

**Testimony before the United States China Economic and Security Review Commission**

***Hearing on China's Healthcare Sector, Drug Safety,  
and the U.S.-China Trade in Medical Products***

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Chairman Shea, Vice-Chairman Reinsch, and members of the Commission, thank you for the opportunity to provide testimony. My name is Allan Coukell. I direct drug and medical device work at the Pew Charitable Trusts. Pew is an independent, nonpartisan research and public policy organization dedicated to serving the public.

**Supply chain globalization & increased complexity**

The geography and complexity of drug manufacturing for products intended for sale in the United States have changed dramatically in recent decades. The number of drug products made at non-U.S. sites for the U.S. market doubled between 2001 and 2008.<sup>1</sup> An estimated 40 percent of finished drugs used in the United States are made outside of the country.<sup>2</sup> An estimated 80 percent of the active ingredients and bulk chemicals in U.S. drugs are also made abroad,<sup>3</sup> and close to half of these are purchased from plants in India and China.<sup>4</sup> In a 2010 study of pharmaceutical executives conducted by the consulting firm Axendia, China was reported as the top source country for pharmaceutical ingredients: seventy percent of the executives surveyed reported having key suppliers in China.<sup>5</sup>

With globalization comes increased complexity. Prescription and over-the-counter (OTC) medications originate in factories all over the world, moving into the American marketplace through supply chains that can involve numerous processing plants, manufacturers, suppliers, brokers, packagers and distributors. This presents serious oversight challenges for both the Food and Drug Administration (FDA) and for manufacturers that outsource production to contractors overseas or purchase ingredients from foreign suppliers.

One of FDA's most important tools for ensuring the safety of drugs sold in the United States – whether they are made domestically or abroad – is the inspection of factories to verify compliance with good manufacturing practice (GMP) standards. The volume of drugs destined for the U.S. market makes it impossible to test samples of all products before they reach patients. Checking manufacturing quality is a critical preventive measure to protect the public from unsafe pharmaceuticals.

Despite our increasing reliance on overseas production plants, the FDA has historically inspected foreign plants much less frequently than those in the United States – about every 9 years on average, compared with every 2 to 3 years domestically. China is home to the highest number of sites subject to FDA inspection outside of the United States (920 in fiscal year 2009), but in the past has received the lowest levels of oversight compared with other countries. FDA inspected only 5.6 percent of Chinese sites in fiscal year 2009 (with 52 inspections that year, up from 19 in 2007).<sup>6</sup> Over an eight-year period (2002–

2009), FDA conducted 182 inspections in China (out of 920 total facilities) compared to nearly a combined 900 inspections in Germany, Italy, the United Kingdom, Switzerland, France and Ireland (out of 938 total facilities).<sup>7,8</sup> The emphasis on European inspections is surprising considering that regulatory oversight and standards for E.U. manufacturers are generally on par with those in the United States, and thus E.U. sites are arguably at lower risk for quality and safety issues. The European Federation of Pharmaceutical Industries and Associations (EFPIA), which regularly surveys its member pharmaceutical companies on the number of regulatory inspections that occur at their sites, has also pointed out inspectional overlap between E.U. and the United States. In 2009, members reported 47 inspections of plants in the U.S. by E.U. regulators, and 102 inspections of E.U. plants by the FDA.<sup>9</sup>

The FDA's inspection program is beginning to change as a result of 2012 legislation, which placed all manufacturing plants, whether foreign or domestic, on a single risk-based inspection schedule, and provided FDA with additional funds to inspect foreign generic drug facilities. The agency is working to implement this new law, but fiscal year 2013 has already shown a marked increase in inspections overseas. The FDA conducted 813 drug inspections in FY 2013,<sup>10</sup> which equates to 23% of the 3,493 foreign drug establishments registered with FDA that year.<sup>11</sup> By comparison, in FY 2009 the FDA inspected 424 foreign drug manufacturing sites,<sup>12</sup> which is 11 percent of the 3,765 that were registered that year.<sup>13</sup>

