



**MEMORANDUM**

**October 25, 2019**

**To: Subcommittee on Health Members and Staff**

**Fr: Committee on Energy and Commerce Staff**

**Re: Legislative Hearing on “Safeguarding the Pharmaceutical Supply Chain in a Global Economy”**

On Wednesday, October 30, 2019, at 10 a.m. in the John D. Dingell Room, 2123 of the Rayburn House Office Building, the Subcommittee on Health will hold a hearing entitled, “Safeguarding the Pharmaceutical Supply Chain in a Global Economy.”

**I. BACKGROUND**

To offer a new prescription drug for sale in the United States, a manufacturer must demonstrate the safety and efficacy of the proposed new drug to the Food and Drug Administration (FDA) prior to coming to market.<sup>1</sup> Once the product is approved by FDA, manufacturers commonly have both intellectual property rights (primarily patent rights) and exclusivity protections for their products.<sup>2</sup> Generic drugs cannot enter the market until such patents and exclusivities have expired. Generic drugs are the same as a brand-name product in dosage, safety, effectiveness, strength, stability, and quality, as well as in the way the product is taken and should be used.<sup>3</sup>

While the two products may look different, generic drugs must contain the same active pharmaceutical ingredients as their brand-name counterparts.<sup>4</sup> An active pharmaceutical ingredient (API) is any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an

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<sup>1</sup> Food and Drug Administration, *Development & Approval Process* (June 2018) ([www.fda.gov/drugs/development-approval-process-drugs](http://www.fda.gov/drugs/development-approval-process-drugs)).

<sup>2</sup> Regulatory Focus, *Patents vs. Market Exclusivity: Why Does it Take so Long to Bring Generics to Market?* (Aug. 17, 2016) ([www.raps.org/regulatory-focus%E2%84%A2/news-articles/2016/8/patents-vs-market-exclusivity-why-does-it-take-so-long-to-bring-generics-to-market](http://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2016/8/patents-vs-market-exclusivity-why-does-it-take-so-long-to-bring-generics-to-market)).

<sup>3</sup> Food and Drug Administration, *Generic Drug Facts* (June 2018) ([www.fda.gov/drugs/generic-drugs/generic-drug-facts](http://www.fda.gov/drugs/generic-drugs/generic-drug-facts)).

<sup>4</sup> Association for Accessible Medicines, *What’s the Difference Between Generics and Brand-Name Drugs?* ([accessiblemeds.org/resources/blog/whats-difference-between-generics-and-brand-name-drugs#targetText=They%20have%20the%20same%20active,quality%20as%20brand%20name%20drugs](http://accessiblemeds.org/resources/blog/whats-difference-between-generics-and-brand-name-drugs#targetText=They%20have%20the%20same%20active,quality%20as%20brand%20name%20drugs))

active ingredient in the drug product.<sup>5</sup> Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body.<sup>6</sup> In other words, API is the component of the drug that produces its desired effect.<sup>7</sup>

Recent recalls of Angiotensin II Receptor Blockers (Valsartan, Losartan, and Irbesartan) and Ranitidine have raised concerns about impurities in finished dosage form (FDF) drug products.<sup>8</sup> The impurities found in the Angiotensin II Receptor Blockers resulted from a change in one ingredient, a solvent.<sup>9</sup> The manufacturer responsible for the impurities in that ingredient had testing information that confirmed the presence of the impurities but omitted such tests from their official reports.<sup>10</sup> As is the case with many products on the market, the manufacturer of both the ingredient that caused the problem and the final product is located in China.<sup>11</sup>

Many of the APIs that supply the U.S. market come from abroad. There are conflicting data, however, as to exactly what percentage of the market comes from China and India. FDA has previously stated that approximately 80 percent of API manufacturers are located outside of the United States<sup>12</sup> Others claim that Chinese and Indian factories manufacture at least 80 percent of the API for all drugs.<sup>13</sup> More recently, FDA has claimed that approximately 22

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<sup>5</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (Nov. 10, 2000) ([database.ich.org/sites/default/files/Q7\\_Guideline.pdf](http://database.ich.org/sites/default/files/Q7_Guideline.pdf)).

<sup>6</sup> *Id.*

<sup>7</sup> The Balance, *What is an Active Pharmaceutical Ingredient (API)?* (Jan. 17, 2019) ([www.thebalance.com/api-active-pharmaceutical-ingredient-2663020](http://www.thebalance.com/api-active-pharmaceutical-ingredient-2663020)).

