurities once corrective measures are implemented by industry.

B. IMPROVEMENT OF EXTERNAL COMMUNICATION

With respect to communication to the public, including patients and healthcare professionals, the lessons learnt group recommended that the communication teams within the network:

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, 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.

C. INTERNATIONAL COOPERATION

The lessons group recommends that the network take steps to expand international collaboration with regulatory authorities around the world, including those in major exporting countries. To this end, the network should:

23) Consider routinely creating a strategic group once a major incident comes to light (as was done in the sartans case).

24) Facilitate exchange of commercially confidential information between the network and other regulators.

25) Exchange information, coordinate and share workload in relation to assessments, GMP inspections, sampling and testing, expert advice, regulatory decisions, communication and advice to patients.

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).

D. DATA SOLUTIONS

The lessons learnt group recommended that the network improve or populate existing databases and develop or acquire, if necessary, EU-wide databases and information technology solutions. The network should:

27) Develop or acquire a data tool for mutagenicity assessments for use by assessors at national competent authorities and EMA.

28) Populate existing databases or linked repositories 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.

29) Put in place a tool to capture and share information and decisions among EMA and national competent authorities when dealing with EU-wide quality incidents requiring a harmonised approach.

30) Put in place a tool for sharing information with international partners.

E. TRAINING

With respect to training within the network, the lessons learnt group recommended that the network:

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.

32) Provide training on the functioning and roles of the Rapid Alert Network and the Incident Review Network and ensure a common understanding of the management of cases that are considered a 'crisis'.

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.

F. OTHER CONSIDERATIONS

The lessons learnt group made other proposals for improving regulatory processes and operating procedures. The group recommended that the network consider ways to:

34) Develop a risk-based model for triggering pre-approval inspections of API manufacturers.

35) Develop a harmonised operating procedure for the sampling of active substances during GMP inspections.

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.

37) Develop a better strategy for identifying parallel imported/distributed products when dealing with quality defects.

38) Revise existing procedures in order to establish a procedure for the Rapid Alert Network and inspectors to share feedback when inspections are required during the management of critical quality defect cases.

39) Ensure that there is an agreed and harmonised definition for the term 'quality defect' across the network.

40) Improve the system for maintaining a single contact list for the various groups within the European network involved in managing incidents.

Next Steps

Based on the recommendations from the lessons learnt group, the European medicines regulatory network will consider measures to protect the quality of EU medicines with respect to *N*-nitrosamines and other impurities. The recommendations will also feed into other *N*-nitrosamine-related initiatives, such as the Article 5 (3) procedure[5] which started in September 2019 to provide guidance to MAHs and

[5] This refers to Article 5 (3) of Regulation (EC) No 726/2004, whereby EMA's Executive Director can request a CHMP opinion on any scientific matter related to medicines. More information is available on EMA's website.

manufacturers of medicines containing chemically synthesised APIs. The outcome of these other initiatives may also complement the recommendations from this exercise.

For those recommendations that impact international guidelines or activities carried out with international partners, the network will consider opening discussions in the appropriate forums.

The recommendations from this lessons learnt exercise are those of the European medicines regulatory network. Other stakeholders are encouraged to conduct similar exercises and consider what actions they should take.

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

Technical background

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List of abbreviations

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios/Spanish Agency for Medicines and Health Products
AIFA	Agenzia Italiana del Farmaco/Italian Medicines Agency
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé/National Agency for the Safety of Medicine and Health Products (France)
API	Active pharmaceutical ingredient
ASMF	Active substance master file
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte/Federal Institute for Drugs and Medical Devices (Germany)
BWP	Biologics Working Party
CDSCO	Central Drugs Standard Control Organisation (India)
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CoC	Cohort of concern
DEA	Diethylamine
DIPEA	Diisoproylethylamine
DIPNA	*N*-Nitrosodiisopropylamine
DMA	Dimethylamine
DMF	Dimethylformamide
EC	European Commission
EU	European Union
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EIPNA	*N*-Nitrosoethylisopropylamine
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GDP	Good distribution practice
GMP	Good manufacturing practice
HMA	Heads of Medicines Agencies
HPRA	Health Products Regulatory Authority (Ireland)
IARC	International Agency for Research on Cancer

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IRN	Incident Review Network
GMP-GDP IWG	Good Manufacturing Practice/Good Distribution Practice Inspectors working Group
MAH	Marketing authorisation holder
MBA	4-methylaminobutyric acid
MEB	Medicines Evaluation Board (Netherlands)
MHLW/PMDA	Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency (Japan)
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MPA	Medical Products Agency (Sweden)
NAP	Nitrosation assay procedure
NCA	National competent authority
NDBA	*N*-Nitrososdibutylamine
NDEA	*N*-Nitrosodiethylamine
NDMA	*N*-Nitrosodiemethylamine
NMBA	*N*-Nitroso-*N*-methylamino butyric acid
NMP	*N*-Methylpyrrolidone
NMPA	National Medical Product Administration (China)
NMPA	*N*-Nitrosomethylphenylamine
NO_x	Nitrosating agent, generally an oxidised nitrogen-containing compound
OGYEI	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet/National Institute of Pharmacy and Nutrition (Hungary)
OMCL	Official Medicines Control Laboratory
QWP	Quality Working Party
RAN	Rapid Alert Network
SUKL	Státní ústav pro kontrolu léčiv/State Institute for Drug Control (Czechia)
SWP	Safety Working Party
TBA	Tributlyamine
TBAB	Tetrabutylammonium bromide
TEA	Triethylamine
TGA	Therapeutic Goods Administration (Australia)

TTC	Threshold of toxicological concern
WHO	World Health Organization

1. Introduction

This technical background document is the outcome of an exercise conducted by the European medicines regulatory network[6] to determine what lessons can be learnt from cases of unexpected *N*-nitrosamine impurities in angiotensin II receptor blockers (also known as sartans) which came to light in mid-2018 and to make recommendations to prevent and manage such cases in the future.

Since the 1980s, the International Agency for Research on Cancer (IARC) has classified *N*-nitrosamines as 'probable human carcinogens',[7] while the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has for several years considered them, along with other *N*-nitroso- compounds, to be part of a cohort of concern (CoC) because of their mutagenic potency.[8] Although present in trace amounts in foods, air and water,[9] until 2018 these compounds were not known to be present in sartan active pharmaceutical ingredients (APIs) and were therefore not recognised as impurities in the quality dossiers of any sartan products.

On 6 June 2018, an API manufacturer, Zhejiang Huahai Pharmaceuticals, was informed by a potential customer of an unexpected impurity in the manufacturer's valsartan API. After an initial investigation, on 20 June 2018 Zhejiang Huahai sent a letter to its customers informing them of the presence of 'a previously unknown impurity that may have genotoxic potential' and requested that they immediately put on hold the use of its valsartan API. Six days later, Zhejiang Huahai contacted its customers again, noting that the presence of the impurity (now identified as *N*-nitrosodimethylamine [NDMA]) was likely to be 'process related' and that the company expected to be able to resume supply 'in a short period of time'.

A customer of Zhejiang Huahai who received Zhejiang Huahai's letter of 20 June 2018 subsequently informed the Spanish Agency for Medicines and Health Products (AEMPS). EMA became aware of the impurity on 25 June 2018 following an email from Germany's Federal Institute for Drugs and Medical Devices (BfArM), who received the letter of 20 June 2018 from a German customer of the same Spanish company that had informed AEMPS. EMA, taking a coordinating role, subsequently sent an email on 26 June 2018 to all members of the Rapid Alert Network (RAN), apprising them of the presence of a genotoxic impurity and stating that a report on the root causes was being awaited.

When in late June 2018 Zhejiang Huahai's customers in the European Union (EU) notified authorities in the EU of the impurity,[10] little was known about the extent of the problem or the levels of NDMA in Zhejiang Huahai's valsartan API.

Regulatory responses in the EU

The immediate regulatory response in the EU took the form of quarantining batches of medicines containing Zhejiang Huahai's valsartan API by national competent authorities (NCAs).[11] By 4 July

[6] Participants came from the European Commission (EC), the European Medicines Agency (EMA), national competent authorities (NCAs) in the European Economic Area (EEA) and the European Directorate for the Quality of Medicines & HealthCare (EDQM).

[7] See *IARC Monograph Volume 17, Supplement 7 (1987).*

[8] See *ICH Harmonised Guideline. Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7(R1).* This guideline was adopted by EMA in February 2018.

[9] See Keszei et al 2013 and the Concise International Chemical Assessment Document 38 on *N*-nitrosodimethylamine cited in the CHMP's assessment report from the Article 31 review of sartans.

[10] For information about reporting obligations for quality defects, see Chapter 8 of Volume 4 of *The Rules Governing Medicinal Products in the European Union* 13 August 2014. EMA has further procedural information on its website as do NCAs.

[11] AEMPS sent a rapid alert notification on 27 June 2018 stating that distribution of potentially affected products in Spain was being put on hold by the manufacturers.

2018, NCAs began precautionary recalls from pharmacies across the EU and informing the public of the reason for the recalls.

On 5 July 2018, with tests by Zhejiang Huahai now showing an average NDMA level of 66.5 parts per million (ppm) in affected batches, the European Commission (EC) triggered a review in accordance with Article 31 of Directive 2001/83/EC to be carried out by EMA's Committee for Medicinal Products for Human Use (CHMP).[12] As a precaution, this review was to cover all valsartan medicines in the EU and not only those containing the API from Zhejiang Huahai.

Four days later, the European Directorate for the Quality of Medicines & HealthCare (EDQM) suspended Zhejiang Huahai's certificate of suitability to the monographs of the European Pharmacopoeia (CEP)[13] for valsartan (CEP 2010-072), effectively barring the release onto the market of valsartan medicines containing the company's API.

An evolving situation

In the following weeks, several events confirmed that *N*-nitrosamines were not confined to the valsartan API from Zhejiang Huahai (see Figure 1.). First, on 3 August 2018, the Taiwan Food and Drug Administration alerted regulators worldwide of the discovery of NDMA in valsartan APIs manufactured by two other companies, Zhejiang Tianyu and Zhuhai Rundu Pharma. Second, on 30 August 2018, Zhejiang Huahai confirmed the presence of a second *N*-nitrosamine, *N*-nitrosodiethylamine (NDEA), in some batches of its valsartan API.[14] Third, on 14 September 2018, authorities in Germany informed the European regulatory network of trace amounts of NDEA, in another sartan, losartan, from Hetero Labs.[15] Fourth, on 17 September 2018, EDQM informed the network of the detection of traces of NDEA this time in irbesartan from another API manufacturer, Aurobindo Pharma Limited.[16]

Meanwhile EDQM reassessed previously submitted data in all CEP dossiers for sartans to provide accurate information to NCAs to support their decisions on potential batch recalls and to ensure that API manufacturers take appropriate corrective actions where necessary.

[12] See the European Commission's justification for referral in the published notification.

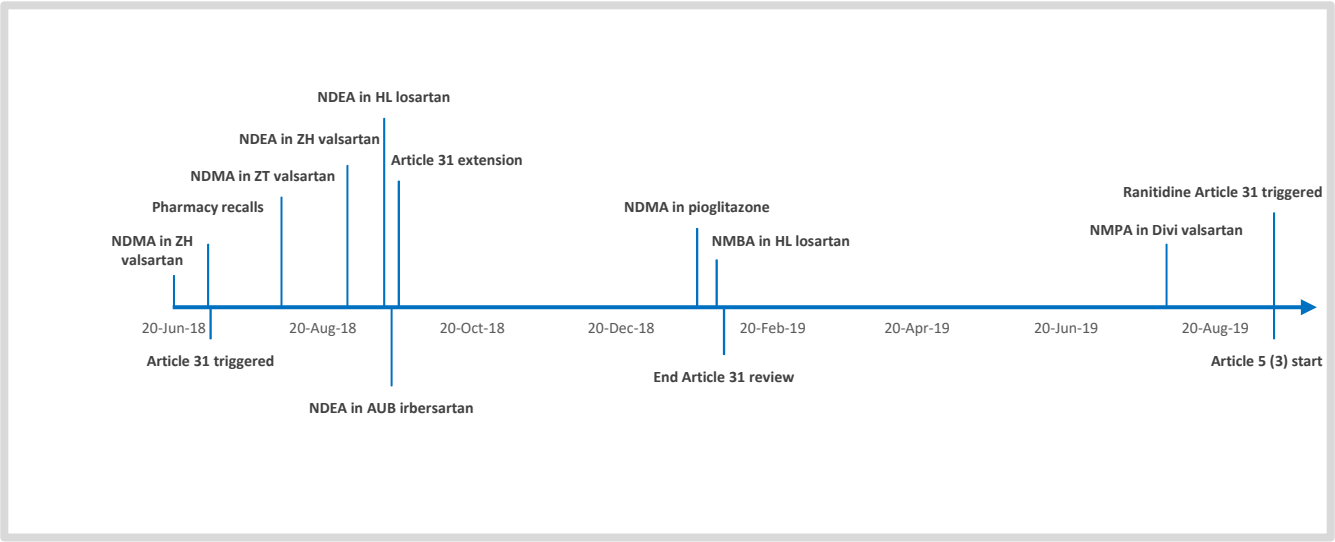
[13] Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP). A CEP certifies that if a substance is manufactured in a certain way (described in the CEP dossier) that substance can be considered suitably controlled in accordance with the European Pharmacopoeia. Information on CEPs suspended by EDQM is posted on EDQM's website.

[14] Information sent to EDQM in 30 August 2018.

[15] A rapid alert notification was issued by the government of Upper Franconia (Oberfranken) in the German state of Bavaria.

[16] EDQM informed the network at the 14th RAN teleconference of 17 September 2018.

Figure 1. Timeline of main events



In response to the rapidly evolving situation, on 20 September 2018 the EC extended the scope of the ongoing Article 31 review to include all sartans at risk of containing *N*-nitrosamines (i.e. those with a tetrazole ring) based on an understanding of how *N*-nitrosamines may have formed.[17]

Later that month, a joint EU/EDQM inspection of Zhejiang Huahai's manufacturing site in Linhai identified significant failings in the way the company investigated *N*-nitrosamine impurities in its valsartan API. As a result, a certificate of non-compliance with good manufacturing practice (GMP) was issued, which prohibited EU marketing authorisation holders (MAHs) from using the valsartan API produced at the site.[18] Subsequently, Zhejiang Huahai's site was placed under increased supervision with authorities monitoring the company's corrective measures on a regular basis. In addition, MAHs for EU medicines were required to perform additional tests on all other active substances supplied by Zhejiang Huahai.[19]

Sartans Article 31 outcome

The Article 31 review of sartans and the recalls of some medicines generated worldwide interest in the media and among patients and healthcare professionals. Questions raised by the public concerned why regulators allowed *N*-nitrosamines to be present in sartans in the first place, whether other medicines were affected and what risks patients had been exposed to. On 31 January 2019, EMA's CHMP concluded the review,[20] publishing a final retrospective risk estimate as follows:

> '…if 100,000 patients took valsartan from Zhejiang Huahai (where the highest levels of impurities were found) every day for 6 years at the highest dose, there could be 22 extra cases of cancer due to NDMA over the lifetimes of those 100,000 patients. NDEA in these medicines

[17] The additional sartans covered by the Article 31 review were candersartan, irbesartan, losartan and olmesartan. The notification of the extension of scope is published on EMA's website. Non-tetrazole sartans such as azilsartan, eprosartan and telmisartan were omitted from the scope of this procedure.

[18] Zhejiang Huahai's valsartan API was already effectively banned in EU medicines following EDQM's earlier suspension of the company's valsartan CEP in July 2018.

[19] See EMA communication issued on 15 October 2019.

[20] The CHMP conducted the scientific evaluation, which concluded in January 2019. The EC issued legally binding decisions for the different sartan products in April 2019.

could lead to 8 extra cases in 100,000 patients taking the medicine at the highest dose every day for 4 years.'[21,22]

These risk estimates, based on worst-case scenarios for valsartan consumption and a very conservative extrapolation from animal studies, were considered low. Furthermore, for the vast majority of sartan medicines, *N*-nitrosamines were either not found or were present at very low levels. Given the greater risk to patients from stopping necessary treatments, EU and national authorities advised patients throughout the review not to stop taking their sartan medicines without speaking with their healthcare professional.

On the question of protecting patients' health, the CHMP did not find evidence to support cancer screening or additional monitoring of patients exposed to *N*-nitrosamines. First, the theoretical risk of cancer was very low and was itself based on a worst-case scenario. Second, the screening methods themselves carry risks for patients. Third, there was considerable uncertainty as to which organs or tissues could be at risk from cancer.

The CHMP found that the presence of NDMA in sartan APIs with a tetrazole ring was due to the use of dimethylformamide (DMF) and other reagents during the manufacturing process. DMF, which is used as a solvent, can decompose under certain conditions to form small amounts of dimethylamine (DMA). Under acidic conditions, this amine then reacts with another chemical used in the manufacturing process called sodium nitrite ($NaNO_2$)[23] in the presence of an acid to form NDMA.

It is the simultaneous presence of these compounds (dimethylamine, sodium nitrite and acids) which gives rise to NDMA, and the same holds for some other *N*-nitrosamines (the only difference being the type of amine reacting with $NaNO_2$ in the presence of an acid).

The potential formation of *N*-nitrosamines from these side-reactions was not identified by the concerned API manufacturers, MAHs or regulators at the time the affected sartan medicines were authorised. Moreover, *N*-nitrosamines would not generally be detected or quantified by standard analytical methods used during process development or quality control. (Indeed, a significant part of the EU regulatory response involved developing and validating testing methods able to quantify the levels of *N*-nitrosamines potentially present in sartan products.)

During the review, the CHMP and regulators also noted another important source of *N*-nitrosamines: contamination from other sources, including solvents, reagents and poorly cleaned manufacturing equipment already contaminated with *N*-nitrosamines, leading to potential cross contamination.

Having identified the sources of *N*-nitrosamine impurities, the CHMP considered both short- and long-term measures. In the short-term, it set interim limits for NDMA and NDEA in APIs based on acceptable intake calculated in accordance with ICH M7 (R1) (Table 1.); these limits were to apply for a 2-year transition period after the Commission Decision (issued on 2 April 2019).[24] During this period MAHs must conduct a risk assessment and ensure a control strategy is in place for sartans API batches used in their finished products.

In the longer term, after the 2-year transition period, all concerned MAHs were required to make necessary changes to their API manufacturing processes to minimise nitrosamine contamination. They

[21] The 6 and 4 years refer to the duration of time NDMA and NDEA are believed to have been present in valsartan from Zhejiang Huahai based on the manufacturing processes the company was using.

[22] See communication announcing at the end of review.

[23] $NaNO_2$ is used to remove another reagent called sodium azide, which is highly toxic and potentially explosive.

[24] Subsequently, EMA's Safety Working Party, applying the same principles used to set limits for NDMA and NDEA, established limits for three additional *N*-nitrosamines: EIPNA, DIPNA and NMBA.

were also required to meet a stricter limit (0.03 ppm) set on the basis of the technical feasibility (limit of quantification) of analytical methods validated by Official Medicines Control Laboratories (OMCLs).[25]

Table 1. Temporary limits for NDMA and NDEA impurities set during Article 31 review.

	NDMA		NDEA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**	**Maximum daily intake (ng)**	**Limit (ppm)**
Candesartan (32 mg)	96.0	**3.000**	26.5	**0.820**
Irbesartan (300 mg)	96.0	**0.320**	26.5	**0.088**
Losartan (150 mg)	96.0	**0.640**	26.5	**0.177**
Olmesartan (40 mg)	96.0	**2.400**	26.5	**0.663**
Valsartan (320 mg)	96.0	**0.300**	26.5	**0.082**

The temporary limits for NDMA and NDEA were used at national level as recall limits for sartans on the market. These limits were based on an understanding of the analytical capability at that time and on the fact that *N*-nitrosamines could be limited by choice of appropriate synthetic routes and reaction conditions.

Further developments

In late January 2019, as the review was concluding, EU authorities became aware of the presence of *N*-nitroso-*N*-methylamino butyric acid (NMBA) in batches of losartan API from Hetero Labs, which led to a recall of products in some EU countries.

In the same month, Hetero Labs informed the EU authorities and EDQM that it had discovered NDMA in some batches of its pioglitazone API, an active substance used in diabetes medicines. Fifteen out of 161 API batches had NDMA levels of between 0.65 ppm and 1.5 ppm (limit of quantification: 0.63 ppm). As the provisional limit based on the equivalent toxicology assessment in the sartans is 1.9 ppm, these levels all fell below that limit.

Although no recall was considered necessary, the presence of an *N*-nitrosamine in a non-sartan API was, from a regulatory point of view, a significant finding. As a precaution, EDQM immediately reviewed all CEP applications for this substance and, in April 2019, EMA and NCAs requested that MAHs for pioglitazone who were using certain reagents in their manufacturing processes check their processes to rule out the presence of *N*-nitrosamines.[26]

In July 2019, regulators received information of a new *N*-nitrosamine - *N*-nitrosomethylphenylamine (NMPA) – in valsartan from Divi's Laboratories Ltd. The levels detected were below the acceptable limit based on the ICH M7 (R1) guideline.

[25] The assessment report for the Article 31 review containing details of the requirements is published on EMA's website.
[26] See public communication on the matter.

In September 2019, EMA at the request of the EC started an Article 31 review for ranitidine medicines after tests showed that some of these products contained NDMA.[27] In a number of EU countries, national authorities initiated recalls of ranitidine medicines from pharmacies.

Independently of these new developments, the network had been coming to the view that the outcome of the Article 31 review of sartans should be considered by MAHs for other medicines. In mid-September 2019, EMA and national authorities in the context of an Article 5(3) procedure[28] sent a formal request to all MAHs for medicines containing chemically synthesised active substances requiring them to evaluate the risk of *N*-nitrosamines being present in their products and to take appropriate risk mitigation measures.[29]

The lessons learnt exercise

As set out in further detail in this document, the discovery of *N*-nitrosamines in medicines posed unique challenges for authorities around the world. The European regulatory network needed to act swiftly in the face of uncertainties and intense public pressure to protect public health while preserving access to essential medicines.

To deal with issues as they arose, the network, including EDQM and the EC, coordinated actions via the Rapid Alert Network, which had regular teleconferences from late June 2018, and the Incident Review Network (IRN) which held teleconferences to deal with major developments.[30] The Co-ordination group for Mutual Recognition and Decentralised Procedures – Human (CMDh) was also a crucial forum for coordinating actions among NCAs.

EMA's CHMP, making use of expertise from across the EU, led the investigation into the root causes of the presence of *N*-nitrosamines in sartans and made EU-wide recommendations in the context of the Article 31 review. EDQM coordinated the development of appropriate analytical methods as well as sampling and testing within the network.

On a wider front, two international working groups (one on strategy and another on public communication) were set up to coordinate actions of regulators from the EU, United States, Canada, Japan and, later Australia, Switzerland, and Singapore to hone strategies for dealing with what was an evolving situation.

Drawing on experience from the sartans case, the lessons learnt group have considered ways that European regulatory network can prevent and manage similar cases in the future. In this context the group took a broad view of what incident management means, taking in aspects such as international collaboration and public communication – the latter particularly in relation to the cancer risk, which was not always certain or easy to communicate.

This document consists of 5 main sections, covering prevention, incident management, market surveillance, communication and international cooperation. Each of these sections discusses the regulatory actions in relation to the presence of *N*-nitrosamines in sartans and proposes improvements for the consideration of the network. These considerations form the basis of the recommendations which are published separately in an 'Overview and recommendations' document.

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[27] Procedure number: EMA/H/A-31/1491. Information about the review of ranitidine is available on a dedicated page on EMA's website.

[28] This refers to Article 5 (3) of Regulation (EC) No 726/2004, whereby EMA's Executive Director can request a CHMP opinion on any scientific matter related to medicines. The procedure number is: EMA/H/A5(3)-1490

[29] EMA published a public communication as well as a notice to companies and a questions-and-answers document. CMDh also published instructions on its website.

[30] The roles of RAN and IRN are described in more detail in section 3.

2. Preventing the presence of mutagenic impurities

2.1. Current guidelines for controlling mutagenic impurities

Since the 1960s, European authorities have introduced a raft of new or stricter measures to protect patients, including the requirement for MAHs to declare the qualitative and quantitative composition of their products.[31] European authorities have also worked with international partners to develop guidelines to ensure companies comply with new and evolving requirements concerning the quality of medicines (Table 2.).

Table 2. Relevant guidelines for controlling impurities

Guideline name and scope
• European Pharmacopeia (Substances for Pharmaceutical Use) – general legally binding quality requirements
• *Guideline on the Chemistry of Active Substances* (2017) – information required in quality dossiers
• *Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier* (2005) – general requirements on information in quality dossiers
• ICH Q11 (2013) – developing manufacturing processes for APIs
• ICH Q3A (R2) (2006) – impurities in APIs
• ICH Q3B (R2) (2006) – impurities in finished products
• ICH Q3C (R6) (2019) – residual solvents
• ICH Q3D (R1) (2019) – elemental impurities
• ICH M7 (R1) (2018) – controlling mutagenic impurities
• ICH Q7 (2000) – good manufacturing practice for APIs
• ICH Q9 (2006) – quality risk management
• ICH Q10 (2014) – pharmaceutical quality system

The European Pharmacopeia, first published in 1969, is a collection of almost 3,000 monographs setting out legally binding standards for the quality of medicines and their ingredients in the EU and beyond.[32] Requirements concerning impurities are found in specific monographs and in the general monograph, *Substances for Pharmaceutical Use*, which covers the control of related substances, mutagenic impurities, elemental impurities, residual solvents and other parameters.

How companies should declare information on the quality of their APIs is outlined in the CHMP's *Guideline on the Chemistry of Active Substances*.[33] This guideline details information that they must

[31] See Article 5 and 11 of Council Directive 65/65/EEC whose promulgation in 26 January 1965 can be seen as the beginning of the EU pharmaceutical legislation and birth of what would become the European regulatory network.

[32] See factsheet on the European Pharmacopeia on EDQM's website.

[33] The CHMP adopted this guideline on 21 July 2016 (Document reference number: EMA/454576/2016). It replaces two previous guidelines, *Guideline on the Chemistry of New Active Substances* (CPMP/QWP/130/96, Rev 1) and *Chemistry of Active Substances* (3AQ5a).

include in their dossiers irrespective of the route of submission of data on the active substance. In relation to impurities, the guideline states:

> 'Information on impurities and their carry-over should be provided. This includes related substances, residual solvents, elemental impurities, reagents and those derived from reagents. The related substances considered as potential impurities arising from the synthesis and degradation products should be discussed and described briefly including an indication of their origin. The mutagenic potential of impurities should be addressed.'[34]

Furthermore, companies must describe possible routes of degradation and the analytical methods (with limits of detection and limits of quantitation) used to detect each of the likely impurities or other related impurities, the exact identities of which may be unknown. They are also required to give a summary of the nature and levels of the actual impurities detected in batch samples of their materials and provide justification for the limits selected on the basis of safety and toxicity data and the methods used to control the impurities.

The ICH guideline *Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological entities)* and its associated questions-and-answers document[35] describe approaches to developing and understanding the manufacturing processes of active substances, including steps designed to reduce impurities. It requires companies, at a minimum, to identify potential critical quality attributes[36] and develop appropriate manufacturing processes and control strategies.

For the development of chemical entities, ICH Q11 emphasises the importance of companies understanding the formation, fate (whether the impurity reacts or changes its chemical structure) and purge (whether the impurity is removed via, for example crystallisation or extraction) of impurities and of establishing appropriate controls for impurities as they progress through multiple process operations. As part of the development, companies should also justify how each proposed starting material is appropriate in the light of factors such as the ability of analytical procedures to detect impurities in the starting material, and the fate and purge of impurities and their derivatives in subsequent processing steps.

ICH Q11 also specifies that the development and improvement of the manufacturing process for a drug substance should continue over its lifecycle. There should be a systematic approach to managing knowledge related to both the drug substance and its manufacturing process. The knowledge of the manufacturing process should be shared as needed to implement the control strategy across sites involved in manufacturing the drug substance.

Furthermore, companies should evaluate any proposed change to the manufacturing process to determine how it could affect the quality of the drug substance and, when appropriate, that of the drug product. This evaluation should be based on a scientific understanding of the manufacturing process and should determine appropriate testing to analyse the impact of the proposed change. For chemical entities, the evaluation of the impact of the proposed change could include, but is not limited to, an assessment of current and potential new impurities and an assessment of the test procedures' abilities to detect any new impurities. This testing should be performed at an appropriate point in the process (e.g., on an intermediate or drug substance) after the proposed change has been implemented.

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[34] See section 4.3.2 Impurities 3.2.S.3.2.