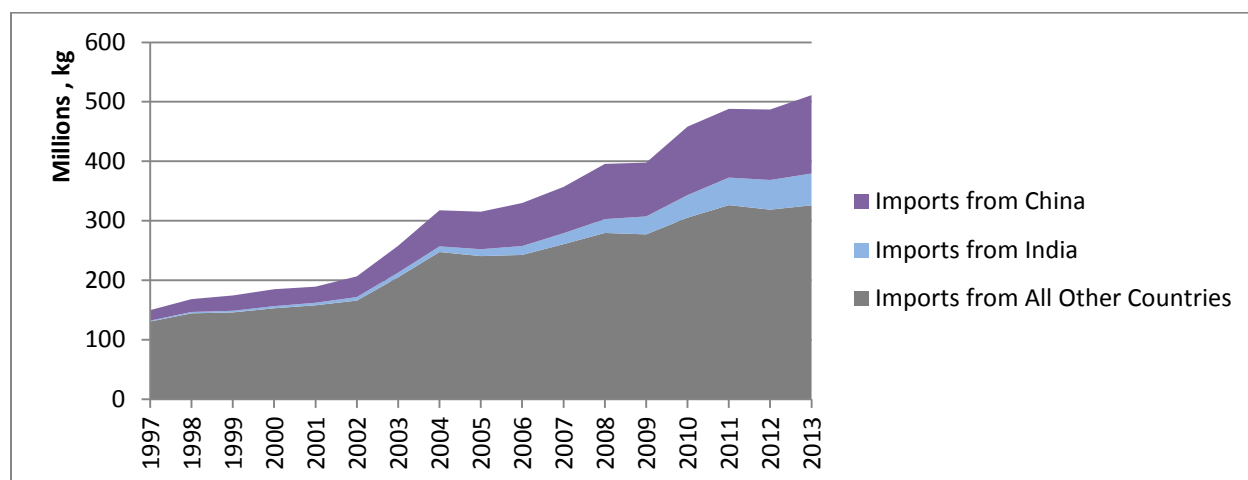
In the absence of sufficient expectation of oversight, some manufacturers may not rigorously observe quality measures. The FDA has over the years identified a number of quality problems at overseas plants. In China, 33 pharmaceutical plants have been placed on import alert – preventing them from exporting certain products to the U.S. – two in March of 2014.<sup>14</sup>

It is important to note that there is a range of manufacturing quality in all countries. There are well-run plants in China doing high quality manufacturing. There are also U.S. facilities with significant quality problems. For example, many of the drug shortages the U.S. is grappling with today have been linked with sterile production failures at domestic plants. Ultimately, the FDA must ensure plants, wherever they are, meet a baseline set of quality standards if they wish to supply the U.S. market.

