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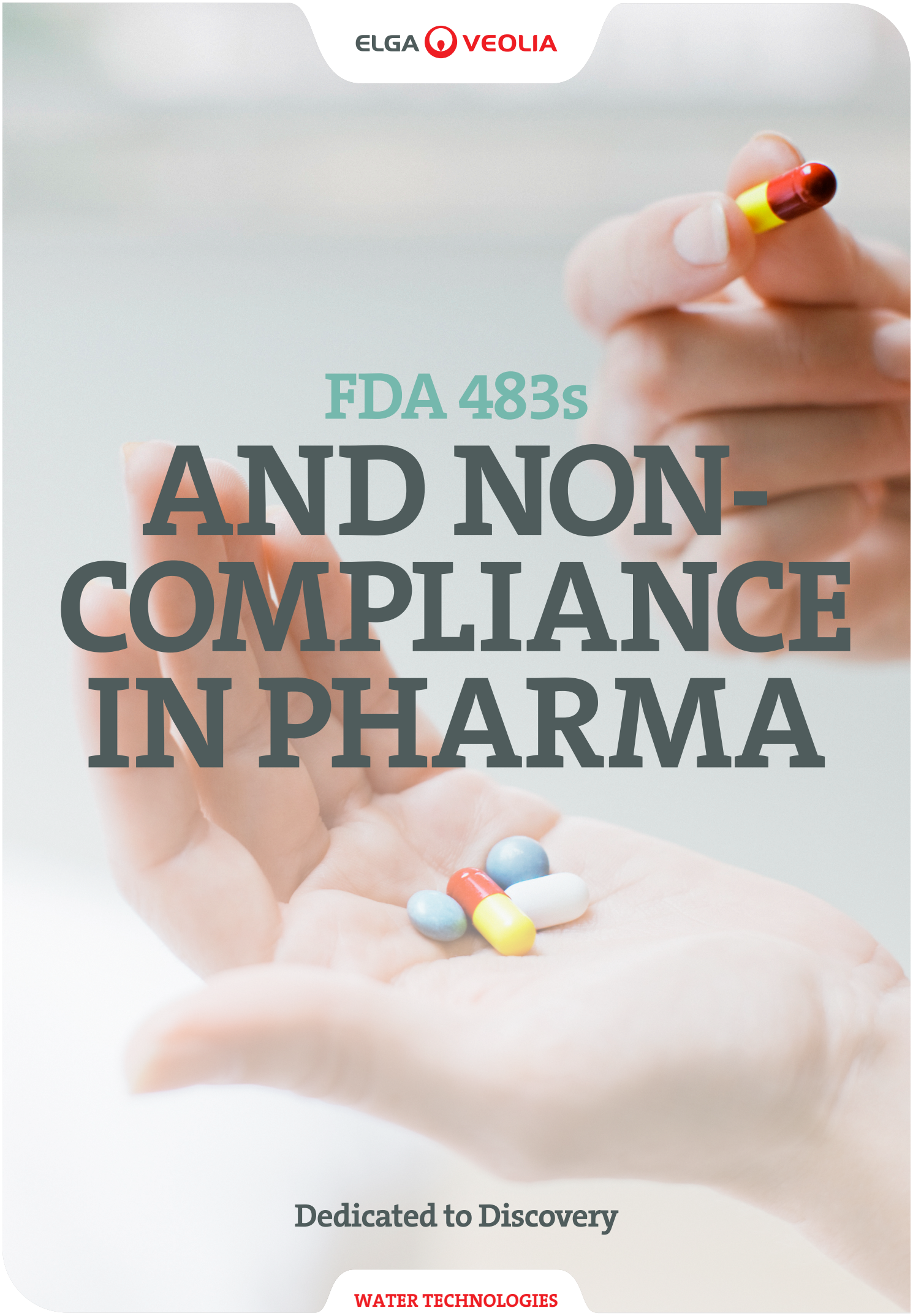

FDA 483s

AND NON-COMPLIANCE IN PHARMA

Dedicated to Discovery

WATER TECHNOLOGIES

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SECTION 1

Non-compliance in pharma: FDA 483

The United States Food and Drug Administration (FDA) has the authority to inspect pharmaceutical companies that manufacture FDA-regulated products at any time, and write down their observations on Form FDA 483, commonly abbreviated to "483".

