Journal of Pharmaceutical Sciences 000 (2023) 1–2

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Editorial

N-Nitrosamines Impurities in Pharmaceuticals The Abrupt Challenges that Resulted, the Evolving Science, and the Regulatory Framework

In mid-2018, N-nitroso-dimethylamine (NDMA) was unexpectedly detected in a valsartan active pharmaceutical ingredient (API). NDMA, like many other nitrosamines, is mutagenic and a probable human carcinogen. In contrast to many other newly discovered impurities, the observation of nitrosamines in pharmaceuticals was not restricted to one manufacturer and one drug but was the start of a significant wave of separate cases and different root causes. To start, for valsartan, not only one manufacturer was affected, but many companies producing the drug by different processes. In addition, it quickly became clear that the whole class of sartan drugs may be at risk of containing NDMA and other small nitrosamines. Concerns grew further as it became obvious that the issue may not only occur with sartans but, in principle, with any API containing a vulnerable amine and a nitrosation source. Hence not only NDMA but a whole plethora of potential nitrosamines could be created.

Since the abovementioned sudden detection of nitrosamines in valsartan about four and a half years have passed. During that time industry, regulatory authorities and academia have been working in close collaboration to tackle the risk, i.e., making sure that patients are not jeopardized by drugs containing nitrosamines at levels that are not safe. However, this implies keeping in mind the benefit to patients from having access to the drugs that they need. Ultimately, there is a balance between mitigating nitrosamine risks and keeping lifesaving drugs available to patients if alternative treatment options are not readily available. Accordingly, it has been clear from the very beginning that withdrawing all affected drugs, even if this was the only solution in rare cases such as ranitidine, would not be an adequate solution as a whole. Instead, optimization of manufacturing processes of many APIs and drug products has been required. This has been an enormous workload especially for industry and regulators during these years with the goal to guarantee quality and safety of drugs as well as to keep them available for patients. In this regard, interdisciplinary thinking and collaboration has been required.

At the beginning, the focus was on the development of suitable analytical techniques. Limits for nitrosamines are extremely low, typically in the parts per billion (ppb) range. Consequently, ultra-sensitive methods with a high selectivity were suddenly required. Fortunately, modern analytical technology and methods developed for trace analysis of nitrosamines in food, tobacco and rubber products could be quickly adapted to the analysis of pharmaceuticals. Because of the prior need, the required analytical technology such as LC-MS/MS and GC-MS/MS instruments had become standard in many laboratories since the beginning of the new millennium.

Once suitable analytical procedures were available, the focus shifted to the analytical screening of APIs. This was mainly triggered by the fact that the root-cause for the appearance of NDMA in sartans was connected to the API synthesis. Hence, when the source for NDMA in metformin was identified in the drug product and the result of the tablet formulation rather than the API, industry and regulators got another surprise. The contamination of metformin pharmaceuticals was of particular concern, as these drugs are taken in high doses over extended time intervals, quite often decades. Accordingly, both analytical and manufacturing science for APIs and drug products have turned out to be essential areas of study for overcoming the nitrosamine crisis.

Root cause investigations have frequently led to findings that can be considered logical and obvious in retrospect, e.g., the fact that nitrite impurities in excipients introduce a risk of nitrosamine formation. But there have also been much more surprising root-causes, such as recycled solvents used in API manufacturing or even inks used for printing primary packaging materials. These examples show that, beyond close interdisciplinary collaboration, additional factors are fundamental, including,

- detailed understanding of API and drug product manufacturing processes
- in-depth knowledge of impurity profiles of staring materials, intermediates, reagents, excipients, and other materials used in the manufacturing process
- advanced chemistry knowledge to find respective reactions leading to nitrosamines or to educts such as vulnerable amines and nitrosating agents
- specific and sensitive analytical procedures for trace amount quantitation of nitrosamines and their precursors

While marketing authorization holders (MAHs) were digging deeply into these topics, health authorities worldwide were simultaneously establishing a respective regulatory framework. Regulators introduced a three-step process of risk-assessments, confirmatory testing where risk was identified and root cause analysis along with process optimizations to tackle the risk. Setting up this framework in a very timely way has allowed an efficient assessment of a plethora of drug products over a short time.

Today, several major nitrosamine risks in drugs have been overcome while others are being investigated by industry and regulators with the help of academia, but even new topics are still coming up.

https://doi.org/10.1016/j.xphs.2023.01.016

To name one such example, the initial focus has been on small dialkyl nitrosamines such as NDMA. However, nitrosamines can also be formed from APIs, intermediates or impurities that contain a vulnerable amine. For such nitrosamine drug substance related impurities (NDSRIs) one might speculate about reduced genotoxicity and carcinogenicity, but much remains to be understood in this area of active research and discussion in the field. Universally accepted scientific and regulatory framework has to be established that takes this difference into account. This latest twist of the nitrosamine story shows that not only quality aspects matter, but also safety aspects such as toxicology and pharmacokinetics come into play and will trigger progress by *in-silico*, *in-vitro* and maybe also *in-vivo* approaches in the future.

One key element which has allowed the industry and regulators to address nitrosamine risks in a very fast and efficient manner - one must bear in mind that the need to evaluate risk did not just refer to one or a few drugs but to all (!) drugs on the market – is the open exchange of available scientific and regulatory information as well as observations and experiences made. In part, this has been a matter of personnel interactions between industry, regulators, and academia. Nevertheless, another important source have been manuscripts available to the public. With this special issue on nitrosamines in pharmaceuticals we would like to further contribute to this sharing of knowledge in a focused way. Therefore, the special issue contains several manuscripts dealing with diverse aspects of nitrosamines in pharmaceuticals, e.g., advances in analytical methods, organic and process chemistry relevant for formation of nitrosamines in APIs and drug products, regulatory science and even pharmacokinetics and some clinical aspects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Justin Moser
Merck & Co., Inc. 770 Sumneytown Pike WP78-110 West Point, Pa 19486, United States of America

Jörg Schlingemann
Merck Healthcare KGaA, Frankfurter Straße 250, 64293 Darmstadt, Germany

Christoph Saal*
Merck KGaA, Frankfurter Straße 250, 64293 Darmstadt, Germany

*Corresponding author.
E-mail address: christoph.saal@gmx.de (C. Saal).

Received 15 January 2023
Accepted 17 January 2023