

REPORT 04 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (N-21)  
Pharmacovigilance  
(Res 518-A-19, Chemical Variability in Pharmaceutical Products)  
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. In past AMA House of Delegates meeting, confusion about several concepts detailed in the multiple resolutions related to the quality of pharmaceutical products and concepts related to pharmacovigilance (PV) in general was recognized. Your Council on Science and Public Health (CSAPH) noted that there are several issues related to PV, track and trace, and testing and verification of pharmaceuticals that could benefit from further study, in addition to addressing referred Resolution 518-A-19, Chemical Variability in Pharmaceutical Products.

Methods. English-language articles were selected from a search of the PubMed database through August 2021 using the search terms “pharmacovigilance,” “pharmaceutical/drug quality,” and “pharmaceutical/drug impurities.” Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society and international, national, and local government agency websites were conducted to identify clinical guidelines, position statements, and reports.

Results. The originally referred resolution that initiated this report was in response to the recalls of multiple drug products because of impurities present in the medications. These impurities were identified by the FDA and partner testing. The FDA subsequently informed the public about the problem, continues to investigate the issue, and continues to take corrective action. The source of detected impurities is linked to manufacturing issues and subsequent inspections revealed systemic problems of supervision that could have created the conditions for quality issues to arise; corrective action is underway. Importantly, FDA procedures identified the issue.

Conclusion. PV is a continuous process requiring active participation and combined efforts from physicians, other authorized prescribers, the pharmaceutical industry, government regulators, public health officials, clinicians, and health care organizations. Informed participation by all in PV processes is necessary to continually improve drug product safety, drug supply chain integrity and to identify safety signals. The AMA already has significant, relevant, and well-written policy related to PV and drug quality. Therefore, your Council recommends updating two outdated policies and reaffirmation of several existing polices.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 04-N-21

Subject: Pharmacovigilance  
(Res 518-A-19, Chemical Variability in Pharmaceutical Products)

Presented by: Alexander Ding, MD, MS, MBA, Chair

Referred to: Reference Committee E  
(E. Christopher Bush, MD, Chair)

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1 INTRODUCTION

2  
3 Resolution 518-A-19, “Chemical Variability in Pharmaceutical Products,” introduced by the  
4 American College of Cardiology and referred by the House of Delegates (HOD) asked:

5  
6 That our American Medical Association (AMA) do a study and report back by the 2019  
7 Interim Meeting regarding the pharmaceutical variability, both in active pharmaceutical  
8 ingredient and dissolution, the impact on patient care and make recommendations for action  
9 from their report findings; that our AMA advocate for legislation requiring independent testing  
10 and verification of the chemical content of batches of pharmaceuticals; and that our AMA  
11 advocate for the logging of batches at the patient level, so the batches can be traced and  
12 connected to patient outcomes or adverse events.

13  
14 In addition, two resolutions were introduced and debated at I-19 on the topic of pharmaceutical  
15 production and quality. At both A-19 and I-19, there was confusion about several concepts detailed  
16 in the resolutions and the concept of pharmacovigilance (PV) in general. Your Council on Science  
17 and Public Health (CSAPH) noted that there are several issues related to PV, track and trace, and  
18 testing and verification of pharmaceuticals that could benefit from further study. This report  
19 summarizes and explains the current state of PV for medications taken by patients in the United  
20 States; describes the role of the U.S. Food and Drug Administration (FDA) in PV; explains Drug  
21 Supply Chain and Security Act (DSCSA, also called “track and trace”) and its implementation;  
22 clarifies testing and verification procedures for medications; comments on issues associated with  
23 the pharmaceutical supply chain related to medication safety and quality; and provides  
24 recommendations related to PV policy. Additionally, CSAPH acknowledges the delay in this report  
25 due to the COVID-19 public health emergency and shifting of priorities for Council staff. This  
26 report from the Council also includes new developments related to pharmaceutical quality that have  
27 arisen during the COVID-19 public health emergency.

28  
29 METHODS

30  
31 English-language articles were selected from a search of the PubMed database through August  
32 2021 using the search terms “pharmacovigilance,” “pharmaceutical/drug quality,” and  
33 “pharmaceutical/drug impurities.” Additional articles were identified from a review of the  
34 references cited in retrieved publications. Searches of selected medical specialty society and

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Action of the AMA House of Delegates 2021 November Meeting: CSAPH Report 4  
Recommendations Adopted as Amended, and Remainder of Report Filed.

