FDA STATEMENT

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Media Inquiries: Jeremy Kahn, 301-796-8671; jeremy.kahn@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

Millions of Americans take medication daily to control their blood pressure. We recently found that some generic versions of one medication, valsartan, contain an impurity that doesn't meet FDA's safety standards. Valsartan is an angiotensin II receptor blocker (ARB) that treats high blood pressure and heart failure. The FDA currently has a major operation underway to investigate and address this troubling finding. This investigation is led by a dedicated task force of experts focused solely on this important work. Their mandate is to oversee the investigation and track new developments and information coming in from valsartan manufacturers. This multidisciplinary team of chemists, toxicologists, medical doctors, pharmacists, investigators, communication specialists, and analytical lab staff coordinates across the FDA, and acts on the newest available information.

As our investigation continues to identify the root cause of this impurity, we want to take the opportunity to describe to the public what we are doing to find the cause of the impurity, to prevent a recurrence of this episode and to protect patients who need this medication.

On June 19, a U.S. manufacturer of valsartan products, Prinston Pharmaceuticals Inc., contacted the FDA's Center for Drug Evaluation and Research (CDER) about its products containing valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceutical Co. (ZHP). Prinston informed CDER that they had stopped making valsartan products because ZHP had detected an impurity in the API – a chemical known as N-nitrosodimethylamine (NDMA). NDMA is a probable cancer-causing chemical found in trace amounts in water and some foods. However, the levels of NDMA in ZHP's valsartan API – while still trace amounts – were unacceptable.

Although the risk to patients taking the affected products is extremely low, we take matters of pharmaceutical quality very seriously. We took immediate steps to address these findings.

Shortly after initiating our investigation, we learned that a foreign regulator was also reviewing medications containing valsartan API manufactured by ZHP and considering a recall. We have closely coordinated with the European Medicines Agency, European Directorate for the Quality of Medicines, Regulatory Operations and Regions Branch and Therapeutic Products Directorate of Health Canada, and the Pharmaceuticals and Medical Devices Agency in Japan since that time, sharing information about our investigation with them and other regulatory bodies and learning about their findings.

We recognized that we had to find answers to several important questions: How many U.S. valsartan products are affected? Where did the impurity come from? What are the potential health consequences of the impurity? How many patients are affected? How long have patients been exposed to NDMA? How do we ensure that patients and providers are informed so that health care is minimally disrupted? How do we prevent drug shortages? And could similar drugs also contain this impurity?

Our first priority was to inform patients and health care providers. To do this, we had to verify the information about ZHP's API to understand the risk to U.S. patients and the scope of APIs and products

potentially affected by this impurity. We identified four manufacturers using valsartan API from ZHP for the U.S. market. We contacted them to ask if they knew about NDMA in their products and to recommend recalls of affected products. In addition to ZHP, we identified 13 other API manufacturers who supply more than 20 drug companies that make valsartan for the U.S. market. We made plans to determine if their products could also contain NDMA.

By July 13, we had the information we needed to issue a press release stating that three companies had products containing NDMA and were voluntarily recalling them. One of the four manufacturers we initially identified required further investigation, but has since voluntarily recalled its products.

However, we did not want patients taking valsartan to hear this news and abruptly stop their medications, possibly suffering serious medical issues, such as stroke. We needed to let patients know the specific products impacted by the recalls, so they could talk to their health care providers and get prescriptions for products that had not been recalled. We began posting frequent updates to our website, listing first the valsartan products affected by the recall, followed by a list of the hundreds of products not affected at that time. We shared this information broadly across other communication channels known to reach consumers and health care providers, such as social media, newswires and email listservs. Because this is a continuing investigation, more manufacturers may discover that their valsartan products contain NDMA and take steps to voluntarily recall them. We encourage patients and prescribers to check these lists frequently for potential changes in the recall status of their medicine. We are continuing to update this information on a regular basis and update consumers over our social media platforms to ensure broad reach.

