Olon case, Management of nitrosamine standards

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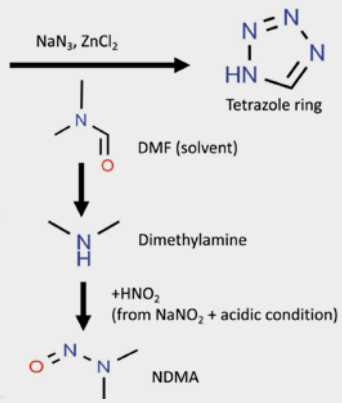
olon

1. Background

The white paper exposes the current status and Olon response to potential contamination of pharmaceutical products by the genotoxic impurities known as nitrosamines.
During the summer 2018, EU Regulators become aware of the trace amounts of some nitrosamines in a class of commonly prescribed heart protection drugs known as angiotensin II receptor blockers, frequently referred to as “sartans” (Figure 1). Subsequently, also the widely used H2 (histamine-2) blocker drugs, ranitidine and nizatidine, have been found to contain nitrosamine compounds, and a little later also in batches of pioglitazone, and metformin.



Proposed chemistry of NDMA formation from DMF during sartan production. **In June 2018**, Zhejiang Huahai Pharmaceutical became aware of an unknown impurity in its generic angiotensin II receptor blocker, Valsartan. **It was identified as the nitrosamine, N-Nitrosodimethylamine (NDMA)**, a potent genotoxin in several species and probable human carcinogen. The impurity may have originated in use of sodium nitrite to remove excess sodium azide used to yield tetrazole during the manufacturing process. This may have allowed the formation of nitrous acid, which then reacted with trace amounts of dimethylamine from DMF to produce NDMA. This change in manufacturing process from the originator (which previously used tributyltin azide) was approved in 2012.

Figure 1.

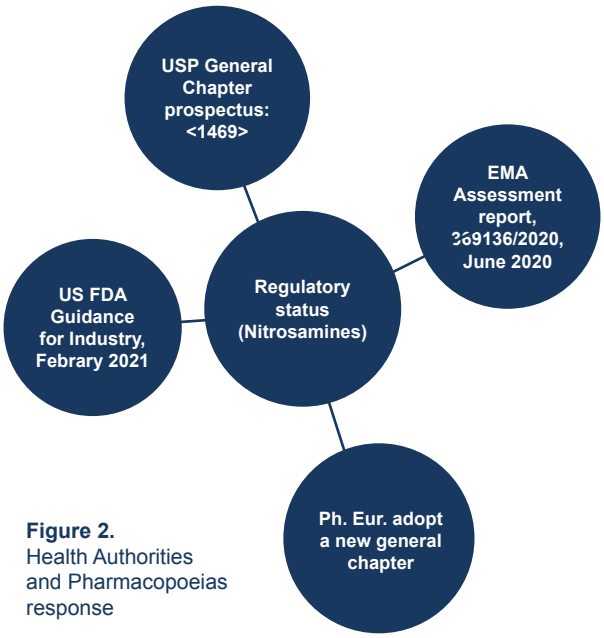


Figure 2.
Health Authorities and Pharmacopoeias response

In October 2019, this discovery of small-molecule nitrosamine impurities in marketed drugs has led to significant regulatory response, including drug recalls, Ph. Eur./USP new chapters, publication of acceptable daily exposure limits, publication of analytical methods and specific controls (Figure 2). **Most international regulatory authorities have provided regulatory guidelines regarding evaluation of nitrosamines in products** including complete retrospective analysis of all approved DPs for the potential presence of nitrosamine impurities (FDA Guidance for Industry, EMA/369136/2020, EMA/409815/2020, Health Canada, PMDA, Anvisa), regulations that which followed one another with considerable frequency in a few years. Health authorities worldwide have rescinded GMP certification, sent Warning Letters, and imposed import alerts or recalls on manufacturers of both the active pharmaceutical ingredients (API), the packaged drug products, and even manufacturing intermediates or solvents. The group of potential carcinogens known as nitrosamines has then become one of the biggest challenges to the pharmaceutical industry today.