[35] This guideline was adopted by CHMP in May 2012 (Document reference number: EMA/CHMP/ICH/425213/2011). The Q&A document was adopted in September 2017 (Document reference number: EMA/CHMP/ICH/809509/2016).

[36] The guideline describes a critical quality attribute as 'a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.'

The ICH guideline *Q3A (R2) Impurities in New Drug Substances*[37] is a guideline that deals with the content and qualification of impurities in new drug substances produced by chemical synthesis. It addresses two main aspects:

- chemistry aspects such as 'the classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures';
- safety aspects such as 'specific guidance for qualifying impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.'

This guideline recognises several categories of impurities, one of which is a category for organic impurities, which can also be mutagenic. The guideline requires companies to summarise the actual and potential impurities most likely to arise during the synthesis, purification and storage of the new drug substance. The summary should be based on a sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected to be present based on knowledge of the chemical reactions and conditions involved.

The guideline also reminds companies that analytical procedures should be developed for those potential impurities that are expected to be unusually potent or produce toxic or pharmacological effects. Taking into account the patient population and duration of use, companies should consider conducting genotoxicity studies or general toxicity studies for these impurities.

The ICH guideline *Q3B (R2) Impurities in New Drug Products*[38] is a complementary guideline that deals with impurities present in the finished product which are generally degradation products formed during manufacture and storage. ICH guideline *Q3C (R6) Residual Solvents* discusses control of residual solvents not completely purged following use in manufacturing operations, while ICH guideline *Q3D (R1) Elemental Impurities* concerns elemental impurities which could originate from a range of sources including deliberately used metal-based reagents and catalysts, impurities in raw materials, or leachables from manufacturing equipment and/or packaging.[39]

A guideline of particular relevance to the presence of *N*-nitrosamine impurities in sartans is the ICH guideline *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*,[40] which was first issued in 2014 with the most recent revision adopted by CHMP in February 2018. This guideline, which complements ICH Q3A, Q3B, Q3C and Q3D provides guidance on identifying, categorising, qualifying and controlling mutagenic impurities to limit potential carcinogenic risk.

The ICH M7 (R1) guideline applies to new products in the authorisation phase and to previously authorised products when changes to the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities or when changes in the formulation, composition or the manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products. This guideline also applies to marketed products if there is specific cause for concern (e.g., the presence of a newly discovered impurity that is a known class 1 or class 2 mutagen).

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[37] This guideline with document reference number CPMP/ICH 2737/99 was last updated by EMA in October 2006.

[38] This guideline was adopted in February 2003 with revisions attached in June 2016.

[39] ICH Q3C (R6) adopted in December 2016; ICH Q3D (R1) adopted in March 2019.

[40] This guideline was adopted in 2018 and supersedes *Guideline on the Limits of Genotoxic Impurities* which came into effect in 2007.

One of the concepts addressed in the ICH M7 (R1) guideline is the threshold of toxicological concern (TTC), which defines an acceptable intake for any impurity without existing carcinogenicity data, below which it poses a negligible risk of carcinogenicity or other toxic effects. The guideline, however, noted that 'some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the 'cohort of concern' (CoC), comprises aflatoxin-like-, *N*-nitroso-, and alkyl-azoxy compounds.' Therefore, CoC compounds, including *N*-nitrosamines, are excluded from the TTC concept and 'compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC-based acceptable intakes where sufficient carcinogenicity data exist.'

The guideline notes that a 'thorough knowledge of the chemistry associated with the drug substance manufacturing process and of the finished product manufacturing process, along with an understanding of the overall stability of the drug substance and drug product is fundamental to developing the appropriate controls for mutagenic impurities.'

The guideline also notes that a control strategy 'that is based on product and process understanding and utilisation of risk management principles will lead to a combination of process design and control and appropriate analytical testing, which can also provide an opportunity to shift controls upstream and minimize the need for end-product testing.'

It further states that 'the development and improvement of a drug substance or drug product manufacturing process usually continues over its lifecycle. Manufacturing process performance, including the effectiveness of the control strategy, should be periodically evaluated and verified after certain post-approval changes. Knowledge gained from commercial manufacturing can be used to further improve process understanding and process performance and to adjust the control strategy.'

In addition to the guidelines discussed above, the following guidelines on quality systems and risk management are important for controlling mutagenic impurities:

- EU GMP Part II[41] (equivalent to ICH guideline *Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients*), which provides guidance regarding GMP for the manufacturing of APIs under an appropriate system for managing quality.
- ICH guideline *Q9 Quality Risk Management*,[42] which describes a systematic approach to quality risk management[43] that may be used to complement other quality guidelines and practices in order to enable more effective and consistent risk-based decisions.
- ICH guideline *Q10 Pharmaceutical Quality System*,[44] which describes a model for an effective quality management system to support the development and manufacture of drug substances and drug products.

How these guidelines are implemented and how adequately they capture available scientific knowledge and best practices are at the heart of the discussion on preventing mutagenic impurities such as *N*-nitrosamines from being present in medicines. The following sections (2.2. and 2.3.) examine the root causes of the presence of *N*-nitrosamines in sartans and some other medicines and explore gaps and weaknesses that may need to be remedied to improve the prevention of such incidents in the future.

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[41] See the EC's website for details of GMP part II.

[42] ICH Q9 was adopted by CHMP in November 2005.

[43] Quality risk management is a systematic process for assessing, controlling, communicating and reviewing risks to the quality of the drug (medicinal) product across the product lifecycle

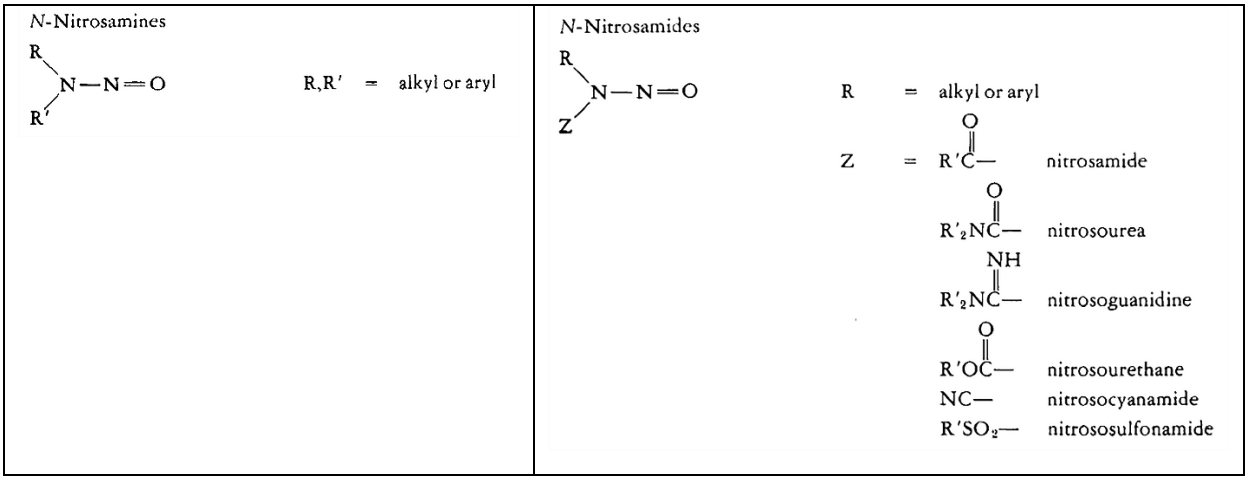
[44] ICH Q10 was adopted by CHMP in June 2008.

2.2. The chemistry of N-nitrosamines

Properties

N-Nitrosamines, which are derived from alkyl, alkaryl, aryl or cyclic amines, belong to a larger group of potent carcinogens known as *N*-nitroso compounds. It is a group they share with *N*-nitrosamides (see Figure 1.), which are derived from *N*-alkylureas, *N*-alkylcarbamates, and simple *N*-alkylamides.[45, 46]The carcinogenicity of *N*-nitrosamines is based on the fact that they can react with DNA base pairs after cytochrome P450-mediated metabolic activation to form unstable α-hydroxymethyl-*N*-nitrosamines, finally yielding alkyl- or aryl diazonium ions as the ultimate carcinogens (see Figure 2.).[47, 48]

Figure 1. Structure of *N*-nitroso compounds



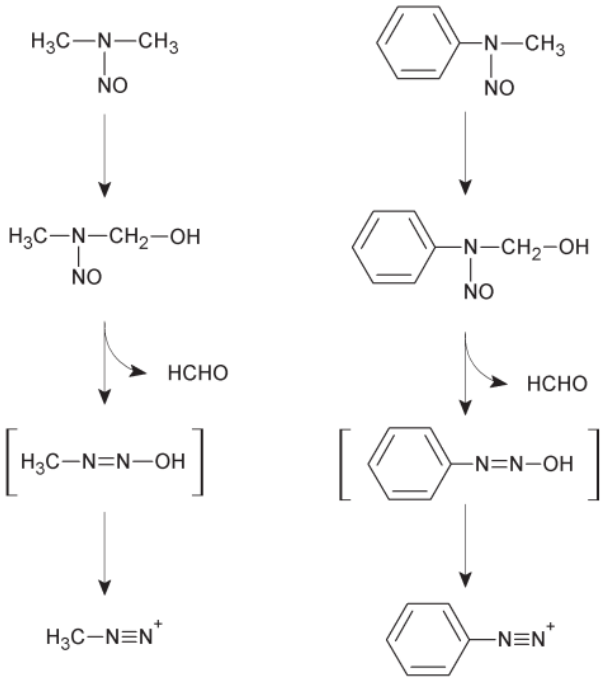
[45] See S. S. Mirvish, Toxicology and Applied Pharmacology, 31 (1975) 325 – 351

[46] M. L. Douglass, J. Soc. Cosmet. Chem., 29 (1978) 581–606

[47] M. Sulc et al., Gen. Physiol. Biophys., 29, (2010), 175–185

[48] R. Preussmann, Trends Pharm. Sci., 8, (1987), 185–189

Figure 2. Cytochrome P450-mediated metabolic activation to unstable α-hydroxymethyl-*N*-nitrosamines, finally yielding alkyl- or aryl diazonium ions



In terms of their physical properties, *N*-nitrosamines are stable organic compounds that can be isolated either as distillable liquids or crystalline solids. The relative ease of dissociation of the N-NO bond, induced by thermal treatment, is a common physical property of *N*-nitroso derivatives, but requires exposure to high temperatures between 400 °C and 500 °C. This attribute of *N*-nitroso derivatives allowed the development of the thermal energy analyser in the 1970s as a highly sensitive detector for *N*-nitrosamines.[49] They are also susceptible to photolytic degradation processes, which is why the photostability of analytical samples should be considered when developing and validating analytical methods. Due to the large dipole moment, they are partially soluble in aqueous media and readily soluble in organic solvents. The larger and less polar the alkyl substituents, the less soluble a given *N*-nitrosamine will be in water. This fact has important implications when considering how *N*-nitrosamines can be removed from reaction mixtures by aqueous work-up.[50]

N-Nitrosamines can undergo several organic-synthetic transformations (Figure 3. and Figure 4.). They act mainly as Lewis bases and hydrogen bond acceptors. Under acidic conditions, denitrosation (the reverse of the nitrosation process) can occur to afford secondary amines and nitrous acid. They can be reduced under various conditions, for example, by catalytic hydrogenation to tetrazenes, or transformed into the corresponding hydrazine derivatives by dissolving metal and hydride reductions. *N*-Nitrosamines can also be further oxidised to *N*-nitramines. They can be converted by photolytic rearrangement to the corresponding amidoximes upon ultraviolet irradiation in the presence of hydrochloric acid. After metallation in α-position, they can be alkylated and acylated to form the corresponding adducts. α-Hydroxy-*N*-nitrosamines have been found to be extremely reactive, showing *in vitro* instability in aqueous solutions at physiological pH with half-lives of seconds.[51]

[49] A. M. A. Perera in Chromatographic analysis of the environment (Third Edition) 2006, 93, 419-452

[50] For more information on the chemistry of N-nitrosamines please see A. L. Fridman et al. Russ. Chem. Rev., 40 (1971) 34-50; M. L. Douglass, J. Soc. Cosmet. Chem., 29 (1978) 581–606; J.-P. Anselme in N-Nitrosamines ACS Symposium Series,101 (1979) 1-12; J. E. Saavedra, Org. Prep. Proced. Int., 19 (1987) 83-159

[51] M. Mochizuki et al. Tetrahedron Lett., 21, (1980) 3693-3696

Figure 3. Tautomeric and rotameric equilibria of *N*-Nitrosamines[52]

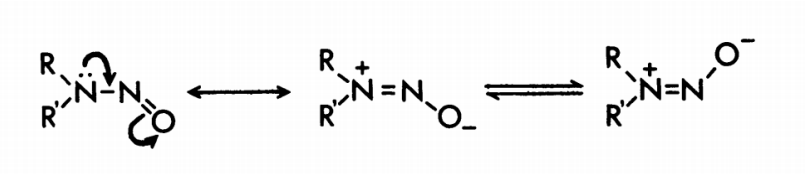
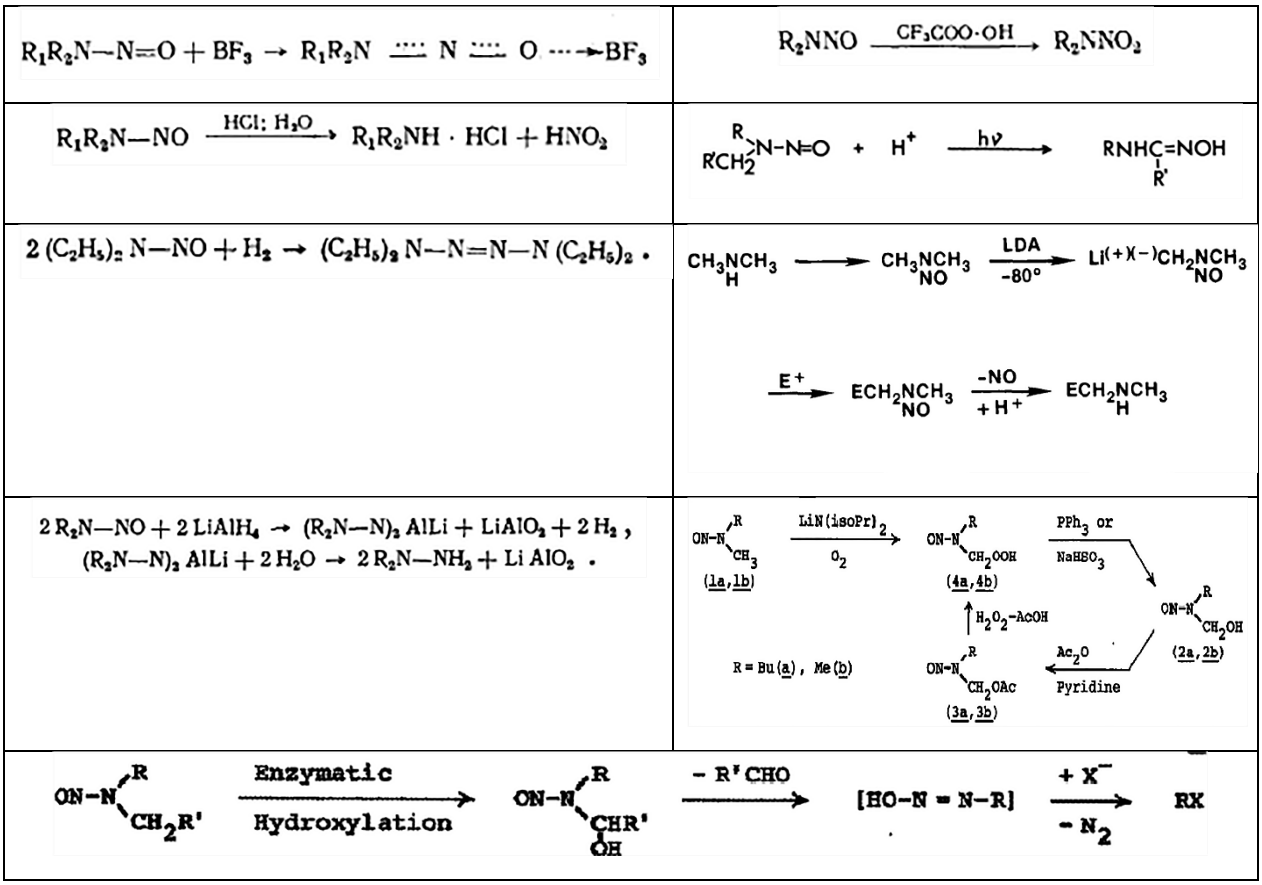


Figure 4. Chemical reactivity profile of *N*-Nitrosamines[53]



Formation of *N*-nitrosamines

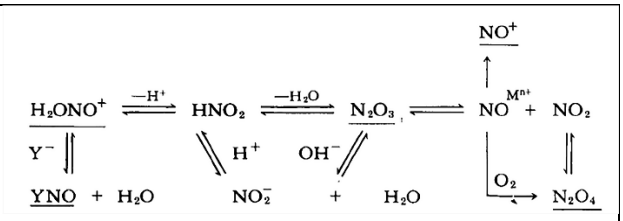
N-Nitrosamines can be formed from amines and nitrosating agents (generally oxidised nitrogen containing compounds, NO_x) under certain reaction conditions (Figure 5.). These NO_x species have different reactivities and can react with amines differently depending on, for example, the pH of reaction media and the nature of the solvent. At low pH, the more powerful nitrosating reagents are present, but the amine is more protonated, and thus, less reactive. Therefore, effective nitrosating conditions depend both on the pH and the basicity of the amine. Nitrous acid forms salts with basic amines which, when heated, can further react to afford *N*-nitrosamines.

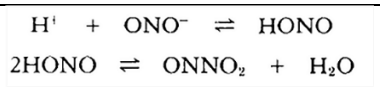
[52] From J.-P. Anselme in N-Nitrosamines ACS Symposium Series, 101, (1979) 1-12

[53] See A. L. Fridman et al., Russ. Chem. Rev., 40 (1971) 34-50; J.-P. Anselme in N-Nitrosamines ACS Symposium Series, 101 (1979) 1-12; J. E. Saavedra, Org. Prep. Proced. Int., 19, (1987) 83-159; M. Mochizuki et al., Tetrahedron Lett., 21 (1980), 3693-3696

Figure 5. Inorganic species as nitrosating agents and their interrelationships; H_2ONO^+ and N_2O_3 as nitrosating species in aqueous solutions at low pH and at moderately acidic pH[54]

Substance	Medium
N_2O_3	gas (20, 21)
	water (19, 22–27)
	organic solvent (2)
NO_2/N_2O_4	water (25–27)
	organic solvent (28, 29)
	gas (21, 30)
YNO	water (19, 22, 23, 31–37)
H_2ONO^+	water (19, 22, 38–40)
NO	plus O_2 (25, 27, 36)
	anaerobic, M^{n+} (19, 27)





The mechanism is thought to proceed via different nitrosating species formed preferentially under acidic conditions. In the case of sartan medicines, sodium nitrite and potentially nitrous acid, formed *in situ*, were identified as the probable nitrosating agents responsible for *N*-nitrosamine formation.

Nitric oxide does not generally lead to nitrosamine formation, although some metals and organometallic complexes are able to catalyse nitrosation using nitric oxide. However, other NO_x species are known to nitrosate amines, for example other nitrite salts and alkyl nitrites, as well as nitrous anhydride (N_2O_3), dinitrogen tetroxide (N_2O_4), nitrosyl chloride (NOCl) or other halides, nitrosylthiocyanate and nitrosophenol. Some of these are available as reagents but they also form during other processes (for example during meat curing, malt kilning prior to brewing, or during chemical reactions). Some antioxidants are known to inhibit nitrosamine formation, for example ascorbic acid, which is added to cured meats for this reason.

Primary amines react readily with nitrite, but the presence of adjacent hydrogens allows rapid conversion of the nitrosamine species to a diazonium salt. Therefore, formation of *N*-nitrosamine impurities is not considered a major risk when only primary amines are present, although *N*-nitrosamine formation in low yield has been observed in some cases. For secondary amines, the pathway to diazonium species is blocked by the presence of adjacent alkyl groups. Secondary amines and their ammonium salts react readily with nitrite to form the associated nitrosamine species, a process which can also be catalysed by aldehydes via iminium ion formation. Tertiary amines and their ammonium salts are also known to react directly with nitrites to form *N*-nitrosamines via a dealkylative mechanism. As demonstrated for trimethylammonium chloride and tetramethylammonium chloride, quarternary ammonium salts are able to form *N*-nitrosamines almost at the same level by a similar dealkylation reaction. These findings have been attributed to dealkylation processes similar to nitrosative dealkylation. [55] The various processes are exemplified in Figure 6. and Figure 7.

[54] M. L. Douglass, J. Soc. Cosmet. Chem., 29, (1978), 581–606

[55] W. Fiddler et al. Nature 236, (1972), 3079

Figure 6. Formation of *N*-nitrosamines

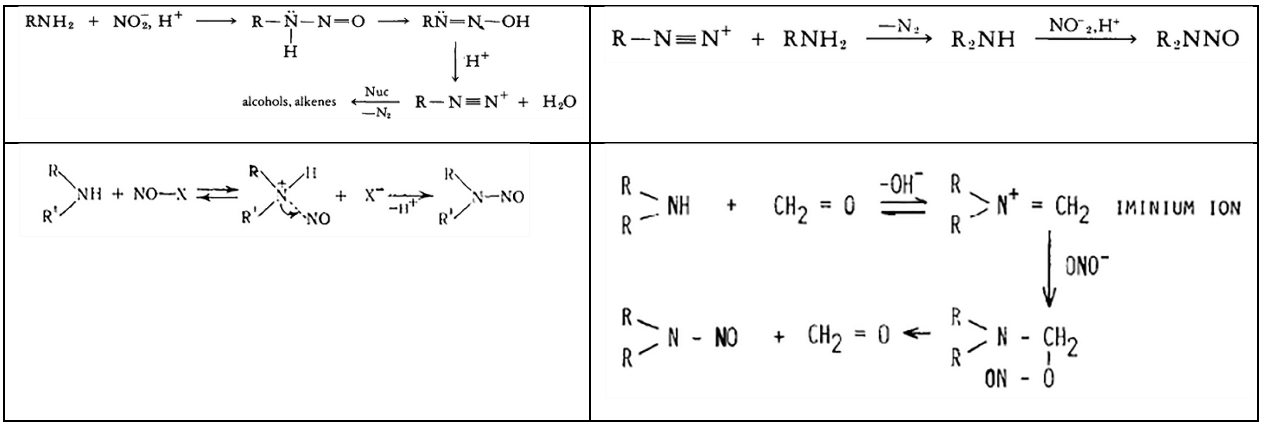
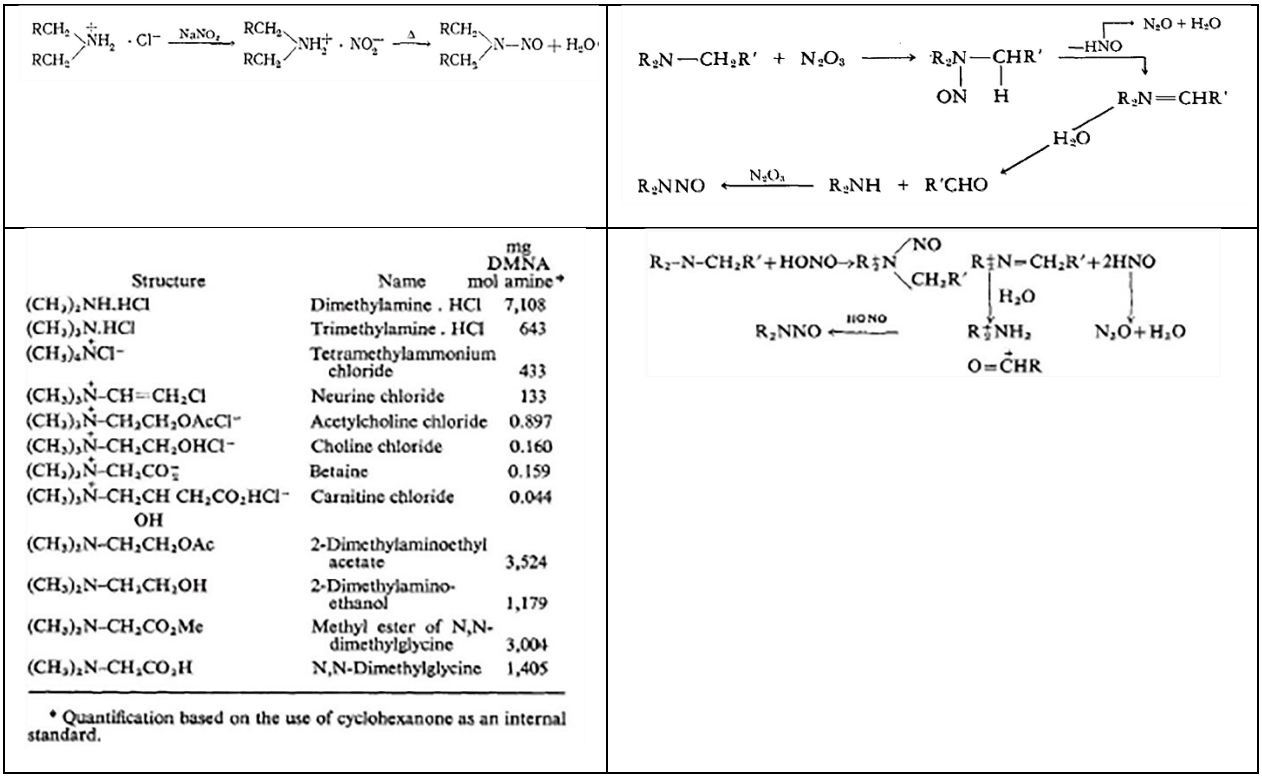


Figure 7. Primary amine to diazonium salts and nitrosamines, secondary amines to *N*-nitrosamines, tertiary amines to *N*-nitrosamines and quarternary ammonium salts to *N*-nitrosamines by dealkylative processes[56]



Structure	Name	mg DMNA mol amine*
$(CH_3)_2NH.HCl$	Dimethylamine . HCl	7,108
$(CH_3)_3N.HCl$	Trimethylamine . HCl	643
$(CH_3)_4\overset{+}{N}Cl^-$	Tetramethylammonium chloride	433
$(CH_3)_3\overset{+}{N}-CH=CH_2Cl$	Neurine chloride	133
$(CH_3)_3\overset{+}{N}-CH_2CH_2OAcCl^-$	Acetylcholine chloride	0.897
$(CH_3)_3\overset{+}{N}-CH_2CH_2OHCl^-$	Choline chloride	0.160
$(CH_3)_3\overset{+}{N}-CH_2CO_2^-$	Betaine	0.159
$(CH_3)_3\overset{+}{N}-CH_2CH(OH)CH_2CO_2HCl^-$	Carnitine chloride	0.044
$(CH_3)_2N-CH_2CH_2OAc$	2-Dimethylaminoethyl acetate	3,524
$(CH_3)_2N-CH_2CH_2OH$	2-Dimethylamino-ethanol	1,179
$(CH_3)_2N-CH_2CO_2Me$	Methyl ester of N,N-dimethylglycine	3,004
$(CH_3)_2N-CH_2CO_2H$	N,N-Dimethylglycine	1,405

* Quantification based on the use of cyclohexanone as an internal standard.

A range of alternative synthetic procedures for *N*-nitrosamines have been documented. These include the use of sodium nitroprusside,[57] Fremy's salt ($K_2[NO(SO_3)_2]$),[58] trichloronitromethane,[59]

[56] See A. L. Fridman et al. Russ. Chem. Rev., 40, (1971), 34-50; M. L. Douglass, J. Soc. Cosmet. Chem., 29, (1978), 581–606; S. S. Mirvish, Toxicology and Applied Pharmacology, 31, (1975), 325 – 351; W. Fiddler et al. Nature 236, (1972), 3079

[57] H. Maltz et al. J. Org. Chem,. 36, 1971, 363 – 361; J. Casado et al. Ber. Bunsenges. Phys. Chem. 89, 1985, 735-742

[58] L. Castedo et al. J. Chem. Soc. Chem. Commun. 1983, 1598-1599

[59] A. S. Demir et al. Synthetic Communications, 22, 1992, 2607-2611

bromonitromethane,[60] 2-nitropropane[61] and nitromethane.[62] The latter two reagents require addition of an external oxidant. With the exception of nitromethane, which is a common solvent and reagent, the use of these reagents and solvents in API manufacture seems to be limited at this moment.

The common feature of these methods seems to lie in the oxidative release of the known nitrosating agents HNO_2/NO^+ and subsequent *N*-nitrosamine formation by reaction with secondary or tertiary amines as previously discussed.