Form 483s are very important to FDA-regulated companies, regardless of how many, if any, they have received. A single 483 tells a company exactly which areas to improve - or to correct - to remain compliant (and therefore operational). Downplaying the 483 content and, more importantly, not responding seriously and completely to the observations can have costly consequences.[1]

Inspections where investigators make notes on observations that may be violations of regulations will lead to a 483. After a 483 is issued, FDA officials may conclude that a serious violation could exist, and a warning letter is then issued. Warning letters usually result from:

- **Failure to adequately address the observations of previously issued 483s**
- **Unsatisfactory or incomplete corrective actions proposed by the sponsor**
- **Other issues that are much more serious and require rapid escalation.**

CITATION	SHORT DESCRIPTION	2016	2017	2018	2019	2020
Total Form 483s issued using the FDA tool for Drug Inspections		691	694	716	779	349
§211.192	Investigations of discrepancies	227	278	183	167	128
§211.22(d)	Procedures applicable to the quality unit shall be in writing and shall be followed	153	185	208	215	111
§211.160(b)	Lab controls should include scientifically sound specifications	133	207	209	145	84
§211.100(a)	Production and process controls shall be supported by written procedures	110	118	102	129	59
§211.68(b)	Appropriate controls shall be exercized over computer systems					57
§211.42(c)	Facilities shall include defined areas of sufficient size	227	148	134	156	56
§211.188	Master production and control records	100	208	93	123	54
§211.166(a)	Stability testing	124	72	111	135	42
§211.67(b)	Equipment cleaning and maintenance	102	91	112	124	45
§211.113(b)	Control of microbiological contamination	118	92	71	121	43
§211.67(a)	Equipment shall be cleaned/sanitized or sterilized	94	54	81	99	42
§211.25(a)	Personnel qualifications	99	113	47	113	39
§211.160(a)	Following / documenting laboratory controls					38
§211.68(a)	Automatic, mechanical, and electronic equipment	80	67	60	67	33
§211.110(a)	Sampling and testing of in-process materials and final product	65	68	88	94	33

Table 1. Summary of drug-related 483s from 2016-2020.[2]

By listing deficiencies in a warning letter, the FDA has determined that the practice violates a regulation to which the firm must comply. Issuance of 483s themselves tends not to make headlines: they are an integral part of ensuring that quality management and compliance remain central to a pharma company's operations and culture. However, warning letters and product recalls posted on the FDA website often make headlines in the industry, or even in the general news media.

Expressed in simple terms, 483s for pharmaceutical drug production tend to be issued in the following areas:

- **Failure to Follow Written Procedures**
- **Failures in Laboratory Controls**
- **Faulty Production Record Reviews**
- **Absence of Written Procedures**
- **Improper Cleaning/ Sanitizing/Maintenance.**

A summary of the 483s issued for drugs, from 2016-2020, can be found in Table 1, and is expressed graphically in Figure 1.