<sup>8</sup> Food and Drug Administration, *FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)* (October 2019) ([www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine](http://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine)); Food and Drug Administration, *FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)* (October 2019) ([www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan](http://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan)).

<sup>9</sup> Bloomberg Businessweek, *Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.*, (Sep. 12, 2019) ([www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda](http://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda)).

<sup>10</sup> *Id.*

<sup>11</sup> *Id.*

<sup>12</sup> Food and Drug Administration, *FDA At A Glance: FDA-Regulated Products and Facilities*, (April 2017) ([www.fda.gov/media/104402/download](http://www.fda.gov/media/104402/download)).

<sup>13</sup> Bloomberg Businessweek, *Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.*, (Sep. 21 2019) ([www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda](http://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda)).

percent of the API manufacturing facilities and 14 percent of FDF manufacturing facilities are located in China, at least with respect to registered foreign human drug manufacturing facilities that are subject to current good manufacturing practices (CGMP) surveillance inspections.<sup>14</sup> Further, more recent data regarding API manufacturing facilities indicates that only 48 percent of API comes from China and India and only 60 percent of finished generic doses come from outside of the United States, with only 8.5 percent coming from China and 24.5 percent coming from India.<sup>15</sup> Some have suggested that the lack of a reliable and complete API registry makes it difficult to ascertain the actual market share of Chinese-made API, in particular.<sup>16</sup>

Though available estimates of the exact percentages of API and FDFs manufactured abroad vary widely, two things remain constant: the role of manufacturers to ensure the safety of the API they use and FDA's role in ensuring the safety of products through the preapproval process and post-approval surveillance.

## II. FDA REGULATION OF DRUG MANUFACTURERS AND MANUFACTURING

Many FDA requirements apply to API, either directly or as a component of the finished product, in the pre-market FDF drug product, testing requirements and other requirements related to demonstrating safety and efficacy of a finished product inevitably include testing of the product containing the API.<sup>17</sup> FDA requires that manufacturers of finished products include information about the manufacturing facilities that produce the API in their New Drug Applications (NDAs).<sup>18</sup> Prior to approval, FDA evaluates establishments by conducting a preapproval inspection.<sup>19</sup> Facility evaluations are typically conducted for: FDF manufacturers, API manufacturers, FDF and API testing sites, and primary packaging and labeling sites.<sup>20</sup> Once

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<sup>14</sup> United States-China Economic and Security Review Commission, *Hearing on Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products*, Statement of Mark Abdo, FDA Associate Commissioner for Global Policy and Strategy 116th Cong. (July 31, 2019).

<sup>15</sup> The Association for Accessible Medicines (@AccessibleMeds), Twitter, (Oct. 18, 2019, 4:22 AM), (<https://twitter.com/AccessibleMeds/status/1185157048750739457?s=20>).

<sup>16</sup> See note 14 (Statement of Christopher Priest, Principal Deputy, Deputy Assistant Director, Healthcare Operations, Defense Health Agency).

<sup>17</sup> Food and Drug Administration, *New Drug Application (NDA)* (June 2019) ([www.fda.gov/drugs/types-applications/new-drug-application-nda](http://www.fda.gov/drugs/types-applications/new-drug-application-nda)).

<sup>18</sup> Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.50, 2019; Food and Drug Administration, *Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products*, (February 1987) ([www.fda.gov/media/131685/download](http://www.fda.gov/media/131685/download)).

<sup>19</sup> Food and Drug Administration Small Business and Industry Assistance REdl Conference, *FDA's Pre-Approval Inspection (PAI) Program and How to prepare for a successful outcome* (2015) ([www.fda.gov/media/94064/download](http://www.fda.gov/media/94064/download)).

