



## Your Generics and Biosimilars Industry

February 8, 2018

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Office of the United States Trade Representative  
600 17th Street, N.W.  
Washington, DC 20508

**Ref:** Docket Number USTR - 2017-0024: 2018 Special 301 Review: Identification of Countries Under Section 182 of the Trade Act of 1974

Dear Ms. Kendall:

The Association for Accessible Medicines (AAM) welcomes the opportunity to submit comments to the Office of the United States Trade Representative (USTR) regarding the 2018 Special 301 Review on matters related to trade and the protection of intellectual property rights. AAM is the nation's leading trade association for manufacturers and distributors of generic prescription drugs and biosimilar therapies, manufacturers of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic drug and biosimilar industry. Our core mission is to improve the lives of patients and enhance the U.S. health care system by advancing timely access to more affordable FDA-approved generic and biosimilar medicines.

The story of the U.S. generic industry is one of success for the American people based on a healthy domestic market characterized by strong competitive bidding. Since 1984, when the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) was adopted, generic pharmaceuticals have grown from just under 20 percent of prescriptions filled to 89% of the prescriptions dispensed in the United States today. At the same time, generics represent just 26% of total drug expenditure and saved the U.S. health system \$253 billion in 2016.<sup>1</sup> For the past 30 years, the generic industry has played a vital role in ensuring patients' access to more affordable drugs and controlling U.S. health care expenditures which exceed \$3 trillion.<sup>2</sup> Without the generic industry, American consumers would face even harder challenges to pay for much-needed drugs.

Generic drug companies have also been a steady source of new manufacturing jobs in the U.S. In fact, in 2016 the generic drug industry manufactured over 61 billion doses of medicines in the U.S.,

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<sup>1</sup> AAM, "Generic Drug Savings and Access in the United States," 2017, p. 16.

<sup>2</sup> AAM, "Generic Drug Savings and Access in the United States," 2017, p. 8.



February 8, 2018

Page 2

employing over 36,000 U.S. workers and contract manufacturers.<sup>3</sup> We expect to continue generating more U.S.-based jobs as the industry continues growing globally. We hope that USTR and the Trump Administration pursue trade policies that will facilitate the growth of the U.S. generic and biosimilar drug industry.

### EXECUTIVE SUMMARY

President Trump has called current drug prices "out of control" and has promised to take action to lower prices. Policies that promote the growth of generics and biosimilars in both the United States and abroad are key to that objective. The U.S. generic and biosimilar pharmaceutical industry has demonstrated that, with the right policy environment, it can bring life-saving pharmaceutical therapies to consumers while achieving substantial savings for both patients and governments. Policies that promote the growth of generics and biosimilars in both the United States and abroad are key to the President's goal of bringing down U.S. drug prices. After achieving an 89% generic utilization rate in the United States, our members have increasingly become global players as they look to grow their business in new markets. Many countries, including Japan and some EU countries, continue to have low generic medicine utilization rates. Expanding opportunities for generic and biosimilar products abroad not only supports U.S. jobs and exports, it will also help those countries achieve health care savings and provide more affordable medicines for their citizens. In addition, AAM member companies have become significant investors in the development of innovative pharmaceutical products, while continuing to provide patients access to quality and more affordable generic pharmaceuticals throughout the world.

IPR frameworks must address and equally support public health needs and industry interests in fostering innovation, while ensuring patients' access to more affordable drugs. AAM believes that the standard of balancing innovation and access to medicines set forth in the TRIPS Agreement, the bipartisan May 10<sup>th</sup> Agreement of 2007, and the 'Bipartisan Congressional Trade Priorities and Accountability Act of 2015' reflect the appropriate balance.

This critical balance should be reflected in the Special 301 report as well. In assessing our trade partners' implementation of IPR standards, USTR should also ensure that the IPR standards it pursues do not unnecessarily disrupt the positive economic impact that additional generic and biosimilar exports could otherwise have in the U.S. USTR should focus instead on the interests of U.S.

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<sup>3</sup> AAM, "Generic Drug Savings and Access in the United States," 2017, p. 7.



February 8, 2018

Page 3

pharmaceutical exporters as a whole (generic and brand) and refrain from using the Special 301 process to create unnecessary barriers to entry that delay generic and biosimilar competition or cause uncertainty for generic and biosimilar manufacturers. For example, AAM is strongly opposed to creating additional mandatory years-long periods of exclusivity for biologics. Access to new markets is critical to the development of biosimilars and policies that delay their introduction in a market will impact not only consumers abroad, but in the United States as well. More markets for biosimilars means producers can spread development costs across larger populations, keeping prices lower. Without the ability to grow markets, some products may not be cost-effective to develop, decreasing competition and leaving patients without life-saving medicines. The U.S. government, as the largest purchaser of prescription drugs, would risk losing much of the cost savings that biosimilars could provide in the Medicare, Medicaid, Tricare, VA and other federal programs. Moreover, putting a mandatory years-long period of exclusivity for biologics within the NAFTA – an internationally binding treaty that will be incredibly difficult to change – will limit U.S. sovereignty by removing the ability to make changes to U.S. law in the future. Rather, NAFTA is an opportunity for the U.S. government to promote incentives for generic and biosimilar competition in Canada and Mexico similar to that provided in U.S. law such as an exclusivity for first approved generic medicines.

### I. GENERICS AND BIOSIMILARS ARE KEY TO LOWERING DRUG PRICES

President Trump has called current drug prices “out of control” and has promised to take action to lower prices. Policies that promote the growth of generics and biosimilars in both the United States and abroad are key to that objective. As detailed in AAM's 2017 report, “Generic Drug Savings and Access in the United States,” the use of generic drugs in the United States resulted in \$253 billion dollars in savings in 2016 and \$1.67 trillion in the ten-year period (2007-2016).<sup>4</sup> Generic drugs are also a critical tool to tackle the U.S. deficit by securing Medicare savings of \$77 billion dollars in 2016 corresponding to \$1,883 per person and Medicaid savings of \$37.9 billion in the same period corresponding to \$512 per enrollee.<sup>5</sup>

The potential savings are even more significant in the area of expensive biologic drugs which can cost a patient as much as several hundred thousand dollars per year. The developing biosimilars industry

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<sup>4</sup> AAM, “Generic Drug Savings and Access in the United States,” 2017, p. 20.

