Pharmaceutical impurity profiling & custom synthesis

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Product recalls can have far-reaching consequences

The overall aim of the pharmaceutical industry is to produce drugs that give the maximum desired effect with minimum side effects. Impurities are inevitable in any chemical process, but pharmaceutical impurities, even in minute quantities, can significantly influence the behaviour of a drug, with implications for both safety and efficacy.[1] The resulting product recalls can have far-reaching consequences for both patients and pharmaceutical companies. There are huge costs associated for manufacturers, both in lost revenue and regulatory fines, in addition to the negative impact on public perceptions of the pharma industry and the potential for drug shortages.[2]

A prime example of the negative impact impurities can have on the industry can be seen in the case of impurities in angiotensin receptor blockers (ARBs), which are widely used to treat hypertension, heart failure and kidney disease. In August 2018, the US Food and Drug Administration (FDA) announced that *N*-nitrosodimethylamine (NDMA) impurities had been detected in the ARB drug valsartan.[3] The quantities of the probable carcinogenic impurity were above acceptable levels, leading to a chain of voluntary product recalls. Over the following months, two further impurities were identified in the ARB drugs irbesartan and losartan, as well as valsartan, resulting in further recalls. The timeline below highlights the scale of the crisis, with an estimated 2 million patients exposed to the impurities prior to the FDA's findings.[4]