<sup>20</sup> *Id.*

a product has been approved, FDA has additional post-market requirements that impact the sourcing and quality of API. For example, FDA requires manufacturers to consider the possible effects of any change to their API and to their finished product and requires notice for such changes.<sup>21</sup> The Agency published a guidance for industry describing how industry should consider such changes and when industry should alert FDA of such changes prior to marketing a product containing the change.<sup>22</sup> FDA first published a Compliance Policy Guide explaining CGMP requirements for API manufacturers in 2001 and recently updated and finalized this guidance, consistent with requirements of the International Council on Harmonization, in 2016.<sup>23</sup>

FDA also conducts inspections of domestic and foreign manufacturing facilities, including API manufacturing facilities, to further its oversight of the pharmaceutical market.<sup>24</sup> While there have been persistent concerns related to the number of facilities FDA inspects and the frequency of those inspections, FDA continues to increase the number of inspections it does in accordance with the risks posed by various facilities and in proportion to the resources the agency has available for such activities.<sup>25</sup> Further, FDA conducts testing of products at the border to determine whether the products meet FDA's standards. In 2018, FDA reported that there were 45,000,000 lines of products imported into the United States.<sup>26</sup> In that same year, China claimed 13.4 percent of all import lines—defined as distinct regulated products within a shipment through customs—among countries that export drugs and biologics to the United States. Of these import lines for drugs and biologics, about 83 percent were finished drugs, and only 7.5 percent were APIs.<sup>27</sup>

### III. PRIOR CONGRESSIONAL ACTION

Generic API manufacturers are required to register, list, and pay fees with the FDA as a result of recent action by Congress. Congress acted in 2017 to reauthorize the Generic Drug User Fee Amendments (GDUFA II), which requires that facilities identified in at least one

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<sup>21</sup> Food and Drug Administration, *Changes to an Approved NDA or ANDA* (April 2004) ([www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda](http://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda)).

<sup>22</sup> *Id.*

<sup>23</sup> Food and Drug Administration, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Guidance for Industry* (September 2016) ([www.fda.gov/media/71518/download](http://www.fda.gov/media/71518/download)).

<sup>24</sup> U.S. Government Accountability Office, *FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices* (December 2016) ([www.gao.gov/assets/690/681689.pdf](http://www.gao.gov/assets/690/681689.pdf)).

<sup>25</sup> *Id.*

<sup>26</sup> Food and Drug Administration, *Import Program – Food and Drug Administration (FDA)*, (September 2019) ([www.fda.gov/industry/import-program-food-and-drug-administration-fda](http://www.fda.gov/industry/import-program-food-and-drug-administration-fda)).

<sup>27</sup> See note 14 (Statement of Mark Abdo, FDA Associate Commissioner for Global Policy and Strategy).

generic drug submission that is approved, to produce a FDF of a human generic drug or an API contained in a human generic drug be subject to user fees.<sup>28</sup> Subject to this requirement, FDA also maintains the GDUFA Paid Facilities List, which identifies API facilities in China, India, among other countries, which have paid their GDUFA fees.<sup>29</sup>

Congress also acted to address concerns with counterfeit drugs and the drug supply chain in 2008 by passing the Ryan Haight Online Pharmacy Consumer Protection Act of 2008 (Ryan Haight Act), the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), and the Drug Quality and Security Act of 2013 (DQSA). The Ryan Haight Act restricted online sales of prescriptions that contain controlled substances. DQSA gave FDA track and trace authority that improves the detection of potentially dangerous drugs in the supply chain.

FDASIA included additional authorities for FDA to address the challenges posed by an increasingly global supply chain, including establishment of a risk-based inspection schedule, clarification that CGMP apply to the safety of ingredients and other components, an extension of FDA's administrative detention authority, registration of importers, and additional authorities to destroy imported drugs that have been refused admission.<sup>30</sup>

#### **IV. WITNESSES**

##### **PANEL I**

**Janet Woodcock, M.D.**

Director, Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

**Michael Wessel**

Commissioner  
U.S.-China Economic Security Review Commission

##### **PANEL II**

**David Gaugh, R.Ph.**

Senior Vice President, Sciences and Regulatory Affairs  
Association for Accessible Medicines

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<sup>28</sup> Food and Drug Administration, *Generic Drug User Fee Amendments* (August 2019) ([www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments](http://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments)).

<sup>29</sup> Food and Drug Administration, *GDUFA Paid Facilities List* (October 2019) ([www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-paid-facilities-list](http://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-paid-facilities-list)).

<sup>30</sup> Pub. L. No. 112–144 (July 2012) ([www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf](http://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf)); Food and Drug Administration, *Food and Drug Administration Safety and Innovation Act (FDASIA)* (March 2018) ([www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-safety-and-innovation-act-fdasia#supplychain](http://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-safety-and-innovation-act-fdasia#supplychain)).

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