<sup>5</sup> AAM, “Generic Drug Savings and Access in the United States,” 2017, p. 21.



February 8, 2018

Page 4

has been projected to create as much as \$250 billion in additional savings over the next decade.<sup>6</sup> Today's advanced medicines will become available at a lower cost to millions of patients thanks to biosimilars and interchangeable biologic products that will ease strained health care budgets and benefit patients, taxpayers, insurers, providers and state and federal governments. The global biologics sector is still young and is rapidly evolving. Pressing countries to adopt years-long periods of exclusivity will remove the flexibility needed to keep pace with changes in the sector in the years ahead and could needlessly delay access for biosimilar products in export markets.

As is the case for many goods, high saturation in the U.S. generics market has driven an increasing *need to expand abroad for future growth opportunities*. The Department of Commerce's 2016 "Top Markets" report for pharmaceuticals, estimated that "U.S. generic drug sales reached an estimated \$70 billion, representing a quarter of the global market, due to a large number of drugs going off-patent and health care reforms favoring generics."<sup>7</sup> This report also predicted that growth in generics "is driving, and will continue to drive, most of the projected growth in emerging markets over the coming decade."<sup>8</sup> Many countries have low generic utilization rates, as is the case of Japan and other OECD countries, where generic penetration can be as low as 10 percent.<sup>9</sup> Thus, balanced IPR policies would level the playing field, allowing the U.S. to maximize the export of both originator and generic pharmaceutical products and satisfy the demand for safe and more affordable drugs. AAM's members have expanded their international operations acquiring companies around the world and making very significant investments to seize the new frontier: to grow globally. Most generic and biosimilar companies are now also involved in the innovation process, conducting research and development (R&D) to generate their own patented products and processes while continuing to provide more affordable generic and biosimilar products.

Growing export markets for generic and biosimilar products is also in the United States' interest. Given the low profit margins for many widely-used generic medicines, any increase in the cost to produce must be passed on to patients in the form of higher drug prices, if companies are to continue to manufacture such drugs. Moreover, being able to sell newly developed products in markets beyond the

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<sup>6</sup> *The \$250 Billion Potential of Biosimilars*, Express Scripts. April 2013. [http://lab.express-scripts.com/lab/insights/industry-updates/the-\\$250-billion-potential-of-biosimilars](http://lab.express-scripts.com/lab/insights/industry-updates/the-$250-billion-potential-of-biosimilars)

<sup>7</sup> U.S. Department of Commerce, International Trade Administration, "2016 Top Markets: Pharmaceuticals," 2016, p. 5.

<sup>8</sup> U.S. Department of Commerce, International Trade Administration, "2016 Top Markets: Pharmaceuticals," 2016, p. 6.

<sup>9</sup> OECD, "Tackling Wasteful Spending on Health. Highlights", January 2017. <http://www.oecd.org/els/health-systems/Tackling-Wasteful-Spending-on-Health-Highlights-revised.pdf>



U.S. allows the fixed costs of developing these products to be spread over a much broader patient base. If access to new markets is delayed, such as by requiring those countries to provide additional market exclusivity to brand name drugs, patients in the United States will have to shoulder more of the cost of developing these medicines. In some cases, new products may not be cost-effective enough to bring to market at all, depriving patients of more affordable life-saving therapies.

Moreover, putting a mandatory years-long period of exclusivity for biologics within the NAFTA – an internationally binding treaty that will be incredibly difficult to change – will limit U.S. sovereignty by removing the ability to make changes to U.S. law in the future. Europe and Asia have adopted policies to facilitate competition, which have resulted in greater access to biosimilars and lowered treatment costs by an estimated 40 percent.<sup>10</sup> Over 25 biosimilar medicines have been approved in Europe; while less than 10 have been approved in the U.S., and only three are available on the market.

## II. MARKET ACCESS BARRIERS & IMPEDIMENTS BY COUNTRY

Section 182 of the Trade Act of 1974 requires the USTR to identify countries that “...deny fair and equitable market access to U.S. persons who rely on intellectual property protection.” The U.S. generic and biosimilar medicines industries depend on patented products to provide the pipeline for the high quality and cost-competitive medicines they export when patents expire. In addition, many producers of generic and biosimilar drugs themselves hold patents and, thus, rely directly on the protection of intellectual property rights.

AAM believes that in order to achieve the balance envisioned in the May 10 Agreement, the Special 301 report should include a focus on market access barriers that prohibit or deter the adoption of generic and biosimilar products in foreign markets. Eliminating these measures will enable U.S. exporters to be more competitive in global markets by eliminating burdensome, duplicative or divergent regulatory requirements for pharmaceutical products. For instance, regulatory agencies could agree on the mutual recognition of inspections of manufacturing sites, the adoption of global standards of serialization of pharmaceutical products instead of costly national ones, the elimination of the need to reproduce clinical trials and lengthy approval timelines for drug applications, as well as avoiding the adoption of unreasonable pricing policies that may ultimately prevent the launch of generic products, to mention a few.

In an era when increasing demands are being made on the world’s health care services, generic and biosimilar medicines provide a major benefit to society by ensuring patient access to quality, safe and

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



## Your Generics and Biosimilars Industry

February 8, 2018

Page 6

effective medicines while reducing the cost of pharmaceutical care. The availability of generic and biosimilar medicines helps facilitate global access to cost-competitive medicines. The companies that manufacture and market these products are also major contributors to the U.S. and other national economies through their R&D and manufacturing activities, and the highly skilled workforce these companies employ.

Discriminatory, non-transparent or otherwise trade-restrictive measures have the potential to hinder market access in the pharmaceutical sector, potentially resulting in higher health care costs. Unfortunately, the launch of generic and biosimilar medicines in some countries can be unnecessarily curtailed due to their domestic legislation, regulations, policies, and practices.