2.3. Root causes of the presence of N-nitrosamines in sartans and other medicines

2.3.1. The sartans case

Synthesis of sartans with a tetrazole ring

The presence of *N*-nitrosamines in sartan APIs containing a tetrazole ring[63] is for the most part due to the reagents, solvents, catalysts and reaction conditions used in the synthesis of the tetrazole ring in the final step of the manufacturing process (see Figure 8.). 5-Substituted-1*H*-tetrazoles, which are known to exist in equilibrium between the 1*H* and 2*H*-tautomeric forms, can be synthesised by various procedures (see Figure 9.), including by the reaction of organic nitriles with inorganic and organometallic azide reagents via a concerted 1,3 dipolar cycloaddition reaction or closely related ionic mechanisms.[64]

To avoid the use of toxic and explosive hydrazoic acid (HN_3), alternative reagents or reagent/catalyst combinations such as sodium azide (NaN_3), tributyltin azide (Bu_3SnN_3), triethylammonium chloride (TEA HCl)/sodium azide, tributyltin chloride (Bu_3SnCl) /sodium azide or zinc bromide ($ZnBr_2$)/sodium azide are often used for synthesizing tetrazoles.[65,66] Most of the tetrazole synthesis processes registered in the sartan dossiers used genotoxic azide reagents.

In order to speed up reactions and shift the equilibrium of the cyclisation reaction towards the product, catalysts (phase transfer, Lewis acids) were added, reagents were used in excess and the reactions were performed at high temperatures in polar aprotic solvents with high boiling points (e.g., DMF, dimethylsulfoxide and *N*-methylpyrrolidone [NMP]) over several hours.[67]

[60] B. C. Challis et al. J. Chem. Soc. Chem. Commun. 1990, 301-302

[61] B. Franck et al. Angew. Chem. 82, 1970, 876-877

[62] See H. K. Potturi et al. J. Org. Chem. 2012, 77, 626−631; J. Zhang et al. J. Org. Chem. 2013, 78, 11366−11372; N. Sakai et al. Chem. Commun., 2015, 51, 11638-11641; S. Azeez et al. Asian J. Org. Chem. 2018, 7, 2113–2119

[63] Candersartan, irbesartan, losartan and olmesartan

[64] F.R. Benson, Chem. Rev., 41, (1947), 1–61; R. J. Herr, Bioorg. Med. Chem., 10, (2002), 3379–3393

[65] R. J. Herr, Bioorg. Med. Chem., 10, (2002), 3379–3393

[66] K. B. Sharpless et al, J. Am. Chem. Soc., 125, (2003), 9983-9987

[67] R. J. Herr, Bioorg. Med. Chem., 10, (2002), 3379–3393

Figure 8. Sartans with a tetrazole ring

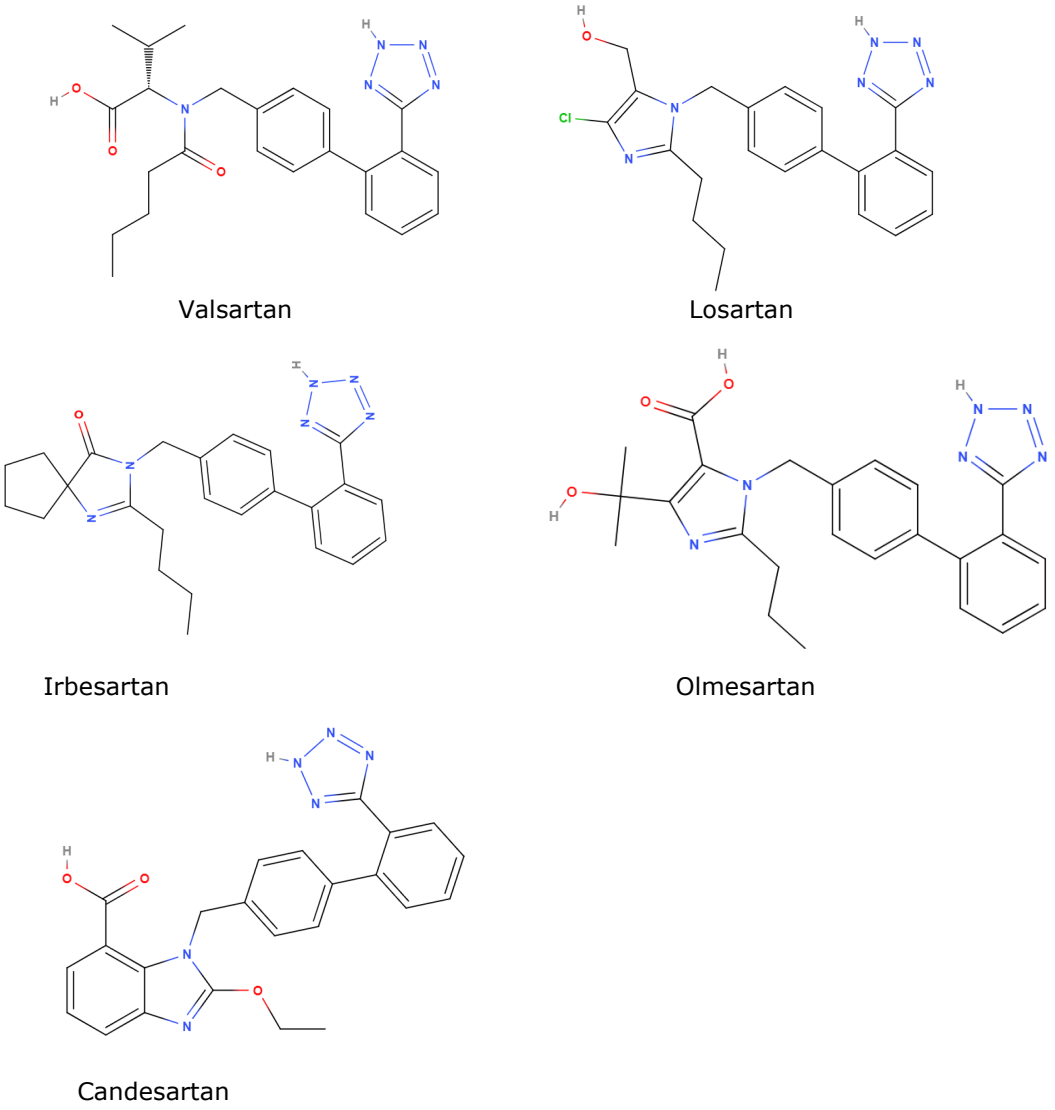
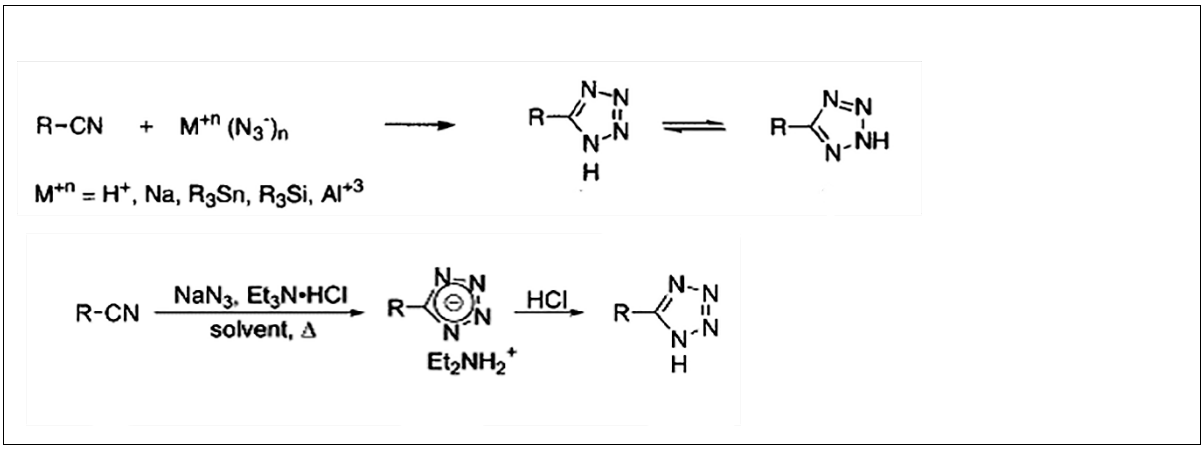


Figure 9. Basic structural features and standards synthesis of tetrazoles[68]



[68] See Wittenberger, S. J., Org. Prep. Proced. Int., 26, (1994), 499-531; R. J. Herr, Bioorg. Med. Chem., 10, (2002), 3379–3393

A typical drawback of using azide reagents is that upon hydrolytic work-up under acidic conditions required for isolation and extraction of tetrazoles, hazardous hydrazoic acid is liberated.[69] Residual quantities of azide can be decomposed to gaseous by-products such as nitrogen and dinitrogen oxide (N_2O) by adding sodium nitrite ($NaNO_2$), which is how the mother liquors are treated during industrial production of sodium azide.[70] In most processes to manufacture sartans, azide reagents are used in excess, and therefore, manufacturers choose to use at least equimolar quantities of sodium nitrite in relation to the azide reagent to ensure complete depletion of the hazardous by-products (Figure 10.).

Figure 10. Depletion of hydrazoic acid by sodium nitrite

$$HN_3 + HNO_2 \rightarrow N_2 + N_2O + H_2O$$

In principle, quenching procedures in the cyclisation step of sartan processes can be performed in the presence or in the absence of APIs and intermediates, i.e., before or after phase separation of liquids or after separation of solids from the mother liquor by filtration. Quenching procedures in the presence of the product (i.e., before separation procedures) enhances process safety as any hydrazoic acid is quenched rapidly. However, extensive exposure of API and intermediate solutions to nitrite risks *N*-nitrosamine formation and subsequent contamination. By contrast, quenching procedures in the absence of the product (i.e., after separation procedures) bear an inherent process safety risk in that unquenched hydrazoic acid is present for longer but prevents *N*-nitrosamine formation in the presence of the APIs or intermediates. Any subsequent re-extractions from quenched aqueous solutions or recovery processes from quenched mother liquors to increase the overall yield of the process step can also result in *N*-nitrosamine contamination with by-products formed during quenching operations.

According to the Article 31 review of sartans, the following solvents, reagents and catalysts were used in the tetrazole forming cyclisation step: toluene, xylene, DMF and NMP as well as corresponding solvent mixtures (also with water and alcohols). These were selected as high boiling solvents for the cyclisation reaction, while products were often extracted with less polar organic solvents such as ethyl acetate and dichloromethane during working-up procedures.

In addition to tributyltin azide, sodium azide alone or in combination with tributyltin chloride and bis(tributyltin)oxide [$(Bu_3Sn)_2O$] were frequently chosen as the azide source. Some processes required the addition of auxiliary bases such as triethylamine (TEA) and diisoproylethylamine (DIPEA). Zinc bromide ($ZnBr_2$), triethylammonium chloride (TEA HCl) and tetrabutylammonium bromide (TBAB) represented typical catalysts to accelerate reaction rates.

During the review of drug substance manufacturing data, it became evident that $NaNO_2$ was only added in a minority of cases, especially those conducted on the largest scale where hydrazoic acid build-up is most hazardous. In some cases, inconsistencies were identified concerning the documentation supporting sodium nitrite: it was generally declared as a raw material in module S.2.3 (control of materials) complete with specifications but was sometimes omitted from reaction schemes and the process description in module S.2.2 (description of manufacturing process and process controls). Going forwards, all materials used in the process should be included in all relevant sections of the dossier, irrespective of the intended use.

According to the assessment reports on sartan CEPs suspended by EDQM, a few API manufacturing processes were changed over time and $NaNO_2$ was added into the processes as part of scale up

[69] Wittenberger, S. J., Org. Prep. Proced. Int., 26, (1994), 499-531

[70] S. Bräse et al. in Hydrazoic Acid and Azides Ullmann's Encyclopedia of Industrial Chemistry, 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

activities. In some cases, these changes were introduced by variation procedures for already granted CEP dossiers in order to ensure process safety for large-scale production by azide quenching in order to minimize genotoxic azide impurities, treat waste streams and optimize efficiency. An increase in scale up to ten-fold can be made via submission of a type 1A variation, provided certain conditions are met, including that the API specification remains the same. It is acknowledged that scale-up activities may not always be low risk, and more consideration should be given to the impact on quality during development and assessment. The appropriateness of this classification, along with the required conditions and documentation, should be considered by the variations working group.

The Article 31 review of sartans found that *N*-nitrosamines such as NDMA, NDEA, *N*-nitrosodiisopropylamine (DIPNA), *N*-nitrosoethylisopropylamine (EIPNA) and NMBA were generated when amines and nitrosating agents were present simultaneously in manufacturing steps. The review found that the use of recycled solvents, reagents or catalysts from third party suppliers were further causes of *N*-nitrosamine contamination as were GMP violations that resulted in cross-contamination in multi-purpose facilities and operator-related issues such as inadequate phase separations.

After the Article 31 review was concluded, *N*-nitrososdibutylamine (NDBA) and *N*-nitrosomethylphenylamine (NMPA) were also found in batches of sartan medicines. Based on analysis of the synthetic processes, secondary and tertiary amines such as dibutylamine, tributylamine and *N*-methylaniline could be present either as impurities or degradation products of the phase transfer catalyst TBAB and the solvent/reagent *N*,*N*-dimethylaniline. When combined with sodium nitrite, these were postulated to be the sources of NDBA and NMPA.

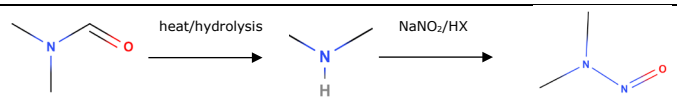
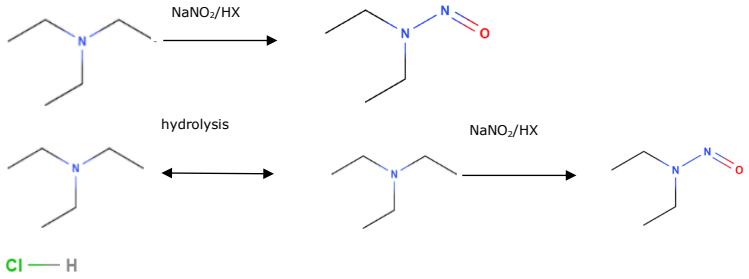
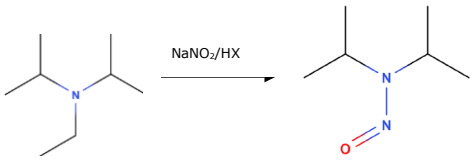
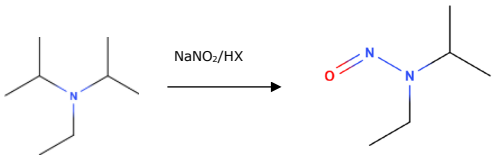
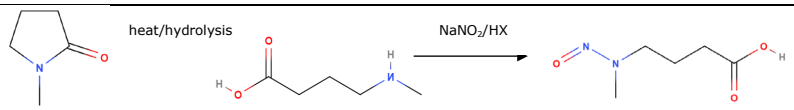
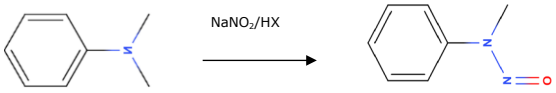
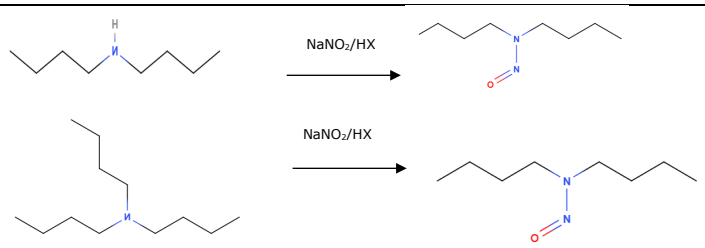
Drug substance manufacturers identified deliberately added $NaNO_2$ as the common source of NOx in tetrazole containing sartans. In contrast, different materials were stated to be responsible for the concomitant presence of secondary and tertiary amines in the processes. Solvents such as DMF and NMP were cited as sources for secondary amines such as *N*,*N*-dimethylamine (DMA) and for 4-methylaminobutyric acid (MBA). Reagents such as the tertiary amines TEA and DIPEA were cited as the origin of the secondary amines *N*,*N*-diethylamine (DEA), diisopropylamine and ethylisopropylamine respectively. The phase transfer catalyst TEA HCl was identified as the source of the tertiary amine TEA and the secondary amine DEA.

Formation of *N*-nitrosamines in sartans

According to the Article 31 review of sartans, *N*-nitrosamine formation was caused by the reaction of $NaNO_2$ as the common NOx source with different sources of secondary and tertiary amines (see Figure 11.). Two principle routes of *N*-nitrosamine generation were identified which can be classified into two main reaction types:

- Hydrolytic and/or thermal degradation of the solvents DMF and NMP to give the secondary amines DMA and MBA respectively, followed by subsequent *N*-nitrosation, finally yielding NDMA and NMBA.
- *N*-nitrosative de-alkylation of the reagents TEA, DIPEA and *N*,*N*-DMA (trialkyl amines), finally yielding NDEA, DIPNA, EIPNA and NMPA; and hydrolytic dissociation of the catalyst TEA HCl (quaternary ammonium salt) to give the tertiary amine TEA, followed by *N*-nitrosative de-alkylation, finally yielding NDEA.

Figure 11. *N*-Nitrosamine formation routes and classification of reaction types

	Route of Formation	Reaction type classification
NDMA		Hydrolytic and/or thermal degradation of DMF to give DMA and subsequent *N*-nitrosation
NDEA		*N*-nitrosative de-alkylation of the tertiary amine DIPEA Hydrolysis of quaternary ammonium salt TEA HCl to give the tertiary amine TEA and subsequent *N*-nitrosative de-alkylation
DIPNA		*N*-nitrosative de-alkylation of the tertiary amine DIPEA
EIPNA		*N*-nitrosative de-alkylation of the tertiary amine DIPEA
NMBA		Hydrolytic and/or thermal degradation of NMP to give the secondary amine MBA and subsequent *N*-nitrosation
NMPA		*N*-nitrosative de-alkylation of the tertiary amine *N*,*N*-dimethylaniline
NDBA		Nitrosation of the secondary amine DBA and/or *N*-nitrosative de-alkylation of the tertiary amine tributlyamine (TBA)

The proposed root causes were considered plausible during the Article 31 review and in line with literature data summarized above (see section 2.2.). However, it became evident that the root-cause analysis focussed only on degradative mechanisms for amine generation and *N*-nitrosamine formation without considering the potential presence of secondary and tertiary amine impurities in the applied solvents, reagents and catalysts. It should be borne in mind that the following discussion on impurities does not relate to recycled materials which may have different impurity profiles depending on their previous use and how they are purified.

DMF is produced on industrial scale by the reaction of carbon monoxide with DMA and sodium methanolate in methanol or by direct reaction of methyl formate with DMA. The content of DMA in DMF is usually limited to ≤ 20 ppm. DMF is known to be degraded to carbon monoxide and DMA by heating and to formic acid and DMA by hydrolysis in aqueous solution.[71] It is concluded that DMF represents a potential source of DMA due to its production process and due to potential thermal and hydrolytic degradation.

NMP is produced on industrial scale by the reaction of γ-butyrolactone with an excess of methylamine at high pressure and temperature. The content of methylamine in NMP is usually limited to ≤ 0.02%. NMP is known to be quite stable to thermal challenge but susceptible to degradation to 4-methylaminobutyric acid under strong acidic or alkaline conditions. Since this impurity is not limited in industrial specifications, 4-aminobutyric acid could theoretically be present as an impurity up to 0.4%.[72] It is concluded that NMP represents a potential source of 4-methylaminobutyric acid due its production process and due to hydrolytic degradation.

Lower alkylamines such as triethylamine are produced on industrial scale by alkylation of ammonia with the corresponding alcohols at high temperature and pressure. Since primary and secondary amines are intermediates in the reaction sequence to tertiary amines, they are likely impurities, purged to an extent by purification procedures. For instance, the content of diethylamine in triethylamine is usually limited to ≤ 0.01 %.[73] In general, monoalkylamines, dialkylamines and trialkylamines represent potential sources of secondary and tertiary amines due to their industrial production processes.

Unsymmetrical trialkylamines such as DIPEA are produced on industrial scale by alkylation of secondary amines with alcohols. Quaternary alkyl ammonium salts such as TEA HCl or TBAB are produced on industrial scale by acid base reaction or alkylation of tertiary amines.[74] Considering that both unsymmetric trialkylamines and quaternary alkyl ammonium salts are derived from the corresponding secondary and tertiary amines, these precursors represent potential impurities.

As discussed above (Figure 11.), the Article 31 sartans review uncovered multiple root causes of *N*-nitrosamine formation. Discreet combinations of nitrosating agents and amine-derived reagents, solvents and catalysts were identified which result in *N*-nitrosamine formation under certain conditions. These critical compound combinations (CCCs), summarised in Figure 12. , therefore present a high risk of *N*-nitrosamine formation and should be avoided in manufacturing processes by first intent, unless it can be demonstrated that they are unavoidable.

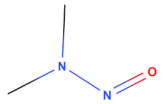
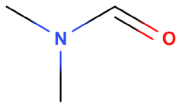
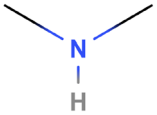
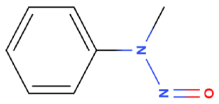
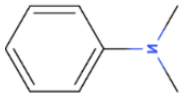
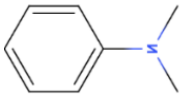
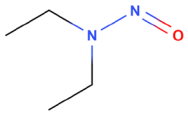
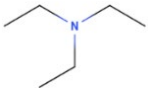
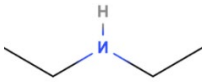
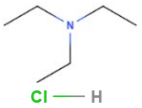
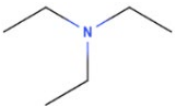
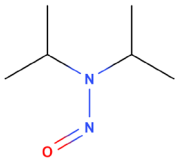
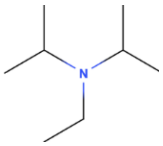
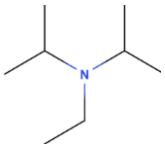
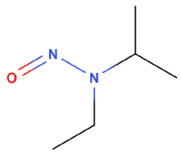
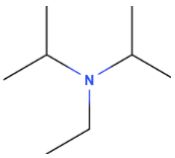
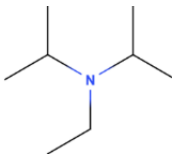
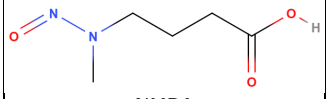
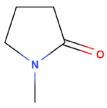
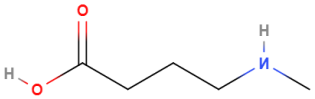
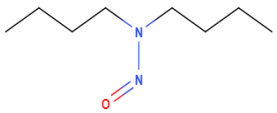
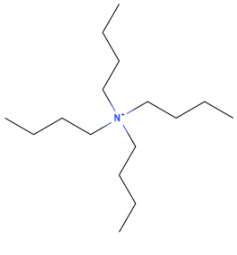
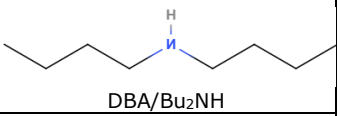
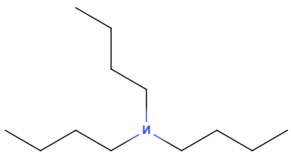
[71] H. Bipp et al. in Formamides Ullmann's Encyclopedia of Industrial Chemistry, 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[72] A. L. Harreus et al. in 2-Pyrrolidone Ullmann's Encyclopedia of Industrial Chemistry, 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[73] P. Roose et al. in Amines, Aliphatic Ullmann's Encyclopedia of Industrial Chemistry, 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[74] P. Roose et al. in Amines, Aliphatic Ullmann's Encyclopedia of Industrial Chemistry, 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Figure 12. Critical compound combinations responsible for *N*-nitrosamine formation

Nitrosamine	NOx Source	Amine Source	Amine nitrosated by NOx	Critical Compound Combination
 NDMA	$NaNO_2$	 DMF	 DMA	reagent/solvent
 NMPA	$NaNO_2$	 N,N-DMA	 N,N-DMA	reagent/solvent
 NDEA	$NaNO_2$	 TEA	 DEA	reagent/reagent
		 TEA HCl	 TEA	reagent/catalyst
 DIPNA	$NaNO_2$	 DIPEA	 DIPEA	reagent/reagent
 EIPNA	$NaNO_2$	 DIPEA	 DIPEA	reagent/reagent
 NMBA	$NaNO_2$	 NMP	 MBA	reagent/solvent
 NDBA	$NaNO_2$	 TBAB	 DBA/Bu_2NH	reagent/catalyst
			 TBA/Bu_3N	

During the Article 31 review of sartans, two valsartan-related *N*-nitrosamine impurities were identified. One was found not to be mutagenic following Ames testing. No data was provided for the second structurally related impurity, although the MAH argued that the structural similarity was sufficient to

consider it non-mutagenic. The assessors considered that the second impurity was likely to have significantly different physicochemical properties and *in vivo* behaviour. Therefore, Ames testing was requested. Data from Ames testing was subsequently submitted and deemed by EDQM to adequately demonstrate non-mutagenicity of the second impurity. This demonstrates that some compounds containing *N*-nitrosamine functionality may not be mutagenic.

2.3.2. The aminophenazone case and historical data

In the 1970s, *N*-nitrosamines were known to form from active substances (*in vitro* and *in vivo*) and were found in APIs for aminophenazone (also known as aminopyrine), a product widely used in the past as an antipyretic and analgesic.[75] In 1972, W. Lijinsky et al. investigated the *in vitro* formation of *N*-nitrosamines from drug substances incubated with sodium nitrite under physiological conditions (37 °C, pH = 3.5 – 5.5).[76] In their study, a variety of *N*-nitrosamines were produced from different APIs in variable yields depending on their structure. Aminophenazone and oxytetracycline were the most reactive substances, yielding 73% and 65% NDMA (abbreviated as DMN in Table 3.) respectively.

In the following year, W. Lijinsky et al. reported an increase in the incidence of liver tumours in rats administered with various drug substances such as aminophenazone and nitrite twice weekly for 50 weeks in doses of 40-53 mg/animal/week (Table 4.).

Table 3. In vitro formation of *N*-nitrosamines from APIs

Reaction of drugs with nitrite								
Compound	Wt.	Nitrite	Acid	Vol.	pH	Temp.	Time	Yield of nitrosamine
Oxytetracydine	250 mg	0.5 g	1.5 ml AcOH	12 ml	4.0	37° C	4 h	24 mg DMN (65%)
	250 mg	0.5 g	2.3 g NaH_2PO_4	12 ml	4.2	37° C	4 h	4.2 mg DMN (11%)
Aminopyrine	1.0 g	2.0 g	4 ml AcOH	25 ml	4.2	37° C	4 h	234 mg DMN (73%)
	1.0 g	2.0 g	8.6 g NaH_2PO_4	25 ml	4.7	37° C	4 h	106 mg DMN (33%)
Disulphiram	0.74 g	1.8 g	1.5 ml AcOH	12 ml	4.0	37° C	2 h	22 mg DEN (4.4%)
	0.74 g	1.8 g	3.4 g NaH_2PO_4	12 ml	4.6	37° C	2 h	31 mg DEN (6.2%)
	0.74 g	1.8 g	0.01 M HCl	12 ml	2.0	37° C	2 h	3 mg DEN (0.6 %)
Nikethamide	1.0 g	1.7 g	1.5 ml AcOH	12 ml	3.8	37° C	2 h	0.8 mg DEN (0.13%)
	1.0 g	1.7 g	0.01 M HCl	12 ml	2.1	37° C	20 h	0.02 mg DEN (0.003%)
	1.0 g	1.7 g	0.01 M HCl	12 ml	3.0	37° C	20 h	0.06 mg DEN (0.01%)
	1.0 g	1.7 g	0.01 M HCl	12 ml	3.6	37° C	20 h	1.65 mg DEN (0.28%)
	1.0 g	1.7 g	0.01 M HCl	12 ml	4.2	37° C	20 h	1.65 mg DEN (0.28%)
Tolazamide	4.0 g	3.5 g	3 ml AcOH	25 ml	4.4	37° C	4 h	445 mg NHM (28%)
	4.0 g	3.5 g	8.6 g NaH_2PO_4	25 ml	4.2	37° C	4 h	367 mg NHM (23%)
Piperine	100 mg	1.0 g	1.5 ml AcOH	12 ml	3.6	90° C	4 h	11.2 mg NP (27%)
	100 mg	1.0 g	1.5 ml AcOH	12 ml	3.6	37° C	4 h	2.2 mg NP (5%)
	100 mg	1.0 g	0.01 M HCl	12 ml	2.3	37° C	4 h	0.05 NP (0.1 %)

Table 4. Tumour incidence in rats fed with APIs and nitrite in drinking water[77]

					No with primary tumours of*			
Amine and nitrite concentration (p.p.m.)	Treatment duration (weeks)	No of animals	Average dose per animal (mg per week)	Tumour-bearing animals per animals dead	liver	lung	oesophagus	Other

[75] Aminophenazone is no longer widely used in the EU but some aminophenazone drug products are still registered in Italy and Hungary

[76] Nature 239 (1972), 165–167

[77] Nature, 239, (1973), 165–167

						No with primary tumours of*		
Aminopyrine (1,000)	30	15 M 15 F	53 40	14/15 15/15	14 15	0 1	0 0	0 1
Aminopyrine (250)	50	15 M 15 F	20 20	4/4 9/10	4 8	0 0	0 0	0 3
Heptamethyleneimine hydrochloride (2,000)	28	15 M 15 F	156 140	6/8 14/5	0 0	2 11	3 14	4 4
*One of the twelve animals with a liver tumour also had a parotid tumour.								