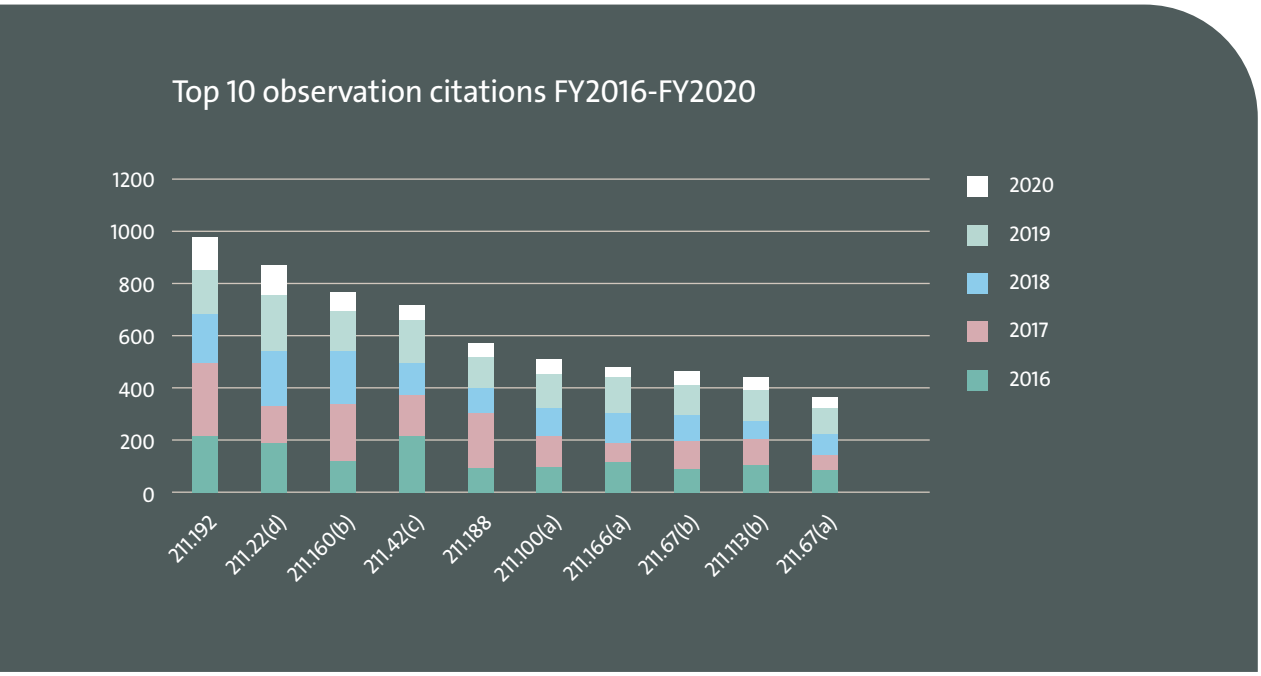


Fig.1: Summary of drug-related 483s from 2016-2020. For key to categories, see Table 1.[2]

The 483s above that refer to physical processes, such as cleaning, sanitizing, sterilizing, sampling, microbial contamination control, and stability testing will inevitably include water at some point in their respective standard operating procedures (SOPs). Given this fundamental importance of water in the drug production and QC process, and the prevalence of microbial and chemical contamination in APIs and finished product recalls, it is self-evident that the water purification systems used in manufacturing need to be compliant.[3,4] This compliance will also include provision for written quality management procedures, whether for installation or maintenance.

In cases where the final product has been compromised by FDA observations outlined in a Form 483, and presents a danger to human health, the FDA will recommend a product recall. A drug recall is the most effective way to protect the public from a defective or potentially harmful product. A recall is a voluntary action taken by a company to remove a defective drug product from the market. Drug recalls may be conducted on a company's own initiative or by FDA request. The FDA's role in a recall is to oversee a company's strategy, assess the adequacy of the recall and classify it.

Recalls will have a negative impact on the company's brand and potentially leave patients at risk. Poorly managed recall procedures can result in devastating consequences with the FDA. The recall procedure is managed by the individual manufacturer, and includes:

- **Timely and adequately notifying FDA, distributors, and customers of the recall**
- **Developing compliant documentation for opening, tracking, and closing the recall**
- **Providing updates to FDA regarding the recall**
- **Performing effectiveness checks that will lead to recall closure.**

Often, a company recalls a product only after the FDA raises concerns in a 483. The FDA may learn about a problem product by inspecting a manufacturing facility, receiving reports of health problems or hearing about it from the Centers for Disease Control and Prevention (CDC). Sometimes, a company discovers a problem on its own and contacts the FDA.

Before the FDA can recommend or conduct a recall, it will conduct a health hazard evaluation. The agency assembles a committee of scientists, which will then consider the following factors:

- **Diseases or injuries that may have already been caused by the product**
- **Existing conditions that could be a contributing factor (documented with scientific evidence)**
- **The level of hazard to special segments of the population, such as children or the elderly, and those who could be at greatest risk**
- **The seriousness of the health hazard and level of risk to exposed populations**
- **Consequences of long-term or immediate health hazards.**

Recalls are then classified in the following categories:

RECALL CLASSIFICATION

Class I: This is the most serious type of recall. There is a reasonable probability that the product will cause serious adverse events or death. Products such as pacemakers, heart devices and lifesaving drugs fall into this category.

Class II: Most recalls fall in this category. Products under a Class II recall can cause temporary or reversible adverse events. Many medical implants, such as hip or knee replacements, fall in this category. Injuries from Class II devices can still be serious, but are not typically life-threatening.