While this submission in no way provides an exhaustive list of the numerous barriers, impediments and intellectual property enforcement issues faced by the generic pharmaceutical and biosimilar medicines industries as they conduct business outside of the U. S., we trust that it will assist USTR in seeking to address barriers for the U.S. generic and biosimilar medicines companies in some of our key markets. AAM is seeking USTR's assistance in addressing the issues identified and hopes to include additional issues of concern to the generic and biosimilar medicines industries requiring action in future submissions, and in our regular interactions with USTR.

In our comments below, AAM has identified market access barriers in 15 countries that pose harmful and unnecessary barriers to U.S. generic pharmaceutical and biosimilar medicines and our member companies seeking to export to the identified countries. The issues identified deny fair and equitable market access to U.S. companies that rely on intellectual property protection, and range from domestic pricing policies to domestic regulatory requirements to blatant bias in favor of products manufactured in a domestic market over those manufactured in the United States and other countries. In addition, this submission highlights concerns with respect to the operation of intellectual property enforcement mechanisms in four countries due to duplicative legal processes that are inefficient and create unnecessary financial risk exposure to generic and biosimilar medicines companies seeking to bring products to that market.

Finally, our companies require clear rules and regulations in order to thrive. Constant changes make it impossible for them to have mid and long-term business plans to achieve their potential. The generic drug and biosimilar industry has made very significant investments to become a global player by acquiring companies around the world, investing in its own R&D and attracting executives capable of implementing global strategies for growth. AAM urges USTR to use the Special 301 Report process to pursue consistent implementation of the TRIPS Agreement provisions on patents – and to ensure, as required by statute, that trade agreements foster both innovation and promote access to medicines -



rather than to pursue additional objectives, which undermines the predictability of the standards under which companies must operate.

## ARGENTINA

The Argentinian Law "Compre Trabajo Argentino," LEY N° 25.551, which was promulgated on December 27, 2001, during the Argentine economic crises, sets market access barriers for the U.S. pharmaceutical industry in Argentina. Especially Article 1 explicitly names a preference for acquiring goods manufactured by Argentinian companies by public administrations, agencies, authorities, services, companies, and their dependencies.

An additional access barrier for U.S. pharmaceutical companies producing abroad (excluding Japan, Sweden, Israel, Canada, Austria, Germany, France, United Kingdom, Netherlands, Belgium, Denmark, Spain and Italy) is the requirement to register their products in Argentina, because the Argentinian Health authorities refuse to delegate the inspections of plants in foreign countries to receive good manufacturing practices (GMP) certificates.

In order to lower market barriers for U.S. pharmaceutical companies in Argentina, it is necessary to change existing restrictive and domestically focused regulations.

## AUSTRALIA

There are GMP considerations for supply and registration in Australia. The Therapeutic Goods Administration (TGA) reserves the right to undertake an audit of an overseas manufacturing site, irrespective of any other evidence supplied. For example, this may happen where TGA has other regulatory information, has concerns regarding compliance, or is auditing an adjacent facility. An audit may take place prior to granting an initial GMP clearance for supply of the relevant product in Australia or at any time following the issue of a GMP clearance.

Moreover, there is a considerable delay for U.S. and overseas manufacturers' GMP clearances from TGA. Some of the clearances take more than 9 months, though the general guideline is 90 working days. There is always a risk that TGA rejects the application and would like to do an on-site inspection themselves resulting in further delay. The on-site inspection schedule is so tight that getting an audit scheduled can take 3 to 6 months and then the audit itself and audit closure can lead to a total delay of at least 12 months. The current cost of a GMP audit is AUD 1250 per hour and a typical audit is with two auditors for 5 days means it can cost AUD 100,000 + the travel costs and the frequency can be as





February 8, 2018

Page 8

regular as every year. This limits the operations of U.S. manufacturers providing products to the Australian market vis-a-vis Australian manufactures.

Australia's GMP requirements may result in delays and could even result in the removal of a product from a U.S. company's submission plan because the cost of the audit impacts the business case to such a degree that it becomes negative.

With regard to standards, the default standards accepted by TGA are the United States Pharmacopeia (USP), the European Pharmacopoeia (Ph.Eur.), and/or British Pharmacopeia (BP) monographs. Where in-house monographs or adaptations of monographs are used, evidence is required to show at least equivalence to the pharmacopeial standards.

With respect to bioequivalence studies, the TGA requires data against the innovator product in Australia. Therefore, if bioequivalence studies have been carried out with the innovator products sourced from the U.S., EU, or another country, additional laboratory analytical work is required to confirm that the overseas product is chemically equivalent to the Australian product. If chemical equivalence cannot be demonstrated, it may be required to conduct bioequivalence studies specifically for Australia.

USTR should encourage the Government of Australia to eliminate duplicative requirements with respect to bioequivalence and GMP, which create barriers and impediments for U.S. generic pharmaceutical companies seeking to bring products to the Australian market.

## **BRAZIL**

There are numerous duplicative regulatory requirements in Brazil that create additional costs and delays for U.S. generic pharmaceutical companies seeking to export their American-made products to Brazil. The Brazilian National Health Surveillance Agency (ANVISA) has implemented a non-transparent and duplicative regulatory framework. The agency may be characterized as non-cooperative on various regulatory and harmonization relevant issues. Nevertheless, ANVISA has a considerable and significant impact on U.S. pharmaceutical companies and the public health system in Brazil.

Brazil will only accept imports of finished products. Companies are not permitted to conduct any manufacturing steps locally, including the packaging of final dosage forms. The imported products must be registered in the country of origin. Foreign companies must also carry all quality control tests in Brazil. There is also a requirement to present the bioequivalence tests and the equivalence tests at labs located in Brazil, which causes three more months of delay since the samples must be imported. World Health Organization (WHO) Zone IVb stability tests are required. The Brazilian sanitary agency





February 8, 2018

Page 9

also conducts international inspections at the finished production site and at the active pharmaceutical ingredient (API) producer site for the same products. There is a requirement of pre-approval of pharmaceutical products importation not only by the Federal Revenue Service but also by ANVISA.