In 1975, these findings led the medicines regulator in the Federal Republic of Germany, Bundesgesundheitsamt, to release a recommendation to re-formulate aminophenazone preparations by adding ascorbic acid as an anti-oxidant to prevent *in vivo* nitrosation and NDMA formation.[78] Two years later, in 1977, Bundesgesundheitsamt was dealing with the detection of high levels of NDMA (up to 340 ng/g or 340 ppb) in some API batches of aminophenazone (Table 5.) and recommended withdrawal of aminophenazone preparations from the market.[79]

Table 5. NDMA quantities detected in aminophenazone finished products and APIs[80]

	Number	Range (µg/kg)
Formulations (tablets, dragees, ampoules, suppositories, drops, syrups, ointments)	35 27 5 1	1 – 10 11 – 50 51 – 100 > 100
Sum	68	1 – 370
Pure substances	8 8 10	20 – 50 51 – 100 > 100
Sum	26	20 – 340

At that time, aminophenazone API was being manufactured using two similar processes, both involving the use of sodium nitrite for a nitrosation procedure, followed by subsequent reduction and methylation reactions (see Figure 13. and 0).[81] The formation of NDMA in aminophenazone APIs has been linked to the reaction with nitrous acid anhydride (N_2O_3) and subsequent formation of the corresponding 4-hydroxypyrazol-3-one derivative.[82] NDMA could also be formed by direct reaction of aminophenazone API with nitrous acid (HNO_2) and subsequent formation of the corresponding 4-hydroxypyrazol-3-one derivative (see Figure 15.).[83]

[78] Eisenbrand et al. Arzneim.-Forsch. / Drug Res., 29, (1979); 867-869; Press release BGA Nr 13/75, 6 May 1975

[79] Eisenbrand et al. Arzneim.-Forsch. / Drug Res. 29 (1979); 867-869; Press release BGA Nr. 16/77, 10 August 1977

[80] NDMA quantities detected in aminophenazone FPs and API [Eisenbrand et al. Arzneim.-Forsch. / Drug Res 29; (1979); 867-869

[81] See Pharmazeutische Wirkstoffe, Synthesen -Patente – Anwendungen, A. Kleemann und J. Engel; G. Thieme Verlag Stuttgart 1978; Lehrbuch der Pharmazeutischen Chemie, 9 Auflage, Wiss. Verlagsgellschaft, Stuttgart

[82] Z. Krebsforsch., 82, (1974), 259-268

[83] Cancer Research, 34, (1974), 255–258

Figure 13. Manufacture of aminophenazone API by synthetic route A[84]

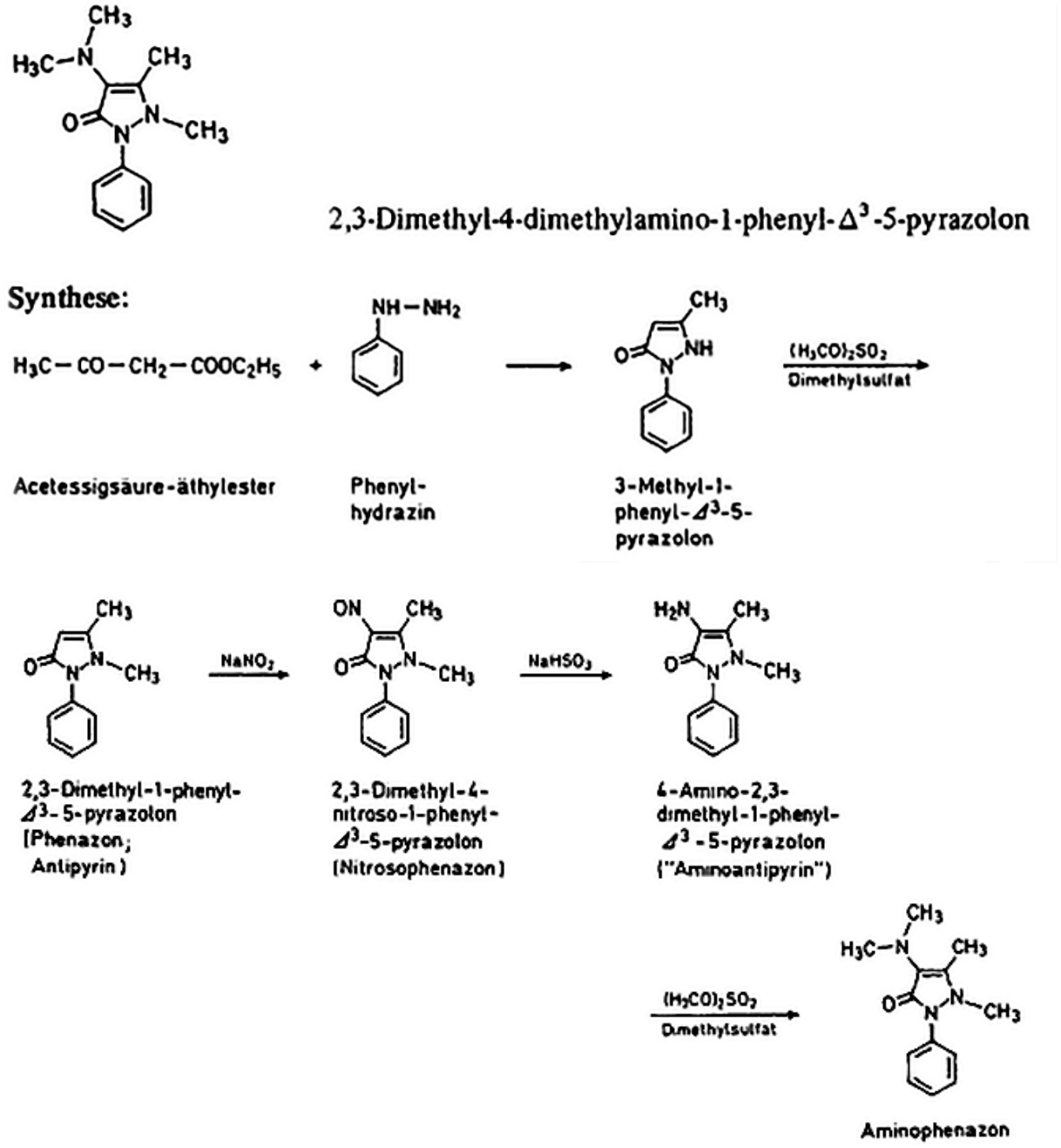


Figure 14. Manufacture of aminophenazone API by synthetic route B[85]

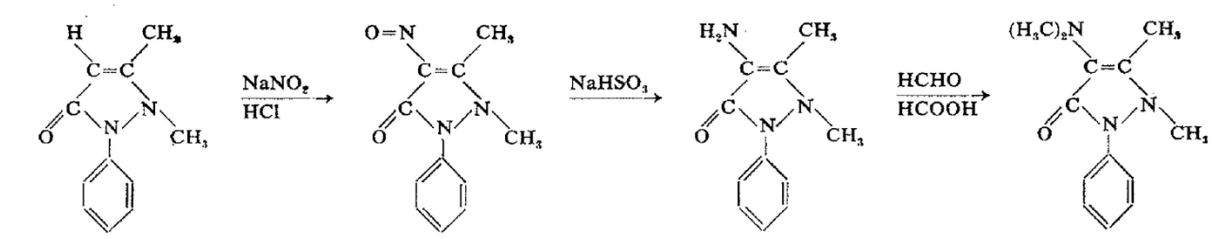
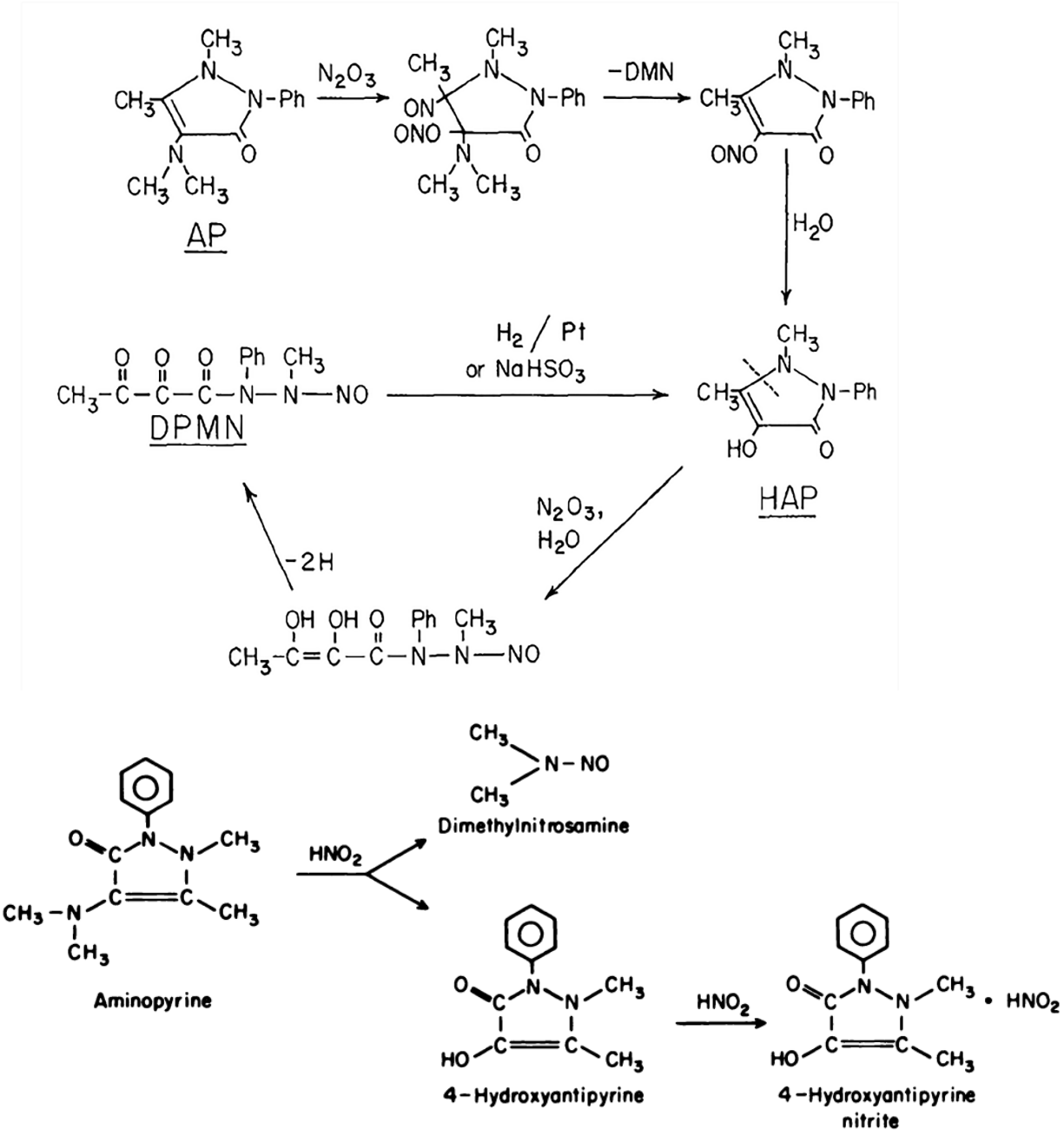


Figure 15. NDMA formation from aminophenazone API by reaction with N_2O_3 and HNO_2[86,87]



Aminophenazone contains a non-aromatic pyrazolone ring substituted with a dimethylamine group at the 4-position. Hydrolytic degradation leads to the generation of the corresponding 4-hydroxypyrazol-3-one derivative and the release of DMA.[88,89]. Although the origin of NDMA is the same as observed for valsartan (i.e. the combination of sodium nitrite and DMA, see Section 2.3.1.), the cases differ in the origin of DMA (solvent degradant vs. API degradant).

[84] Pharmazeutische Wirkstoffe, Synthesen -Patente – Anwendungen, A. Kleemann und J. Engel; G. Thieme Verlag Stuttgart 1978

[85] Lehrbuch der Pharmazeutischen Chemie, 9 Auflage, Wiss. Verlagsgellschaft, Stuttgart (1978)

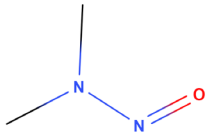
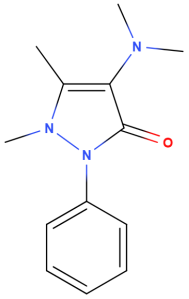
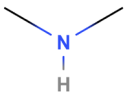
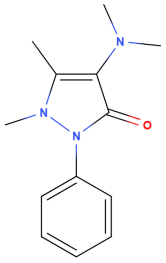
[86] Mirvish et al. Z. Krebsforsch., 82, (1974), 259-268

[87] W. Lijinsky Cancer Research, 34, (1974), 255–258

[88] Reisch et al. Tetrahedron Lett. (1969); 4; 271-272

[89] Reisch et al. Dtsch. Apotheker-Ztg. (1967); 107; 1358-1359

Figure 16. Critical compound combinations responsible for nitrosamine formation in aminophenazone

N-nitrosamine	NOx source	Amine source	Amine nitrosated by NOx	Critical compound combinations
 NDMA	$NaNO_2$	 Aminophenazone	 DMA and/or  Aminophenazone	Reagent/solvent

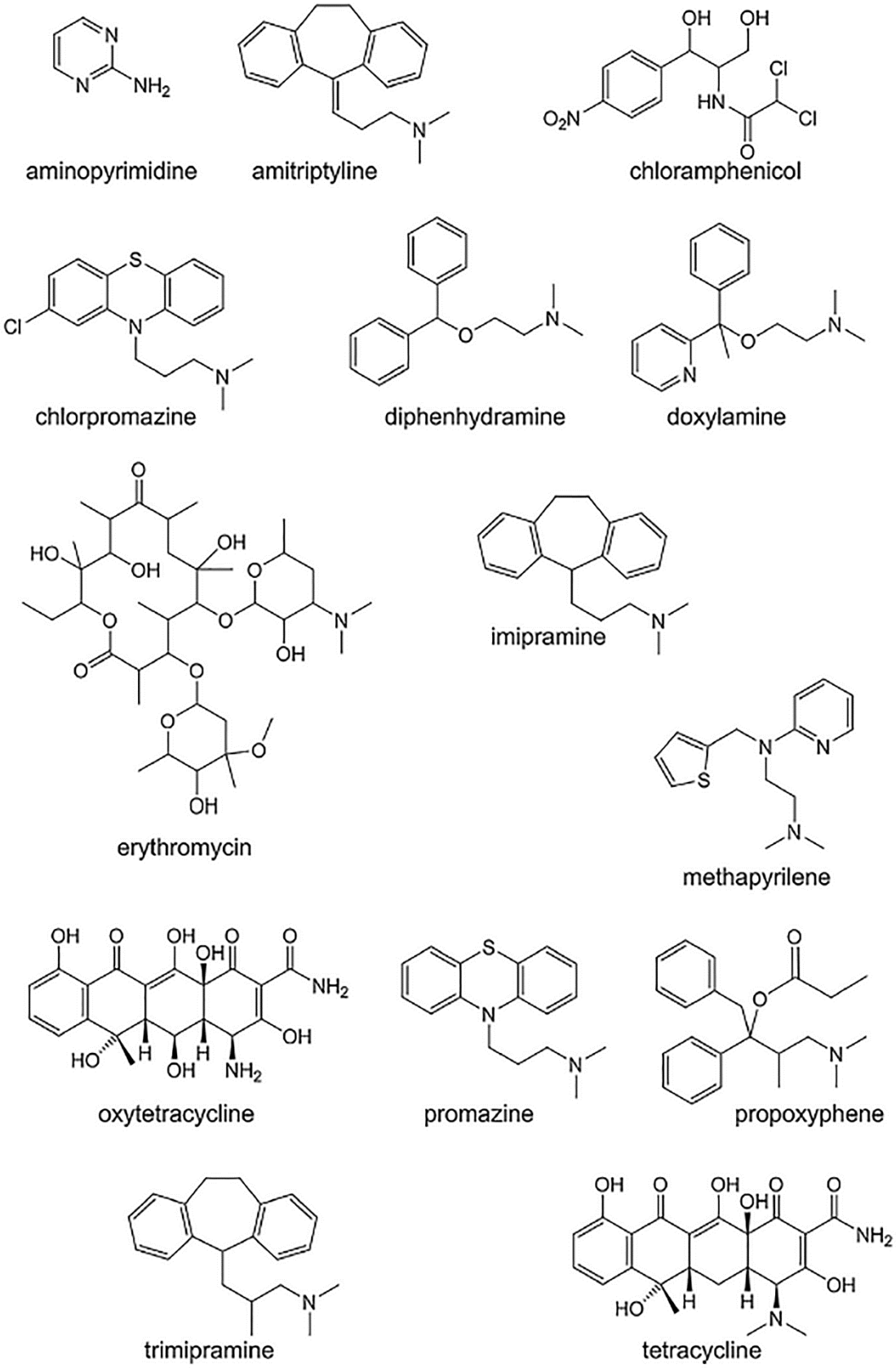
There are various potential routes to aminophenazone,[90,91,92,93] some of which avoid the use of sodium nitrite in the penultimate step, thus reducing significantly the risk of NDMA formation. The fact that a riskier route was chosen demonstrates the need for the choice of synthetic route to be adequately justified, especially with regard to API impurity profile.

In the aftermath of the aminophenazone case, scientists began to investigate *N*-nitrosamine impurities in APIs and finished products. Eisenbrand et al. found none of the 73 products tested within their study to contain NDMA.[94] However, *N*-nitrosamine levels were detected in disulfiram finished products, ranging from 94 – 980 ppb for NDEA[95] and in piperazine formulations, up to 20 ppm mononitroso-piperazine.[96] Concrete concentration ranges in APIs and finished products are available in the literature.[97,98,99,100]

A recent study investigated the potential for generation of NDMA in a range of APIs when treated with nitrite or other oxidizing agents.[101] Those identified from the literature are shown in Figure 17.

[90] H. Thomes et al. Liebigs Ann. Chem. 434, (1926), 396-312
[91] E. Waser Helv. Chim. Acta 8, (1925); 117-125
[92] D. M. Hamel et al. J. Electroanal. Chem. 28, (1970), 197-206
[93] S. R. Amanchi et al. New J. Chem. 43, (2019) 748-754
[94] Arzneim.-Forsch. / Drug Res. (1979); 29; 867-869], Krull et al. [Arzneim.-Forsch. / Drug Res. (1979); 29; 870-874
[95] Castegnaro et al. Food Cosmet. Toxicol (1981), 19, 489 -491)
[96] T. Bellander Toxicology and applied Pharmacology 80 (1985), 193–198
[97] Castegnaro et al. Food Cosmet. Toxicol (1981), 19, 489 -491);
[98] P. Taylor et al. IARC Sci. Publ. (1980) 575-587
[99] BA. Dawson et al. J. Assoc. Off. Anal, Chem. 70 (1987) 554-556
[100] T. Bellander Toxicology and applied Pharmacology 80 (1985), 193–198.
[101] M. K. Parr et al. J. Pharm. Biomed. Anal. (2019), 164, 536-549)

Figure 17. Chemical structures of APIs reported in literature to contain NDMA[102]



[102] M. K. Parr et al. J. Pharm. Biomed. Anal. (2019), 164, 536-549

The NAP test

In 1978, the World Health Organization (WHO) Expert Group proposed the nitrosation assay procedure (NAP test) as a general *in vitro* test system under standard conditions to study the nitrosation ability of drug substances.[103] At that time, aminophenazone API was found to show the highest relative *N*-nitrosation of selected drug substances (Table 6.). In 2007, Brambilla et al. summarised the genotoxic and carcinogenic risk to humans caused by drug-nitrite interactions in a review article.[104] The authors stated that 'since the endogenous formation of *N*-nitroso compounds from nitrosatable amine precursors and nitrosating agents, such as nitrite or nitrous gases, is not usually taken into account in carcinogenicity tests of the parent compound, additional investigations are necessary to evaluate this possible hazard.'

Table 6. NAP test criteria

Nitrosation assay procedure (NAP test) (WHO, 1978)
If valid comparisons are to be made, the reactions must be carried out under standard conditions for set times, and the identity and yield of N-nitroso compounds established by mass spectrometry or other appropriate methods. The WHO Expert Group recommended a 'Nitrosation Assay Procedure' (NAP test) that must conform to the following criteria: • Concentration of drug: 10 mmol/l • Concentration of nitrite: 40 mmol/l • Reaction temperature: 37°C • pH: 3-4 • Reaction times: 1 hour *and* 4 hours

By referring to the above-mentioned IARC conclusion from 1980, these authors state that 'in spite of this recommendation, guidelines for genotoxicity testing of pharmaceuticals do not recommend performing adequate tests in order to assess whether a nitrosatable drug may undergo endogenous nitrosation to a genotoxic NOC [*N*-nitroso compound].' Investigation of the potential nitrosation of drug substances is currently not required in any regulatory guidance document applicable in the EU and could be considered in future.

As outlined above, NDMA formation in aminophenazone has been linked to nitrosative degradation of the API in response to sodium nitrite carry over during drug substance synthesis.[105] Up to 173 drug substances have been found to form *N*-nitroso compounds such as *N*-nitrosamines upon reaction with nitrite under *in vitro* conditions.[106] Therefore, it could be relevant to consider under what circumstances the WHO NAP test should be conducted on relevant materials during process development in future. In case of positive findings, further investigations such as Ames testing may be required in accordance with ICH M7 (R1).

[103] IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Some pharmaceutical Drugs, Volume 24, IARC, Lyon, France, General Considerations on N-Nitrosatable Drugs 1980, 297 - 314
[104] Mutation Research (2007), 635, 15-72
[105] Eisenbrand et al. Arzneim.-Forsch. / Drug Res. (1979); 29; 867-869
[106] Mutation Research (2007), 635, 15-72

2.3.3. The pioglitazone case

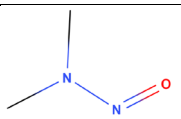
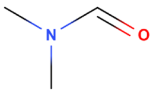
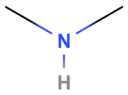
In January 2019, NDMA was reported in some batches of pioglitazone in what was the first such report for a non-sartan since June 2018. The amount of NDMA present in the affected batches would lead to exposure below the 96 ng/day agreed interim limit from the Article 31 review of sartans. The manufacturer of the pioglitazone API concerned, Hetero Labs, proposed that the preliminary root cause was the use of $NaNO_2$ and HBr in an early step of the process, followed by the use of DMF and HCl in a later step. This root cause requires either $NaNO_2$ or another form of nitrosating agent (NOx) to be carried over across several steps before DMF is introduced (e.g., as the nitrous acid salt of the pyridine moiety). Other potential root causes were also considered, including the use of solvents (e.g., DMF) contaminated with NDMA. However, this has not yet been further investigated.

This case was also the first time an *N*-nitrosamine was detected in an API where its formation does not occur in the final synthetic step and where sources of nitrite would need to be carried over across several synthetic steps consisting of multiple unit operations, including aqueous work-ups and crystallisations, before coming into contact with a secondary amine.

Following an inspection, the manufacturing routes of all sources of pioglitazone in the EU were assessed for the risk of *N*-nitrosamine formation. The synthetic routes are documented either in CEPs or ASMFs.[107] Only one of these routes uses sodium nitrite as well as sources of secondary amines.[108] The other manufacturing routes were all deemed not to pose a risk of *N*-nitrosamine formation. MAHs using pioglitazone from those manufacturers using sodium nitrite in their processes were subsequently contacted and requested to provide risk assessments for potential *N*-nitrosamine formation and batch analysis data on batches of their APIs. No other contaminated sources of pioglitazone have been identified as yet.

In summary, the use of $NaNO_2$ and DMF in different but subsequent synthetic steps represents the most likely source of NDMA formation (Figure 18.). In this case, NDMA formation is considered principally avoidable by replacing DMF as the nitrosatable solvent or by selecting an alternative route for the manufacture of pioglitazone HCl. The option to choose between different manufacturing processes demonstrates the need for thorough justification of the entire route during manufacturing process development.

Figure 18. Critical compound combinations responsible for *N*-nitrosamine formation in pioglitazone HCl

N-nitrosamine	NOx source	Amine source	Amine nitrosated by NOx	Critical compound combinations
 NDMA	$NaNO_2$	 DMF	 DMA	Reagent/solvent

2.3.4. Other recent cases of *N*-nitrosamines in medicines

On 12 September 2019, at the request of the European Commission, the CHMP started an Article 31 review of ranitidine medicines following the detection of NDMA exceeding the temporary limits

[107] See more ASMF guidelines on EMA's website.

[108] Kleemann Engel Pharmaceutical Substances Syntheses, Patents and Applications of the most relevant APIs, online edition 2019

calculated based on the Article 31 review of the sartans referral (see section 3.2.3.). As a consequence of these investigations and batch analysis results, all CEPs for ranitidine hydrochloride were suspended by EDQM, pending further information.

At the same time, EMA started a further exercise as part of an Article 5(3) procedure to provide guidance to MAHs for all medicines containing chemically synthesised active substances. The outcome of the implementation of the guidance and of the ranitidine review will be considered by the European medicines network outside the scope of the current lessons learnt exercise.

2.3.5. Presence of *N*-nitrosamines and nitrites in raw materials and water

2.3.5.1. N-Nitrosamines and nitrites in water

When *N*-nitrosamines are present in raw materials used in finished product manufacture, there is a risk that they could end up being present in the finished products. NDMA can occur in drinking water as it is a by-product of several industrial processes and is a contaminant of certain pesticides. NDMA has been identified as a disinfection by-product of chloramination (by the reaction of monochloramine with dimethylamine, a ubiquitous component of waters impacted by wastewater discharges) and, to some extent, chlorination. NDMA can also be formed as a by-product of anion-exchange treatment of water. It is generally removed during water treatment by ultraviolet irradiation. The reaction of dichloramine with amine precursors is likely the dominant mechanism responsible for NDMA formation in drinking waters[109]

The current WHO guideline for drinking water quality defines a limit for NDMA in drinking water of 0.1 µg/L, equivalent to 0.1 µg/kg = 0.1 ng/g = 0.1 ppb in case of ρ = 1 kg/L, due to different sources from the environment.[110] Stricter limits are in place in some parts of Europe and the USA.

APIs are generally organic molecules, more soluble in organic solvents than water. As a result of these properties, aqueous solutions are often used in work-up procedures to quench reactions and separate polar impurities from the organic API solution. Considering the high solubility of NDMA in water (290 g/L at 20 °C),[111] it is highly likely that any NDMA present in process water will remain in the aqueous phase and not be distributed extensively in the organic phase. NDMA present in water used to wash solid APIs will also remain in solution. Therefore, it is highly unlikely that process water constitutes a significant source of NDMA contamination of APIs. The use of contaminated water in finished product manufacturing processes, for example, wet granulation, film-coating, lyophilisation or preparation of aqueous solutions could potentially lead to some level of contamination. Water is generally removed by evaporation and *N*-nitrosamines generally have significantly higher boiling points, making them difficult to purge fully. However, the amount of NDMA present (if present at all) is likely to be so low as to pose no significant risk.

A recent review reported that water disinfection procedures may lead to significant *N*-nitrosamine generation in combination with certain APIs (Figure 19.)[112] She et al. have investigated the susceptibility of 20 drug substances to *N*-nitrosamine formation after exposure to water disinfected with chloramine.[113] Molar yields higher than 1% were observed for eight APIs, with ranitidine showing the strongest potential to form NDMA. Despite lower molar turnover, similar results were reported for

[109] Krasner et al. Water Research 2013; 47, 4433 – 4450

[110] WHO/HSE/AMR/08.03/8; 4th edition, incorporating the 1st addendum

[111] Alaba et al., Critical Reviews in Environmental Science and Technology 2017; 47; 2448–2489

[112] See M. K. Parr, J. F. Joseph J. Pharm. Biomed. Anal. (2019), 164,536-549

[113] Water Res. 45, (2011); 944-952

ranitidine when treated with water disinfected by ozonation (Figure 20.).[114] These potential root causes will be borne in mind during the Article 31 referral on NDMA contamination of ranitidine.