1 international, national, and local government agency websites were conducted to identify clinical  
2 guidelines, position statements, and reports.

### 3 BACKGROUND

4  
5 PV is defined by the World Health Organization (WHO) as comprising the science and activities  
6 relating to the detection, assessment, understanding, and prevention of adverse effects and other  
7 drug-related problems.<sup>1</sup> PV is described as a systematic process involving the collection of  
8 information about the nature, severity, clinical characteristics, and outcomes of adverse effects of  
9 medicinal products; documentation and analysis of the collected adverse-effects data to detect a  
10 causal link between the medicinal product and adverse effect; remedial actions to eliminate (or  
11 minimize) hazards posed by adverse effects of medicinal products, and continued monitoring of the  
12 impact of any such remedial actions.<sup>2</sup> The field of PV has undergone rapid growth over the last two  
13 decades.<sup>3</sup>

14  
15 Various medicinal product-related safety issues not attributable to the pharmacologic properties of  
16 the product are also a part of PV. Safety issues include dosage form problems such as  
17 contamination, physical defects, abnormal odor or taste; product packaging issues such as broken  
18 seals, leaking bottles, and incorrect fill amount; labeling problems such as missing labels, missing  
19 lot numbers, and missing expiration dates; and counterfeit medicines. Upon learning about issues,  
20 regulatory authorities ask manufacturers to take remedial actions, for example, product recalls. This  
21 report addresses many aspects of adverse events and the tracking of those, but also drug product  
22 supply chains and recent and ongoing efforts to improve the tracking of medicinal product  
23 production, distribution, shipping, and location.

#### 24 *Terminology*

25  
26  
27 PV is a growing field and mounting concern in healthcare, which aims to enhance patient care and  
28 patient safety in relation to the use of medicines. However, often in healthcare, the terms including  
29 adverse event, adverse drug reaction, and side effect are used interchangeably. Experts note that  
30 standardization of medication-safety-related terminology is an important goal of PV. With that in  
31 mind, the following terms are provided for clarity:<sup>4,5</sup>

32  
33 Adverse event (AE). All undesirable events occurring after the use of a medicinal product that may  
34 not necessarily be ascribed to the product are AEs.

35  
36 Adverse drug reaction (ADR). A response to a drug which is noxious and unintended, and which  
37 occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease, or used for  
38 modifications of physiological function, is an ADR.

39  
40 AEs or ADRs are considered unexpected if it is not consistent with applicable product information  
41 or characteristics of the drug. Serious AEs or ADRs are untoward medical occurrences that at any  
42 dose results in death, are life-threatening, requires inpatient hospitalization or prolongation of  
43 existing hospitalization, and/or results in persistent of significant disability or incapacity.

44  
45 Side effect. An unintended effect, regardless of dosage, that occurs related to the pharmacological  
46 properties of a medication, is considered a side effect; side effects are not necessarily adverse and  
47 are often foreseen.

48  
49 PHARMACOVIGILANCE AT THE U.S. FOOD AND DRUG ADMINISTRATION (FDA)

1 The FDA has several offices dedicated to drug quality, surveillance, and epidemiology. The aim of  
2 FDA PV processes is to collect information about various broad aspects of medicinal product  
3 safety. These aspects are listed in the FDA's guidance document on good PV practices.<sup>6</sup>  
4 Specifically, the document provides guidance on safety signal identification,  
5 pharmacoepidemiologic assessment and safety signal interpretation, and PV plan development. The  
6 FDA also hosts an informational website that provides and outlines resources related to  
7 pharmaceutical quality.<sup>7</sup>

#### 8 9 *FDA Office of Surveillance and Epidemiology (OSE)*

10  
11 The FDA's Office of Surveillance and Epidemiology (OSE) monitors and evaluates the safety  
12 profiles of drugs using a variety of tools and disciplines throughout the life cycle of the drugs.<sup>8</sup>  
13 OSE has four core functions: pharmacovigilance; pharmacoepidemiology; medication error  
14 prevention and analysis; and risk management. The Office operates across multiple disciplines to  
15 review and assess the safety of medicines and maintains a system of postmarketing surveillance  
16 and risk assessment programs to identify adverse events that did not appear during the drug  
17 development process. OSE evaluates more than 1.5 million adverse event reports (AERs)  
18 submitted every year to the FDA's MedWatch program,<sup>9</sup> part of the FDA Adverse Event Reporting  
19 System (FAERS)<sup>10,11</sup> or Safety Reporting Portal (SRP).<sup>12</sup>