The prices at which generic medicines can be sold in Brazil are regulated by the government based on very subjective analysis.

The process of analysis and registration by ANVISA is delayed (sometimes for more than two years) and does not respect any legal deadlines. Concerning U.S. generic companies, ANVISA prioritizes without any legal basis only the first generic of each drug. Competitors have to postpone their registration for at least 5 years.

The analysis of the marketing authorization depends on the understanding of the responsible technical person and there is no common understanding among the reviewers. There is political and sanitary tendency to protect national companies.

A further market access barrier for U.S. pharmaceutical companies is the extensive approval process of changes related to variations. All critical changes require ANVISA approval prior to implementation, including changes to process optimization, changes leading to a reduction in failures and improvement of the production and quality control. In general, the ANVISA evaluation takes up a period of time that exceeds 3 years.

### CANADA

The pharmaceutical sector is global in nature, and U.S. companies are currently unable to fully leverage their global supply chains when seeking to bring new generic medicines to Canada. The regulatory environment for generic medicines has not kept pace with the market-driven globalization of pharmaceutical supply chains.

Canadian-specific requirements that are not scientifically justified appear as early as the initial product development phase, which increases costs, resources, and uncertainty for sponsors. Some examples include:

- Requirement to use a Canadian reference product, with few exceptions. Health Canada has just published their current position with respect to foreign reference products and is titled "Guidance on the Use of a Foreign-sourced Reference Product as a Canadian Reference Product" effective 24-Nov-2017. This guidance replaces the previous 1995 policy entitled



February 8, 2018

Page 10

“Canadian Reference Product”. This new guidance has expanded the criteria for acceptance of a foreign product as a Canadian reference product but does not include all dosage formats.

- Lack of a generic drug pathway in Canada for certain complex dosage forms and/or complex mixtures.
- Practice requiring the generic drug to match the branded drug with respect to the scoring of tablets that limits the ability to use global product. Health Canada issued a Notice 28-Mar-2017 for Scoring of Subsequent-entry Pharmaceutical products that under certain circumstances allows for different scoring as compared to the Canadian reference listed drug.
- Tighter in-process control specifications compared to other jurisdictions prevent the use of a global bulk drug substance or a global bulk drug product.
- Adoption of full scale-up and post-approval changes (SUPAC) guidance would provide for the use of a global product in reference to proportional formulations.
- Identical Medicinal Ingredient policy that limits the ability to use global product development. Some progress has been made with the recent *Updated Notice: Interim Policy on Health Canada’s Interpretation of Medicinal Ingredient and Assessment of Identical Medicinal Ingredient* on October 5, 2017. The expanded scope of applications that may be acceptable as an abbreviated new drug submission (ANDS) and for which a declaration of equivalence may be issued aligns with current science and the practices of peer regulatory authorities. This revised interpretation would permit different salts of the same therapeutic moiety to be acceptable as an ANDS, provided safety and efficacy remain equivalent.
- Additional data and/or clinical trials required by some provinces even after the drug has been reviewed and authorized for sale by Health Canada.

While Health Canada has been active in global convergence initiatives involving generic medicines, these efforts have not yet yielded improved convergence of generic medicines requirements in Canada. Increasingly, U.S. generic companies are unable to build a business case that supports bringing new generic medicines to Canada, particularly for complex generic products. We ask USTR to encourage Health Canada to expedite the convergence of its regulatory requirements for generic medicines with the US Food and Drug Administration (FDA) and other leading regulatory authorities

With the impending renegotiation of the North American Free Trade Agreement (NAFTA), we urge USTR to take these considerations regarding the Canadian market into account.



## CHINA

### *Different Technical Requirements for Imported Products and Domestic Products*

Under Chinese drug registration regulations, in the context of the draft of Drug Registration Regulation (changes on the generics submission), local generic companies can submit the application at any time before the patent expiry date, but for imported generic medicines, companies have to provide the Certificate of Pharmaceutical Product in the clinical trial application. This creates the concrete risk that the review and approval of imported generic medicines drop behind those of local manufacturers.

### *Lengthy Approval Timeline for All Types of Applications*

Despite the efforts put forward by the Chinese authorities to reduce the lengthy approval timeline for all medicines applications, there is still prolonged technical evaluation in the Center of Drug Evaluation (CDE). Significant deviations in approval timelines create a lack of predictability with respect to product launch dates. The registration timeline for generic medicines is typically more than 7 years – much longer than in the U.S. and far beyond international norms.

### *Prolonged Review and Approval Timeline for Clinical Trials*

The statutory and actual timeline for clinical trials in China are relatively longer than in most other countries. While the statutory timeline in China is 145 working days, actual clinical trial approvals typically take between one to one-and-a-half years. This has had the effect of lengthening the average period for new drug research and development and has seriously affected new drug accessibility.

### *Approval number for domestic vs. imported medicines*

Currently, management of approval number for imported medicines and domestic medicines is different. The approval number for domestic medicines in the renewal remains unchanged, but for imported medicines, it is changed. Since the approval number should be printed on the label and package insert, the latter for imported medicines have to be changed after the renewal. This increases production and management cost for imported products. It may even lead to out of stock during the renewal of imported medicines.

### *Recent change in CFDA review policy*

With the recent change in the Chinese Food and Drug Agency (CFDA) review policy, innovative medicines manufactured locally in China will be granted priority review (performance goals are as



February 8, 2018

Page 12

follows: reduction to 35 days for investigational new drugs (IND) and 150-190 days for new drug applications (NDA). In addition, applications through this pathway will not go through the normal waiting queue. Companies investing in China will definitely benefit from this. Companies importing from the U.S. will follow the "classical" import pathways and risk to be negatively affected as these products will have to queue in the already overcrowded waiting queue and the new pathway will definitely divert review resources from there.