2. Nitrosamines formation, presence and potency

Nitrosamines are substances **produced essentially unintentionally during chemical synthesis**. The terms “nitrosamine” or “N-nitrosamine” are referring to the chemical structure $R_2N{-}N{=}O$, where R is usually an alkyl group. They feature a nitroso group (NO+) bonded to a deprotonated amine. Nitrosamines are a group of carcinogens that are formed by the reaction of a nitrosatable substrate precursor (amine source) with a nitrosating agent (e.g. nitrous acid, nitrites, or nitrogen oxides) . The more known mechanism of N-Nitrosamine formation occurs when secondary amines are present in combination with a nitrosating agent, generally under acidic conditions (Figure 3).

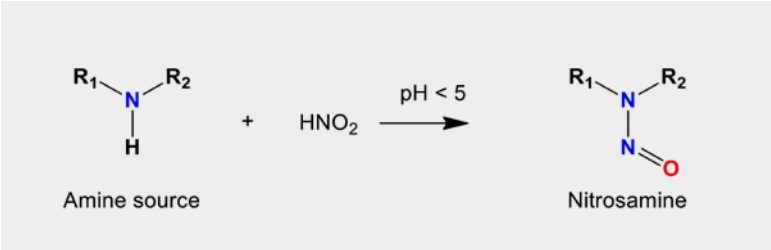


Figure 3.

The ubiquity of the precursors and the facile nature of the nitrosation reactions under acidic and neutral pH have made nitrosamines a common and an unwelcomed guest in the world of foods, consumer goods, and pharmaceuticals. As a consequence of this pervasiveness, **nitrosamines are organic compounds that we are exposed to in our everyday lives and the presence of nitrosamines continues to be problematic in the human environment** (Figure 4). They are common in foods, including cured and grilled meats bacon, beer, preserved fish, dairy products, and vegetables. They can be formed when meats are heated to high temperatures. Nitrosamines can also be found in drinking water (WHO, 2008). Some of the most well-known sources of nitrosamines are tobacco, cosmetics (creams, lotions, shampoos), rubber products, pesticides and pharmaceuticals, either during manufacture or product storage. Nitrosamines are also formed endogenously in stomach and oral cavity, suitable environment for nitrosation based on of amines and nitrites intake (Figure 4).

Figure 4.

N-nitrosamines are a class of compounds that have been shown to exhibit carcinogenic and mutagenic effects in animal models at several different tissue sites and by several different routes of exposure. Several nitrosamines were classified as carcinogens 2A (probable carcinogens) and more recently in Group 1 (human carcinogens) for N-nitrosonornicotine (NNN). The REACH regulations also list N-Nitrosodimethylamine (NDMA), Methylnitronitrosoguanidine (MNNG), N-Nitrosodiethanolamine (NDELA); N-Nitrosodi-n-propylamine (NDPA) as category 1B carcinogens. Several nitrosamines are also categorized by the International Agency for Cancer Research (IARC) as 2A and 2B – Probable and Possible Carcinogens, respectively, based on study data of some species.

The carcinogenic properties of nitrosamines have been known for more than 50 years since Peter Magee and John Barnes **reported in 1956** that N-nitrosodimethylamine (NDMA), a simple water-soluble compound with only 11 atoms, readily **induced liver tumors in rats and since then hundred nitrosamines have been tested for carcinogenicity**, N-nitrosodimethylamine (NDMA), N-nitroso-diethylamine (NDEA), N-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-nitroso-diethanolamine (NDELA), nitroso morpholine (NMOR), N-nitroso-N-methyl-N-ethylamine, and N-nitrosopyrrolidine (NPYR), being some of the well-known among these. Of all the nitrosamines, NDMA have been researched the most. **NDMA have been found to be carcinogenic in more than 20 species of animals and it is believed that no species is exempt from the carcinogenic activity of this compound**. Because of this higher potency, nitrosamine impurities are considered by the ICH M7(R2) guideline as high potency mutagenic carcinogens referred to as compounds that are part of the "cohort of concern" and as such are classified as Class 1 impurities ─ "known mutagenic carcinogens" ─ based on both rodent carcinogenicity and mutagenicity data and need to be controlled at or below compound-specific limits. Cohort of concern (CoC) is indeed defined as a group of high potency mutagenic carcinogens comprised of aflatoxin-like-, N-nitroso, and alkyl-azoxy compounds. These compound-specific limits might be much lower as compared to the limit of 1.5 µg/day acceptable intake (AI) for other potentially mutagenic impurities which lack carcinogenicity data, as defined by ICH M7 if treatment lasts more than 10 years. The EMA and FDA in 2020 published a **list of the most common volatile nitrosamines deriving from common reagents and solvents**, which emerged from the learn lesson of the case sartans, with their acceptable intakes, which are 15-50 times lower than the ICH M7 TTC.