Figure 19. Chemical structures of APIs reported in literature to form NDMA by contact with disinfected water[115]

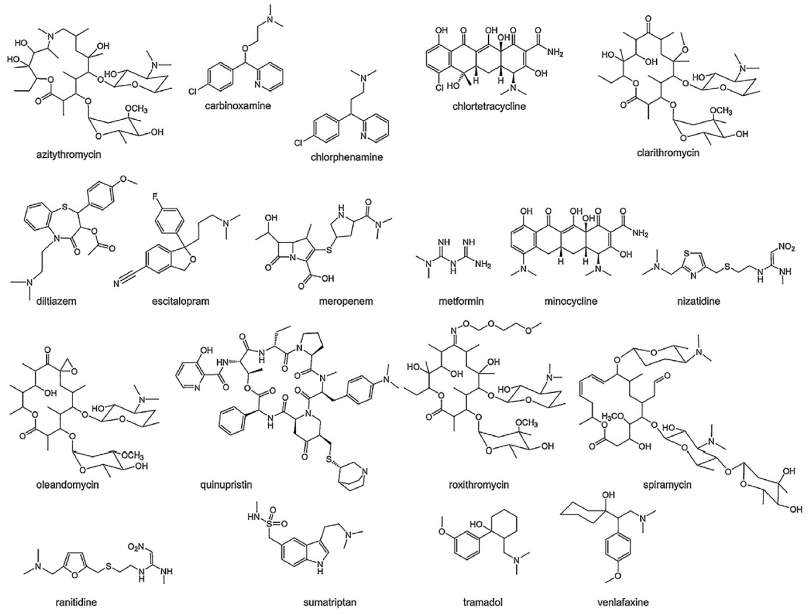
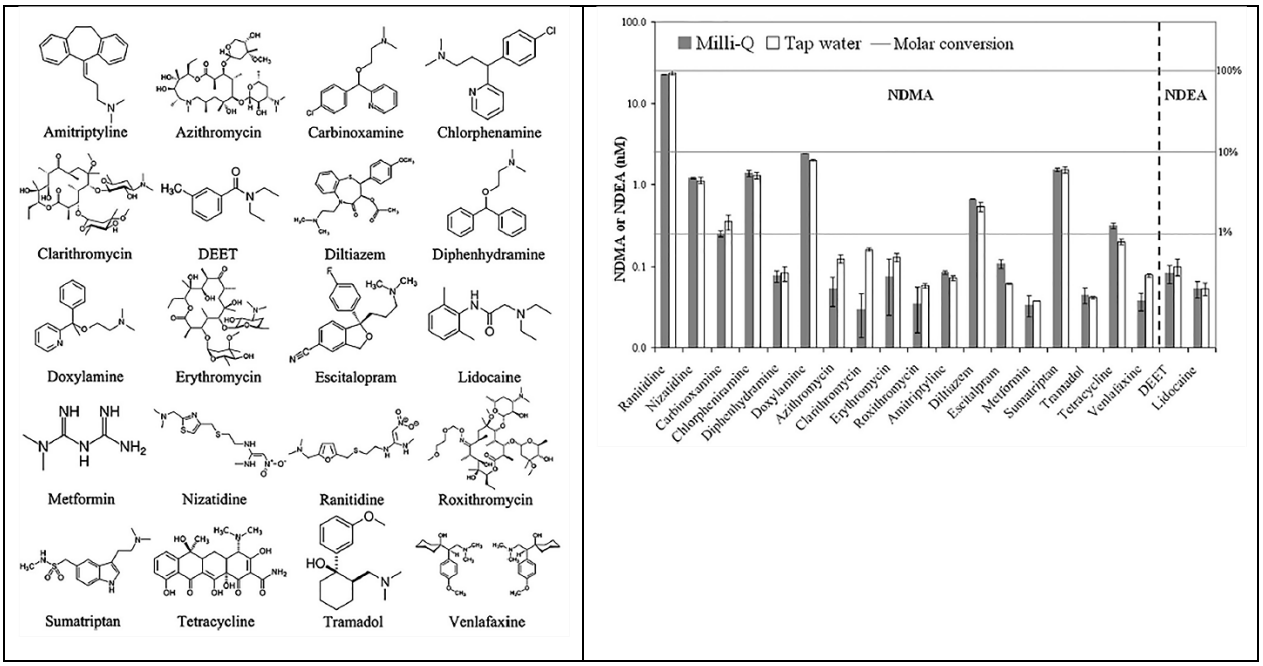


Figure 20. Chemical structures of APIs reported in literature to form NDMA by contact with water disinfected by chloramine



The presence of nitrites in raw materials could also cause *N*-nitrosamines to be present in the finished products as they could react with amines (ubiquitous in APIs), their precursors, reagents and many solvents, to form *N*-nitrosamines. Nitrites have been found in various reagents, often when sodium

[114] J. Lu J. Environ. Sci. 58; (2017); 116-126

[115] M. K. Parr et al. J. Pharm. Biomed. Anal. (2019), 164, 536-549

nitrite has been used in their preparation (for example, sodium azide). This is another route by which nitrites could be inadvertently introduced into a synthetic process.

Nitrite is generally also present in drinking water, and thus likely, process water. The WHO has set a guideline value for nitrite in drinking water of 3 mg/L as nitrite ion (equivalent to 0.9 mg/L as nitrite nitrogen). [116] Limits for nitrites in food have also been set in the EU, following input from the European Food Safety Authority. With such low concentrations, nitrosation of amines in APIs or intermediates would be very slow. Furthermore, suitable conditions for nitrosamine formation (temperature, acid) would need to be present.

In summary, *N*-nitrosamines in water are not likely to represent a significant source of contamination of APIs. Nitrosation during API degradation processes linked to the presence of nitrites in water is considered theoretically possible but unlikely. Drug substance degradation processes caused by the use of disinfected water cannot be excluded currently as a contributing factor. However, neither *N*-nitrosamines from water nor *N*-nitrosamines from API degradation processes mediated by nitrites in water have yet been identified.

2.3.5.2. N-Nitrosamines and nitrites in solvents, reagents and catalysts

During the Article 31 review of sartans, *N*-nitrosamines were identified in recovered solvents and reagents, which were identified as likely root causes of API contamination.

It is common for manufacturers to recover and recycle materials from their waste streams. This is especially common for solvents, since they are readily purified by fractional distillation. This practice is desirable for environmental reasons to reduce waste, and is allowed under GMP rules.[117] Recycled solvents may be re-used in the same process, or different processes, provided that the recovery process is controlled, documented and that they meet appropriate specifications. However, recovery processes are often outsourced to third party manufacturers who may not have full knowledge of the content of the waste streams they are processing. Therefore, tighter constraints may be required on such practices to prevent inadvertent contamination of APIs with unknown impurities.

As outlined above, solvents such as DMF, NMP and TEA represent sources of amines such as DMA, MBA and DEA susceptible to *N*-nitrosamine formation. In addition, the solvent/reagent TEA can be converted to NDEA by nitrosative dealkylation. Similar to DMF, dimethylacetamide is expected to be susceptible to hydrolysis and subsequent nitrosation. In contrast, nitromethane should be regarded a potential nitrite source and nitrosating agent. *N*-Nitrosamines have been found as minor impurities in a range of common secondary and tertiary amines. For example, NDMA was detected in DMA batches (0.65-17.3 ppm), NDEA was found in batches of TEA (0.03 ppm) and *N*-nitrosopyrrolidine was found in batches of pyrrolidine (up to 53 ppm). These results and those for other common amines are summarised in Table 7. and Table 8. Given the low levels reported, this is not considered to be a likely root cause of contamination but cannot be excluded currently.

[116] See the background document for development of WHO guidelines for drinking-water quality
[117] See GMP Part II, section 14.4

Table 7. Contamination of secondary and tertiary amines with the corresponding dialkyl-*N*-nitrosamines[118]

Amine investigated	Concentration (mg/kg)	Average value from several samples	Number of samples from different sources
Dimethylamine solution	0.65 – 17.3	6.72	6
Dimethylamine hydrochloride	0.21		1
Dimethylamine	0.1 – 7.3	1.78	1
Dipropylamine	1.9 – 13.0		2
Diisopropylamine	0.25 – 0.39		2
Dibutylamine	0.3 – 2.95	1.34	6
Diisobutylamine	8.35		1
Dipentylamine	0.31 – 2.6	1.4	3
Dihexylamine	0.4		1
Piperidine	1.6 – 2.1		2
Pyrrolidine	3.65 – 53.0	25.65	4
Triethylamine	0.03*		1
* Diethylnitrosamine			

Table 8. Alkylamines used in manufacturing screened for *N*-nitrosamine contamination[119]

Sample	Ingredient	GLC-TEA, ppm	LC-TEAA, ppm	LC-UV, ppm	GLC-Hall, ppm
N-28	Dimethylamine	34	–	26	–
N-31	Dimethylamine	28	–	29	–
N-67	Triethanolamine	–	Neg	–	–
N-69	Diethanolamine	–	Neg	–	–
N-85	Dimethylamine	4	6	–	–
Negative means less than 1ppm; a blank indicates sample was not analyses by that method					

3.3.6 Presence and formation of *N*-nitrosamines in drug products as API degradation products and as contaminants from primary packaging

Nitrates and nitrites can be found in many excipients at parts per million levels. Sodium starch glycolate, croscarmellose sodium, pre-gelatinised starch, povidone, crospovidone, and lactose are excipients that carry trace levels of nitrate or nitrite impurities.[120] The exact source of these trace impurities has not been investigated, but it is possible that they could come from process water, processing steps requiring acid titration, bleaching, and potentially from oxidation in air during high temperature drying.

As yet, there have been no reports of the formation of *N*-nitrosamines in drug products attributed to the interaction of drug substances with nitrates and nitrites in excipients. However, this possibility is considered a potential root cause and cannot yet be ruled out.

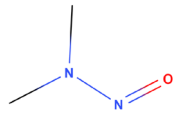
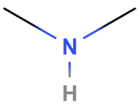
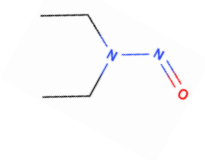
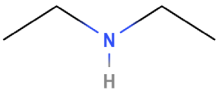
In September 2019, a new root cause for contamination of finished drug products with NDMA/NDEA was identified in relation to primary packaging materials. The levels observed were well below the temporary limits for *N*-nitrosamines agreed in the Article 31 review of sartans. The MAH's preliminary investigation report revealed that the formation of *N*-nitrosamines was caused by reaction of nitrocellulose in the lidding foil with amine constituents of printing ink (Figure 21.). These impurities were, in some cases, transferred to the drug product during the heat-sealing blistering process via vaporisation and condensation.

[118] Spiegelhalder et al. Angew. Chem. Int. Ed. Engl. (1978), 17, 367-368
[119] Bontoyan et al. J. Agric. Food Chem. 27, (1979), 631-635
[120] Y. Wu et al. AAPS PharmSciTech 12; (2011); 1248-1263

The MAH has proposed to eliminate this root-cause by replacing lidding foils containing nitrocellulose printing primer with nitrocellulose-free lidding foils. Considering that nitrocellulose printing primer is very common in lidding foils, this issue could potentially affect many products. However, it should also be borne in mind that the levels observed are low, and that a switch of packaging materials is a straightforward solution.

In conclusion, *N*-nitrosamine formation in and contamination of finished drug products during primary packaging, performed in line with good manufacturing practice, is considered principally avoidable by eliminating nitrocellulose as the responsible nitrosating agent in the lidding foil (i.e., via a minor change in the container closure system).

Figure 21. Critical compound combinations responsible for *N*-nitrosamine contamination of finished drug products

N-Nitrosamine	NOx source	Amine source	Amine nitrosated by NOx	Critical compound combination
 NDMA	Nitrocellulose lidding foil	Printing ink	 DMA	Lidding foil/printing ink
 NDEA	Nitrocellulose lidding foil	Printing ink	 DEA	Lidding foil/printing ink

2.4. Lessons learnt

The European network has robust guidelines aimed at controlling mutagenic impurities in APIs and finished products, many developed in conjunction with international regulators under the auspices of the ICH. In addition, the European Pharmacopeia sets out legally binding standards for the quality of medicines and their ingredients. These regulatory guidelines have been updated over the years to take account of growing experience from regulating medicines and new insights into how impurities can be controlled. Building on these new insights and the experience gained from the presence of *N*-nitrosamines in sartans, the lessons learnt group made observations on how such mutagenic impurities could be avoided in future.

First, in the case of the ICH M7 (R1) guideline, new requirements may need to be applied retroactively to ensure that the bulk of medicines on the market are subject to the latest best practices.

ICH M7 (R1) states that the TTC concept does not apply to CoC impurities. During the sartans referral, it was agreed that temporary limits for NDMA and NDEA should be applied based on extrapolation of animal toxicology data. However, given that the root causes identified were primarily related to the choice of synthetic route and that contamination could be minimised by choosing a different process, it was agreed that stricter limits for these highly potent impurities should be imposed in the long term, based on the capability of analytical methods at that time. Subsequently, additional root causes have been identified, not always relating to the choice of synthetic route. As a result, how to apply the principles of ICH M7 (R1) to CoC compounds is still under discussion within the network.

Second, the importance of the chemistry of *N*-nitrosamine formation and potential side reactions occurring in their manufacturing processes may not have been appreciated. More forensic assessment of potential impurities, especially those not structurally related to the active substance and its precursors, was required. In addition, better GMP compliance could reduce the risk of *N*-nitrosamine contamination, for example, from using contaminated recycled solvents, not cleaning properly between the manufacture of different batches and non-adherence to batch records for individual unit operations.

Third, there is a need to thoroughly investigate the interactions between starting materials, intermediates, drug substances, solvents, reagents and catalysts as well as potential side reactions leading to impurities during manufacturing process development. If regulators rely on the information provided in the dossier and no discussion of the potential formation of impurities is included, assessment of their potential presence by regulators can be hindered.

Fourth, although MAHs are fully responsible for the quality of their medicinal products, including the APIs and other raw materials used in the manufacturing process, they are not privy to all the information about the manufacture of the APIs by the API manufacturers. For APIs, the full information is usually documented in CEP or ASMF dossiers, which were considered during the Article 31 review and submitted to competent authorities as part of marketing authorisation applications.

For ASMFs, sufficient information should be included in the open part of the dossier, including sections S.2.2 (manufacturing process and applied controls) and S.3.2 (characterisation of impurities), and shared with MAHs so that they have adequate knowledge of the process to fulfil their responsibilities. In the case of CEPs, the information on the certificate and corresponding monograph alone is not sufficient for the MAH to have sufficient knowledge of the manufacturing process and the potential impurity content of the API. Furthermore, there is no regulatory mechanism to force the CEP holder to provide the additional information to the MAH. This situation should not prevent the sharing of relevant information between API manufacturer and MAH, especially as such information would be needed to adequately qualify a supplier. In some cases, during the referral, MAHs reported that they did not have access to information on the synthetic process.

Fifth, after the presence of *N*-nitrosamines in sartans came to light, most API manufacturers who discovered *N*-nitrosamine impurities in their APIs could have conducted better investigations into the root causes. The principles described in ICH Q9 guideline on quality risk management need to be better understood and implemented.

Sixth, MAHs do not always identify the appropriate class of variation to submit. The class of variation to submit is indicated in the EU variations classification guideline,[121] which contains a list of conditions and documentation associated with some individual change, but in some cases, the information was insufficient to guide MAHs to the correct change category. The incorrect change type could be noted during validation or assessment and further documents can be requested from the MAH. However, this rarely happens because type IA variations are minor variations following the 'do and tell' principle and are therefore subject to minimal scientific assessment. If a significant change is incorrectly submitted as a type IA variation, it is unlikely that a sufficiently in-depth scientific assessment will be conducted.

Considerations

Taking these observations into account, the lessons learnt group proposed that the following improvements be considered. These considerations form the basis of the recommendations in the 'Overview and recommendations' document.

[121] Available on the website of the European Commission

With respect to ensuring that MAHs fulfil their legal responsibilities for the quality of their products, the European medicines regulatory network could take further steps to:

- Remind MAHs of their responsibilities.
- Encourage improved quality agreements between MAHs and API manufacturers. These should be technical quality agreements rather than just purchasing agreements.
- Require better quality audits of API manufacturers by MAHs and improve the qualified person declaration system to ensure it is reliable.
- Review the CEP procedure 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 the 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.
- Consider requiring MAHs to generate and submit their own information on impurities rather than just relying on information provided by their API suppliers.

With regard to guidelines for controlling impurities:

- 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.
- 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.
- 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.
- 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, 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., $NaNO_2$) 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.

- 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.

- 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.
- 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.
- 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.
- 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.

In addition, the European regulatory network should consider:

- Establishing 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.
- 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 in view of the increasing complexity of active substance manufacturing processes.
- Re-assessing older API dossiers in pending authorisation/relevant variation applications to align with current EMA/ICH guidelines and lessons learnt with *N*-nitrosamines.

3. Handling incidents effectively

3.1. Current framework for incident management

Irrespective of the original source of the information about a defect, marketing and manufacturing authorisation holders must report immediately to the relevant competent authorities once they become aware of it.[122,123]These authorities then take swift action to assess and the control the risks to patients, following procedures set out in the *Compilation of Community Procedures on Inspections and Exchange of Information* with EMA taking a coordinating role.[124] Risk assessment and the application of quality risk management principles are significant elements of this quality defect-related work at the competent authorities in the European Economic Area (EEA)

[122]EMA for a centrally authorised medicine and NCAs for a non-centrally authorised medicine
[123]See EMA's website for more information on reporting of quality defects.
[124]Published on the European Commission's website.

The regulatory response to quality defects reflects the decentralised and collaborative nature of the regulatory system itself. Comprising NCAs, EMA, the EC and EDQM, the regulatory network has established a number of tools for coordinating activities while allowing individual members of the network (particularly NCAs) to take independent actions to protect patients.

The RAN, comprising experts from EMA and all NCAs, coordinates key actions in relation to quality defects. Typically, the first member to become aware of a defect informs the rest of RAN via a rapid alert notification, providing information about the nature of the defect, what actions they have taken and what actions they propose other RAN members should take. Follow-up RAN teleconferences can then be arranged to discuss strategies for coordinating actions across the EU.

If a quality defect could have a major health impact, EMA convenes the IRN. Comprising staff members from EMA, the EC and the NCAs closely concerned with the defect, the IRN typically considers risk minimisation and management and other regulatory options. It makes recommendations on whether a regulatory procedure (e.g., an Article 20 or 31 review[125]) should be triggered and on communication activities (e.g., the need for a press release or lines-to-take). If the IRN considers that the urgency of the situation is such that routine measures are not adequate, the 'incident' is considered a 'crisis' and an EU Executive Task Force is subsequently convened.[126]

Ultimately, the EU network has several regulatory options for handling defects, from recalling products at pharmacy or patient level to prohibiting the use of an API or medicinal product to suspending or revoking the authorisation of medicines. Some of these decisions are urgent and need to be taken shortly after a defect has been reported based on an understanding of the risk.

For the vast majority of quality defects, coordination within the network is necessary to properly evaluate risk to patients, including the risks from shortages that may result from regulatory action. EMA's CHMP provides an important scientific forum to evaluate both the risks and the nature of the quality defect and is called upon to make recommendations if a referral procedure such as an Article 20 or 31 review is triggered. A review can be triggered by NCAs or by the EC.

Finally, the CMDh, which represents Member States, plays an important role in coordinating regulatory actions of NCAs and in keeping the regulatory network updated.

3.2. Response to presence of N-nitrosamines

3.2.1. Initial response (June-July 2018)

As discussed in the introduction to this document, it was a potential customer of Zhejiang Huahai that informed the company of an unexpected impurity in its valsartan API.[127]

In the rapid alert notification sent to the RAN by AEMPS on 27 June 2018, Zhejiang Huahai was listed as having a CEP for valsartan (CEP R1-CEP 2010-072-Rev 00) and a manufacturing site based in Linhai, a city in the Zhejiang province of China. AEMPS advised the RAN that it was quarantining valsartan medicines containing the Zhejiang Huahai's API in Spain. AEMPS proposed that authorities

[125] An Article 20 pharmacovigilance procedure follows the provisions of Article 20 of Regulation (EC) 726/2004. It applies when the procedure is initiated as a result of the evaluation of data relating to pharmacovigilance of medicinal product(s) authorised via the centralised procedure only. An Article 30 'harmonisation' referral procedure follows the provisions of Article 30 of Directive 2001/83/EC. It applies when divergent decisions have been adopted by the Member States (MSs) concerning the authorisation of a nationally authorised medicinal product, in order to promote harmonisation of authorisations. It also applies when divergent decisions have been adopted by MSs concerning the suspension or revocation of a medicinal product.

[126] These steps are part of the EU incident management plan, which has been in operation since 2009. Details of this plan are published on EMA's website.

[127] According to an undated report from Zhejiang Huahai submitted to AIFA on 28 June 2018.

across the network take similar actions and evaluate the situation in their countries in order to decide if a recall from pharmacies was needed.

In the morning of 28 June 2018 when the first IRN teleconference was held, the levels of NDMA in valsartan from Zhejiang Huahai (and hence the scale of the potential risk to patients) was not known.

Based on the information available, the IRN made a number of urgent decisions to manage the situation: a list of questions was sent to Zhejiang Huahai; the Italian medicines authority (AIFA) led the investigation with the support from AEMPS; lines-to-take (for media queries) were drafted and shared with the IRN; international partners with whom EMA had a confidentiality agreement were to be alerted and a RAN teleconference was to be set up so NCAs could coordinate activities at the Member State level.[128]

At the RAN teleconference held on the same day, members agreed with recommendations from AEMPS to quarantine affected products across the EU, with several NCAs confirming that quarantines were already in place in their territories.[129]

Subsequently, Zhejiang Huahai sent a report of its internal investigation to AIFA. This report concluded that the presence of NDMA was process related and was due to the use of DMF as a solvent in its manufacturing process since 2012. By the company's measurements, levels of NDMA in its valsartan ranged from 3 ppm to 120 ppm, with an average of 66 ppm. The company's risk assessment concluded that 4.7 ppm was acceptably safe and proposed that batches of medicines containing NDMA below this level be allowed to remain on the market. This proposed limit was at odds with a preliminary toxicological assessment by AEMPS sent to the RAN on 29 June 2018, which concluded on an interim limit of 0.3 ppm for NDMA in valsartan APIs.

On 4 July 2018, AEMPS sent a second rapid alert notification to the RAN notifying members of its decision to recall products containing Zhejiang Huahai's valsartan from pharmacies in Spain and recommending that other NCAs follow suit. By 5 July 2018, an EU-wide recall of products from pharmacies was underway, with some authorities (in Cyprus, Denmark and Finland) going further with direct recalls from patients.[130]

Given the possible impact on public health in the EU, the EC triggered an Article 31 review to be carried out by EMA's CHMP.[131] As a precaution, this review was to cover all valsartan medicines in the EU and not only those containing APIs from Zhejiang Huahai.

In its notification for the review, the EC noted that 'NDMA is a genotoxic and carcinogenic agent in animals and it is classified as a probable human carcinogen by IARC…Zhejiang Huahai Pharmaceuticals provided an initial investigation report. This initial investigation…indicated that NDMA formed at a specific step in the valsartan API manufacturing process.' The Commission also confirmed that according to principles of ICH M7(R1), the levels of NDMA detected in some batches of the company's valsartan 'raise concern'.[132]

Subsequently, EMA published communication addressing both the start of the Article 31 review and the ongoing EU-wide recalls of valsartan medicines containing the API from Zhejiang Huahai.[133] In order to

[128] There were other recommendation, including those related to clinical trials and the need for a follow up IRN teleconference. See meeting minutes (document reference: EMA/436338/2018).

[129] See post meeting note in minutes of IRN teleconference 28 June 2018 (document reference: EMA/436338/2018)

[130] Based on updates from national authorities during the 6th RAN teleconference held on 19 July 2018

[131] The decision to trigger an Article 31 review was discussed at a follow up IRN teleconference held on 2 July 2018.

[132] See full published notification from the European Commission.

[133] This communication was the first of many EMA publications and was linked to many NCA websites. EMA was not the first regulator to publish material of NDMA in valsartan. The Hungarian medicines authority (OGYEI) for instance published on the quarantine on 30 June 2018.

prepare the network for queries from the media and the general public, EMA also drafted lines-to-take, which were shared with communication teams across the network on 3 July 2018.[134]

The main messages in early communication from the network were that medicines containing valsartan from one company were being recalled; that patients may be given alternative treatments but must not stop taking their medicines unless they have been told to do so by their doctor or pharmacist; and that regulators were carrying out a review. Importantly, patients were informed that there was no immediate risk from their medicines and that there was a greater risk from stopping treatments. (For further information on public communication see section 5.).

Four days later, EDQM suspended Zhejiang Huahai's CEP[135] for valsartan, effectively barring the release onto the market of valsartan medicines containing the company's API.

A major part of the initial response was identifying whether any other medicines containing sartan APIs could also have the impurity of concern. This work was led in part by EDQM, which devoted immediate resources to reviewing the processes used to manufacture active substances included in a large number of sartan medicines worldwide. This exercise resulted in the identification of a number of manufacturing processes and related medicinal products potentially at risk of contamination. The information gathered during this exercise was pivotal for NCAs' decision making on the market actions required to safeguard public health.

In addition to the above, the need for market surveillance and sampling and testing by OMCLs was recognised at an early stage and therefore an ad hoc market surveillance testing plan was agreed across the EU Member States. The agreement and implementation of this programme was coordinated by EDQM together with EMA and OMCL network (see section 4.).

To ensure that all regulators were kept abreast of developments, several RAN teleconferences were held in the coming months). IRN teleconferences were held when there were major new developments but were less frequent.

3.2.2. An evolving situation (from August 2018)

Beginning in August 2018, a number of events confirmed initial concerns that the presence of *N*-nitrosamines may not be confined to valsartan APIs from Zhejiang Huahai (see Figure 1.) In response to the rapidly evolving situation, on 20 September 2018 the EC extended the scope of the ongoing Article 31 review to include other sartans with a tetrazole ring (candesartan, irbesartan, losartan and olmesartan). The EC extended the scope of the review because there were 'sufficient reasons to believe that the quenching of azides used to synthesize the tetrazole ring with sodium nitrite in an acidic environment could lead to the generation of *N*-nitrosamines.'[136]

In dealing with the expanding nature of the review, EMA and NCAs faced the challenge of rapidly determining which products could be at risk. A number of shortcomings of the system when dealing with an incident on such a scale became apparent. First, regulators did not have appropriate databases that could quickly yield information linking API manufacturers with the finished products, taking into account the use of ASMFs and CEPs. Second, MAHs did not have readily available information on which finished products were manufactured with concerned API batches and the markets to which they were distributed. Third, API manufacturers had little information on which finished products contained their APIs. Fourth, the tracking of impacted products was affected by the presence of parallel imports. Fifth,

[134] See Guideline on good pharmacovigilance practices (GVP) – Module XV on safety communication (updated October 2017) for information on coordination of communication within the network.

[135] Full name: Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP). A CEP certifies that if a substance is manufactured in a certain way (described in the CEP), that substance can be considered suitably controlled in accordance with the European Pharmacopoeia. Information on any CEP suspended by EDQM is posted on EDQM's website.

[136] See full justification in the letter from EMA to the EC which is appended to the EC's notification.

the use of ASMF and CEPs were additional sources of complexity in tracking affected products. Often there were discrepancies between the dossiers, CEPs and ASMFs in important details such as names and addresses of companies.

Tracking products was not the only considerable challenge regulators faced as the review expanded. The lack of validated analytical methods to test samples of the potentially affected sartan products meant that some MAHs and manufacturers did not know how to test for *N*-nitrosamines. The OMCL network, which is coordinated by EDQM, subsequently developed methods for testing for specific *N*-nitrosamines in sartans, and the CHMP liaised with OMCLs to conduct risk-oriented sampling and testing of APIs and/or finished products and to inform the network of any non-compliant results.[137]

By the end of September 2018 2 for-cause GMP inspections were conducted at manufacturing sites of Zhejiang Huahai and Zhejiang Tianyu by EU Authorities on behalf of EMA and EDQM. These inspections were requested as part of the review and were performed by GMP inspectors accompanied by quality assessors. The aim of these for-cause inspections was to evaluate the root-cause analysis of the contamination of valsartan and the potential impact of the issue on the other sartans APIs, as well as to examine the potential for cross-contamination of other APIs and to verify that the identified issues were reported to relevant national and international authorities as required.