### *The sequential approach*

The approach represents a challenge to generic products: A submission can only be done after obtaining approval in the country of origin or in the country of manufacturing. Then, the assessment of an application relating to its chemistry and manufacturing has to take place and, only after that, clinical trial approval is given, i.e. the bioequivalence study can be started.

This results in a significant extension of approval time for a generic product when compared to other countries. There is no progress so far on a possible adjustment to the standard process of conducting bioequivalent (BE) studies upfront and submitting a complete package of chemistry manufacturing and controls (CMC) and BE study results.

### *The following barriers relate to biosimilar medicines specifically:*

#### *Requirement clinical trial*

A multinational biosimilar producer can only apply for clinical trials in China once it gets approval in the U.S. or EU. This requirement is even more stringent than what is required for developers of new medicines, for which China has established the International Multicenter Clinical Trial pathway (IMCT). Using the IMCT, new drug developers can conduct a clinical study in China as part of a regional clinical trial involving China and a few other countries. The IMCT pathway seems to be currently blocked for biosimilars, putting American producers at disadvantage compared to local producers.

#### *Market access delay*

The new Chinese biosimilar guideline includes positive aspects. However, multinational companies are disadvantaged on the basis of the fact that any clinical trial in China cannot be started before another authority approves the biosimilar. This results in a market access delay of up to five years or even more, taking into account the lengthy approval process for a clinical trial application in China (18-24 months), execution of trial, dossier submission and, again a lengthy dossier review (about 2.5 years).



## INDIA

The nature and diversity of the Indian pharmaceutical market, health care objectives, and legal system pose unique challenges for the pharmaceuticals sector in India. The diversity of the challenges is very complex.

In India, handling of drugs, as well as drug manufacturing, quality, and marketing are regulated in accordance with the Drugs and Cosmetics Act of 1940 ("1940 Act") and Rules 1945. This act has been amended several times over the last few decades to improve the ease of doing business in India under the stringent regulatory umbrella. The Drugs Controller General of India (DCGI), who heads the Central Drugs Standards Control Organization (CDSCO), assumes responsibility for amendments to the acts and rules under the Health Ministry. Other major related acts and rules include the Pharmacy Act of 1948, The Drugs and Magic Remedies Act of 1954 and Drug Prices Control Order (DPCO) 1995 and various other policies instituted by the Department of Chemicals and Petrochemicals.

Some of the important schedules of the 1940 Act include: 1) Schedule D, which deals with exemptions in drug imports; 2) Schedule M, which deals with Good Manufacturing Practices involving premises and plants; and 3) Schedule Y, which specifies guidelines for clinical trials, imports, and manufacture of new drugs, etc.

### *Dual Licensing Authority:*

In accordance with the 1940 Act, India operates a system of dual regulatory control or control at both Central and State government levels. The central regulatory authority undertakes approval of new drugs, clinical trials, standards setting, control over imported drugs and coordination of state bodies' activities. State authorities assume responsibility for issuing licenses, registration of the facilities and monitoring manufacturing activities, distribution and sale of drugs and other related products.

Central and State Licensing Authorities work independently in India, hence there is no harmonization or uniformity in the practices followed across authorities. The Central Licensing Authority is supposed to be the controlling authority, but in applying multiple regulations, State Authorities show a difference of opinion with the Central Authority. This leads to delays in completing the process, which hampers the export business. India should identify common, agreed practices for specific regulatory requirements to streamline the process and decrease the waiting period.



*DAVA portal (Track and Trace):*

On January 10, 2011, the Directorate General of Foreign Trade (DGFT), announced the adoption and implementation of a track and trace system incorporating serialization for all pharmaceutical products exported from India. The stated purpose of the requirement is to “address counterfeit and ineffective product recall challenges, which affects the entire health care supply chain, from manufacturers all the way to patients, wholesalers, distributors, exporters and health care providers.

Specifically, exported drug products must carry a one or two-dimensional barcode encoding a universal global product identification code in the form of a 14-digit Global Trade Item Number (GTIN), along with the product’s batch number, expiration date, and unique serial number. For all products manufactured on or after April 1, 2016, non-small-scale industry (non-SSI) manufacturers must serialize the secondary and tertiary package. Serialization of the primary package is optional for exported products. Manufacturers must aggregate lower-level packaging to higher-level packaging and upload this “parent-child” information to the Drugs Authentication and Verification Application (DAVA) database—a central, country-wide database for storage of serialization data developed and managed by the National Informatics Center (NIC).

The US has its own Serialization and Track and Trace mechanism scheduled for an implementation in various phases; the Indian DGFT regulations would pose additional complications on the labeling of drug products. As per the DGFT regulations, the manufacturer is supposed to imprint additional barcodes on the product labeling which would complicate the process of drug authentication. As per DGFT directives, if companies secure an exemption from imprinting the barcode on the primary and secondary packaging components if the country has its own existing regulations; the mandate still directs the manufacturer to secure a Dummy barcode for the labeling components (primary and secondary). The DAVA database is designed to accept only aggregated data and aggregation is possible between two level of packaging when both are serialized. The Dummy or Virtual serial numbers for aggregation is a serious threat to GMP quality measures. In case of products planned to be imported to India from US, there is no clear input from DGFT whether the product being imported to India will be accepted based on US allocated Trace and Track barcode or not. It is unclear whether products being imported to India should be affixed with additional barcodes as per DGFT regulations for further commercialization in India.

Much of the information required by the DAVA portal does not appear to be necessary for a track and trace system. A group of manufacturers has made recommendations (listed below) to DGFT/Ministry of Commerce regarding proposed changes to the system, but there has been no modification of the portal.