The initial list was subsequently significantly expanded, and EMA has published a more comprehensive list of common nitrosamines over time. Table 5 shows a selection of the limits that EMA has currently established for some specific N-nitrosamines.

N-Nitrosamine	EMA AI Limit (ng/day)
4-(methylnitrosoamino)-1-(3-pyridinyl)-1-butanone, NNK	100
N-methyl-N-nitrosophenethylamine, NMPEA	8
N-nitroso-1,2,3,6-tetrahydropyridine, NTHP	37
N-nitroso-diethanolamine, NDELA	1900
N-nitroso-diethylamine, NDEA	26.5
N-nitroso-diisopropylamine, DIPNA	26.5
N-nitroso-dimethylamine, NDMA	96.0
N-nitroso-di-n-butylamine, NDBA	26.5
N-nitroso-diphenylamine NDPh	78000
N-nitroso-dipropylamine, NDPA	26.5
N-nitroso-ethylisopropylamine, EIPNA	26.5
N-nitroso-morpholine, NMOR	127
N-nitroso-N-methyl-4-aminobutyric acid, NMBA	96.0
N-nitroso-N-methylaniline, NMPA	34.3
N-nitroso-piperazine, NPZ	400
N-nitroso-piperidine, NPIP	1300
N-nitroso-pyrrolidine, NPYR	1700

3. Carcinogenicity Mechanism

Afterwards, the subsequent in-depth analysis and risk assessments led to the discovery of a truly vast panorama of possibilities given the almost ubiquity of nitrogens vulnerable to nitrosation in processes of drug substance and dry product manufacturers. Although a very large amount of the amines may be nitrosated, it must be considered that a consensus has been reached with the regard to the mechanism related to the high level of carcinogenicity of N-Nitrosamines, in fact **to achieve a highly carcinogenic potency, metabolic activation to form a diazonium salt (e.g. methyldiazonium, ethyldiazonium, etc.) is required**. In this context it would be more correct to refer to vulnerable amine rather than all nitrosatable nitrogens. The term vulnerable amine corresponds to an amine function having extractable α-proton and that could form an alkylating diazonium salt as described in below (Figure 6). A vulnerable amine corresponds to (but not limited to): secondary and tertiary amines, quaternary ammonium salts, N,N-dialkylamines (e.g. N-methyl-2-pyrrolidone, dimethylformamide, dimethylacetamide), N,N-dialkyl carbamates or N,N-dialkylhydrazines.

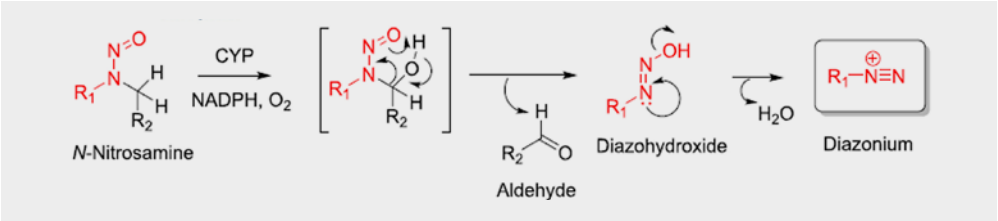


Figure 6.

4. Nitrosamine Drug Substance Related Impurities (NDSRIs)

Due to the wide range of potential routes of formation for nitrosamines, many active pharmaceutical ingredients (APIs) and impurities are themselves liable to be nitrosated, either during the later stages of the synthetic process of the API, during drug product manufacturing, or in the finished and packaged drug product. Several recent drug recalls were conducted due to contamination with such API-derived complex nitrosamines, also called Nitrosamine Drug Substance Related Impurities (NDSRIs). Due to the lack of compound-specific limits for most of the complex nitrosamines (e.g., NDSRIs or other API-related structures), an AI of 18 ng/day as nitrosamine class-specific TTC is required by many Health Authorities as a precautionary approach.