CDER toxicologists and chemists evaluated the risk to the public. On July 27, we shared what our scientists were able to estimate was the theoretical risk that the impurity could pose to patients. We estimated that if 8,000 people took the highest valsartan dose (320 mg) from NDMA-affected medicines daily for four years (the amount of time we believed the affected products had been on the U.S. market), there may be one additional case of cancer over the lifetimes of these 8,000 people beyond the average cancer rate among Americans. This estimate represented the highest possible level of NDMA exposure. It was a measure of the risk under the most extreme circumstances. Most patients who were exposed to the impurity through the use of valsartan received less exposure than this worst-case scenario.

In St. Louis, the FDA maintains the most advanced pharmaceutical laboratory of any regulatory agency in the world. As soon as we were aware of the NDMA impurity in certain valsartan drugs, we began collecting samples of all valsartan API and products marketed in the U.S. At the same time, our scientists began developing a test to detect and quantify NDMA in valsartan API. NDMA's properties make it difficult to find. To determine if valsartan products do contain this impurity, CDER's scientists have now developed the gas chromatography-mass spectrometry (GC/MS) headspace testing method. We posted this method to the web to help manufacturers and regulators detect NDMA in valsartan API and tablets.

Based on information provided regarding ZHP's manufacturing processes, we believed (but did not have proof) that the impurity resulted from changes that ZHP made to the manufacturing process for its API. We needed to identify the root cause of the problem and evaluate ZHP's explanation. After assessing information about ZHP's manufacturing processes and the changes ZHP made over time, we identified how its processes could have led to the presence of NDMA in their API.

Specifically, a combination of conditions, which include certain chemicals, processing conditions and production steps, could lead to formation of the NDMA impurity. We believe that these risks are introduced through a specific sequence of steps in the manufacturing process, where certain chemical reactions are needed to form the active ingredient. Before we undertook this analysis, neither regulators nor industry fully understood how NDMA could form during this process. We are still not 100 percent sure that this is the root cause of the problem. Full understanding will require correlation of multiple test results from valsartan APIs made by different processes with the various process steps used by different manufacturers or at different times. We need to determine how NDMA can be formed and why it is not separated from the API during purification.

Once we understand the way or ways that the NDMA impurity can occur as a by-product of the manufacturing process, we will make sure these conditions are evaluated in API synthetic processes so that, in the future, testing for this impurity would be required if there was a risk of NDMA formation.

NDMA is one chemical in a class called "genotoxic impurities". These chemicals are of special concern to global regulators because, unlike most impurities in drugs, they have the potential to cause harm at very low levels. The FDA has worked with international regulators to create standards for mitigating the risk of such impurities. We have robust policies and procedures in place to guard against these risks.

The FDA will continue to improve its procedures for guarding against these impurity risks. We will use the information that we learn from our investigation into valsartan to strengthen our oversight.

In March 2018, the FDA issued a guidance for manufacturers that lays out risk assessements that manufacturers can use to evaluate the presence of genotoxic impurities. This is an internationally-harmonized guidance that both regulators and industry have agreed to. To implement the risk assessment for any genotoxic impurity, there has to be recognition that it can occur in the manufacture of the product. The guidance lays out the conditions under which these risks can occur, and the steps that manufacturers should take to test for these potential impurities.

Under the agency's longstanding policies, manufacturers are required to test for impurities that may be introduced or develop during their manufacturing processes. We review that information in product applications, including requests to change the manufacturing process. We employ robust teams of organic chemists, as part of our newly established Office of Pharmaceutical Quality, to review applications and referenced information to look for steps – and manufacturing changes – where these risks could be introduced.

The FDA also inspects manufacturing facilities across the world, and in routine current good manufacturing practices inspections, we can review a manufacturer's records regarding impurity testing. However, the review of records depends on appropriate tests to detect the impurity. Tests are selected based on assessments of what impurities may develop based on the manufacturing process. In other words, it needs to be recognized that the risk of an impurity can occur in order to know that it should be tested for.