Class III: A product that is unlikely to cause any adverse health reaction, but that violates FDA labeling or manufacturing laws.

Not all recalls are announced on FDA.gov or in the news media. Public notification is generally issued when a product is recalled that has been widely distributed or poses a serious health hazard. However, if a company does not issue public notification of a recall, the FDA may do so, if it determines this necessary to protect patients. Patients also may learn that their medicine has been recalled through notification from the manufacturer, their health care professional or pharmacist.

All recalls are posted weekly in an FDA enforcement report. Recalls are classified as Class I, Class II or Class III. Unclassified ongoing recalls are published as "not yet classified" until their classification has been determined. The FDA evaluates the effectiveness of a recall by evaluating a company's efforts to properly notify customers and remove the defective product from the market, working with them to develop and implement their recall strategy.

The FDA then requests that the company submit periodic recall status reports, so the appropriate FDA district office can assess the progress of the recalls. In many cases, a report must be submitted every two to four weeks, but the frequency may vary depending on the urgency of the recall.

Using these status reports, the FDA will evaluate whether "all reasonable efforts have been made to remove or correct a product." The agency will terminate a recall after it reviews the manufacturer's actions and determines they meet the criteria laid out in the recall strategy. Sometimes the problem cannot be corrected, but in other cases, a manufacturer will return the drug or device back to the market.

What are the consequences of non-compliance in drug production and QC, and how must a company respond to a 483 or to the need for a product recall? Let us look at this in more detail by exploring some recent and ongoing cases where 483s and product recalls have been issued.

SECTION 2

Drug production, compliance and QC

We have established that 483s are an essential tool for keeping up the high standards of compliance and quality management required of companies that produce drugs. In some cases, 483s may lead to product recalls, in other cases recalls arise post-distribution and result from adverse event reporting.

On average, about 4,500 drugs and devices are pulled from U.S. shelves each year.[5] The recalled products have U.S. Food and Drug Administration (FDA) approval and in many cases, are widely ingested, injected or implanted before being recalled. Reasons for a recall can range from issues with the packaging to reports of life-threatening and even fatal injuries or diseases.[5]

Of the 261 drug recalls ongoing as of 21 October 2021, at least 22 of these are due to microbial contamination, 9 of which implicate *Burkholderia cepacia* complex (Bcc).

Bcc bacteria are known for their capacity to endure severe environmental stresses, and that includes the ability to survive in nutrient-scarce environments, such as water supplies. Whilst Bcc is low virulence, it is a frequent colonizer of fluids used in hospitals e.g., irrigation solutions, intravenous fluids. Bcc rarely causes infection in healthy hosts, but as an opportunistic pathogen it frequently causes pneumonia in immunocompromised patients.[6] A further 22 recalls cite lack of sterility assurance, or potential for non-sterility, **making microbial contamination one of the most common reasons for recall.**[3]

Another common element which figures highly in drug recalls is chemical contamination, with 31 cases of NDMA contamination noted in sartan derivatives, such as Valsartan and Losartan.[3] These drugs belong to a group of angiotensin receptor blocker (ARB) medications and are very commonly prescribed for high blood pressure and heart failure. The initial findings, which first came to light for Valsartan in 2018, and continue at time of writing, were initially the consequence of using poor quality low-cost generic APIs, and triggered recalls of at least six generic versions of the medication in more than 20 countries.[7]

When we look at the root causes of microbial contamination found in the raw materials or in the final product, most of them come from the environment not being sufficiently sterile (e.g., inadequate lab hygiene and sanitation), or from the water that is being used (e.g., contamination of APIs).[8] It follows that if the water purification systems used in the manufacturing and formulation of the final products meet regulatory compliance, including 21 CFR Part 11, and USP 643 and USP 645 regulations, the less likely it is that the water itself will be contaminated. Water problems will also be more easily ruled out when it comes to the various QC tests which are routinely carried out on the intermediates and the final formulations.

For chemical contaminations, the purity of the water used in the chemical synthesis process could potentially be an issue, and water must also be ultrapure when it comes to performing accurate and sensitive QC testing. Similarly to microbial contamination, the only way to guarantee the purity of the water used in the synthetic process and in QC testing is to ensure that the systems producing it meet regulatory compliance.