20  
21 OSE is part of the Center for Drug Evaluation and Research (CDER) and houses the Office of  
22 Pharmacovigilance and Epidemiology (OPE) as well as the Office of Medication Error Prevention  
23 and Risk Management. OPE's Division of PV (DPV) evaluates the safety of drug and therapeutic  
24 biologic products, engages in monitoring/surveillance, analyzes safety signals, recommends  
25 regulatory actions, and communicates relevant safety information. OPE and DPV recognize that  
26 pre-approval clinical trials of drugs have limitations and that the pharmaceutical industry and the  
27 FDA must rely on postmarket surveillance and AE reports to monitor medications and monitor for  
28 safety signals. OSE and its office and divisions are responsible for:

- 29
- 30 • Postmarketing safety surveillance for all marketed drug and therapeutic biologic products;
- 31 • Conducting active drug safety surveillance;
- 32 • Reviewing drug safety-related epidemiologic study protocols and study reports;
- 33 • Ensuring that the postmarketing requirements conducted by sponsors meet the best  
34 practices in epidemiology and can provide robust and actionable evidence to inform  
35 regulatory decision making following initial approval;
- 36 • Procuring, managing, and analyzing pharmaceutical sales and health care data to describe  
37 and characterize drug utilization levels and treatment patterns in the United States;
- 38 • Working with drug companies to reduce medication errors related to confusing labels,  
39 labeling, drug packaging, and drug names that look alike or sound alike; and
- 40 • Providing risk management expertise on development and implementation of programs and  
41 initiatives to support policies related to Risk Evaluation and Mitigation Strategies (REMS).
- 42

43 In May 2021, OSE issued its first annual report highlighting the key OSE initiatives to detect,  
44 assess, prevent, and monitor the risks of medicines, with a special focus on its efforts to respond to  
45 the COVID-19 pandemic.<sup>13</sup>

#### 46 47 *FDA Office of Pharmaceutical Quality (OPQ)*

48  
49 FDA's CDER also houses the Office of Pharmaceutical Quality (OPQ) which works to assure that  
50 quality medicines are available for the American public.<sup>14</sup> OPQ integrates assessment, inspection,  
51 surveillance, policy, and research activities to strengthen pharmaceutical quality on a global scale.

1 OPQ oversees the quality of marketed drugs over the entire drug lifecycle and monitors the state of  
2 quality for all regulated manufacturing sites and drug products by establishing quality standards,  
3 including current good manufacturing practices (cGMP); identifying quality problems which  
4 require corrective action; and encouraging the adoption of emerging technologies to enhance  
5 pharmaceutical quality. OPQ works closely with other FDA offices if enforcement decisions need  
6 to be made and strives to balance potential quality risks with the risk of a patient not getting a  
7 needed medication. It also attempts to anticipate quality problems before they develop so as to help  
8 prevent drug shortages.

9  
10 The OPQ 2019 annual report described activities in 2019 and over the office's five-year life,  
11 including efforts in drug assessment, inspection, surveillance, policy, and research. The report also  
12 detailed the number of additional FDA staff hired to work on pharmaceutical quality.<sup>15</sup> The 2020  
13 annual report on the state of pharmaceutical quality contains select quality indicators and trends  
14 that provide insight into the quality of the U.S. drug supply chain and includes an analysis of the  
15 impact of the COVID-19 public health emergency on the pharmaceutical supply chain and on the  
16 quality of drugs.<sup>16</sup>

### 17 *Facility Inspections*

18  
19  
20 A U.S. Government Accountability Office (GAO) report from December 2019, *Preliminary*  
21 *Findings Indicate Persistent Challenges with FDA Foreign Inspections*, noted that more than 60  
22 percent of drug manufacturers for the United States market are located overseas. The FDA inspects  
23 foreign and domestic drug manufacturers to ensure drug safety and effectiveness; however, the  
24 number of inspections of foreign drug manufacturers has declined since FY 2016 and most foreign  
25 inspections are preannounced. The report notes concerns about FDA's ability to oversee the global  
26 supply chain.<sup>17</sup>