1. CDSCO and DGFT should delegate an independent body to undertake (i) an economic impact assessment for domestic serialization and traceability requirements under consideration, and (ii) a regulatory impact assessment of existing requirements for serialization and traceability of exports.
2. With regard to product exported to a country that has its own serialization requirements, the “tertiary package” should be considered the highest level of shipping container used for export. For example, the pallet will typically be the tertiary package for exports to the United States or the European Union. For some markets, however, the homogeneous case is the highest level of container exported. All levels of packaging below the tertiary package (as defined here) should then be exempt from unique identifier and labeling requirements under the India serialization and traceability regulations.
3. DGFT should grant exemptions on a country-by-country basis, not a manufacturer-by-manufacturer or product-by-product basis.
4. Regulators should not define the GTIN indicator digit; it should be set by the manufacturer, as provided in the GS1 GTIN General Specifications.
5. NIC should revise the DAVA database and portal to:
  - Segregate the portal interface for exports and domestic product.
  - Eliminate the primary package serial number field, or at a minimum, permit the field to be left blank.
  - Eliminate the pricing information field, or at a minimum, permit the field to be left blank.
  - Eliminate the requirement to upload product photos.
  - Permit a single manufacturer to repeat serial numbers for different GTINs.
  - Provide the option and interface for automatic upload of data via web service.
  - Prevent a company’s data from being visible to other companies.
  - NIC should establish a clear, predictable process for communicating revisions to the DAVA portal.
  - CDSCO and DGFT should consider alternative approaches that limit data volumes.
6. NIC should maintain development and simulation environments to support revisions to the DAVA portal.
7. NIC should establish a clear, predictable process for communicating revisions to the DAVA portal.
8. In the initial phase of requirements for domestic product, CDSCO should require serialization of the saleable unit.
9. CDSCO should not require manufacturers to capture, maintain, or report any information related to the movement of products by downstream trading partners.
10. CDSCO should adopt a four-year, phased implementation timeframe for domestic requirements.
11. CDSCO and DGFT should consider alternative approaches that limit data volumes.





*Import/ Re-Import:*

Regulation to import the innovator samples for clinical trials, in-vitro, and in-vivo bio study should be flexible and harmonized. India's current system requires multiple approvals for sample uses over multiple time frames. Instead, it should be flexible and allow the same set of samples from the same lot granted an approval to be used to carry out all required studies for registration, since applying to use the same lot multiple times is a cumbersome task.

A proper system should be developed for avoiding delays in re-importing an exported finished drug product back to India for any mandatory re-working. This approach would assist the manufacturer in achieving easy reworking of the exported goods and exporting them back to the exporting country after reworking and quality confirmation.

For finished product manufacturers whose sites are either 100% export-oriented units (EOU) or situated in special economic zones (SEZ), difficulties in re-importing product for reworking defeat the benefits of provided by DGFT through these programs. If the product is covered by a "no objection certificate" (NOC) and/or an assistance drug controller ("ADC") certificate, then manufacturers should be permitted to re-import the material to India for re-working.

*Export:*

Customs clearance of goods to be exported to the United States and other countries should be followed as outlined by Ministry of Health and Director General of India. Under the current practice, Customs Clearance Ports impose different sets of regulation instead of following the mandate published by the Govt. Of India.

**INDONESIA**

The new Regulation on Drug's Criteria and Registration (*Regulation of the Chairman of NADFC RI No. 3 Year 2013, Amendment of Regulation of the Chairman of NADFC RI No. HK.03.1.23.10.11.08481 Year 2011 on the Drug's Criteria and Registration; This Regulation was also notified to the TBT Committee of the WTO*) adds an additional step in the registration of medicines in Indonesia. Indeed, before issuing a Marketing Authorization (MA), the National Agency of Drug and Food Control (NADFC) will issue a first "Approvable Letter." The company will then need to submit evidence that it has made the importation/started local production before it can get the MA. The regulation has been in fact issued to ensure that the company not only registers but also markets the product once it gets the MA.



However, the approvable letter, just introduced in the Regulation, requires that imported products have an Indonesia-specific pack that, according to the letter, will need to be prepared in the exporting country, and no action can be conducted in the local territory. This represents a potential barrier for U.S. companies, especially for medicinal products with lower sales levels in Indonesia. This might force companies that have already invested to supply the Indonesian market to discontinue the launch of some products in Indonesia.

A more efficient process would be to allow companies to finish the packaging (with the Indonesian-specific packaging requirements) in the Indonesian territory instead of obliging companies to finalize the packaging process in the exporting countries, i.e. the U.S.

The Indonesian national Law No. 33/2014 on halal product certification could become another potential market access barrier for U.S. pharmaceutical companies in Indonesia. According to this law, all components of a drug have to be deemed halal, which is an insurmountable impediment for the whole branch. The effects of such a regulation will be that companies are forced into other markets. Instead of the Indonesian compulsory Halal-guideline, which includes medicinal product, the Malaysian “positive Halal-regulation” legislation is advisable. All products that are not specifically labeled Halal are by default Non-Halal. A regulation similar to the Malaysian regulation will prevent the generation of additional costs for U.S. pharmaceutical companies and is further in accordance with a “positive Halal-regulation” that allows the U.S. pharmaceutical companies to maintain the security and freedom of choice for the Indonesian consumers.

As an Association of Southeast Asian Nations (ASEAN) country, Indonesia requests applicants to provide 12 months of WHO Zone IVb stability data with the drug submission. The approval process then takes an additional 1-2 years after the submission is filed. The total process lasts 2-3 years from the beginning of the stability testing until the product approval. An alignment with International Conference on Harmonisation (ICH) stability Guidelines would be appreciated for the U.S. pharmaceutical industry.

Another market access barrier is the potential discrimination against U.S. pharmaceutical companies in favor of local companies in registering unbranded products, despite the fact that the product is manufactured in Indonesia. This unofficial regulation is already in place and limits the ability of multinational companies with local production facilities to compete for government tenders.

### **KOREA, REP.**

A standard agreement for the “Supply and Sales of Pharmaceuticals” limits the freedom of contracting parties in agreements between local pharmaceutical companies and multinational pharmaceutical



companies. Indeed, even when multinational companies intend to terminate the agreement for not obtaining minimum order quantity or minimum sales target etc., such agreement prohibits its immediate termination. This is a legal obstacle for multinational companies in handling local partners. As a result, this is one of the barriers that prevent the introduction of advanced pharmaceutical products into the Korean market and burden businesses.