These restrictive limits have changed following the two revisions of the Q&A EMA/409815/2020 issued in July 2023. Many new possibilities have been introduced, both in terms of the opportunities offered by the **Enhanced Ames Test Conditions for N-nitrosamines** and in terms of the permitted limits. In fact, EMA has shared a system for calculating the potency of nitrosamines without known TD_{50}, i.e. without long-term rodent carcinogenicity studies. The system applied by EMA is called **Carcinogenic Potency Categorization Approach (CPCA)** and allows nitrosamines to be categorized into 5 potency categories, exploiting the concept of the metabolic activation mechanism that was already well-known in the literature, as illustrated in the previous paragraph 3. This major update on how to set limits would be particularly helpful for NDSRIs, as it is based on the ability to metabolize the α-carbon in combination with activating/deactivating features present in the molecule. EMA has therefore made available a useful list of new acceptable intakes for the most significant nitrosamines, and has also made the calculation possible in a scientific and rational way for all other NDSRI.

Following the EMA's initial step in July 2023, the FDA also took a formal implementation in early August 2023, publishing a specific guidance document on NDSRIs. The FDA uses a predicted carcinogenic potency categorization approach to assign a recommended AI limit to an NDSRI based on the NDSRI's activating and

deactivating structural features, in close alignment with the July 2023 updates of the EMA QAs. Both agencies then classify nitrosamines without experimental carcinogenicity data into 5 potency categories with identical criteria. The only difference between the agencies is the acceptable intake value for the worst-case nitrosamines that fall into potency category 1, the most potent category (18 ng/day for the EMA, 26.5 ng/day for the FDA). Additionally, the FDA also publishes a useful extended list of NDSRIs.

5. Olon approach to Nitrosamine issue

Since the presence of nitrosamines may be associated with health risks; taking into consideration the primary importance of the patient health and with reference to the recent Authorities notifications, **Olon in 2019 timely issued a nitrosamine policy, applied by all Olon manufacturing plants**, and started a systematic review of the potential presence of nitrosamines in all of its active pharmaceutical ingredients (APIs), about 300 APIs. **The revision involved a multidisciplinary team composed by R&D, QA, Regulatory Affairs, QC both at Site and Corporate level**.

First Phase

Priority ranking and risk assessment

To achieve this goal, the interdisciplinary task force was set up, to evaluate all drug substance by applying the ICH Q9 quality risk management approach. In this way each Olon production site has defined for its manufacturing processes the potential risk of nitrosamines (high or low) and the priority in which the high nitrosamine risk APIs should have been subjected to **analytical verification** by means of confirmatory tests to verify or exclude the validity of the hypothesized potential risk.According the risk-based approach described in internal policy, Olon performed an evaluation of the potential sources of nitrosamines based on the API structure, manufacturing of the APIs (both the regulatory steps and the starting materials manufacturing steps), packaging and other factors **to determine the level of risk associated with the API**. The aspects of potential cross contamination for the use of multipurpose plants have not been underestimated, nor an implementation of the request for documentation for the risk aspects of nitrosamines as an additional material necessary for the qualification of suppliers.

For the aspect related to manufacturing process, it is useful that many of the steps are made in GMP in Olon sites (sometimes even the starting material itself is made in-house). Therefore, there is a **prompt control of all the materials used, coming from validated suppliers, and the information are easily available**. Nevertheless, a lot of information is therefore needed, and some of this must be provided by the suppliers.

In this data retrieval, we took advantage by the presence of global Olon offices, well integrated with local suppliers which have allowed us a cooperative contact and prompt retrieval of information. Thanks to this close contact, a lot of evidence was recovered and allowed to set the risk appropriately (high or low). In case of lack of relevant information the worst case scenario was considered.

The risk assessments editing of the global Olon API portfolio was carried out in strictly collaboration between QA and R&D departments, and was completed well before pre-established times in order to facilitate the planning of the confirmation tests and the submission of the update to the authorities.

This policy, risk assessment and the ranking of priority are **continuously updated** since new root causes for nitrosamine formation are discovered periodically and, more recently, the issue of APIs which are themselves vulnerable to nitrosation leading Nitrosamine Drug Substance Related Impurities (NDSRIs) has strongly emerged. They involve a risk in the manufacturing or storage phase, even in the apparent absence of nitrosating agents in the process, for example due to environmental pollutants (nitrous acid, nitrogen oxides).

