PRESS RELEASE

Nitrosamine regulation implemented on time for many customers thanks to modular solution approach of Aenova Group

- **Aenova developed a comprehensive process and solution approach for marketing authorization holders.**
- **Already within the first regulatory deadline, all risk assessments for customers could be prepared.**
- **The deadline extension for biologic drugs expires July 1, 2021.**

Starnberg, June 29, 2021 - After the regulatory authorities had already become aware of products containing valsartan in July 2018, the worldwide recall of medicines containing metformin also attracted great attention just over a year ago. The reason for this was a contamination with carcinogenic nitrosamines. In a report, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) called on companies to take actions to limit the presence of nitrosamines in medicines for human use as far as possible and to ensure that the strict limits are not exceeded. This posed a particular challenge, first for API manufacturers, then for marketing authorization holders, as well as for contract manufacturers working for pharmaceutical companies. Within a short period of time, the Aenova Group, as the world's leading contract developer and manufacturer for pharmaceutical and healthcare companies, was able to implement a comprehensive, scientifically based modular solution for risk assessments, both in terms of content and process, and to execute this together with the customer companies for their products.

The first specifications of the EMA

In the interest of patient safety, marketing authorization holders were made responsible by the EMA to review their manufacturing processes, first for all products containing chemically synthesized active ingredients and later also for biological active ingredients, in order to identify and mitigate the risk of nitrosamine contamination where applicable. Similarly, strict nitrosamine limits were set for products. Furthermore, for all affected products marketing authorization holders needed to also implement appropriate control strategies and to further improve manufacturing processes where necessary.

The risk assessment of all products should be completed at the latest within six months after the publication of the "Information on Nitrosamines for Marketing Authorization Holders". Thereupon, the authorization holders were to inform the competent authorities when the risk assessment was completed. For this purpose, an initial deadline of 26.03.2020 applied. In the course of last year, this had to be extended initially until 01.10.2020, then again until 31.03.2021 due to the COVID19 pandemic, and applies to biological medicinal products until 01.07.2021. Aenova was able to complete all risk assessments for its own customers on time by the first deadline. Thanks to the flexible, modular structure of the Aenova approach, it can also be modified for biological medicinal products.

The impact of nitrosamines in patients: Patient safety is top priority

In June 2018, EU authorities became aware of the presence of the nitrosamine N-nitrosodimethylamine (NDMA) in valsartan from a manufacturer of active pharmaceutical ingredients (APIs). Valsartan is a drug used in the treatment of hypertension in mild to moderate heart failure. Shortly thereafter, another nitrosamine, N-nitrosodiethylamine (NDEA), was detected, and later other sartans from other API manufacturers. NDMA and NDEA are classified as probable human carcinogens; their presence in sartans was unexpected at this time.

However, it is now known that these contaminants can also arise under certain production conditions and when using certain solvents, reagents and other starting materials such as excipients or packaging materials. In addition, manufacturers must ensure that contaminants

are not transferred through the use of contaminated equipment or reagents during the manufacturing process.

The consequence for marketing authorization holders

Marketing authorization holders are responsible for the quality, safety and efficacy of their products. This includes the value chain from the quality of active ingredients, excipients and other raw materials to the actual manufacture of finished products.

Despite the low risk of the presence of nitrosamines, Marketing Authorization Holders (MAHs) are encouraged to take precautions to mitigate the risk of the formation or presence of nitrosamines in the manufacturing process of all drugs containing chemically synthesized APIs or biologically-sourced API respectively.

Confirmatory testing activities should begin as soon as the risk of the presence of nitrosamine is identified in the risk assessment. For high risk products, these should be initiated immediately. Confirmatory testing for all affected drug products and submission of required manufacturing authorization changes should be completed no later than three years after publication of this notice, or sooner if otherwise warranted.

The consequences for manufacturers and contract manufacturers (CMO / CDMO)

Manufacturers were asked to actively support the compilation of information for the risk assessment, as a result of which manufacturers now had to review their manufacturing processes. In the case of metformin-containing products, Aenova was even able to point out to customers / marketing authorization holders non-regulatory changes to minimize nitrosamine contamination to an absolute, legally accepted minimum. As a result, Aenova designed a structured approach that further developed the processes in the manufacturing process - up to formulation changes for metformin - which is considered by the customers as exemplary, pragmatic and extremely efficient.

The Aenova process for solving the impurity problem in terms of content

First, Aenova developed a template for a standardized comprehensive group-wide harmonized risk analysis of nitrosamines. As an assessment aid for a safe and comprehensive scientific approach, Aenova first had compiled a complete toxicological

literature review by an independent toxicologist. In close coordination with the respective customer, this holistic approach was then offered as a harmonized service for all Aenova Group manufacturing sites. The various service packages range from a minimal assessment of general manufacturing process to the full service “ready-to-acknowledge” complete risk assessment. Aenova can also offer the analytics for the control strategy as a service. In this way, Aenova is able to continue offering customer companies a full service on low-nitrosamine products - from consulting to manufacturing.

The Aenova approach to the process-based solution of the contamination problem

Aenova first demonstrably reviewed manufacturing processes and - if necessary - made necessary adjustments to minimize the generation of nitrosamine impurities during the manufacturing process as much as possible. Through the additional specific analyses of starting materials and knowledge of the manufacturing process, the levels of nitrosamines in the final product have become controllable.

Excellent results within the deadline

The initial deadline set by the authorities was met at all operational sites thanks to Aenova's standardized approach. All requested risk assessments were thus completed on time. At the same time, services for various risk analyses could be established in order to support the customer companies, the MAHs, appropriately and comprehensively.
Manufacturing processes were reviewed at all sites and possible adjustments made to minimize nitrosamine contamination as much as possible. Aenova was also able to offer its customers the analytical testing of confirmation tests as a service. The procedure and the results led to full satisfaction of the customers involved.

About Aenova Group

The Aenova Group is a leading global contract manufacturer and development service provider to the pharmaceutical and healthcare industries for human and animal health. Our services include end-to-end manufacturing and development of all dosage forms and potencies (from nutraceuticals to highly potent APIs) at 15 sites in Europe and the USA. With our comprehensive know-how, many years of experience, innovative technologies and highest quality standards, we are a reliable, long-term partner for pharmaceutical and

consumer health care customers worldwide. Around 4,300 well-trained employees contribute to the success of the Group. www.aenova-group.com

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