### MAGHREB (ALGERIA, MOROCCO, TUNISIA)

Pharmaceutical exports to Maghreb (Algeria, Morocco, Tunisia) are mainly hindered by a preference for locally manufactured products. There are specific lists of products that are banned from importation as these products are produced locally. The registration of products in the Maghreb requires that the products be both registered and marketed in the U.S. or another country of origin. This blocks exports of products that are licensed or are not currently registered and marketed in the U.S. but are manufactured in the U.S.

### MALAYSIA

Local and U.S. pharmaceutical manufacturers are unequally treated in the process of granting government tenders. U.S. owned, or U.S. majority-owned manufacturers have the possibility of being awarded government tenders, but the inconsistency in tender policies restricts their participation. National policy is mainly dictating the award of government tenders to local pharmaceutical manufacturers. Furthermore, local companies could act as an intermediary to participate in government tenders. U.S. companies are not given this opportunity.

Another market access barrier is the restriction on fund transfers and the interdiction of the global pooling of funds with netting of payments under Act 17 of the Exchange Control Act from 1953. The exchange of Dollar to Ringgit can only be done by the Malaysian Central Bank, which allows the government to control every transaction companies are doing in or to Malaysia. As a consequence, the Foreign Direct Investment (FDI) to and also from the country will be limited.

As an ASEAN country, Malaysia requests applicants to provide 12 months of WHO Zone IVb stability data with the drug submission. The approval process then takes an additional 1-2 years after the submission is filed. The total process lasts 2-3 years from the beginning of the stability testing until the product approval.



## RUSSIA

### *Exclusive Product Sourcing*

Only one product can be marketed per dossier. As a consequence, licensors can only out-license their products to one marketing company in Russia. As a result, economies of scale cannot be achieved and cost of goods increase, resulting in higher prices and limited opportunities for licensors. In certain cases, this regulation is not supporting the creation of a competitive environment.

### *GMP Audit of Local Authorities*

The amendment to the federal law N61-FZ (came into force on July 1, 2015) includes an obligatory requirement for a GMP certificate submission issued by the Russian drug regulatory authority during registration of new products beginning in January 2016, and for variations and renewals beginning in January 2017. Timelines for GMP inspections could delay the market entry of products from sites that have not yet been inspected by the Russian authorities.

### *Registration*

The registration of any generic medicine in Russia can only be done if the bioequivalence study has been performed in Russia. This leads to repetition of bioequivalence studies. Clinical studies have to be repeated for Russia before launching new medicines.

### *Imports*

The import of finished products and APIs into Russia attracts a high and variable amount of customs clearance charges. In addition, local producers may have a monopoly on the production of certain APIs or finished products. They can undercut the price of sourcing from a foreign supplier by a significant margin, making the option of sourcing from within the foreign supplier's internal network very unattractive.

### *Prices*

Prices for essential drugs on a list maintained by Russia's Ministry of Health can be adjusted each year to inflation. This right is denied to foreign manufacturers. For essential drugs to be imported, the Russian price registration system has a minimum price threshold requirement (out of 20 reference countries). This policy prevents U.S. and other generic pharmaceutical companies from obtaining a reasonable retail price.



February 8, 2018

Page 20

### TAIWAN

Taiwan requests Pharmaceutical Inspection Convention (PIC) GMP approval for a manufacturing site and a site validation/inspection for a manufacturing site before the file can be approved. The site validation and PIC/s GMP approval processes each take approximately 1.5 years and are separate processes from the file registration process.

### THAILAND

The ASEAN countries request applicants to provide 12 months of WHO Zone IVb stability data with the drug submission. The approval process then takes an additional 1-2 years after the submission is filed. The total process is 2-3 years from the beginning of the stability testing until the product approval.

Any production site transfer is considered to be a new registration, which means a new application must be submitted along with 12 months of WHO Zone IVb stability data from the new site. This means that approval of a new site can take 2-3 years. This differs from most other non-ASEAN markets.

### TURKEY

Pharmaceutical pricing in Turkey is based on international reference pricing whereby the price in Turkey will be the lowest price available amongst France, Italy, Portugal, Greece, and Spain. The prices set by the international reference pricing regime are then converted to local currency (TL) by using the Government €/TL conversion rate.

In April 2009, the Government fixed the €/TL exchange rate for pharmaceutical pricing purposes only to 1.9595TL/€ and has not adjusted it since. The pricing legislation dictates that if the Central Bank Rate is 15% higher than the fixed rate for 90 days rolling average, the government should revise the rate. The rolling average has been at least 15% higher since 2011, and it is now approximately 50% higher.

In April 2016, according to the "64th Action Plan of the Turkish government for 2016," Action Nr. 46, the Turkish Ministry of Health plans to request suppliers of certain pharmaceutical products to produce through a local Turkish company if local suppliers already hold more than 30% market share in the respective market.

In case of non-compliance with this request, suppliers will automatically lose their reimbursement status with the Turkish health insurance. As doctors will not prescribe products that are not being



reimbursed, this regulation will, in fact, mean that the concerned products lose significant market shares or are completely squeezed out of the Turkish market.

## UKRAINE

Ukraine has local manufacturer preferences, which unfavorably impact importers of generic medicines from the U.S. and other countries.

### *GMP Requirements*

During the state registration process, companies are required to submit a huge list of documents to obtain a local confirmation that a medicinal product is produced in according to GMP requirements. This is an unnecessary duplicative, time-consuming, and costly process for foreign companies.

### *Quality Controls at Customs*

Long quality controls are conducted at customs on each product. In addition, different distributors selling the same product have to pass the controls on the same products separately.

## VIETNAM

The ASEAN countries request applicants to provide 12 months of WHO Zone IVb stability data the drug submission. The approval process then takes an additional 1-2 years after the submission is filed. The total process is 2-3 years from the beginning of the stability testing until the product approval.

Any production site transfer is considered to be a new registration, which means a new application must be submitted along with 12 months of WHO Zone IVb stability data from the new site. This means that approval of a new site can take 2-3 years. This differs from most other non-ASEAN markets.