Second Phase

CONFIRMATORY TEST

After the first phase of priority ranking, the analysis was carried out through **confirmatory tests of all the APIs that were found to be high risk**. The safety levels of these nitrosamines need to be ascertained based on the maximum daily dose of the drug substance and according the extremely low acceptable intake required by Health Authorities based on TD_{50}, consequently it was mandatory to establish very sensitive analytical methods for their analysis. To do this, **Olon has equipped itself with an UHPLC-HRMS with a Q Exactive™ Hybrid Quadrupole Orbitrap™** Mass Spectrometer, in order to be able to internalize the analyses by quality control corporate (QCC) in its own headquarters of Rodano. In addition to that, in order to diversify the analytical techniques available in Olon, a new Agilent 6495C triple quadrupole LC/MS system (6495C LC/TQ) was recently acquired. The Orbitrap instruments will be used for identification and quantification of unknown nitrosamine, while the new instruments will be dedicated to the quantification of nitrosamine, for which we have reference standard, down to the ppb level. Sometimes the experience and instrumentation of third-party laboratories certified by our QCC was used for a timely response to the needs of authorities and customers.
This type of instrument has been subsequently put beside by high-resolution masses also in the R&D analytical laboratories located in the various production sites, to assist in the R&D centers through the development of analytical methods and the R&D works for the implementation of existing processes.

Results

OLON PORTFOLIO UNDER CONTROL

The Step 1: Risk evaluation of the global Olon API were completed within the required EMA timeline (31 March 2021 for chemical medicines; 1 July 2021 for biological medicines).
The Step 2: Confirmatory testing performed on the products identified to be at risk of N-nitrosamine formation was also fully finalized within the pre-stablished EMA deadline (26 September 2022 for chemical medicines) and the outcome reported to the authority.
Furthermore, Olon is actively taking care of the aspect related to NDSRIs and is already in an advanced stage of evaluation having already carried out numerous confirmatory to exclude the risk, or instead to include in the release specifications if the risk has been confirmed.

Rifampicin

A particular case of the impact of environmental agents is the oxidation by the air of a dialkyl hydrazine to the corresponding N-nitrosamine. In fact, in addition to the concept of vulnerable amines, capable of supplying nitrosamines when used in combination with a nitrosating agent, we must remember the term “vulnerable hydrazine” (or hydrazide or hydrazone), that correspond to a hydrazine, hydrazide or hydrazone function that can lead to N-nitrosamine derivative by mean of an oxidation step. This N-nitrosamine should as well be able to lead to an alkylating diazonium salt as described in below (Figure 7).

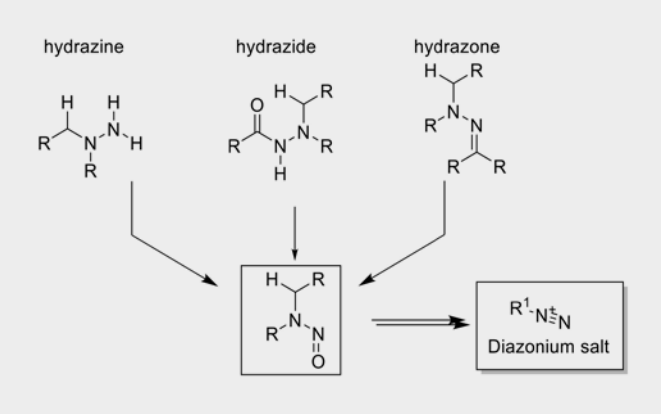


Figure 7.

We report the example of what was implemented in the Olon Mahad site to control this last effect which was maximized since the vulnerable dialkyl-hydrazine is an inherent by-product due to the intrinsic instability of the API itself. We talk about Rifampicin, and its known impurity 1-methyl-4-amminopiperazine which spontaneously generates 1-methyl-4-nitrosopiperazine (MNP, MeNP) on exposure to atmospheric oxygen (Figure 8).