The findings from these inspections were communicated to the RAN and the IRN. Overall, while the for-cause GMP inspections were an important part of the regulatory response, in some cases their scope was not clear to the RAN, which had expected them to have a wider scope covering a general GMP inspection at the site. It was recognised that the scope of the planned inspections should have been communicated to the RAN at an earlier stage and in a clearer way.

Both testing of samples and GMP inspections were a key part of the European regulatory network's response to the sartans incident and are described in further detail in section 4.

In December 2018, due to the growing number of impacted products identified and following the publication of validated analytical test methods by the OMCL network and EDQM, EMA and NCAs decided, as a precaution, to request that all MAHs of sartan products conduct NDMA and NDEA testing *before* using APIs in finished product manufacturing.

As 2018 came to a close, the CHMP held its penultimate plenary session before it concluded its review of sartans. To arrive at its conclusions, the Committee availed itself of the expertise of a number of bodies: an ad hoc expert group in July 2018, EMA's Safety Working Party (SWP) in November 2018 and Quality Working Party (QWP) in December 2018. The CMDh also played an important coordinating role and was kept abreast of developments during the review, given that NCAs would be called upon to implement its recommendations.

The CHMP concluded its Article 31 review on 31 January 2019, with the EC issuing decisions in April 2019. The outcome and post-Article 31 developments are discussed in section 1.

Table 9. Topics discussed by expert groups during Article 31 review of sartans[138]

Expert consultation
• Ad hoc expert group – Calculation of patients' cancer risk based on toxicology data

[137] The information on these methods are published on EDQM's website, along with links to pages with information on test developed by authorities in the United States, Canada and Taiwan.

[138] The outcome of CHMP's expert consultations are discussed in the assessment report for the Article 31 review of sartans.

Expert consultation

- Safety Working Party
  - Calculations of limits on intakes for NDMA and NDEA*
  - Excess carcinogenic risk for NDMA and NDEA as found in sartans
  - Ames test to screen mutagenic impurities in APIs
  - Potential target organs in humans
- Quality Working Party
  - Root causes of presence of *N*-nitrosamines
  - Avoiding *N*-nitrosamines in sartans
  - Need for NDMA and NDEA limits

*After the conclusion of the article 31 review, the SWP gave opinions also for DIPNA, EIPNA,NMBA and NDBA impurities

The CHMP's Article 31 review was one aspect of the response to the presence of *N*-nitrosamines, feeding into and taking account of other actions by members of the European medicines regulatory network. All these actions required increasing amounts of coordination and information gathering. By the year's end, over 20 RAN and 6 IRN teleconferences had been held to discuss *N*-nitrosamines in sartans, with a high amount of information sharing occurring between teleconferences in relation to activities being carried out across the EU. Keeping track of these activities was a challenge in itself as there was no central database to capture the fast moving and evolving nature of the incident.

3.2.3. CEP suspensions

Based on the reviews of responses from API manufacturers and assessments of CEP dossiers in relation to *N*-nitrosamine impurities, EDQM suspended 11 CEPs for sartans, including 7 valsartan CEPs, 2 irbesartan CEPs and 2 losartan potassium CEPS,[139] triggering recalls of the concerned drug products by NCAs. The vast majority of sartan CEPs (over 90 %) were not affected, indicating a high probability of process-specific root causes.

Despite the fact that most CEPs for sartans did not warrant suspension (and were therefore potentially available), recalls of valsartan, irbesartan and losartan potassium medicines containing APIs for which CEPs were suspended had a sizeable impact on market supply and caused significant shortages of these medicines. However, all olmesartan and candesartan CEPs remained valid throughout the Article 31 review and beyond, and the corresponding medicinal products were available as alternative medicines to satisfy market and patient demand.

3.2.4. Other aspects of the regulatory response

As mentioned above, sampling and testing and inspections were a key part of the regulatory response to manage the sartans incident but also to explore why *N*-nitrosamines came to be present in the first place. Other aspects of the regulatory response that took on great importance were public

[139] As of September 2019 the following CEPs had been suspended, some of which were subsequently restored: CEP 2009-247 losartan potassium (restored), CEP 2009-283 irbesartan (restored), CEP 2009-396 valsartan (restored), CEP 2010-033 irbesartan, CEP 2010-072 valsartan, CEP 2010-139 losartan potassium, CEP 2011-174 valsartan, CEP 2011-231 valsartan (expired), CEP 2013-159 valsartan (restored), CEP 2014-162 valsartan, and CEP 2016-069 valsartan. For current status, check EDQM's website.

communication and international collaboration due to the public concern and global implications of the *N* -nitrosamine findings. All these aspects are discussed in detail in sections 4. to 6.

3.3. Lessons learnt

The network reacted swiftly once the presence of *N*-nitrosamines became known, taking immediate measures to protect patients and the quality of medicines in the EU. These measures included coordinating recalls of medicines across the EU, prohibiting the use of affected APIs in EU medicines (via CEP suspensions or issuance of certificates of non-compliance with Good Manufacturing Practice (GMP)), sampling and testing of medicines on the market, carrying out inspections of manufacturing sites and conducting a review of sartans medicines in the EU, including the risk to patients and the root cause of the presence of *N*-nitrosamines.

The scale of the actions taken by regulators, the speed with which they were carried out and the urgency of the safety concerns they addressed provide some opportunities to assess the impact of the regulatory response with a view to highlighting areas for improvement should the network face similar challenges in the future. A number of observations in relation to several aspects of the regulatory response, including information gathering and coordination within the network are discussed below.

First, the regulatory response could be more efficient if appropriate tools were available to quickly provide information on the links between marketing authorisations and currently used API manufacturers, considering that some APIs were registered using ASMFs and CEPs.

Second, not all MAHs and manufacturers had readily available information on which batches of their finished products contained active substances from an API manufacturer of concern. In the same vein, some API manufacturers had little or no information on which finished products their API batches were used in and in which countries. These observations underline the need to strengthen requirements for keeping records on traceability.

Third, the ability to speedily trace affected medicines was also impacted by the availability of parallel imports, which in some cases were labelled with originator brand names even though the source packs were generic versions. This led to challenges in quickly identifying which parallel imported products contained the valsartan API from using Zhejiang Huahai and other API manufacturers of concern. While the parallel imported products of concern were determined and recalled, the process could have been more efficient.

Fourth, the regulatory response could have been enhanced by the use of appropriate IT tools to capture NCA activities and to keep the network updated. Spreadsheets had limited value given the scale of activities recorded and the evolving situation. Furthermore, the email system used to keep the network updated relied on the use of single email addresses with the risk of some contacts being omitted in error.

Fifth, two important forums for coordinating actions for quality defects – the RAN and IRN – were particularly active in the second half of 2018. Both were instrumental to ensuring concerted action across the EU but in practice there was some duplication in effort and the remit of each group was not always clear.

Sixth, the SWP was called upon to give an assessment on the risks presented by the *N*-nitrosamine issue within a very limited time period; this was challenging given the high complexity of issue.

Seventh, this incident showed that when a very large number of medicinal products containing an API sourced from the same manufacturer and distributed globally is concerned by a quality defect, the impact on patients and healthcare systems can be substantial. In addition, the high reliance placed

upon the one API manufacturer (and the related medicinal product manufacturers and MAHs) to ensure the quality and safety of the API represents an issue that should be recognised and addressed.

Eight, there was some inconsistency in the regulatory terms and definitions initially used by authorities in the EU, with potential consequences on regulatory actions. For instance, the discovery of *N*-nitrosamines in valsartan was considered an 'incident' by some authorities and a 'crisis' by others. Furthermore, the *N*-nitrosamine issue was not initially classified as a quality defect in all countries and was considered by some to be a process impurity issue.

Considerations

Taking these observations into account, the lessons learnt group proposed that the following improvements be considered. These considerations form the basis of the recommendations in the 'Overview and recommendations' document:

Short-term considerations

- 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.

Long-term considerations

- 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.)
- Develop an appropriate IT tool able to capture information updates and NCA decisions in one centralised way as an incident evolves. Such a tool would improve the way information is shared and keep all relevant stakeholder groups updated in an efficient manner.
- 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.
- Revise existing procedures in order to establish a procedure for sending feedback during critical defect cases between RAN and the inspectors conducting related GMP inspections when needed.

Other considerations

- 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.
- Provide clarity on respective roles of the RAN and the IRN so that they are clearly understood by both parties in order to avoid duplication of effort.
- Ensure that there is clarity and understanding across the network of exactly when an issue is to be formally considered a 'crisis'.

- 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.

4. Improving market surveillance

4.1. Sampling and testing

4.1.1. Current framework for sampling and testing

Regulatory authorities carry out tests on samples of medicines and active substances placed on the market in order to supervise the quality of medicines and check that they comply with specifications.[140] Typically, samples are drawn by inspectors during routine GMP/GDP inspections or requested by NCAs from active substance and medicinal product manufacturing sites, wholesalers and retail or hospital pharmacies. In most cases, sampling covers only finished medicinal products available at the site or pharmacy. At times, the batches of the active substance used to manufacture the medicines are included in the sampling operation. In all cases, samples are taken in such a way as to ensure that they are preserved appropriately during their transport and storage (e.g., by protecting samples from light or moisture and by storing in a fridge or freezer where appropriate).

Most NCAs have set up risk-based annual surveillance plans for sampling and testing medicines in their territories. The degree to which OMCLs and the assessors (who evaluate the marketing authorisation applications) are involved in the planning of sampling differs between Member States. [141]

Coordinated sampling and testing programmes are in place at European level for products having undergone central authorisation, mutual recognition or decentralised procedures applying risk-based selection criteria. A harmonised risk-based model for medicinal product testing (based on pre-marketing information) covering all products has been developed by a Heads of Medicines Agencies (HMA) working group and the development of the appropriate IT capabilities to support this new approach across the EU Member States is underway.

In establishing such risk-based sampling plans, there is a need, among other things, to have oversight of the sources of active substances used for the manufacture of a given medicinal product. Furthermore, during GMP inspections of active substance manufacturers or manufacturing sites, sampling of active substances has not been routinely done for practical reasons in view of the limited time available for inspections. Furthermore, active substances are sampled when there is a suspicion of non-compliance with GMP noted during the inspection. Active substances are therefore not sampled on a routine basis.

OMCLs

OMCL routine testing of samples is normally based on approved release and/or shelf-life specifications of the medicinal products and aims to confirm compliance of the collected sample with those specifications up to their expiry date. This may also provide information with respect to products where storage is an important factor in determining product quality throughout their shelf life.

OMCLs perform a range of testing on a wide variety of medicines, including formulations such as tablets, capsules and liquid medicines but also creams, gels and injectable products. Physico-chemical and biological testing, including testing for the appearance and identification of products, may be performed to verify that the correct product is present as well as other tests to ensure that the active

[140] The obligation to conduct sampling and testing is enshrined in EU legislation. See Article 111 of Directive 2001/83/EC (products for human use) and Article 57f of Regulation (EC) No. 726/2004.

[141] OMCLs are the official laboratories of Member States charged with conducting tests on samples. Since 1994, OMCLs in the EEA have been part of a network (OMCL network) coordinated by EDQM. See EDQM's website for further information.

substance is present in the correct amount and that impurities do not exceed specified values. Microbiological testing is also performed to ensure that the product is not contaminated by microorganisms.

Validated test methods for each medicine are described in approved marketing authorisation dossiers and can be provided to OMCLs. As far as impurity (related substances) tests are concerned, the specifications are based on the requirements set out in ICH Q3A and B as implemented by CHMP guidelines and the European Pharmacopoeia. Accordingly, the specifications for unspecified impurities are (depending on the dosage) defined in the range of 0.05 to 0.1% with reference to the active substance. For impurities that are expected to be unusually potent (e.g., because they are carcinogenic), lower limits are applied, and these are derived from toxicology data for the impurity. Testing for such impurities requires specialised testing methods and is generally conducted when they are predicted to be potentially present based on analysis of the synthetic route and potential degradants.

4.1.2. Challenges faced in responding to the sartans incident

Identifying medicinal product batches of concern

When the presence of *N*-nitrosamines in sartans came to light, the European regulatory network faced the challenge of immediately identifying which medicines contained active substances from particular API manufacturers. However, as this information was not captured in a central database, the process of identifying medicines of concern (with each NCA performing their own search) was laborious and time-consuming.

As such the coordination of sampling and testing campaigns throughout the European regulatory network was more challenging.

Coping with increased demand for analytical capacity

Typically, the classical market surveillance approach involves selecting a number of samples to be analysed. However, during an incident, such as the discovery of a probable human carcinogen, regulators employ a more exhaustive approach to cover all batches of potential concern on the market. This requirement led to an increased demand on resources and some OMCLs had to put on hold routine laboratory work while the testing of sartan medicines was underway. The workload was increased further by the need to analyse samples recalled from the market in order to estimate *N*-nitrosamine exposure of patients who had taken medication from affected batches.

In response to the discovery of *N*-nitrosamines in sartans, for-cause inspections, coordinated by EDQM and EMA, were also carried out at API manufacturing sites by GMP inspection services. During some of the inspections, active substance samples were collected as supporting evidence and used to verify the accuracy of testing results reported by the active substance manufacturers.

Obtaining suitable equipment

In contrast to requirements for routine testing of impurities, the requirements for mutagenic impurities set out in the ICH M7(R1) guideline mean that tests must be more sensitive to be able to detect lower levels of impurities. These require highly sensitive and specific equipment (e.g., liquid chromatography–mass spectrometry and gas chromatography–mass spectrometry) which are not available to all OMCLs or at least are not available in the capacity required during the sartans incident.

Developing and validating testing methods

As manufacturers and OMCLs had not previously been testing for *N*-nitrosamines in sartans, rapid analysis of medicines on the market was not possible. Methods first had to be developed and adapted to each active substance or medicinal product and then validated by various OMCLs before the results obtained could be accepted and used as a basis for deciding on regulatory actions. In addition, some OMCLs faced difficulties in obtaining direct access to testing methods developed by MAHs or manufacturers.

Defining intended target limits

The development of an adequate test method should consider the intended analytical target range. Since the assessment of the toxicological data (initially only for NDMA) had to be carried out and their harmonisation with international partners took some time, the development of test methods was delayed. Additional test methods were required for NDEA which required the detection of even lower amounts of impurity than for NDMA.

Obtaining samples

Reference samples of finished medicinal products are not always suitable for specific tests (e.g., mutagenic impurities in active substances) due to matrix effects and low concentrations in the medicinal product. Therefore, preferably active substances should be tested. As most of the medicines are manufactured in third countries, retained samples of active substances are usually kept outside of the EU/EEA and access to these active substance samples is limited. Authorities are usually not on-site to collect suspected samples and when routine or suspected samples are requested directly from manufacturers in third countries, national competent authorities and their OMCLs have to be confident that these samples are representative, given that independent sampling cannot be performed.

In urgent situations the availability of active substance samples from distant non-EU locations can significantly delay testing due to transport and customs constraints.

Obtaining reference material

As the *N*-nitrosamine impurities were unexpected, there were no reference standards for pharmaceutical purposes. Instead, chemical reagent grade materials had to be used for testing and these sold out shortly after the beginning of the incident. In some Member States, it took several weeks or months and extra effort for OMCLs to obtain these materials, some of which were costly. Regulators explored the option of a supplier synthesising a quantity of a reference material for OMCL use, but this was prohibitively expensive. It has been proposed that in urgent cases, standards could be made available through a central incident/crisis management budget to expedite the OMCL response time for providing test results.

Setting priorities and coordinating sampling and testing

Market surveillance

Given the challenges outlined above, EDQM together with certain NCAs and OMCLs set priorities and made recommendations which were shared with all OMCLs that volunteered to participate in testing sartans. Where possible, OMCLs were asked to consult their inspectorates in order to identify potentially concerned products as testing candidates. The difficulties described in identifying batches of concern and the fact that not all inspectorates participated limited the coverage of the exercise. Nevertheless, the sampling and testing worksheets elaborated by EDQM were well received by all OMCLs and provided a good overview of the sartan active substances and medicinal product batches

that were scheduled for sampling. With these measures, duplication of work was avoided. The same data worksheets were used to disseminate the results on a frequent basis amongst all OMCLs and regulatory authorities. In view of the scarce resources, a more formal role of EDQM in managing the testing programme could be considered. Continuous exchange of information between EDQM and OMCLs within the OMCL network was crucial during the incident. Only with this information was it possible to react in time to shift testing activities to batches of medicines that were still on the market.

Analysis performed in support of the Article 31 review

The assessors working on the Article 31 review requested the testing of products already withdrawn from the market in order to estimate the risk to patients exposed to the concerned products. This request had resource implications given the testing being carried out on medicines on the market. A further challenge faced by OMCLs was the requests to verify results provided by MAHs and to examine a correlation between levels of impurities in the medicinal products compared with the corresponding active substance batches. In certain cases, expectations, deadlines and priorities of the assessors were not clear to the OMCLs.

4.1.3. Outcome of sampling and testing measures

The sartan incident triggered a sampling and testing operation throughout the EEA, the outcome of which informed important regulatory actions (e.g., recalls and CEP suspension) and the Article 31 review of sartans. In order to guide these regulatory decisions, the European medicines network first had to have access to reliable validated testing methods. OMCLs developed several methods shortly after the presence of *N*-nitrosamine contamination came to light and by September 2019 nine testing methods had been developed, details of which were made available to other OMCLs and industry via EDQM's website.[142]

The scale of testing both during and after the Article 31 review was immense. By April 2019, a total of 249 active substance batches and 2,000 medicinal product batches had been tested for NDMA, and 637 active substances batches and 1,007 medicinal product batches tested for NDEA**.** From these tests, including those for other *N*-nitrosamines, a number of out-of-specification results (presence of *N*-nitrosamines at levels higher than the interim limits) were obtained (see Table 10.).

Table 10. Number of out-of-specification results as of 15 April 2019

	Valsartan		Losartan		Irbesartan	
	Active substance	Medicinal product	Active substance	Medicinal product	Active substance	Medicinal product
NDMA	70 out of 141	253 out 621	0 out of 16	0 out of 312	0 out of 20	0 out of 260
NDEA	53 out of 200	36 out of 246	1 out of 149	2 out of 188	28 out of 160	29 out of 175
NMBA	-	-	13 out of 72	-	-	-

Whilst the vast majority of samples tested did not contain *N*-nitrosamines at levels higher than the interim limits, in some cases the results triggered batch recalls or CEP suspensions. Samples taken during four GMP inspections were analysed by the OMCL network and contributed to the outcome of those inspections. In terms of quality of analytical results, the reliability of the OMCL testing results was confirmed in several ring trials and sample exchanges between laboratories.

[142] See more information on EDQM's webpage for the OMCL network

The OMCL testing provided important information to the assessors involved in the Article 31 review. However, only in a limited number of cases were both samples of withdrawn product batches and the corresponding active substance batches used for their manufacture available for analysis. As a result, no firm statistical correlation could be established between the *N*-nitrosamine content in the active substances and the content in the finished products. Establishing such a correlation would require a dedicated sampling strategy throughout the entire market, ideally with a central coordination.

4.1.4. Lessons Learnt

The scale of the sampling and testing operations carried out in relation to *N*-nitrosamines illustrates the ability of the network to react speedily to cases of unexpected impurities despite resource constraints and the need to develop and validate testing methods. The experience gained to date affords the network the opportunity to build on its strengths and consider improvements. To this end, the lessons learnt group made a number of observations.

First, the testing of the actual active substance batches that were used to manufacture medicinal products would have been a preferred approach for detecting trace levels of impurities. However, in some cases, the MAHs' dossiers listed alternative active substance suppliers and current databases available to competent authorities could not always be used to trace which active substance sources were currently used for a given medicine or batch.

Second, access to active substance and excipient batches used to manufacture medicinal products is sometimes restricted, for example, due to geographic location. Based on the current legislation and inspection practices, sampling of these materials is only possible during inspections conducted within the EEA. Inspections of API manufacturers located in third countries are restricted to certain cases as defined by the legislation such as suspicion of non-compliance with GMP requirements, or are carried out using a risk-based approach at the request of a Member State, the European Commission or EMA. Hence there are only limited opportunities for API sampling.

Third, as noted above, analysis of active substances is the most appropriate way for determining the presence of trace levels of impurities such as *N*-nitrosamines. It could therefore be advantageous for GMP inspections to perform more active substance sampling during inspections.

Fourth, only a restricted number of OMCLs were able to embark on testing since the testing equipment required was not available to all OMCLs within the network. Additional barriers were the lack of suitable reference materials and the cost of such materials.

Fifth, having a clear contact point for each group (e.g., EMA, EDQM, Article 31 Group, CHMP, SWP and QWP) involved managing the sartan incident could have facilitated better communication and dialogue between various groups and avoided the need for each OMCL and NCA to contact their own national experts and potentially receive conflicting advice in relation to timelines for delivery of sample results or priorities.

Sixth, OMCLs did not always have access to details of testing methods employed by companies. In incidents such as this, better access to relevant information would have been desirable.

Considerations

Taking these observations into account, the lessons learnt group proposed that the following improvements be considered. These considerations form the basis of the recommendations in the 'Overview and recommendations' document.

- 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.

- 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 product or APIs are manufactured in the EEA.
- Strengthen the legal basis for active substance sampling and elaborate a harmonised standard operating procedure for sampling of active substances during GMP inspections.
- 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.
- 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.)
- Support central sourcing and dispatch of reference material by EDQM and finance these activities through an emergency fund.
- 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.
- 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.
- Carry out a coordinated market surveillance exercise at the European level once corrective measures are implemented by the industry.

4.2. GMP Inspections

4.2.1. Current framework for inspections

EU legislation authorises competent authorities to conduct inspections of manufacturing sites, including sites producing medicines and active substances, to ensure that manufacturers are complying with legal requirements.[143] Authorities may also inspect the premises of MAHs. The inspections, both in and outside the EU, are carried out in accordance with the guidelines adopted by the EC, with similar guidelines applying to veterinary medicinal products.[144]

While manufacturers of medicinal products located in the EU or in third countries are subject to repeated inspections based on risk, manufacturers of active substances located in third countries are only inspected by authorities if there are specific grounds for suspecting non-compliance.

Current legislation foresees inspections of marketing authorisation holders, however there are no guidelines on the occasions when marketing authorisation holders should be inspected.

[143] See Article 111 of Directive 2001/83/EC
[144] See Article 80 of Directive 2001/83/EC

4.2.2. Challenges faced in responding to the sartans incidents

Challenges at the level of the active substance manufacturer

One reason for the presence of *N*-nitrosamines in sartans was the fact that manufacturers of active substances lacked sufficient product and process knowledge and the most serious gaps related to the process development phase, which occurs prior to the production environment being subject to GMP. If process knowledge is not sufficient, manufactures may not identify all potential impurities and may not consider these impurities when taking steps to manufacture their products in compliance with GMP.

Furthermore, once *N*-nitrosamines are present, poor application of GMP (e.g., inadequate investigation of complaints, out-of-specification results and out-of-expectation results) can contribute to the spread of the impurities (e.g., from solvent recovery processes performed incorrectly, unsatisfactory cleaning procedures and cross-contamination in multipurpose facilities).

As a consequence, inspection teams faced challenges during the initial for-cause inspections carried-out jointly by GMP inspectors and quality assessors to evaluate the root cause analysis performed by manufacturers. In order to be able to propose immediate risk mitigation measures, it was necessary that GMP inspections covered areas not normally included in routine GMP inspections as they are not subject to GMP, notably manufacturing process development. Together with assessors, who had the specific competencies to support the inspectors, the process development was analysed, and the manufacturing process was assessed to determine whether it could potentially form any additional impurities.

Challenges at the level of the medicinal product manufacturer

The EU manufacturer or importer of a medicinal product has to verify compliance of the manufacturer of the active substance with GMP through audits. Although, according to chapter 5.28 of the EU GMP guide, appropriate aspects of the production, testing and control (including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures for active substances) should be documented in a formal quality agreement or specification, in practice medicinal product manufacturers often have only limited access to relevant technical information from the active substance manufacturer. In some cases, this situation can impact the conduct of audits at the active substance manufacturing site by the finished product manufacturer.

Challenges at the level of the marketing authorisation holder

As indicated in Annex 16 of the GMP guidelines, the ultimate responsibility for a medicinal product over its lifetime, including its safety, quality and efficacy, lies with the MAH. While certain activities of an MAH may be delegated to a manufacturing authorisation holder, the MAH retains the responsibility for these activities.

However, MAHs may have only limited information regarding the detailed route of synthesis of an active substance and no information on the development data, because for existing active substances (e.g., pharmacopoeial substances) there is no requirement to submit data on process development in the regulatory dossiers.

As a consequence, in such cases the MAH may not be able to adequately assess quality defects linked to the development or the route of synthesis of the active substance. The MAH therefore has to rely on information provided by the active substance manufacturers when assessing the impact of a quality defect on any other medicinal products.

So, while being fully responsible for the safety, efficacy and quality of medicinal products, MAHs face difficulties in complying with legal requirements when the supply chain is fragmented, and only limited or no information provided by the holder of an ASMF or a CEP is available to them.

The holder of an ASMF or a CEP located outside the EU has no such legal responsibilities for their APIs in the EU, as the MAH has overall responsibility for the medicinal product.

4.2.3. The conduct of inspections in response to the sartans incident

GMP inspections were a key part of the regulatory response to the presence of *N*-nitrosamines in sartans and contributed to the investigation of root causes and the response of manufacturers once the presence of these impurities was known.

As of October 2019, several GMP inspections had been performed in relation to the sartans incident and these were conducted jointly by several authorities. Furthermore, in order to make best use of inspectional resources, information on GMP inspection planning and outcomes was extensively exchanged as part of the cooperation with international partners (see section 6.), and, where possible, joint inspections with several authorities were conducted.

Two for-cause GMP inspections were conducted jointly by inspectors and quality assessors from EU authorities and EDQM at 2 manufacturing sites in China, Zhejiang Huahai and Zhejiang Tianyu, at the request of the CHMP in the context of the Article 31 review procedure on sartans with *N*-nitrosamine impurities. These inspections were conducted to specifically look into the manufacturing processes for valsartan employed by the manufacturing sites as well as their investigations into the root cause of *N*-nitrosamine impurity formation. The for-cause inspections also included areas not routinely covered by GMP inspections, such as the development of the active substance.

As many active substances are manufactured outside the EU, any deficiencies and recommendations for improvement raised during EU inspections have to also be brought to the attention of the competent authorities in the concerned third countries and to the medicinal product manufacturers which are required to audit all manufacturers of active substances.

Insufficient knowledge of the development of their active substance and poor design of the active substance manufacturing process were identified as the main causes for the presence of *N*-nitrosamines. The MAHs and the holders of the CEPs and ASMFs are responsible for these activities which are not required to be conducted under GMP, hence are not subject to inspection at the level of the MAHs and holders of the CEPs and ASMFs.

4.2.4. Lessons Learnt

Taking into account the experience with, and outcomes of, inspections conducted in response to the sartans incident, including investigations of manufacturers' processes for avoiding impurities, the lessons learnt group has made a number of observations. These observations could point to ways to improve the ability of inspection regimes to identify potential problems in relation to impurities and to provide more guidance to manufacturers and MAHs.

First, GMP inspections conducted in response to the sartans incident revealed that the cause can be attributed to shortcomings in the process development phase and to the insufficient product and process knowledge on the part of manufacturers. In addition, inadequate application of GMP principles may have contributed to the contamination of products with *N*-nitrosamines from other sources.

Second, some aspects of GMP, even if already mentioned in GMP guidelines, are not clear and therefore ended up in a grey area; as a consequence, these aspects were not always fully addressed during GMP inspections because they were considered to belong solely to the pre-GMP development

phase, for example the GMP requirement for verifying that process validation activities should be based on documented and robust development studies (EU GMP guideline Part II, 12.11).

Third, it is important to note that GMP inspectors do not evaluate development studies and impurity profiles, but rather verify that companies have adequate systems in place to guarantee they have sufficient information in order to safely introduce new processes or changes to existing processes into in their facilities. In this context, should any gaps be identified with respect to the development of the active substance, inspectorates should be made aware of the importance of providing the information collected on site during a GMP inspection to the relevant licencing authority for further actions, as appropriate.

Finally, it should be emphasised that even though the available GMP guidelines already provide a basis for regulating manufacturers in relation to areas of concern identified during the sartan inspections,[145] some improvements in the current regulatory guidance would provide additional support during GMP inspections and would also help clarify so called 'grey areas'.

Considerations

Taking these observations into account, the lessons learnt group proposed that the following improvements be considered. These considerations form the basis of the recommendations in the 'Overview and recommendations' document:

Short- or medium-term measures

- 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.
- 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.
- 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:[146]
  - Cross-linking between non-GMP activities (e.g., research and process development and process transfer) and the operations performed under GMP (e.g., manufacturing process and analytical methods validation, and the routine manufacturing).