The chemical contaminant initially implicated in the Valsartan recalls, NDMA, is classified as a probable human carcinogen, even at µg/kg levels.[9] NDMA contamination was thought to be caused by the changes in the production process of the Valsartan API. Since the recall, an HPLC analytical method has been developed that can detect trace amounts of NDMA in the final product, in the same chromatograph as the API, Valsartan (see Fig 2).[10]

This figure clearly demonstrates the limits at which we are working when it comes to detection of contaminants: without "clean" chromatograms, it would be impossible to detect these trace amounts in QC testing processes, and batches of potentially dangerous drugs would continue to be released into the market.

We have touched on the importance of compliance, and the implementation and maintenance of quality management systems in pharmaceutical production and QC testing, to avoid issues such as microbial and chemical contamination of APIs.

The final section of this paper explores the contribution of compliant water purification systems to the success of drug production and QC.

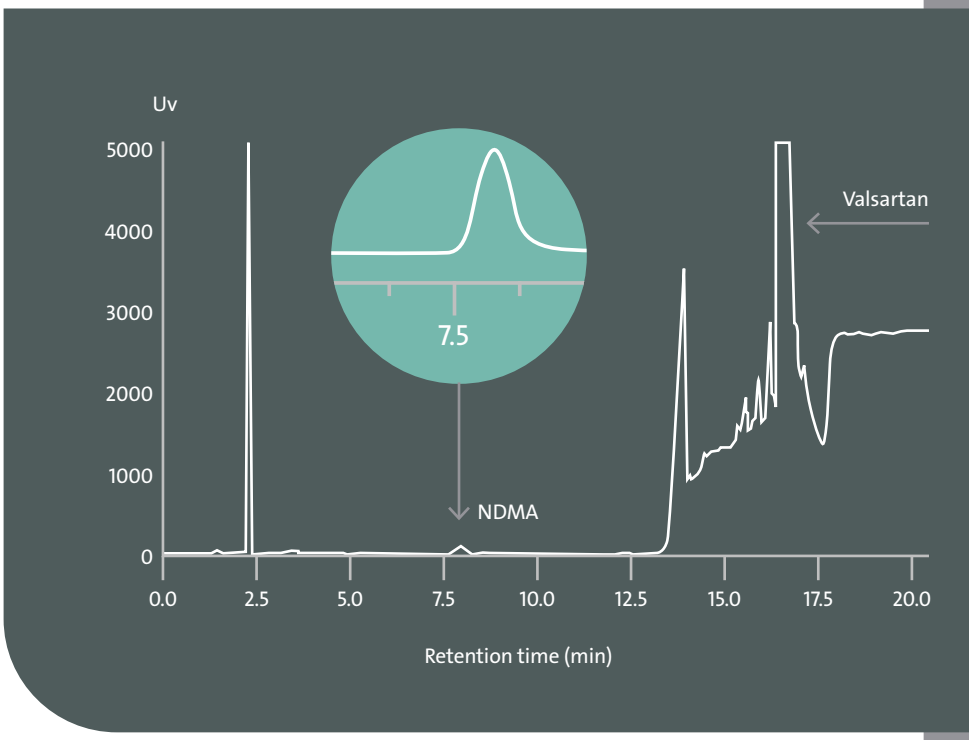


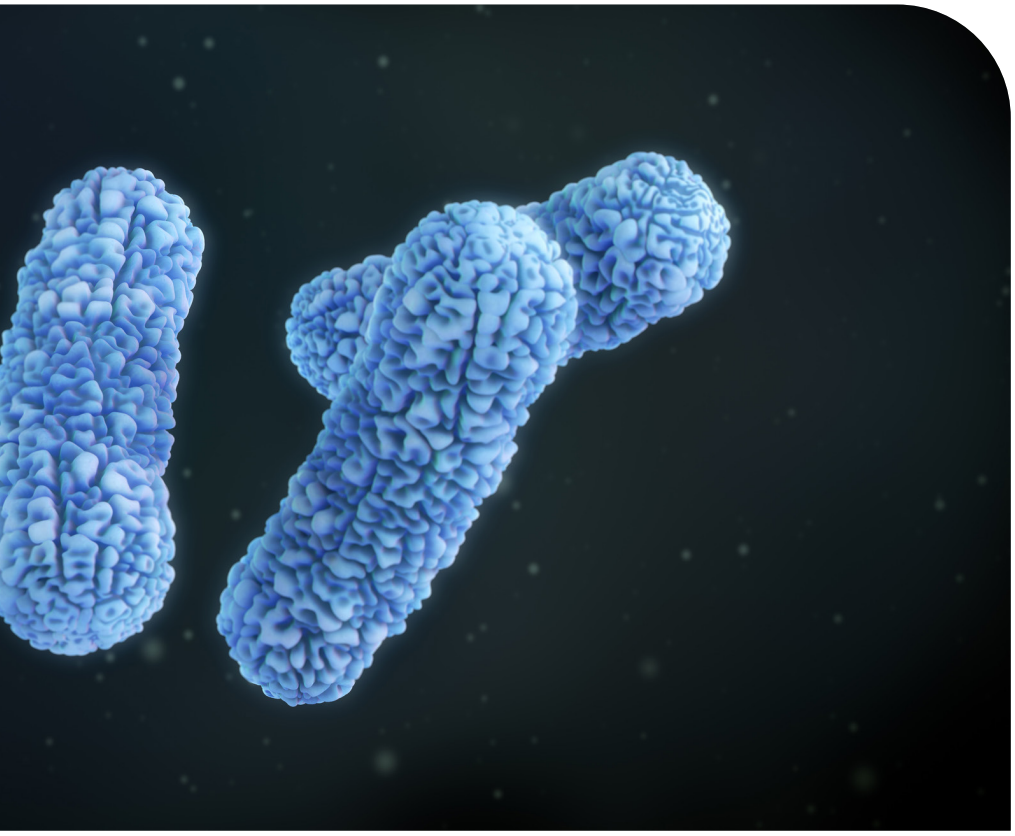
Fig. 2 HPLC chromatograms of a sample solution of Valsartan drug substances produced by Zhejiang Huahai Pharmaceutical Co., Ltd.[10]

SECTION 3

Water purification for QC success

Compliance becomes especially important when it comes to the design, installation and maintenance of the water purification systems needed in pharmaceutical processes. In effect, the unique role of water as both reagent and product in the drug production pathway means that its own quality control processes must be as stringent as possible, so that water can be immediately eliminated as a root cause when issues arise, such as contamination.

The United States Pharmacopoeia (USP) has clear guidelines that contribute towards the elimination of - or at least help minimize - microbial contamination in pharmaceutical production. For example, it notes that water systems for pharma manufacturing should have ready access to built-in sanitization systems, including super-heated water at all locations, ozone or UV-C (ultraviolet) radiation, or ensure an adequate amount of residual chlorine.