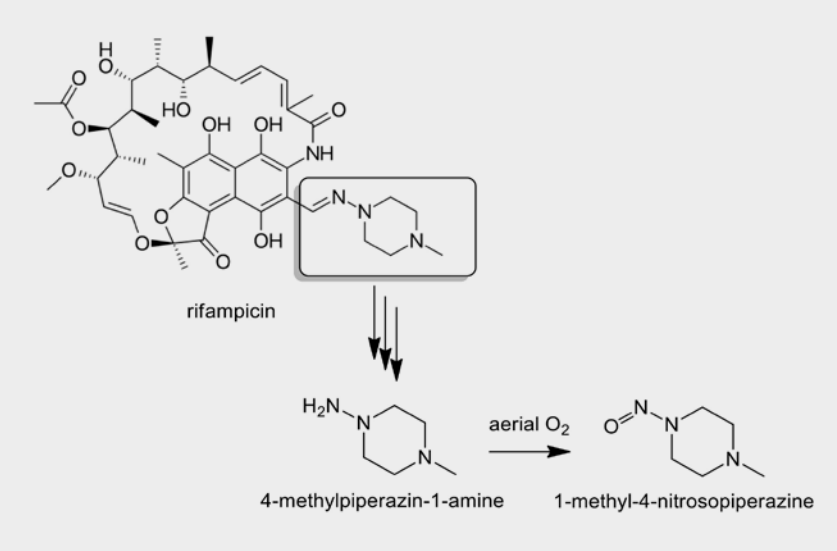


Figure 8.

Rifampicin is a dialkyl-hydrazone which by its intrinsic nature is subject to simple hydrolysis for exposure to atmospheric humidity, generating the two well-known by-products in a sort of equilibrium. Several authors report that 1-amino 4-methylpiperazine is a typical degradation product of Rifampicin in acidic conditions and well documented in extensive kinetic studies. The *in vivo* stability of Rifampicin in the acidic environment of the stomach is finally reported and the physiological decomposition varies between 8.5% and 50% over the time. The challenge was therefore managing the presence even at the level of a few ppm of this impurity, which is then easily converted through the atmospheric oxidation to the corresponding nitrosamine.
Thanks to a large investment in technology, the production plant of the Mahad site has been adapted to completely avoid contact with the air at all levels, which means in all phases of the process, from the loading of the raw materials, to the reaction and work up steps, continuing with the purification, isolation and drying to conclude with the finishing, blending and final packaging. All in a system completely isolated from the atmospheric air. In particular, the packaging system in the inert atmosphere, both in terms of methodology and materials, has been specially designed to extend the stability of the final product. The results of all these efforts is that the Rifampicin produced in Mahad complies with all the strictest international regulations ensuring a level below the required threshold in 1-methyl-4-nitrosopiperazine (MNP, MeNP). All these precaution and devices guarantee the availability of an high quality of Rifampicin which plays a fundamental role in the control and cure of tuberculosis mainly in the third world countries. The successes obtained have been the subject of two proprietary patents relating both to the manufacturing method and to the innovative packaging designed
.

7. Conclusion

This is a new sudden challenge that came from the authorities, in which **Olon is responding quickly and thoroughly, in the spirit of collaboration with suppliers, customers and authorities themselves**.
It is at the forefront in dealing with the regulatory requirements for risk assessment and analysis of nitrosamines as evidenced by the results obtained in terms of timing and quality of the analyzed APIs, which largely comply with the highest safety standards determined by the EMA, FDA and Health Authorities. As a virtuous adjustment for nitrosamine control, it is highlighted how the Mahad site has successfully implemented the air-free process for the manufacture of Rifampicin.
Alongside compliance with the regulatory requirements, on the other hand, **it's also a great noteworthy opportunity and occasion to deepen and review the knowledge of the processes, of all the materials, and to tighten and strengthen relationships with the suppliers**. And the result of this great effort is certainly the achievement of a better product, from both points of view of controls and overall quality. With the evident advantage of providing more safety and quality both to customers and the final consumer, with a view to an overall long-term gain of global public health.

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8. Olon Group

Olon Group is a global leader in the development and production of active pharmaceutical ingredients (APIs) for CDMO and generic markets, integrating chemical synthesis and biological processes while always embracing the highest international safety, quality, and environmental standards.

With one of the longest track records of the API industry, having deep development expertise and a broad set of advanced technologies, we are the partner of choice which enables our client's molecules to enter the market successfully.

Olon has a global network of **11 manufacturing sites and 7 R&D centers across the globe**. Thanks to our **2,300 employees, including 300 highly experienced and qualified R&D experts, we represent a highly innovative and reliable partner**.

At Olon, expertise and competent flexibility throughout the organization help build successful outcomes for our clients in custom chemical synthesis and microbial fermentation, while always maintaining the highest levels of safety, quality, and environmental compliance.

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