[145] These are related to unsatisfactory development studies, shortcomings during introduction of new molecules, process changes in the facility, unsatisfactory risk assessments and deficiencies concerning solvent recovery, laboratory controls and the evaluation of unknown peaks, production and outsourced activities.

[146] In case of contract manufacturing organisations, these aspects should be appropriately covered in the quality agreements with the contract givers, in the context of outsourced activities review.

- 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.

Long-term measures

- 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.
- Consider a change in 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.
- Develop a risk-based model for triggering pre-approval inspections of API manufacturers during the assessment of marketing authorisation applications, CEPs and ASMFs.
- Amend ICH M7 (R1) guideline so that it applies retroactively (similar to implementation of the ICH Q3D guideline).
- Draft specific guidelines or a questions-and-answers document to clarify the regulatory expectations on GMP topics like technology transfer and supplier qualification.
- 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.

- 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.

5. Communicating to the public

5.1. EU and national communication strategies

5.1.1. Early strategies

The discovery of NDMA in the valsartan API from Zhejiang Huahai in mid-2018 presented communication teams of the European regulatory network with significant challenges. From the beginning the urgency of the situation was clear.[147] Not only was cancer a sensitive topic, many patients were taking valsartan and the NDMA could have been present in some of these medicines for several years. Compounding the situation was the lack of information in the early stages, including information on the risk to patients, just as NCAs were embarking on one of the biggest recalls in recent years.

A major part of communication strategies, particularly for NCAs, involved contacting healthcare professionals directly in advance, or at the start, of national recalls and giving them the necessary information to advise their patients. In line with normal procedures, NCAs also published information about the recalls on their websites.[148] Although the messages given out by NCAs were generally aligned, the timing of the public communication on the recalls was not and the lag time between them may have led to difficulties in handling queries for those who published later.

On 5 July 2018, EMA published communication addressing both the EU-wide recalls and the start of the Article 31 review of valsartan medicines.[149] To prepare the network for queries from the media and the general public, EMA also drafted lines-to-take,[150] which were shared with communication teams across the network on 3 July 2018.[151]

The main messages in early communication from the network were that medicines containing valsartan from one company were being recalled; that patients may be given alternative treatments but must not stop taking their medicines unless they had been told to do so by their doctor or pharmacist; and that regulators were carrying out a review. Importantly, patients were informed that there was no immediate risk from their medicines and there was a greater health risk if they abruptly stopped their treatment. See Table 11. for information on key messages used by the network.

Table 11. Key messages delivered by European regulatory network

- *N*-nitrosamines were unexpected impurities in sartans
- Some products are being recalled as a precaution
- Valsartan from *one* company is affected (initially)

[147] In a survey of communication professionals within the network, some did indeed agree that the situation was a 'crisis'.

[148] BfArM published information about recalls on 4 July 2018. This was not, however, the first publication on valsartan by a regulator in the EU. The Hungarian medicines authority (OGYEI) had announced the quality defect on its website on 30 June 2018.

[149] This communication was the first of many EMA publications and was linked in many NCA websites.

[150] Lines-to-take are prepared to assist staff dealing with press enquiries to reply in an accurate and consistent manner. They are not published.

[151] See Guideline on good pharmacovigilance practices (GVP) – Module XV on safety communication (updated October 2017) for information on coordination of communication within the network.

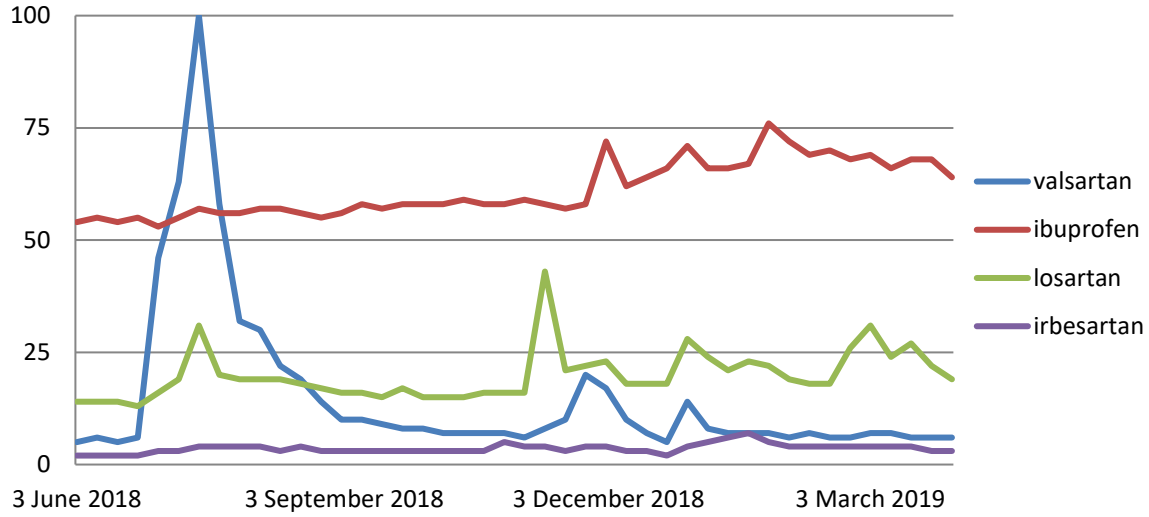
Table 11. Key messages delivered by European regulatory network
• There is no immediate risk from these impurities • Alternatives are available • Risk of cancer seen so far is very low (once estimates were available);the risk of stopping treatment is higher than any potential risk from the impurities • Patients should not stop taking any treatments without speaking to their healthcare professionals • A lessons learnt exercise will be conducted and the outcome made public • Authorities will provide updates as more information becomes available. • Authorities in EU are working closely together and with international partners

Both EMA and NCAs were aware of the need to avoid unnecessary alarm among patients.[152] However, limited information on the level of risk that patients may have been exposed to meant that more reassuring messages were absent in the early communication from both EMA and NCAs. In addition, the list of medicines being recalled from pharmacies was not included in EMA's communication as these were being determined and updated on websites of the NCAs initiating the recalls. Also, missing from the early communication was any detail of how NDMA (and later NDEA) came to be present in valsartan beyond vague references to changes in the manufacturing process used by Zhejiang Huahai.

As shown in Figure 22. in the weeks immediately following the initial communication from EMA and NCAs there was a high level of online public interest worldwide. It was during this period, however, that much of the information needed to advise and reassure the public was limited as investigations were ongoing.

[152] The possible adverse impact of alarm among patients was explored in a Canadian study which reported incomplete replacement of patient's medicines following recalls of valsartan and increased levels of hospitalisation. The authors stated that, 'Patients may have been willing to risk the short-term potential of uncontrolled hypertension to avoid ingesting a potential carcinogen.'

Figure 22. Worldwide Google searches for sartan medicines with searches for ibuprofen as a comparator[153]



Source: Google Trends, accessed 7 August 2019

In the early stages, both EMA and NCAs communicated proactively and frequently. The frequency of the communication was driven in part by the need to provide updates on the ongoing recall and to address fears of the public in relation to the cancer risk. Regulators also acted with a high level of transparency to keep the public abreast of the ongoing investigation.

A common means of communication by EMA and NCAs was the posting of material online, in many cases with separate sections for the public and expert audiences on their web pages. But regulators also employed other means including direct communication with healthcare professionals (including healthcare professional organisations) and the media, and the use of social media platforms such as Facebook, Twitter and LinkedIn. EMA and NCAs also gave interviews to the media.

5.1.2. Later strategies

In the beginning of August 2018, in the early stages of the Article 31 review, EMA's CHMP provided a preliminary estimate of the risk for patients exposed to valsartan from Zhejiang Huahai. EMA communicated this risk as follows: 'Following a preliminary evaluation, EMA estimates that there could be one extra case of cancer for every 5,000 patients taking the affected medicines at the highest valsartan dose (320 mg) every day for 7 years. This is based on average levels of this impurity detected in the active substance from Zhejiang Huahai (60 parts per million).' [154,155, 156]EMA also put the risk in the context of the lifetime risk of cancer in the EU and mentioned NDMA exposure from other sources, including food and water supplies.

[153] 100 in the figure represents the highest number of searches over the selected period. Google Trends does not give the exact number of searches. Ibuprofen, as one of the most widely known and googled medicine in the world, is used as a comparator to help gauge public interest.

[154] Communication published on 2 August 2018.

[155] See communication on final risk assessment published at the end of review.

[156] FDA published preliminary risk estimates on 12 July 2018. The FDA estimated that there could be one extra case of cancer for every 5,000 patients over 4 years.

Although a cause for concern, this worst-case risk estimate was nonetheless considered very low. It enabled the network to reinforce the advice being given to patients not to stop taking any medicines, unless told to do so by a doctor or pharmacist.

On 9 August 2018, the FDA announced a recall of medicines containing valsartan from Hetero Labs Limited as it was becoming clear that the *N*-nitrosamine issue went beyond Zhejiang Huahai. As valsartan from Hetero Labs was not sold to any EU manufacturers, EMA sent updated lines-to-take to the network[157] but announced on 10 August 2018 that EMA was reviewing valsartan produced by another company, Zhejiang Tianyu, which was supplied to the EU and where NDMA had been detected.[158] A month later, EMA announced that another *N*-nitrosamine – NDEA – had been found in valsartan from Zhejiang Huahai.[159]

From September 2018 onwards, although online public interest in most countries had fallen from its July/August peak, the network dealt with broader questions from the public and media. No longer was one company's manufacturing process the sole focus of concerns. (On 5 July 2018 EMA had announced that a change in the manufacturing process may be linked to NDMA formation.) Media queries to EMA and NCAs became more technical and these queries concerned CEPs, ASMFs, the role of EDQM, and EU inspections of manufacturing sites in and outside the EU as well as the chemistry of *N*-nitrosamine formation. To deal with these queries, EMA sent regular updates of lines-to-take to the network, but the key messages generally remained simple and consistent with previous ones.

For some enquiries, communication teams had to refer to the then ongoing Article 31 review and the lessons learnt exercise, which were expected to provide answers. Some enquirers were seeking to know which entities were responsible for what was viewed as a systemic failure. In such cases, NCAs and EMA avoided speculative replies. The replies sent out reflected knowledge available at the time.

On 31 January 2019, EMA's CHMP concluded its Article 31 review. EMA and NCAs communicated on the outcome, which included an updated risk assessment for patients previously exposed to *N*-nitrosamines and information on requirements for manufacturers to review their manufacturing processes and make necessary changes. Furthermore, with the subsequent publication of the assessment report, more detailed information on the manufacturing steps that led to the formation of *N*-nitrosamine became public knowledge.[160] The information published by EMA remains the most detailed public information available.

From the release of the first public communication, communication teams have had to adapt their practices to fit the rapidly evolving situation. This meant, for example, producing ad hoc web pages or adapting web pages intended for single news items so they could be used for regular updates. In some cases, lists of medicines being recalled were supplemented or replaced by lists of medicines not being recalled. Because of the scale and timing of this critical incident (during July and August), teams faced challenges replying to enquiries and had to dedicate a significant amount of additional resources to preparing public communication.

5.2. EDQM communication strategies

EDQM plays a distinctive role in the regulation of medicines in Europe. A directorate of the Council of Europe rather than the EU, EDQM publishes the European Pharmacopoeia which sets out legally binding standards for the quality of medicines and their ingredients in the EU and beyond. Although it

[157] Updated lines-to-take were sent to the network on 10 August 2018.

[158] Review was presented as an update of the ongoing Article 31 review of all valsartans.

[159] Press release published on 13 September 2018

[160] The assessment report was published on 2 May 2019 after the EC had issued its decisions.

does not assess medicinal products for authorisation, it plays an important role supporting authorities in the evaluation of both nationally and centrally authorised medicines in the EU.

From the outset it was clear that media were not familiar with the complexities of the existing legal framework for medicines and the responsibilities of the different players, not least those of EDQM. One important role of the directorate is the evaluation and granting of CEPs, certificates that companies can submit to EMA or NCAs in the context of a marketing authorisation application. Put simply, a CEP certifies that if an API is manufactured in a certain way (described in the CEP) that substance can be considered suitably controlled by the tests of the European Pharmacopoeia (and those additional tests mentioned on the CEP).[161,162, 163]

As the regulatory response to the discovery of *N*-nitrosamines included suspensions and re-evaluations of CEPs, the importance of these certificates and the relationship between EDQM and EU regulators was an essential part of the messaging for the public and media.

EDQM aimed to provide factual information while reassuring the public. In its first public communication in July 2018,[164] EDQM announced the suspensions of certain CEPs for valsartan APIs and gave details of other actions being taken in relation to other CEPs. In the coming months, EDQM continued its investigations and took actions to address the presence of *N*-nitrosamines, including NDMA, NDEA and other *N*-nitrosamines in valsartan and other sartans covered by CEPs. EDQM's communication team published several updates to inform stakeholders and received and responded to a number of media queries from both the pharmaceutical and mainstream media in relation to CEPs and their approval. Most of the queries came from the media (as opposed to members of the public).

The enquiries received by EDQM in many ways mirrored those handled by EMA and NCAs. However, EMA and NCA responses to queries about CEPs, inevitably meant that enquirers returned to EDQM for further clarifications.

In early August 2018, at the height of media interest, EDQM's communication team started working directly with EMA's team, sharing lines-to-take and communication materials – initially just prior to publication but later more in advance. This cooperation allowed teams to align messaging, prepare for queries that may result following publication and, where possible, provide comments on the text. EDQM's communications team was also in regular contact with BfArM, the authority in Germany, where most of the press queries came from.

5.3. International cooperation

While it is true that EU regulators have for several years provided advance notice of communications to some third country regulators (e.g., in the United States, Canada and Japan) and received notices from them in return, even in such cases communication teams were not in direct contact with each other and did not engage with their international counterparts on a regular basis.

At the height of the worldwide public interest in the sartans review, communication teams from EMA, FDA, Health Canada and Japan's Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency (MHLW/PMDA) set up an international working group dedicated to communication in

[161] See the missions page on EDQM's website.

[162] The European Pharmacopoeia provides a legal and scientific reference for the quality control of medicines. It has 38 European countries (including all EU Member States) and the EU as signatory parties to its legal basis, the Council of Europe Convention on the elaboration of a European Pharmacopoeia and 30 observers of which 6 are non-EU European countries and 22 are non-European countries. See the page Membership & Observership on EDQM's website.

[163] It is important to note that a CEP is one of three options according to which the documentation on an API can be submitted in the context of a marketing authorisation application in the EU. Alternatively, the same data can be submitted in an ASMF or in the API part of a marketing authorisation application to EMA or NCAs.

[164] See communication published 27 July 2018

relation to sartans and *N*-nitrosamines.[165] A kick-off teleconference was held on 4 September 2018, after which communication teams regularly exchanged communication material, including very early drafts, by email in advance of publication.

The increased cooperation between communication teams did not mean that the messages were the same, as each team's primary objective was to reflect regulatory actions taken at home. However, it did mean that teams were prepared to react to communication from other agencies, as communication in one region or country can and did trigger questions and concerns in others. Furthermore, when regulatory actions were aligned, communication teams were better able to align their messages. Indeed, the key messages in Table 11. were similar to those of international partners.[166]

On 7 December 2018, the Swiss authority, Swissmedic, joined the working group. Although EDQM and NCAs were not members, EMA's team had direct and regular contact with their counterparts in EDQM and were able to liaise with NCAs using established communication channels. One of these channels was the HMA Working Group of Communication professionals.[167] NCAs also had some direct contact with international partners such as the US FDA.

Feedback from the NCAs and members of the international working group about coordination in general has been very positive, with some regulators calling for more coordination based on the experience to date.[168]

5.4. Public and media response

5.4.1. Feedback from public

Patients and general public

As discussed in previous sections, public interest in the discovery of *N*-nitrosamines in sartans was very high. Online searches for affected medicines surged, initially on the back of communication by authorities in the EU, and remained higher than normal for several months (see Figure 22.).

Patient queries received by EMA and NCAs clearly show that EU patients were worried about the risk of cancer from medicines identified as having *N*-nitrosamines, particularly those who had been taking a sartan for significant periods. Many patients had concerns about alternative treatments, some of which were later recalled because they too were found to contain impurities. A recurring complaint from patients was that there was a lack of clear information from regulators' websites or healthcare professionals as to whether their own medicines were affected.

Patients also wrote in from other regions around the world, where information may not have been readily available from their national regulators. The concerns from the general public both in and outside the EU were predictable, and addressing these concerns was one of main objectives of the communication teams in the European regulatory network (see Table 12.).

Table 12. Main concerns from patients and the general public

- Will I get cancer as a result of *N*-nitrosamines in my medicine?
- Is my medicine affected?

[165] This followed the creation of the international strategic group led by Health Canada. See section 6.

[166] It is also possible that communication teams learnt from each other in matters of phrasing and other editorial decisions, particularly for communication material written in or translated into English. Certainly communications from partner agencies helped others with valuable models and approaches for their own.

[167] See HMA website for information on membership and activities.

[168] Comments received in a survey of communication teams

Table 12. Main concerns from patients and the general public
• Is my replacement medicine any safer?
• Why did regulators find out about the problem late?
• Where can I get more information?
• Why isn't the name of the active substance manufacturer in the package leaflet?
• Is this a problem with generic medicines?
• Can we trust manufacturing outside the EU?

EMA and NCAs have also obtained feedback from patient representatives on the content and drafting of communication for patients.[169] The feedback has been positive, particularly with respect to providing clear and transparent information. Some patient representatives did, however, raise a number of concerns requiring improvement. Patient representatives informed one NCA, for example, that they found parts of the communication 'too technical', the word 'carcinogen' too worrisome or difficult to understand and the layout somewhat unsuited for patients. The key message not to stop taking medicines abruptly was also viewed as not being prominent enough. The representatives recommended the inclusion of photographs of medicines being recalled and more specific guidance about what patients should do with their medicines.

There is also the issue of patients trying to obtain information on regulators' websites. A survey of patients' organisations indicated that patients may have had difficulties in finding relevant the information and in navigating such websites. According to one respondent in the survey, 'The patient shouldn't have to navigate in such an ocean of information. Information to the public should be straightforward and not mixed with information for professionals.'

Healthcare professionals

As part of this lessons learnt exercise, organisations representing patients and healthcare professionals were contacted to assess communication activities carried out by the network. One of the respondents, the Pharmaceutical Group of the European Union, an organisation representing community pharmacists in 32 European countries, had conducted a survey of its own members and identified as a major issue the lack of specific instructions for healthcare professionals on regulators' websites, including on alternative treatments when recalls have been carried out.

Another issue raised was the lack of immediate information on batch numbers of medicines affected, leaving pharmacists unprepared to answer questions from patients. Moreover, healthcare professionals suggested that both EMA and national authorities should have ensured that healthcare professionals received communication well in advance of the public to enable them to deal more effectively with possible supply problems and prevent potential panic among patients.

The Pharmaceutical Group of the European Union noted that, in some countries, pharmacists are not allowed to substitute medicines with a medicine of a different brand and this restriction should be taken into consideration when authorities provide advice to healthcare professionals on how to resolve the situation for patients. Moreover, switching all patients to the same medicine could cause shortages.

[169] Feedback came from direct contact with patient representatives and a survey sent by the lessons learnt group to patients' organisations.

Because of the pressure from concerned patients, pharmacists' organisations in the EU were keen for updates on websites of authorities. [170]On the overall assessment of communication from authorities, the response from healthcare professional organisations surveyed by EMA was mixed with respondents noting that communication to healthcare professionals was better in some countries than others.

The public reaction from healthcare professionals was not limited to these practical issues. Starting in September 2018, several journals published articles, mostly editorials, on the presence of *N*-nitrosamines in sartans, with some critiquing the regulatory response. A BMJ editorial[171] which was itself prompted by a Danish publication on the cancer risk of valsartan contaminated with NDMA,[172] appeared positive about the regulatory response in the EU at the time and called for the long-term monitoring of patients.

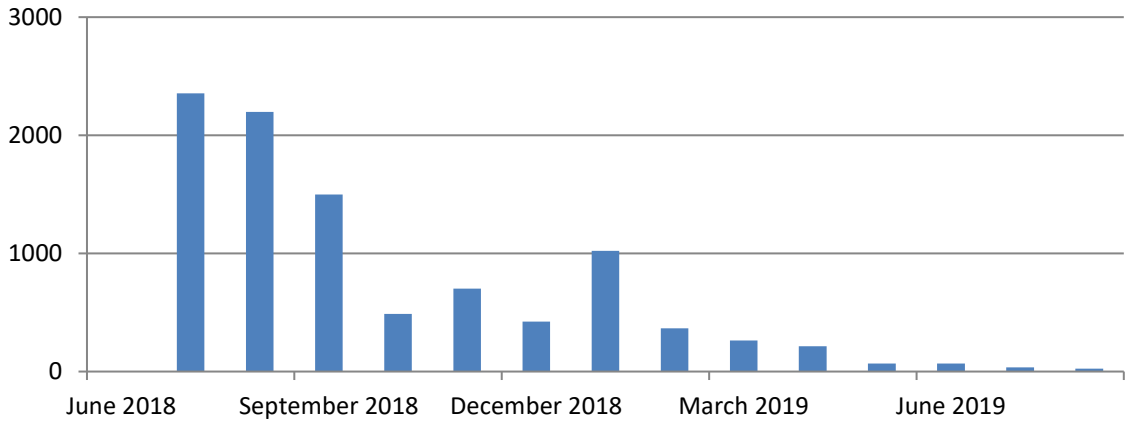
The overall tone of the commentary in the scientific literature has been measured, but the relatively high number of articles[173] published over a short period of time indicates real eagerness in the scientific community to contribute to a swift resolution of the issue of *N*-nitrosamines in sartans.

5.4.2. Media response

Media coverage of the 'valsartan story' did not gain wide interest immediately after the first publication by Hungary's National Institute of Pharmacy and Nutrition (OGYEI)[174] on 30 June 2018 (which was a Saturday) but grew in the following week as NCAs and EMA published information on recalls of some valsartan medicines,[175] with highest coverage occurring throughout July and August 2018 (See Figure 23.).

This coverage largely preceded or coincided with the rise in public interest, and the content of the news material, including the tone and headlines, were crucial in shaping public perception of the both risk from *N*-nitrosamines and the regulatory action taken to protect patient's health.

Figure 23. Worldwide media coverage (print, broadcast and online) of valsartan



Source: Vuelio, accessed 21 August 2019

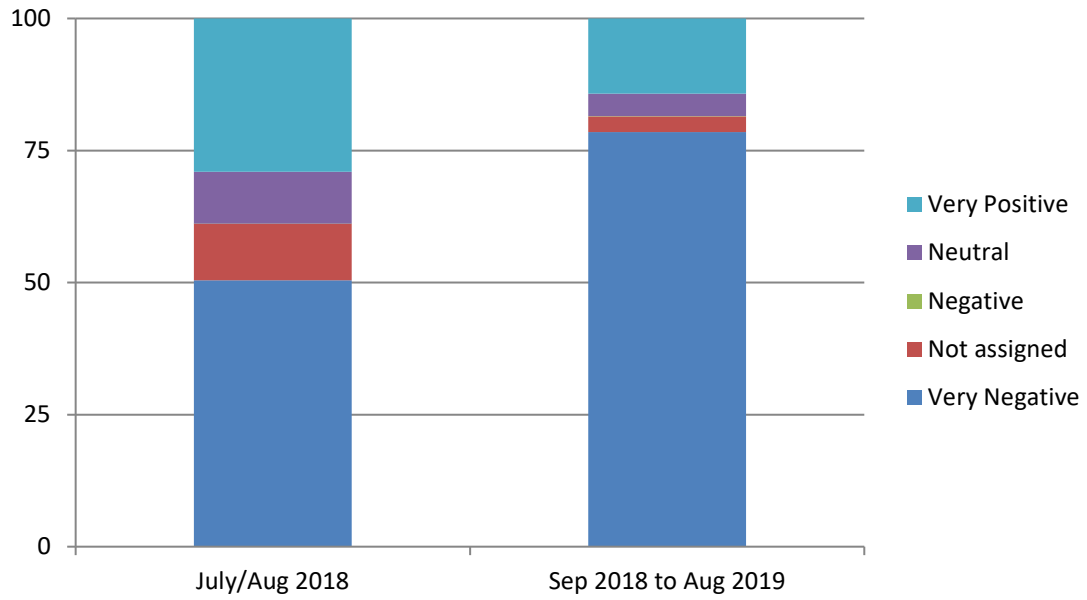
[170] Here is an example of how one national pharmacist organisation used the updates from authorities to inform its members.
[171] Banzi, R., Berele, V., BMJ 2018;362:k3855
[172] Pottegard, A., Kristensen, K., Ernst,M.T., BMJ 2018;362:k3851.
[173] 11 publications were identified in PubMed for valsartan and nitrosamines with addition publication for losartan and irbesartan.
[174] See webpage on OGYEI's website.
[175] Based on information obtained from Vuelio's database.

Communication teams were of the view that the media generally presented the bare facts of the regulatory actions in a clear and understandable way. In some cases, prominence was given to key messages from regulators such as the advice not to stop taking medicines.

It is not unexpected, given the subject matter, that a sentiment analysis showed that the tone and wording of news material was generally negative, with almost half of reports in July and August 2018 classified as 'very negative.' However, the negativity did not subside over time as media and public interest waned but rather increased (see Figure 24.).

There are several possible reasons for this, including the expanding nature and longevity of the investigations and the lack of immediate answers to pressing questions. The media (and their audiences) expect regulators to come to grips with a situation and address it speedily. When information is not available for a long stretch of time while the issue itself is expanding, it becomes more difficult to maintain confidence.

Figure 24. Sentiment analysis of media reports on valsartan



Source: Vuelio, accessed 22 August 2019

The nature of press enquiries, which preceded media output in many instances, can provide regulators with important insights into the perception of journalists covering this story. Overall, queries received by EMA indicate that journalists were generally well informed and aware of the information publicly available. The journalists, including those from the mainstream media, also showed a growing interest in and knowledge of regulatory and scientific matters but, as discussed in section 5.2. , did not appear to understand the role of different members of the European regulatory network.

In some cases, media queries could not be answered in enough detail, mainly because regulators did not have the information, particularly in the early stages (see Table 13.).

Table 13. Paraphrased media queries and level of responses

Background
• Who knew what and when? (*answered fully from regulators' perspective*)

Table 13. Paraphrased media queries and level of responses

- How were impurities detected? (*answered in greater detail as information became available)*
- Why they were not detected earlier? *(limited answers provided)*
- What levels were detected? (*answered in greater detail as information became available)*

Public health

- How many patients were affected? (*precise information not available)*
- What is the risk long-term? (*answered in greater detail as information became available)*
- What was the basis for risk assessments? (*answered fully)*

About the then ongoing review

- When will more updates be available? *(answered fully)*
- What recommendations are expected? *(not answered before finalisation)*
- How are companies complying with the investigation? *(answered to extent possible)*
- What level of impurities will regulators accept? *(answered in greater detail as information became available)*
- Will review expose flaws in regulation of medicines? *(not answered fully)*

Manufacturing rules

- How are manufacturing processes approved? *(answered fully)*
- What are EU regulations regarding or impurities in medicines? *(answered fully)*
- Is this a problem related to third countries (e.g., China and India)? *(answered fully)*
- How are manufactures outside the EU regulated? (*answered fully)*
- What is the link between EMA and EDQM? *(answered fully)*
- What actions did EU regulators take after FDA issued 483 forms? (*answered fully)*
- Why were CEPs suspended? (*answered fully)*
- Should MAHs know full contents of ASMF and CEPs? (not answered)

Manufacturing queries

- Who approved the change in manufacturing that led to formation of NDMA? (*answered fully)*
- How did *N*-nitrosamine impurities form? (*answered in greater detail as information became available)*
- Questions about different *N*-nitrosamines (*answered to extent possible)*
- Questions about specific API manufacturers (*answered to extent possible)*

Inspections

- Have concerned companies been inspected? (answered fully)
- What was outcome of inspections? (*answered to extent possible)*

Table 13. Paraphrased media queries and level of responses
• Who conducted inspections of concerned companies? *(answered fully)* • Did EU regulators not find problems in previous inspections? *(answered fully)* **How widespread** • Are there concerns about other APIs? *(not answered at the time)* • How many medicines were recalled in the EU or individual countries? *(answered to extent possible)* • Which batches were affected? *(answered to extent possible)* • How much valsartan is imported into the EU and what share comes from China? *(not answered at the time)* • How widely is valsartan used or how many patients use such treatments? *(answered to extent possible)*

Aside from responding to media queries, some NCAs initiated direct contact with journalists to publicise key messages. Regulators also organised or agreed to interviews with journalists to help them better understand the situation.