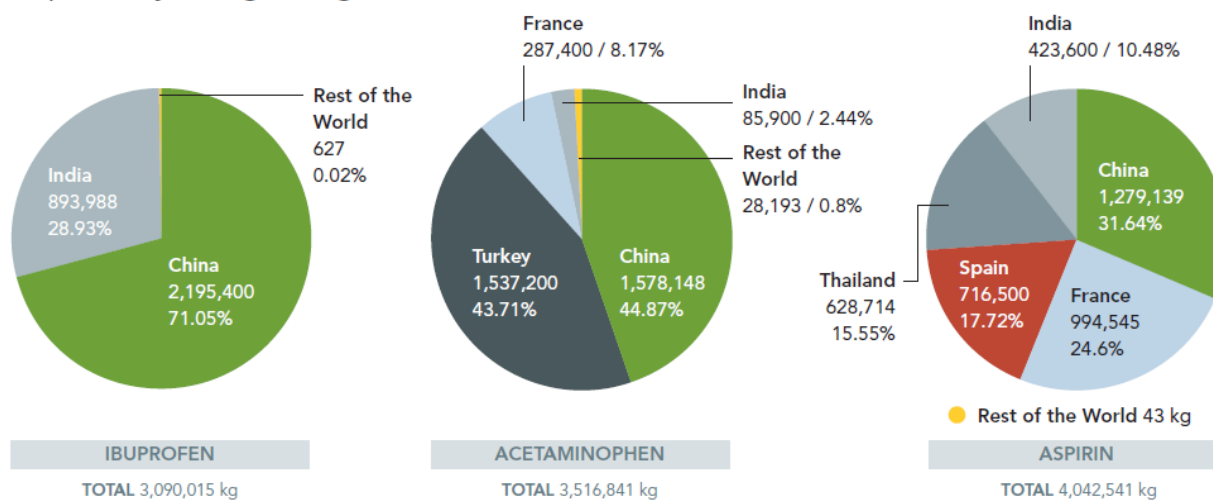
### **Focus: China**

The United States is the number one destination for Chinese pharmaceutical raw material exports—a multi-billion business each year (\$2.2 billion in 2008).<sup>15</sup> The U.S. imported over one hundred million kilograms of pharmaceutical goods from China in 2013, 26 percent of all such imports.<sup>16</sup> In the decade between 2003 and 2013, pharmaceutical imports from China increased 192 percent.<sup>17</sup> In particular, China is a major source for older and off-patent pharmaceutical ingredients in medicines sold in the United States.<sup>18,19</sup> U.S. Census Bureau data from 2009 indicate that the United States imported large quantities of three major over-the-counter (OTC) pain relievers: ibuprofen, acetaminophen and aspirin (3 million, 3.5 million and 4 million kilograms, respectively).<sup>20</sup> For all three products, the largest portion of imports came from China. China is also a major source of a number of older antibiotics. Ninety-four percent of imported tetracycline salts, an important class of antibiotics, originated in China from 2006 to 2008, as did three-quarters of imported streptomycin derivatives and salts used in injectable antibiotics and eye drops.<sup>21</sup>

## U.S. imports of pharmaceuticals by weight (kg), 1997 – 2013 <sup>22</sup>



## Top source countries for U.S. imports of ibuprofen, acetaminophen and aspirin by weight (kg) in 2009



Source: U.S. Census Bureau, Foreign Trade Division.

The Chinese bulk pharmaceutical market has been growing by about 20 percent in production value each year,<sup>23</sup> and China is home to thousands of drug manufacturing facilities.<sup>24</sup> The FDA has estimated that as many as 920 manufacturing plants in China may manufacture drugs and drug ingredients intended for the U.S. market, and therefore may be subject to inspection by FDA,<sup>25</sup> a striking increase from just eleven such sites in 2002.<sup>26</sup>

The Chinese Food and Drug Administration (CFDA) regulates all drugs used domestically in China, as well as some drugs made for export.<sup>27</sup> Although China requires that exported medical products meet the regulatory standards of the destination country; it has in the past placed full responsibility with the receiving party for ensuring that products meet those quality standards.<sup>28</sup> In 2007, China and the U.S. signed a memorandum of understanding to place certain drugs designated for export under greater oversight by the CFDA, including a number of antibiotics.<sup>29</sup> In 2012, China provided the FDA with a list

of Chinese pharmaceutical firms where CFDA had found GMP failures. Sixty one of these firms had shipped products to the United States, and the FDA then targeted these firms as priorities for inspection.<sup>30</sup>

Older measurements of drug quality have indicated that substandard and counterfeit products have been an issue in the Chinese domestic market. A survey of medicine quality by China's State Food and Drug Administration in 1998 found 13.1 percent of 20,000 batches tested to be substandard or counterfeit.<sup>31</sup> China has taken steps over the years to strengthen domestic oversight of pharmaceutical manufacturing and modernize GMP regimes. When GMP standards in China were made mandatory in 2004,<sup>32</sup> up to one-third of Chinese factories were unable to meet the regulations, according to one estimate.<sup>33</sup> China has continued to update its GMP requirements – most recently in 2011<sup>34</sup> – but there are still wide variations in production and GMP capacity among plants producing pharmaceutical products in China.<sup>35,36</sup>

## **Heparin**

Quality problems in China came to the fore in 2008, after dozens of adverse events including some deaths, were linked to the adulteration of heparin, a widely used blood thinner. The drug was manufactured by Baxter Healthcare, a U.S. company that was sourcing active ingredient and precursor ingredients from a complex upstream supply chain in China.<sup>37</sup> Investigations revealed that somewhere in that supply chain, the correct active ingredient was replaced by a substance known as over-sulfated chondroitin sulfate (OSCS), which standard tests then in use were unable to detect.<sup>38</sup> The exact source of the contamination has never been determined, but OSCS is a synthetic product, and its introduction is generally believed to have been intentional, for economic gain.