Timeline of FDA recalls

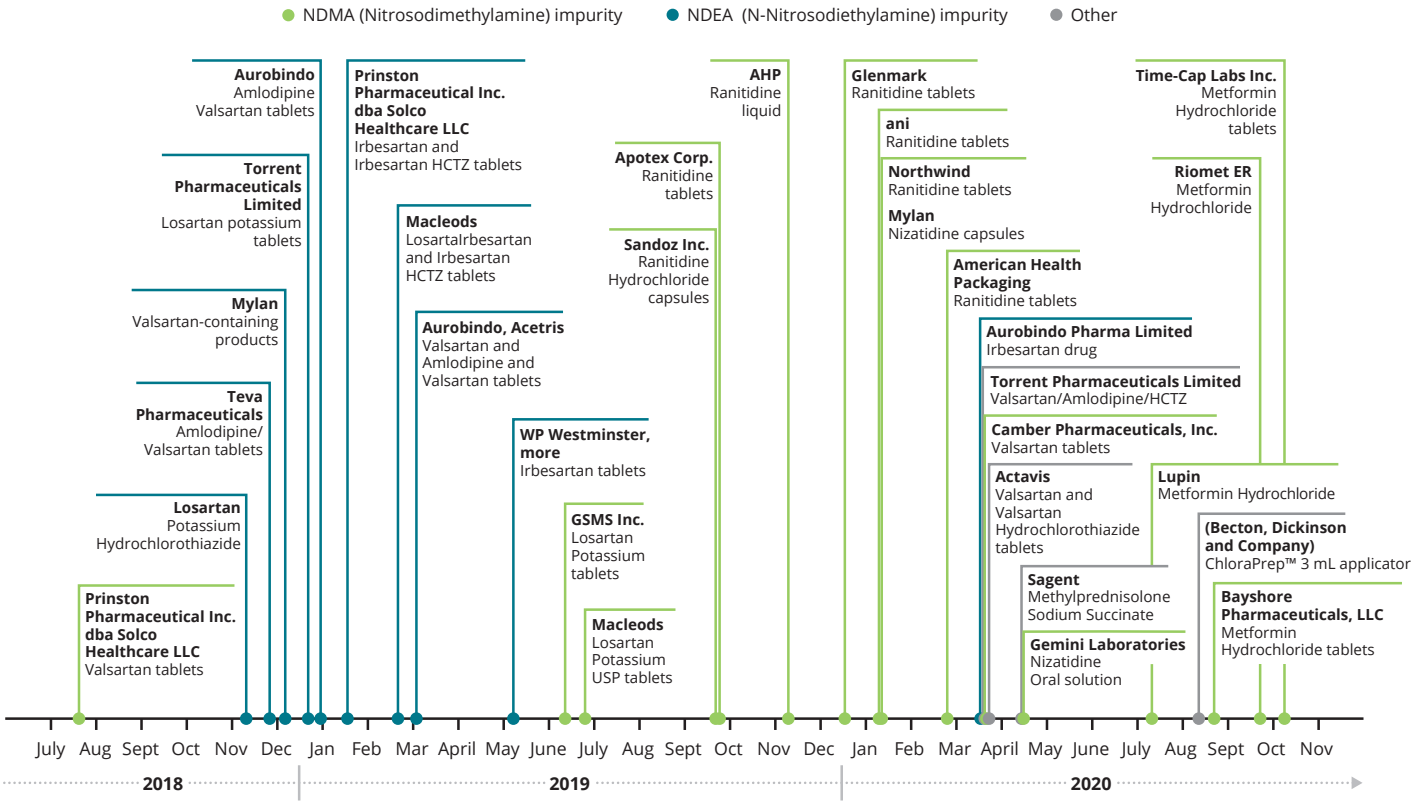


Figure 1: Timeline shows FDA pharmaceutical recalls as the result of NDMA impurities (in green), NDEA impurities (in blue) and other (in grey). Company names refer to the manufacturer and are not always the same as the distributor. HCTZ denotes hydrochlorothiazide.

Impurity control is vital to ensure safe and effective drugs

Similar recalls have since occurred for the diabetes drug, metformin, after NDMA impurities were found to be present.[5] Since the FDA's statement in December 2019, several pharmaceutical companies have recalled all lots of their metformin products. To prevent shortages, patients were advised to continue taking the potentially contaminated medication until a healthcare professional could prescribe an alternative.[6]

As highlighted by the above examples, the presence of pharmaceutical impurities can have a catastrophic effect on the industry as a result of lost revenue and financial penalties. Impurity control is therefore vital to ensure only safe and effective drugs reach the market and prevent large-scale recalls. To this end, pharmaceutical drugs must be highly pure, and drug developers must also have a thorough understanding of the likely impurities for each product, as well as their formation mechanism.[7] Impurity profiling and analysis is essential to inform our understanding of how and why impurities arise and facilitate their detection and prevention.

The origin of impurities in pharma

Impurities can arise at any stage throughout drug formulation and can be broadly categorised into three types: organic, inorganic and residual solvent impurities.[8] It is important to understand the process by which these impurities arise in order to monitor and prevent their formation, and identify other potential contaminants.

Impurities that occur during the formulation process are caused either by the method used or the environmental conditions under which the drug is produced. Method-related impurities can arise from the use of specific techniques or equipment, such as autoclaving, and environment-related impurities are caused by exposure to inappropriate temperatures, UV light, and humidity.[8] In addition, the dosage form of the drug can impact the development of impurities, with liquid dosage forms much more likely to develop microbial contaminants. Such drugs often have a shorter shelf life than solid dosage forms. Impurities are also formed due to the degradation of the drug. There are several causes of this, including the interaction between ingredients and degradation specific to the functional groups present, such as ester hydrolysis, oxidative degradation, photolytic cleavage and decarboxylation.[8] These all produce undesirable products that compromise the purity of the drug and can impact its therapeutic effect and safety.