As indicated above, the media has largely been accurate in relaying the facts concerning *N*-nitrosamines in sartans,[176] covering the story over a long period of time and probing for answers, many of which have now been addressed by the Article 31 review and this lessons learnt exercise. Given the extent of the coverage, communication teams in the network were bound to encounter cases of misleading or unnecessarily sensational information. Such cases included claims that all valsartan medicines were being recalled; that taking valsartan containing *N*-nitrosamines was as harmful as smoking five cigarettes a day; and that valsartan medicines contained impurities used in rocket fuel.[177]

In an article about how EMA and NCAs managed the incident, *Politico* reported on communications concerns by healthcare professionals. The article reported that 'Regulators probing drug impurities in Europe are causing more confusion than confidence' and that nuanced messages had 'generally been lost on the public, thanks in part to communication breakdowns between the regulators and the health professionals on the ground.'[178] The concerns raised in the article have also been highlighted in section 5.4.1.

5.4.3. Social media response

Many members of the European regulatory network used social media in some way, including by posting announcement about recalls or highlighting press releases published on websites. LinkedIn, Facebook and Twitter were the commonly used platforms. The concerns expressed on social media platforms were generally similar to those of patients (see Table 12.).

5.5. Lessons learnt

Since the end of June 2018, communication teams from the European regulatory network had been facing communication challenges in circumstances where relevant information has not always been

[176] Feedback from international partners also indicates the media (including social media) coverage was factual and neutral.
[177] From survey of communication teams in the network
[178] The article was published in Politico's Pro Morning Health Care newsletter.

available. From this experience, described in sections 5.1. to 5.4. , important observations can be made.

First, during a recall, healthcare professionals across the EU need more information, more readily, on specifics such as batch numbers and alternatives available, in order to make treatment decisions and to advise patients. It may not be possible in most cases to inform healthcare professionals before making a wider public announcement, but it is clear that healthcare professionals need information as soon as possible after an incident comes to light. In some cases, publicly available information may not have reached their target audience.

Second, patients visiting websites of EMA and NCAs (usually for the first time) need to be able to navigate and find relevant information in a language and format suitable to them.

Third, given the scale of communication challenge from the start and its expanding scope in the following months, coordination within and outside the EU was a necessity, without which much of the work of the teams may have been less effective.

Fourth, although the urgency of the issue was appreciated by communication teams in late June 2018, few would have predicted how quickly it would escalate to include other products and other *N*-nitrosamines or how long the investigations would last.

Fifth, limited and evolving information during ongoing investigations impacts the effectiveness of public communication, particularly in relation to media queries.

Sixth, social media provides opportunities to engage directly with concerns of the public and potentially improve public health information during periods of intense public interest.

Considerations

Taking these observations into account, the lessons learnt group proposed that the following improvements be considered. These considerations form the basis of the recommendations in the 'Overview and recommendations' document.

- 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 may also add such information to their communication or provide clear easy-to-find guidance as to where the information can be found.)
- 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.
- Continue to implement best practices in communication and seek ways to improve the content, clarity and presentation of materials for target audiences.
- 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.
- Improve coordination of the timing of public communication, particularly when regulatory actions across the network are aligned.
- Increase cooperation between EDQM and NCAs, perhaps in the context of the HMA Working Group of Communication Professionals.

- 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.
- Develop communication strategies for long-lasting communication challenges, for example, by adapting websites and web pages to ensure that they are suitable for dealing with evolving situations.
- 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 communication team is available to others.
- Be active on social media and develop strategies to engage with users of different platforms.
- Consider establishing a hotline with dedicated staff and improve disseminating information to the target audiences.

6. Working with international partners

6.1. Exchange of confidential information and strategies

Even in the absence of a major incident, international collaboration in medicines regulation is the norm rather than the exception. EU and international partners routinely collaborate on topics covering the entire life cycle of medicines from the development stages (e.g., clinical trials and parallel scientific advice) to the monitoring of medicines already on the market (e.g., with respect to warnings on new adverse effects).

EU and international partners regularly exchange information on the outcome of inspections. The EU has also signed mutual recognition agreements on GMP inspections with some third countries, allowing authorities to rely on each other's GMP inspections and share information on planned inspections and quality defects.[179]

In addition, draft regulatory guidelines, public communication and joint workshops and publications[180] are the subject of extensive exchanges of information on a near daily basis. Regular telephone or video conferences known as 'clusters' are also set up for confidential discussions between regulators on topics of common interest.[181,182] To facilitate this international collaboration, EMA and some partners have liaison officials who work from the offices of partner agencies.[183]

EU authorities have the closest ties with the FDA, Japan's MHLW/PMDA, Health Canada, Australia's Therapeutic Goods Administration (TGA), Swissmedic, New Zealand's Medsafe as well as EDQM and the World Health Organization (WHO) all of whom have confidentiality arrangements with EMA and the EC. More restricted, but nonetheless significant interaction occurs with other international regulators, who do not have such arrangements.

6.2. International cooperation in response to the sartans incident

When the presence of *N*-nitrosamines in valsartan from Zhejiang Huahai came to light in June 2018, it was immediately clear that the findings would have far reaching global implications. Zhejiang Huahai's

[179] Countries with mutual recognition agreements with the EU are listed on EMA's website.

[180] See a recent example of a joint publication: A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014–2016: Concordance, Discordance, and Why. Kashoki M, Hanaizi Z, Yordanova S, Veselý R, Bouygues C, Llinares J, Kweder SL. Clin Pharmacol Therap. 2019 July 15. doi.org/10.1002/cpt.1565

[181] A cluster involves two or more agencies or organisations. See more about clusters on EMA's website.

[182] Also see *Are EMA, FDA and other international regulators talking to each other?* Teixeira T, Kweder SL, Saint-Raymond A. Clin Pharmacol Ther. 2019 Aug 26. doi: 10.1002/cpt.1617.

[183] Currently FDA and MHLW/PMDA have officials at EMA, while EMA has an official at FDA

valsartan API was used in medicinal products distributed in many regions and countries in the world, necessitating widespread recalls. Particularly in the early stages, a coordinated approach along with effective communication between international partners was of the utmost importance in making informed decisions.

In August 2018, EMA's Executive Director wrote to counterparts in the US, Canada and Japan emphasising the need for deeper collaboration on what was then an escalating situation and proposing cooperation on scientific matters and public communication. This request was in line the strategy that had been agreed in various forums, particularly the International Coalition of Medicines Regulatory Authorities (ICMRA).[184]

In late August, an ad hoc 'Angiotensin II Receptor Blockers (ARB) International Strategic Group' was created to coordinate activities of the various authorities and ensure that authorities were aware of each other's activities. Health Canada volunteered to lead this group, which included from the outset EMA, FDA and Japan's MHLW/PMDA, and was later enlarged to include Australia's TGA, Singapore's Health Science Authority and Swissmedic. In early September, a second group was created to cooperate in the area of communication to the public. The activities of the communications group are discussed in more detail in section 5.3.

Regular teleconferences by the strategic group provided the necessary platform for exchanging information on recalls, testing methods for the various *N*-nitrosamines and risk assessments. Regulators also informed each other of GMP inspections, sharing information in real time. The work of the strategic group increased over time, initially concerning only NDMA and then expanding to other *N*-nitrosamines as more impurities were detected in medicines (see section 3.2.2.)

From the initial exchanging of information, collaboration intensified over the next few months, with EMA inviting international experts to listen in on and participate in meetings of the CHMP during the Article 31 review of sartans. There were also several joint expert groups on acceptable limits and toxicological risks.

Some other regulators expressed interest in working with the strategic group and subsequently exchanged important information with the group. As this exchange of confidential information was necessary for overriding public health reasons, it was decided to agree ad hoc confidentiality arrangements with EDQM (pending the conclusion of a formal one) and regulators from the Republic of Korea, Taiwan and Singapore, allowing free and open discussions with these authorities. These ad hoc confidentiality arrangements were both time limited and limited in scope to the presence of *N*-nitrosamines in medicines.

There was no such cooperation with either China's National Medical Product Administration (NMPA) or India's Central Drugs Standard Control Organisation (CDSCO), and communication with those two important authorities was minimal. This may be in part because there is no established mechanism for exchange of information.

6.3. Challenges in coordinating responses to N-nitrosamine contamination

Regulators around the world faced a challenging situation dealing with many products on their markets containing one or more *N*-nitrosamines and being sourced through complex supply chains from several global API manufacturers.

Investigations showed that the root causes were complex and they were initially difficult to identify. Furthermore, a range of *N*-nitrosamine impurities with different toxicological characteristics were

[184] See ICMRA's standard operating procedure for global crisis management.

identified for which reliable toxicological data, e.g., on acceptable limits or daily intake, were not always available. In terms of patient exposure, the medicines had been available on the various markets over a variable period and had different daily doses.

A further challenge for the European authorities was the need for EU coordination alongside the wider international coordination. All sartan products were widely available in Member States, many of them approved at national level rather than via the centralised procedure. EMA's role was pivotal and resulted in a single EU voice when interacting with international partners.[185] In addition, obtaining reliable information from companies whose products contained *N*-nitrosamines proved to be a challenge for many regulators.

Despite or perhaps because of these challenges, EU authorities and international partners established a deep collaboration that extended beyond exchanging information to include joint international action. The tendency to manage a situation first and then collaborate with international partners after the fact was reversed, with international collaboration playing a central role in key regulatory decisions.

6.4. Lessons learnt

Following the sartans incident, the European regulatory network enhanced its cooperation with international partners using both new and established tools to work together and improve efficiency. From this experience, some observations can be made which may be pertinent for future incidents.

First, the strategic group model was instrumental in focussing international efforts to manage the incident and these efforts might have benefited from further cooperation with major exporting countries (such as China and India). A significant achievement was establishing agreed interim limits for *N*-nitrosamine impurities, although regulators may have benefited from more coordination on long-term limits.

Second, the exchange of commercially confidential information with partners is essential and should not be hampered by the lack of formal permanent confidentially arrangements. It is important that overriding public health interests take precedence over confidentiality. In this case, EMA quickly put in place time-limited arrangements in order to share vital information with some partners.

Third, ongoing collaboration in the field of GMP inspections was necessary to avoid multiple inspections of the same sites in a short sequence and to free up limited resources.[186] Especially in the case of very large manufacturing sites with several manufacturing units and lines, sharing inspection outcomes supports better regulatory oversight. Furthermore, multiple inspections of the same site on very close dates could also prevent the inspectors from concentrating on corrective measures and necessary improvements. In one case, by sharing information, regulators became aware of a planned inspection by one authority which was to take place at the same time as an unannounced inspection by another. Collaboration could also take the form of joint or observed inspections. More collaboration on quality and GMP in general among international partners could free inspection resources in importing countries.

Fourth, collaboration is necessary if authorities are to investigate root causes, establish validated testing methods, assess toxicology data and set standards for dealing with cohort-of-concern impurities. The possibility of engaging with ICH and the International Pharmaceutical Regulators

[185] This is despite the fact that experts in the EU were not always in agreement, particularly on the issue of acceptable limits for *N*-nitrosamines.

[186] Efforts were made to reduce duplication by having regulators conduct concurrent or joint inspections. The FDA and Health Canada conducted some concurrent inspections of sartan manufacturing sites, while Health Canada discussed the possibility of joining an EU inspection but this was not possible due to timing conflicts.

Programme was considered but was thought more appropriate for longer-term reflection and guidance. In any case, the experience gained from the sartans incident will be discussed at ICH.

Fifth, risk assessment conclusions from each authority may differ for objective scientific reasons (as was the case with sartans, for example, due to different durations of exposure) but authorities should be ready to explain to the public why different conclusions were reached. Collaboration is particularly important in the early stages where information is usually scarce or uncertain.

Sixth, the participation of international partners in discussions of the CHMP during the Article 31 review of sartans was considered useful for both EU and non-EU regulators as was the increased cooperation in the area of public communication.

Seventh, although cooperation with China's NMPA and India's CDSCO was limited, both authorities are members of ICMRA. ICMRA has developed a document on the procedure for global crisis management, which has been revised in light of the sartans incident but should be updated further on the basis of this lessons learnt exercise. This procedure can be used to bring more regulators to the table.

Eighth, it is difficult at this time to see how international collaboration could have prevented *N*-nitrosamines from being present in sartans in the first place. However, this incident raises important questions about what steps regulators can take to improve the control of impurities in medicines. Section 2. explores what such steps could be in the context of the European regulatory system.

Ninth, communication to the public was a key aspect of international collaboration, with authorities sharing embargoed communication material (or even early drafts) ahead of publication and, where possible, coordinating the timing of publications. Some authorities with whom the European network did not work closely with on communication were concerned that public communication suggested that regulators had not adequately scrutinised API manufacturers. Communication aspects are discussed in further detail in section 5.

Considerations

Taking these observations into account, the lessons learnt group proposed that the following improvements be considered. These considerations form the basis of the recommendations in the 'Overview and recommendations' document:

- 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.
- 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 facilitate urgent exchanges of confidential information.
- 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.

- Exchange information, coordinate and share workload in relation to the root-cause investigation of any incidents.
- 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.
- Work together with international partners on the review of toxicological data and risk assessment to establish common acceptable limits for CoC impurities.
- 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.
- Consider ways to improve coordination and, where possible, alignment in areas such as regulatory decisions, communication and advice to patients.
- 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.

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

Timeline of events

6 June 2018	Zhejiang Huahai informed by potential customer of impurity in its valsartan API
20 June 2018	Zhejiang Huahai tells customers to put use of its valsartan API on hold after preliminary investigation
25 June 2018	Zhejiang Huahai tells customers of presence of NDMA in its valsartan API
26 June 2018	Information related to the presence of NDMA in valsartan from Zhejiang Huahai is disseminated within the Rapid Alert Network
28 June 2018	EU network holds the first Incident Review Network (IRN) and the first Rapid Alert Network (RAN) teleconferences
2 July 2018	2nd IRN teleconference and 2nd RAN teleconference
3 July 2018	3rd RAN teleconference
5 July 2018	3rd IRN teleconference
5 July 2018	EC triggers Article 31 review of valsartan medicines; EMA announces start of review and recalls on its website
6 July 2018	4th RAN teleconference
9 July 2018	EDQM suspends Zhejiang Huahai's valsartan CEP (CEP 2010-072)
12 July 2018	5th RAN teleconference
19 July 2018	6th RAN teleconference
30 July 2018	7th RAN teleconference
2 August 2018	EMA publishes preliminary risk assessment for NDMA in medicines containing Zhejiang Huahai's valsartan API
3 August 2018	Taiwan Food and Drug Administration alerts regulators of valsartan API from Zhejiang Tianyu and Zhuhai Rundu Pharma (the latter's API not being present in EU medicines)
6 August 2018	8th RAN teleconference
9 August 2018	4th IRN teleconference
9 August 2018	US Food and Drug Administration (FDA) announces the detection of NDMA in valsartan API from Hetero Labs
10 August 2018	9th RAN teleconference

17 August 2018	EDQM suspends Zhejiang Tianyu's valsartan CEP (CEP 2013-159)
17 August 2018	EDQM suspends Heterolab's valsartan CEP (CEP 2016-069)
17 August 2018	10th RAN teleconference
29 August 2018	11th RAN teleconference
30 August 2018	Zhejiang Huahai confirms the presence of a second *N*-nitrosamine, NDEA, in some batches of its valsartan API
31 August 2018	12th RAN teleconference
5 September 2018	13th RAN teleconference
12 September 2018	Study on cancer risk from NDMA in Denmark published in BMJ
13 September 2018	EMA publishes updated NDMA risk assessment
14 September 2018	OMCL in Germany detects trace amounts of NDEA in losartan from Hetero Labs
17 September 2018	14th RAN teleconference
18 September 2018	5th IRN teleconference
20 September 2018	EC extends scope of Article 31 review to all sartans with a tetrazole ring
24 September 2018	EDQM informs RAN of NDEA in irbesartan from Aurobindo
24 September 2018	15th RAN teleconference
28 September 2018	Following EU inspection, AIFA publishes statement of GMP non-compliance for valsartan API from Zhejiang Huahai
28 September 2018	6th IRN teleconference
4 October 2018	16th RAN teleconference
8 October 2018	EDQM suspends Aurobindo's CEP for irbesartan (CEP 2009-283)
11 October 2018	17th RAN teleconference
23 October 2018	18th RAN teleconference
7 November 2018	Sandoz informs Danish agency of NDEA in losartan from Zhejiang Huahai
8 November 2018	Swissmedic issues notification on NDEA in valsartan from Mylan
13 November 2018	19th RAN teleconference
14 November 2018	AEMPS inform EMA of NDMA in valsartan from Sun Pharmaceuticals, India
16 November 2018	Some Member States start recall of medicines containing Mylan valsartan
16 November 2018	EDQM suspends Mylan CEP for valsartan (CEP 2009-396)
16 November 2018	20th RAN teleconference

19 November 2018	BfArM issues notification on NDEA contamination of irbesartan from Divi Laboratories
20 November 2018	7th IRN teleconference
21 November 2018	21st RAN teleconference
5 December 2018	BfArM issues notification of recall for Irbesartan from Divi Laboratories
7 December 2018	Health Canada informs EU network of NDIPA in valsartan from Signa de CV
10 December 2018	DIPNA, EIPNA known to be present or possibly present in valsartan from Novartis, Mylan and Teva Tapi and candesartan from Aurobindo
	NAP 181-14 known to be in valsartan from Novartis
13 December 2018	EDQM notifies network of NDEA in valsartan from Aurobindo
17 December 2018	BfArM sends notification of recall of valsartan from Aurobindo
17 December 2018	EDQM suspends Signa de CV's valsartan CEP 2011-231
19 December 2018	EDQM suspends Aurobindo's CEP 2011-174 for valsartan
19 to 21 December 2018	BfArM sends notification of recall of 'Valsartan Puren' – API from Aurobindo
21 December 2018	Poland initiates recall of valsartan from Aurobindo and Valsartan from Signa de CV
26 December 2018	ANSM informs network of NDEA above limits in irbesartan and losartan from Zhejiang Huahai
27 December 2018	BfArM informs network of NDEA in losartan from Zhejiang Huahai
28 December 2018	MHRA informs network of NDEA in irbesartan from Zhejiang Huahai
3 January 2019	MHRA recalls irbesartan from Zhejiang Huahai
11 January 2019	22nd RAN teleconference
14 January 2019	EDQM suspends Zhejiang Huahai's CEP 2010-033 for irbesartan and CEP 2010-139 losartan potassium
22 January 2019	23rd RAN teleconference
24 January 2019	EDQM informs network of new impurity NMBA in losartan from Heterolabs and NDMA in pioglitazone from Heterolabs
25 January 2019	24th RAN teleconference
31 January 2019	CHMP concludes Article 31 review and issues recommendations
7 February 2019	8th IRN teleconference
21 February 2019	25th RAN teleconference
26 April 2019	EMA and national authorities agree to request some MAHs for pioglitazone to check their processes to rule out the presence of *N*-nitrosamine impurities

2 May 2019	European network launches lessons learnt exercise
2 April 2019	EC publishes first decisions on the Article 31 review of sartans
17 April 2019	EC publishes final decisions on the Article 31 review of sartans

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

Members of lessons learnt group

Steering group

Member	Organisation
Almeida, Patricia	EMA
Bachman, Peter	HMA/BfArM
Bream, Robert	EMA
Bruguera, Hélène	EDQM
Caplanusi, Irina	EMA
Dias, Monica	EMA
Evandri, Maria Grazia	SWP/AIFA
Garcia-Burgos, Juan (Rapporteur, Communication)	EMA
Girard, Thomas	EMA
Hirschlerová, Blanka (Rapporteur, Prevention)	QWP/SUKL
Horn, Michael	HMA/BfArM
Keitel, Susanne	EDQM
Kovacs, Janos	EMA
Kruse, Nanna Aaby	BWP/Danish Medicines Agency
Lee, Helen	EC
Luigetti, Riccardo	EMA
Mbaeliachi, Nacho	EMA
O'Donnell, Kevin (Rapporteur, Incident Management)	GMP-GDP IWG/HPRA
Pinheiro, Luis	EMA
Ruepp, Robin	EMA
Schoondermark, Priscilla	CMDh/MEB
Solomon, Olga	EC
Spinei, Andrei (Lead)	EMA
Weise, Martina	CHMP/BfArM
Whomsley, Rhys	EMA
Wierer, Michael (Rapporteur, Market Surveillance)	EDQM

Additional nominated experts

Expert	Organisation
Alsasua, Teresa Dannert	CMDh/AEMPS
Andersson, Mikael	SWP/MPA
Byrne, Declan	EDQM
Caroline Letarnec	EDQM

Cogliandro, Eugenia	QWP/AIFA
Conocchia, Roberto	EMA
Cuddy, Brendan	EMA
Dercks-Mueller, Andrea	CHMP/BfArM
Dussa, Jörg	CMDh/BfArM
Filancia, Maria	EMA
Gilchrist, Fiona	EDQM
Gross, Olivier	EC
Letarnec, Caroline	EDQM
Ludwig, Joachim	CHMP/BfArM
Marcal, Anabela	EMA
Mehmandoust, Maryam	QWP/ANSM
O'Mahony, Denise	GMP-GDP IWG/HPRA
Pietz, Roland	CMDh
Saint-Raymond, Agnes	EMA
Schoenfeld, Franz	GMP-GDP IWG/Government of Upper Franconia
Sweeney, Fergus	EMA
Vincent, Frederic	EC
Wanko, Richard	EDQM
Wittstock, Marcus	CMDh/BfArM

20 December 2019

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

Interested parties meeting held on Monday 4 November 2019

Introduction

An interested parties meeting was held as part of an ongoing lessons learnt exercise started by the European medicines regulatory network in May 2019 following detection of *N*-nitrosamine impurities in sartans.

The meeting, co-chaired by Fergus Sweeney (European Medicines Agency EMA), Blanka Hirschlerová (EMA's Committee for Medicinal Products for Human Use/Quality Working Party, CHMP/QWP) and Hélène Bruguera (European Directorate for the Quality of Medicines & HealthCare, EDQM), was attended by organisations representing patients and healthcare professionals, industry and international partner regulatory authorities.

In his opening message, Noel Wathion, EMA's Deputy Executive Director, welcomed participants and reiterated the importance of obtaining feedback from stakeholders in order to prevent and better manage such incidents in the future.

Session 1 – Setting the scene

Andrei Spinei (EMA) provided an introductory presentation and a chronology of events related to the cases of *N*-nitrosamine impurities in sartan medicines that came to light in mid-2018, focusing on the regulatory response of the network as well as cooperation with international partners. The presentation was followed by a discussion on some of the topics raised, such as the communication of risk to the general public and the outcome and impact of some of the regulatory actions taken.

Session 2 – Information, coordination and public communication

Nacho Mbaeliachi (EMA) gave an overview of communication activities carried out by the network in response to the sartans incident. This overview was followed by presentations by Tiago Villanueva (European Union of General Practitioners), Christine Dehn (European Heart Network) and Laetitia Tonel (Medicines for Europe).

During the presentations and subsequent discussion, it was pointed out that healthcare professionals need timely information, so they are not caught off guard when faced with queries from concerned patients. It was suggested that healthcare professionals would benefit from advanced information at least 24 to 48 hours before publication. Furthermore, there is a need for better guidance for doctors in recall situations (e.g., on switching) and for regulators to improve how they reach out to doctors (who may be less organised that pharmacists). One suggestion for the latter was to move away from classic press releases towards more specific and direct communication for healthcare professionals.

It was noted that, in some instances, information did not cascade downwards from medicines authorities to healthcare professionals and it was suggested that regulators could work with other bodies such as medical councils.

With respect to patients, it was suggested that regulators should always give advice to patients in their communication and include lay language versions of their communications. Given the concerns that patients had been following the news about *N*-nitrosamines in sartans, it was suggested that the risk could be put more in context (e.g., by comparing the risk from *N*-nitrosamines in sartans with the risk from dietary sources) and that a better balance could have been struck between alerting and reassuring patients.

Participants also considered the communication tools used by regulators and called for regulators to expand their use of other tools such as SMS, social media and hotlines (including hotlines with recorded messages). It was also proposed that regulators lower the reading age for communication on recalls and use more infographics, particularly to describe risks.

Other proposals include closer ties with media and harmonisation of recalls (e.g., patient or pharmacy-levels recalls) across the EU to aid communication. It was also suggested that regulators should consider the latest communication guidance for shortages when communicating on shortages that may occur following recalls.[1]

Sessions 3 and 4 – Prevention

Blanka Hirschlerová (CHMP/QWP) delivered a presentation on the current applicable guidelines on preventing mutagenic impurities from being present in medicines, as well as an overview of the potential root causes of *N*-nitrosamine formation identified to date. The presentation also covered potential areas for improvement in the light of the lessons learnt from the sartans incident.

This was followed by a presentation by Ron Ogilvie (European Federation of Pharmaceutical Industries and Associations, EFPIA) on the implementation of guidelines for the control of mutagenic impurities in medicines and on how the knowledge and experience gathered as a result of the cases of *N*-nitrosamine impurities in sartans can support future prediction, identification and control of risk for other products. A further presentation by Andreas Hartmann (EFPIA) covered applicable guidance on genotoxic impurities in terms of setting thresholds, duration of exposure and the determination of control limits for genotoxic impurities.

The second part of the prevention discussion started with a presentation from Andrew Teasdale (EFPIA) on the challenges encountered with testing products and active pharmaceutical ingredients (APIs) for *N*-nitrosamine impurities, the available methodologies and how testing at the edge of analytical capability has an impact on available testing capacity.

The last presentation of the prevention session, also delivered by Andrew Teasdale, was about a case study by EFPIA on the application of a risk- and science-based approach to assessing and controlling the risk of *N*-nitrosamine formation during the design and development of the manufacturing process for a sartan API.

The presentations were followed by a plenary discussion on some of the challenges that industry has encountered in this case, such as communication and exchange of information between API manufacturers and marketing authorisation holders and auditing of API manufacturers. It was suggested that in some cases industry would require further clarification from regulators about the requirements for API manufacturers to provide marketing authorisation holders with commercial confidential information in active substance master files and certificates of suitability.

Another topic covered was how to address *N*-nitrosamine impurities in medicines in the future within the framework of the current guidance. It was noted that a more consistent implementation of requirements is necessary and that the knowledge that industry has gained with regard to the root

[1] See information about communication on medicines shortages on EMA's website.

causes and risk of *N*-nitrosamines formation would help prevent similar cases. It was agreed that the network's request for companies to conduct risk assessments for their products to ensure there is no risk of *N*-nitrosamine formation and cross-contamination is necessary to confirm that medicines do not contain these impurities.

Session 5 – Supply chain management and surveillance

The session on supply chain management and surveillance was kicked off by a presentation from Michael Wierer (EDQM) on surveillance activities carried out by the European regulatory network in respect of *N*-nitrosamines in sartans. The presentation included details of the sampling and testing surveillance exercise conducted by the European Official Medicines Control Laboratory network, which was coordinated by EDQM. It also contained details of how the risk-based sampling plan was developed, the objectives and results of the testing and the challenges encountered. Details and the key findings of the for-cause good manufacturing practice inspections conducted at 2 manufacturing sites in China were also presented to the group.

The second presentation of the session was delivered by Josep Maria de Ciura (Medicines for Europe) on behalf of industry associations and covered the implementation of risk mitigation measures across the supply chain to control *N*-nitrosamine formation and cross-contamination in the API manufacturing process and in starting materials, solvents and reagents.

Session 6 – Incident management

The session on incident management started with an overview of how the incident was managed by the network and a chronology of the regulatory actions taken. The presentation also covered the effectiveness and proportionality of actions taken, as well as some of the lessons learnt to improve the response of the network should similar incidents arise in the future.

Machlien De Brabandere (Pharmaceutical Group of the European Union, PGEU) spoke about the experience of the Belgian and European community pharmacists associations and their perspectives on the communication of the sartans recalls in 2018. The presentation covered feedback from a survey of community pharmacists conducted by PGEU regarding the handling of information available from regulatory authorities, the sartan recalls and the translation of information for patients. Recommendations included providing more timely and clear hands-on communication to prescribers and pharmacists and better aligning of EU-level recall practices and communication strategies.

The last presentation of the day was delivered by Luisa Paolo (Active Pharmaceutical Ingredients Committee, APIC). It covered the flow of information between the different supply chain operators during recall procedures and the key elements for a rapid response.

The presentations were followed by a short discussion that reiterated some of the points made in the first session, including the importance of having answers to questions that patients might ask and ensuring that messages from regulators are provided in a language accessible to the public.

Closure of meeting

The co-chairs summed up the main points raised in all the sessions and confirmed that these will be considered during the lessons learnt exercise being conducted by the European medicines regulatory network. The exercise will produce recommendations for improvement in the future.

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