Adulterated heparin exposed a number of significant supply-chain management problems on the part of the manufacturer and the FDA. Baxter began receiving heparin from a new Chinese plant in 2004, but did not conduct its own audit of that plant until 2007, relying instead on an earlier assessment by a different company.<sup>39</sup> FDA approved the plant as a supplier for Baxter without conducting a pre-approval inspection,<sup>40</sup> in part because the agency confused the plant with another site in its database. When FDA finally inspected the plant after the adverse events occurred, its inspectors found a number of manufacturing quality issues,<sup>41</sup> including poor control of incoming raw materials.<sup>42</sup> When, in 2008, Baxter sent inspectors to retroactively evaluate its supply chain, they were denied access to upstream workshops and consolidators.<sup>43</sup> FDA was also denied access to two upstream consolidators of heparin.<sup>44</sup>

Since these events, Baxter reported a number of initiatives to secure its supply chain against future contamination and adulteration, including examining its global supply-chain practices to identify vulnerabilities, reviewing relationships with high-risk suppliers, reducing the number of suppliers, doing more concentrated audits and reviewing test methods.<sup>45</sup> The adulteration of heparin also resulted in an increased FDA focus on global production and in Congressional attention, which led to new authorities discussed below.

## **Ingredient falsification**

Ingredient falsification (such as occurred in the heparin example) is a challenging issue to address when supply chains are long and complex. When an ingredient comes from an unknown source, and is made under unknown conditions, production quality, and by extension product quality and safety, cannot be assured.

Observers of the pharmaceutical manufacturing sector in China describe substandard unknown or unapproved sites. In some cases these deceptions have lasted years. Shanghai No. 1, a Chinese supplier to U.S. manufacturer International Medication Systems, Limited (IMS), claimed to be a manufacturer of heparin but in reality was a “show” factory. Shanghai No. 1 was registered with FDA as an exporter of heparin active ingredient to the United States and had an authorized U.S. agent, Amphastar Pharmaceuticals Inc., which in 2004 declared to FDA that Shanghai No. 1 produced heparin under GMP conditions.<sup>46</sup> In fact, Shanghai No. 1 had been shipping heparin to the United States that was labeled as having been produced at their facility, but was actually made at two external plants.<sup>47</sup> IMS had been importing this falsely labeled heparin as early as 2001, but the fraudulent activity was only discovered seven years later. FDA investigated one of the external plants, and in addition to finding GMP violations, found that the plant had made 19 lots of heparin that were contaminated with Over-Sulfated Chondroitin Sulfate, the same substance associated with adverse events in the U.S., though these lots did not ultimately reach U.S. patients.<sup>\*48</sup>

Pharmaceutical brokers and traders have also been responsible for concealing the source of drug ingredients. For instance, diethylene glycol (an industrial solvent) has been labeled as glycerin (a common inactive ingredient for cold and cough syrups) and sold into distribution numerous times, causing hundreds of deaths.<sup>49,50,51,52</sup> In one of these cases, the Panamanian government prepared cough medicine with diethylene glycol labeled as glycerin that had originated in China.<sup>53,54</sup> The official number of deaths was 78,<sup>55</sup> but unofficial reports suggest the possibility of a much larger toll.<sup>56</sup>



*European inspectors in Zhejiang, China, found empty drums blocking access to part of a certified pharmaceutical plant exporting to Europe and the United States. Further investigation revealed a vast warehouse of substandard or falsely certified drug active ingredients. Image courtesy of Philippe André, Associate Professor at the School of Pharmaceutical Science and Technology at Tianjin University, China (2008).<sup>57</sup>*

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\* Shanghai No. 1 was not part of Baxter Inc.’s heparin supply chain.