Recognizing these risks is based on a deep understanding of the chemistry involved in drug manufacturing, and the theoretical risk that an impurity could be a by-product of an essential step used in the manufacture of an active ingredient. When these impurities are identified, there are ways to re-engineer manufacturing processes to find pathways that don't create these by-products. Because it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it. They would not have records that help identify this issue during an inspection. So this particular risk would not have been identified on an inspection. As we develop a better understanding of the root cause of NDMA formation, and develop a way to detect NDMA in valsartan or other ARBs, we can ensure that appropriate testing is performed in the future.

Based on our analyses of the manufacturing processes, we are now testing all the products in the ARB class to determine if they contain NDMA. In some cases, the steps in the synthesis of other ARBs can have similarities to the synthesis of valsartan. These tests will continue until we identify all products that may contain NDMA in the ARB class, and they are no longer available in the U.S. And our robust investigation continues, as do our efforts to mitigate these risks and prevent them from recurring.

The FDA has also inspected ZHP in response to this problem and the agency may re-inspect ZHP and inspect other manufacturers of valsartan API in the future. The FDA is coordinating with companies to take swift action to remove any products found with unacceptable amounts of NDMA from the U.S. market.

The initial recall has expanded to now include five manufacturers and other companies who repackage those products under a different name. More products may need to be recalled. At the same time, the

FDA is working to make certain that patients have access to the treatment that they need. Currently, more than half of all valsartan products on the market are being recalled. But prescribers can find a similar replacement product within the same class to substitute for patients who require this medication.

We are also working very closely with global regulatory agencies, including the European Medicines Agency. The task force the FDA formed exchanges information with regulatory counterparts around the world including inspection findings, laboratory test method and results, and our scientific assessment of the cause of this problem and its impact on patients. While not every manufacturing site produces drugs for all countries, we believe sharing this information is vital to advancing our ongoing investigation. It enables us to address emerging issues quickly in a way that benefits U.S. patients. This includes monitoring actions other regulators are taking as part of their investigations. For example, international regulators have identified another API manufacturer, Zhejiang Tianyu Pharmaceutical Co., with NDMA in its valsartan API. But the FDA has confirmed that no valsartan products in the U.S. market use this API.

The FDA will continue to work closely with providers and patients to address health care needs.

The news of the recall caused a significant public response. Consumers were rightly concerned. CDER has a skilled group of pharmacists and nurses who manage a toll-free number (855-543-3784) and answer email inquiries (druginfo@fda.hhs.gov) from the public. Since the first news of a recall, the FDA has received more than 6,000 inquiries from patients, physicians, nurses, pharmacists and academicians. We take these inquiries very seriously, and we strive to answer all of them. The public wants to know how to get safe valsartan, what to tell their pharmacists, if they should stop taking their medications and how to calculate their risk for cancer if they have been taking affected valsartan for several years. It was these questions, in part, that prompted the FDA to conduct its analysis of the risk that NDMA posed.

As we develop a better understanding of the manufacturing process conditions that ZHP used that can cause the impurity, we will use that knowledge to inform assessments of product applications being submitted and currently reviewed by the FDA. We will disseminate that information to manufacturers of all drugs and to the scientific community and re-evaluate our existing guidance to manufacturers. In addition, the test method we developed for identifying NDMA helps us to prioritize assessments and inspections of manufacturing sites. The information we gather throughout this investigation will give us a better understanding of the manufacturing processes and will strengthen our efforts to keep the U.S. drug supply safe for patients.

In addition to our ongoing investigation, we will continue to update our website, detailing lists of all recalled and non-recalled valsartan products as well as advice for patients and prescribers. We will also disclose our test results. This is a serious matter that is being managed closely by the FDA's leadership. As described above,we have a robust effort underway to evaluate these risks, led by a team of some of our most experienced scientists and clinicians. As we continue to investigate this episode, and develop new information, we will update the public regularly. We are committed to identifying the root causes of this impurity being found in valsartan, and taking steps to reduce the risk that similar episodes occur in the future.

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The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.