Organic impurities

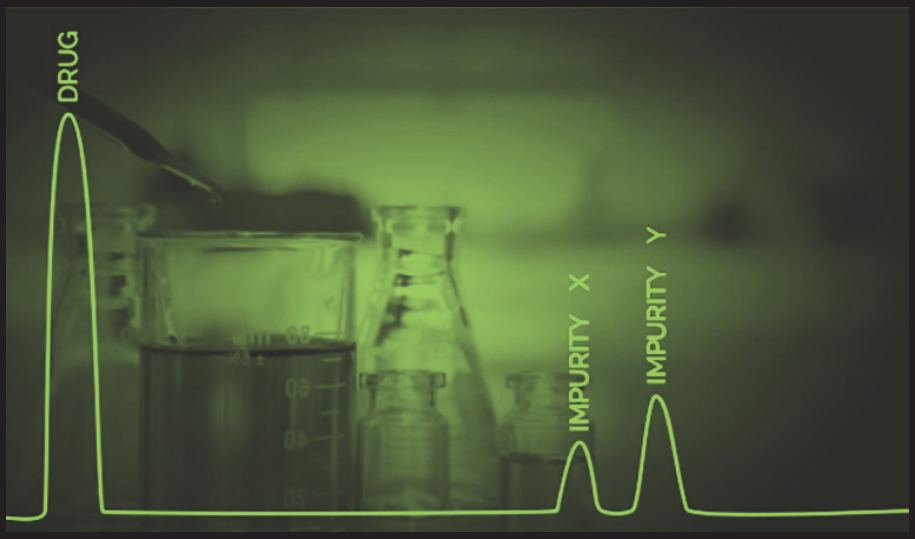
Organic impurities are the most common and can occur as a result of the drug production process. One source of these impurities is incomplete separation from other materials involved in drug synthesis. Unreacted starting materials or intermediates that remain in the compound are the most common source of organic impurity. Further, by-products are formed in the vast majority of pharmaceutical syntheses, and if these are not completely separated from the active compound, they will also contribute to impurity. Organic impurities can also result from the degradation of the end product over time. Finally, for chiral molecules where only one enantiomeric form has favourable properties, the presence of the stereoisomer constitutes an organic impurity.[8]

Inorganic impurities

Inorganic impurities can arise throughout the manufacturing process and are generally easier to prevent than organic impurities, as they result from the equipment and materials used in the process, all of which can be controlled. Sources of inorganic impurity can include the presence of reagents, ligands or catalysts; the presence of heavy metals, from water or the reaction vessel used; and other materials, such as those used in filters. The risk of these types of impurity can usually be easily mitigated, for example by using demineralised water and glass-lined vessels, as well as through careful monitoring each stage of the production process.[8]

Residual solvent impurities

Solvents used in the manufacture of a drug compound can be difficult to fully remove and residues can remain on the product. For this reason, solvents are categorised according to their risk to human health, with strict limits set for safe daily exposure, and only the safest approved for use in drug formulations.[8]



Measures such as the use of appropriate packaging and storage conditions, as well as careful washing and drying of products at every stage of formulation, can help to reduce the occurrence of impurities. These methods alone, however, cannot guarantee the prevention of contamination. Further research into impurities is needed to inform best practice to ensure maximum purity, and therefore safety. TRC's capabilities in this regard are outlined in the following pages.

TRC provides state-of-the-art instrumentation and highly qualified teams

Detection, synthesis and analysis of pharmaceutical impurities

Identifying impurities is the first step in preventing them. By elucidating the structure of impurities, it is possible to understand their formation mechanism, which can then inform industry practice around prevention or control.[9]

For impurity identification, the components of the drug must be separated to isolate any process contaminants, degradants or leachables alongside the active pharmaceutical ingredients (APIs). This can be achieved using high-performance liquid chromatography-mass spectrometry (LC-MS), which will provide mass information for less volatile impurities, enabling structural identification. For more volatile impurities, gas chromatography-mass spectrometry (GC-MS) is required. Following separation, nuclear magnetic resonance (NMR) spectroscopy and Fourier-transform infrared (FTIR) spectroscopy can be used to identify any impurities in the sample. Different combinations of techniques are used on a case-by-case basis, taking into account the complexity of the compound and the purity requirement of the customer.

TRC provides state-of-the-art instrumentation and highly qualified teams to ensure the highest standards throughout impurity analysis. In addition to its catalogue of fully compliant research chemicals, TRC also offers extensive analytical services for impurity identification, including quantitative and qualitative analysis, IR and NMR analysis, mass spectrometry (MS) analysis and purity determination. TRC's expertise can help to ensure accurate data for even the most complex impurities.

Synthesis of impurities is a useful tool in impurity studies. By matching the spectral and chromatographic profiles for the impurity with that of the synthesised compound, its structure can be verified.[10] The synthesised impurity can then be studied further, to understand its toxicological effect, as well as its formation mechanism. This knowledge can inform regulations and be used to optimise the synthetic process and drug formulation, ensuring safe purity levels are maintained.