## **Industry responsibility**

Outsourcing allows pharmaceutical companies to cut costs and reduce manufacturing time,<sup>58</sup> but can also result in diminished control and transparency, particularly when contractors and suppliers are in distant geographic locations. According to a 2010 survey by the Axendia consulting firm, 94 percent of pharmaceutical executives think that raw material sourcing from foreign suppliers is a serious or moderate risk.<sup>59</sup>

Both members of industry and FDA experts recognize the need for strong contractor and supplier management.<sup>60,61,62</sup> In the past, FDA officials have expressed concerns about industry supply-chain vulnerabilities, including insufficient knowledge of contract manufacturing sites, too little on-site auditing of suppliers and over-reliance on supplier-provided documentation of testing.<sup>63,64,65</sup>

Current GMPs require manufacturers to control the quality of incoming drug components through testing. However, they do not explicitly require manufacturers to evaluate component suppliers prior to contracting with them, nor to engage in quality agreements with those suppliers, nor to conduct on-site audits of suppliers' plants.<sup>66</sup> The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, made explicit that GMPs require managing the risks of and establishing the safety of ingredients and raw materials. The FDA has indicated it may issue a proposed rule to update regulations by July 2015, and a final rule by October 2016, but FDASIA's new quality requirements are enforceable even without new regulations.

In addition, a number of companies have taken a private sector collaborative approach to address concerns about supply chain quality control through information sharing and leveraging one another's supplier audit results. Rx360, an industry consortium, has created such a shared audit program and also disseminates information on risk signals to its members.<sup>67</sup>

## **Counterfeits**

In addition to legitimate drugs that are of poor quality, counterfeit drugs – fakes that imitate the product or packaging of a licensed manufacturer – have also entered the U.S. drug supply numerous times over the past few decades. For example, counterfeit cancer medication has been found in the U.S. at least three times since 2012.<sup>68,69,70</sup> The origin of the counterfeits is not known. In 2013, a pharmacist in Chicago was indicted for allegedly purchasing Chinese counterfeits and selling them from his U.S. pharmacy store.<sup>71</sup> And in 2009, a Chinese national was sentenced to prison for distributing counterfeit and misbranded pharmaceuticals in the United States. His counterfeits contained low levels of active ingredient, and many had impurities.<sup>72</sup>

Counterfeits may also be real medicines that are illicitly diluted or otherwise adulterated. In 2002, counterfeit high-dose Epogen<sup>®</sup> was actual low-dose Epogen<sup>®</sup> that had been relabeled as a higher strength, and was successfully sold to legitimate distributors and pharmacies.

The public health risks of poor quality and counterfeit drugs are the same: counterfeits may have little or no active ingredient, or may even contain harmful chemicals. However, while the risks of counterfeit and substandard drugs are analogous, the solutions and players are different. Poor quality drugs enter from within the legitimate supply chain, and the FDA and the regulated industry are responsible for conducting

sufficient oversight to prevent quality failures. Counterfeit drugs, conversely, normally enter from outside the legitimate supply chain. Law enforcement works to catch both suppliers of counterfeits as well as persons knowingly bringing them into the U.S. for further sale. Important new tools were established in the 2013 Drug Quality and Security Act (which is discussed below) to help protect the drug supply from counterfeits.

### **Recently enacted legislation**

Two major laws to safeguard the drug supply were passed in 2012 and 2013: Title VII of the FDA Safety and Innovation Act (FDASIA) focused on “upstream” manufacturing supply chain security, and Title II of the Drug Quality and Security Act (DQSA) laid the groundwork for improving safety of the “downstream” drug distribution system.

#### FDASIA

Title VII of FDASIA enhances overseas inspections by creating a single risk-based inspection framework for both foreign and domestic plants. While there is no minimum frequency for inspections, one risk criteria that must be considered is whether a plant was inspected in the previous four years. The law also requires manufacturing establishments to register annually with FDA and submit a unique facility identification number, which will help FDA accurately identify plants in its internal databases.

FDASIA also requires drug importers to register with FDA, and adhere to Good Importer Practices (GIP) which will be developed by the Secretary; FDA has indicated that it expects to propose a GIP rule by April 2015, and finalize it by January 2017.

Title VII also gave the FDA some important new authorities, including the ability to require importers to provide compliance information as a condition of entry for an imported drug, and the power to block importation of a drug product if the plant making it delays, limits, or refuses inspection. The agency issued at least two warning letters for this reason in 2013.

FDA may also now request documents outside of an inspection. And the agency was given the authority to administratively detain drugs, meaning the FDA can halt the movement of potentially violative drugs while investigating and determining the appropriate response.

FDASIA Title VII also recognized the need for international collaboration to ensure the safety of the global drug supply. It gives the agency explicit extraterritorial jurisdiction, and creates a limited framework for the sharing of confidential information with other foreign regulators. The FDA may also enter into agreements to recognize inspections by foreign regulators that are capable of conducting inspections that meet U.S. standards, and the results of these foreign inspections may be used as evidence of compliance with U.S. law.