### *Quality Standards*

Our member companies welcome the Government of Vietnam's significant efforts towards administrative reforms of the health care system. Particular consideration needs to be given to the general promotion of Codes of Good Practices, such as GMP and Good Distribution Practices (GDP).

However, current policies for generic medicine registration and procurement carry significant risk of widespread use of Vietnamese generics that have not been proven bioequivalent. The level of



supervision and enforcement by Vietnamese competent authorities cannot be deemed equivalent to that fostered within PIC/S.

In order to achieve a level playing field for all manufacturers supplying the Vietnamese market, highest priority should be given to a transparent supervision and enforcement system by Vietnamese competent authorities, based on internationally recognized principles and practices.

It is important that the demonstration of bioequivalence be introduced in Vietnam as a fundamental part of the marketing authorization granting process in order to secure access to safe effective medicines of the desired quality.

*i. Hospital Tenders & Quality Standards*

Hospital/provincial tendering systems disproportionately favor price competition over assurance of quality, safety, and efficacy through compliance with internationally recognized standards, particularly bioequivalence of the generic medicine with its reference product. Recent evolutions of the system have attempted to create different “categories” or “lots” within tenders, to acknowledge differences in regulatory/GMP standards.

While a clear distinction between products based on different levels of assurance of quality, safety, and efficacy is welcome, it would be desirable that medicines produced according to internationally recognized standards become broadly available to the local population.

Additionally, the current criteria to allocate volumes among the different “lots” appear unclear and the associated process arbitrary. As a result, hospitals need to reduce the volume of medicines produced according to internationally recognized standards already planned to be purchased, even when hospitals’ own estimates were based on clinical needs for the different products.

*ii. New Drug Registration Circular*

Under current Circular 22 (issued in 2009), an applicant cannot submit a dossier for the renewal of a marketing authorization registration earlier than six months before the expiry of the product’s existing registration.

According to industry experience over the past several years, renewal times typically exceed 6 months, thus leading to an “off-visa” period for a product for several months. During such off-visa period, importation of the product is not permitted. Providing information to doctors about the product is very restricted, particularly because all promotional materials must be withdrawn, no new materials can get





February 8, 2018

Page 23

an authorization visa from the Ministry of Health, and all materials must get a new visa after the renewal. In addition, participation in hospital tenders is not permitted during the off-visa period because most hospitals will not accept Ministry of Health documents that stipulate the product has been legally registered and is merely under a renewal process. Such a situation restricts access to essential pharmaceutical products both for health care providers and patients in Vietnam.

### III. CONCLUSION

In conclusion, while the Special 301 review is not a trade negotiation covered by TPA, it still should reflect the balance between innovation and access that has been affirmed by Congress in TPA and: 1) ensure implementation of the TRIPS Agreement; 2) secure market access opportunities for exporters of all pharmaceuticals, including generics and biosimilars; and 3) promote both innovation and access to medicines. Both the generic/biosimilar and originator industry need access to foreign markets to continue to grow and generate jobs at home. However, it is important to ensure that any new ex-U.S. IPR provisions do not create more difficult barriers for U.S. generic and biosimilar products to enter foreign markets. Following the guidance set out in TPA to balance innovation with access will result in balanced IPR regimes that give companies' certainty about the regulatory frameworks in which they will operate, which will maximize the economic impact of U.S. exports and domestic job creation. This balanced approach is critical to achieving the President's goal of bringing down prescription drug prices and provides a unique opportunity to address public health concerns while promoting growth in the U.S. economy. This is a win-win opportunity that meets the original intent of Congress to expand pharmaceutical exports while protecting the interest of U.S. businesses abroad and addressing the current needs of the entire pharmaceutical industry and society.

Once again, AAM appreciates the opportunity to contribute to USTR's process and remains available to discuss these issues further and respond to any questions you may have.

Sincerely,

/s/

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Senior Vice President,  
General Counsel

/s/

David R. Gaugh, R.Ph.  
Senior Vice President,  
Sciences and Regulatory Affairs



February 8, 2018

Page 24

**AAM Members**

- 3M Health Care Business
- Accord Healthcare Inc.
- Aceto Corporation
- ACIC
- Alvogen Inc.
- Amerisource Bergen Corp.
- Amneal Pharmaceuticals
- Apotex Corporation
- Argentum Pharmaceuticals
- Aurobindo Pharma USA Inc.
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- Colorcon, Inc.
- Direct Relief
- Dispensary Of Hope
- Dr. Reddy's Laboratories Inc.
- DSquared Pharmaceuticals Inc.
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- Fresenius Kabi USA LLC
- G & W Laboratories, Inc.
- Gedeon Richter USA
- Glenmark Generics Inc., USA
- Greenblum & Bernstein
- GYMA Laboratories
- Haynes And Boone, LLP
- Husch Blackwell LLP
- Impax Laboratories, Inc.
- InnoPharma Inc.
- Interchem Corporation



## Your Generics and Biosimilars Industry

February 8, 2018

Page 25

IPG Pharmaceuticals, Inc.  
Johnson Matthey Pharmaceutical Materials  
Knobbe Martens Olson & Bear LLP  
Lachman Consultant Services Inc.  
Luitpold Pharmaceuticals, Inc  
Lupin Pharmaceuticals, Inc.  
Mayne Pharma  
Midas Pharmaceuticals Inc.  
Momenta Pharmaceuticals Inc.  
Mylan, N.V.  
New Chemic, Inc.  
Novum Pharmaceutical Research Services  
Ren-Pharm International Ltd.  
Rising Pharmaceuticals Inc.  
RT Specialty  
Sagent Pharmaceuticals, Inc.  
Sandoz Inc., A Novartis Division  
Sovereign Pharmaceuticals LLC  
Spear Pharmaceuticals  
Sun Pharmaceutical Industries, Inc.  
Symbio LLC  
Teva Pharmaceuticals USA  
Virtus Pharmaceuticals, LLC  
Walgreen Company  
West Pharmaceutical Services  
West-Ward Pharmaceuticals, A Hikma Company  
Zydus Pharmaceuticals USA