TRC offers a range of products and services to support impurity studies

In addition to providing a broad range of impurities for use in research, TRC's custom synthesis offers further options for pharmaceutical impurity research. Custom synthesis is required when an impurity needed for research is not commercially available, providing synthesised compounds to be used by companies as internal standards for exact impurity quantification. This broadens the research possibilities for newly identified or complex impurities. In such cases, TRC's services can provide development of a new synthetic route as well as optimisation of an existing one, accelerating research into these contaminants. Among the many types of custom synthesis available, TRC's expert teams can develop custom reference compounds, impurities and stable labelled isotopes to support pharma impurity research.

Labelled isotopes can be used to characterise and monitor pharmaceutical impurities for metabolic and pharmacokinetic studies in biological systems, giving further insight into their toxicological effects. TRC provides customised labelling of metabolites, impurities, APIs and intermediates to be used in tracer studies. These products can be customised to the customer's needs and provide robust LC-MS assays by increasing sensitivity and selectivity and reducing the matrix effect, generating more reliable data.

TRC offers a range of products and services to support impurity studies to any extent. The impurities in our extensive catalogue can be used as standards, starting materials or analytical tools to quantify materials, whilst the highly experienced scientists delivering our analytical and custom synthesis services can provide problem-solving advice and specialised support.

Synthesis of atorvastatin epoxy pyrrolooxazin tricyclic impurity

What is atorvastatin?

Atorvastatin is a selective, competitive HMG-CoA reductase sold under the brand name Lipitor. It is the only drug in its class specifically indicated for lowering both elevated LDL-cholesterol and triglycerides in patients with hypercholesterolemia.

What is the atorvastatin epoxy pyrrolooxazin tricyclic impurity?

The epoxy pyrrolooxazin tricyclic potassium salt impurity is a photodegradation product of atorvastatin which can cause adverse effects. It must be included in the mandatory list of impurity testing required by any drug manufacturer before they submit a new drug application.

The challenge

Our customer was unable to obtain the impurity at the level of purity needed to continue the analysis of their product batches, so they approached TRC to synthesise the compound required. Of all the impurities associated with the photodegradation of atorvastatin, the epoxy pyrrolooxazin tricyclic potassium salt impurity is certainly one of the most difficult to prepare. To date, no synthesis has been reported in the literature, making it difficult to obtain for use as a standard.

How TRC helped

Despite its apparent complexity, the product was prepared in two steps from an advanced atorvastatin bicyclic impurity. However, this short sequence proved problematic, requiring a longer duration to optimise. The highly strained tricyclic molecule was susceptible to degradation, limiting our options in terms of reagents to affect both steps of the synthesis, as well as purification methods. After numerous failed attempts, an alternate ether solution proved to be the optimal reagent in order to generate the desired impurity from the methyl ester intermediate. Due to the limited stability of this particular impurity in a suitable solvent for NMR analysis, the structure of the impurity was ascertained indirectly via the ester precursor again. Through our proven methodologies for specific material identification, we were able to thoroughly characterise a problematic impurity and synthesise it with the purity required to enable our customers to progress their analysis.

Conclusion

It is clear that an understanding of pharmaceutical impurities, including how and why they form, is imperative for the manufacture of safe and effective drugs. The presence of potentially harmful impurities can impact the pharmaceutical and healthcare industries through damaging product recalls and drug shortages, but most importantly, such impurities threaten patient health. Impurity formation can occur in a number of ways throughout the formulation process and is not always easy to detect and prevent.

TRC combines a highly experienced team and superior problem-solving skills with state-of-the-art analytical instrumentation to support impurity analysis. Our custom synthesis service can provide complex or commercially unavailable impurities for analysis or internal standards, and our labelled isotopes can facilitate further studies into metabolites in biological systems. While techniques and regulations for impurity control are continually updated, impurity screening and analysis will always have a place in safeguarding therapeutics for patients around the globe. Through our products and services, we can support research into impurities to help ensure that only safe medicines reach the marketplace.

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