Finally Title VII recognizes the responsibilities of the pharmaceutical industry to ensure drug quality. It clarifies that current good manufacturing practices include company control of drug ingredient quality – an important step to ensure industry takes responsibility for managing their suppliers and ensuring the safety of drug ingredients. It allows the FDA to require industry to notify the agency about identified drug theft and counterfeiting.

In addition to Title VII, FDASIA Title III – the Generic Drug User Fee Amendments of 2012 (GDUFA) – also contains provisions relevant to the drug supply chain. Specifically, under GDUFA, the generic drug industry will pay fees that will fund FDA inspections of generic drug plants both here and overseas, with a goal of inspection parity between foreign and domestic sites by 2017. These are critical new resources for the FDA, though they are targeted just for generic drugs, and not for branded products.

One final Title of FDASIA worth noting is Title X, which seeks to help address drug shortages by requiring manufacturers to provide advance notification of an impending shortage to FDA when possible. The FDA has reported that this notification requirement has allowed them to more quickly take steps to prevent and resolve drug shortages.<sup>73</sup>

### DQSA

Title II of the Drug Quality and Security Act, passed in late 2013, establishes a national serialization and traceability system for medicines sold in the United States. This will fundamentally change the distribution system for drugs in this country.

Beginning in late 2017, each package of prescription drugs will be given a unique serial number enabling it to be verified, and, eventually, allowing for its distribution history to be traced. This serialization system will be an important new tool for ensuring the legitimacy of pharmaceutical products, and it should also allow for quicker location of product within the supply chain in the event of drug recalls. It will also aid investigators seeking to trace back the source of problems within the drug distribution chain.

### **Next steps**

As drug manufacturing becomes increasingly global, collaboration between regulators and harmonization of quality standards is essential. Collaboration and capacity development activities are important, such as the FDA's recent cooperative agreement with Indian pharmaceutical regulators.<sup>74</sup> Ideally, each country will eventually provide sufficiently robust oversight of its production facilities to ensure the quality of drug products, whether used domestically or shipped abroad.

Until such harmonization is possible, the FDA must continue to develop its ability to monitor drug production overseas. The FDA has increased drug plant inspections in India, and is also seeking to increase its on-ground inspectorate in China. In-country inspectors can help ensure timely access to plants: while many domestic inspections are surprise visits, foreign inspections are often pre-announced by FDA to ensure that necessary personnel are present.<sup>75</sup>

Congress should conduct ongoing oversight of FDASIA title VII implementation to ensure FDA is using its new authorities to protect the U.S. drug supply. Congress should also make sure the tools the agency has been given are sufficient. For example, the authority provided FDA to share information with foreign regulators is limited by a fairly onerous process wherein the commissioner herself must certify a foreign regulator has the ability to protect trade secrets.

Congress should also monitor implementation of DQSA Title II to make sure the new drug serialization and traceability system is implemented in a robust manner that provides maximum patient protection. In



particular, as the system is phased-in over the years, Congress, FDA, and stakeholders should explore use of the drug serial number as a routine, proactive check to ensure patients are getting legitimate products.

The DQSA contains some requirements for companies in the supply chain to make use of serial numbers, but in most cases only when there is an existing belief that a product is suspect. An even more powerful use of serial numbers would be to use them as a proactive check to identify counterfeit or illegitimate product that otherwise might pass unnoticed into the drug supply chain. Italy and Turkey already require pharmacy authentication of serialized medicines in order to protect their citizens and prevent fraud, and additional countries such as China and Brazil are advancing similar requirements.<sup>76,77</sup> According to one summary, the Chinese system will require serialized drugs to be tracked in a Drug Electronic Supervision Network. Every member of the supply chain must report serial number transaction information to the database, including the retail sector.<sup>78</sup>

Even without a federal requirement, verification should become routine in pharmacies. To achieve this, the system must be designed to ensure that verification is practical and efficient. Waivers of DQSA's requirements should be rare, lest we exempt businesses like the pharmacist in Chicago who was indicted last year for substituting Chinese counterfeits for legitimate products.<sup>79</sup>

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