USP reviews are also available to help in the design, operation, and maintenance of an effective pharmaceutical water treatment system and microbiological testing program to prevent microbial contamination in the first place.[11] This includes the establishment of alert and action levels as part of SOPs for testing, validating and troubleshooting, as well as routine, periodic sanitization procedures for all pharmaceutical water systems. The effective implementation of these SOPs as part of pharmaceutical production and QC testing is only possible with the use of water purification systems that meet 21 CFR Part 11 requirements.

Ultrapure water is also needed for QC testing in the detection of chemical contaminants in APIs. If the water in these QC processes is not delivered from a compliant system, such that the quality of the water is not continuously monitored and regulated, it is entirely possible that trace amounts of contaminants go unnoticed, and dangerous products are released to the market as a result. The ongoing sartan recalls provide us with a salutary tale in the need for continuous monitoring of APIs going into the production process, and the potential knock-on effects of changes in the SOPs for chemical synthesis.

Pharmaceutical production and QC SOPs are notoriously difficult to change, as change requires capital investment and time of those concerned to assess the risks and benefits. In mitigation, it is easy to understand the innate conservatism of the industry when considering such examples as Valsartan, where a small difference in the chemical synthesis of the API had such dramatic consequences. The use of water from systems that meet compliance requirements when it comes to the QC of APIs is essential, especially when we are trying to detect trace amounts of contaminants using water-sensitive techniques such as HPLC.

In conclusion, water is unique in its vast contribution and impact across pharmaceutical processes, whether used as an excipient, in API synthesis, in production and QC of the finished product, or as a cleaning agent. The monitoring and maintenance of the correct level of water purity in all these processes, including the use of water purification systems that are compliant, can only contribute positively towards ensuring continued trust and confidence in the pharmaceutical industry.

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