27  
28 In March 2020, at the beginning of the COVID-19 public health emergency, the FDA made the  
29 decision to pause most foreign and domestic facility inspections, with the exception of mission-  
30 critical inspection work. This decision was made in response to federal guidelines to mitigate the  
31 spread of the COVID-19 virus. The Agency relied on alternative tools such as inspection reports  
32 from foreign regulators, records requests, and product sampling to complement its oversight  
33 activities.

34  
35 The FDA acknowledges that the pandemic had an impact on inspection work in a report titled  
36 "Resiliency Roadmap for FDA Inspectional Oversight," which outlines the effect of the public  
37 health emergency on inspection activities and the detailed plan for inspections and operations  
38 moving forward. The report notes that a significant backlog of both domestic and international  
39 inspections that are likely to persist through much of the next calendar year.<sup>18</sup>

### 40 41 *FDA Drug Quality Sampling and Testing Programs*

42  
43 FDA Drug Quality Sampling and Testing Programs help assure that only safe and effective drugs  
44 are sold.<sup>19</sup> The FDA tests drugs in FDA laboratories and through research contracts and grants.  
45 This includes active pharmaceutical ingredients (API) used to make the product and the finished  
46 drug product sold to consumers. FDA tests drugs using the same standards that are part of the drug  
47 approval process for identity, strength, purity, and bioavailability, which is also used to establish  
48 bioequivalence. Although some research has indicated batch-to-batch variability,<sup>20</sup> FDA offices  
49 and labs evaluate these issues and take corrective action as necessary, including recalls.<sup>21</sup>

50  
51 DRUG SUPPLY CHAIN

1 Of note when discussing the topic of PV is overall pharmaceutical supply chain issues. Because of  
2 the way API are distributed in the supply chain, one source of contaminated API can impact  
3 multiple products from multiple manufacturers. At times, because of a lack of transparency in the  
4 supply chain, it is difficult and time-consuming to determine all links in the supply chain.

5  
6 Recently, considerable attention has been focused on supply chain resilience. In 2021, the FDA  
7 published several guidance documents related to supply chain security,<sup>22</sup> the White House released  
8 a report on policies to support the creation of resilient supply chains,<sup>23,24</sup> and The Duke-Margolis  
9 Center for Health Policy and the COVID Collaborative released a new white paper on challenges  
10 and potential solutions for resilient drug supply chains that complements the White House report.<sup>25</sup>  
11 All of these publications include aspects of AMA policy regarding drug shortage including calls for  
12 increased transparency, global cooperation, resiliency and redundancy in manufacturing capability,  
13 and the creation of a quality rating system. While advanced manufacturing, including continuous  
14 manufacturing,<sup>26</sup> is an important component to drug quality, the specifics regarding implications  
15 and implementation of advanced manufacturing are outside of the scope of this report.

16  
17 Additionally, a recent report from the National Academies of Sciences, Engineering, and Medicine,  
18 *Stronger Food and Drug Regulatory Systems Abroad*, recommends strategies and a framework that  
19 regulatory agencies worldwide can adopt to support the availability of good quality, safe food and  
20 medicines globally and to identify areas of greatest risk. The report also recommends ways that  
21 U.S. government agencies, international development donors, and the WHO can strengthen the  
22 capacity of food and drug regulators, particularly those in low- and middle-income countries. Such  
23 investments should prioritize the expansion of WHO's approval and quality control processes for  
24 priority medicines and vaccines; the development of tools for rapidly screening food and drug  
25 quality; and improving the evaluation of how well regulatory agencies are performing.<sup>27</sup>

## 26 27 PHARMACEUTICAL IMPURITIES

28  
29 The FDA, the International Conference on Harmonization (ICH), and the United States  
30 Pharmacopeia (USP) define an impurity as "any component of a drug substance that is not the  
31 chemical entity defined as the drug substance and in addition, for a drug product, any component  
32 that is not a formulation ingredient."<sup>28-30</sup> Impurities in a drug substance (i.e., an API) or a drug  
33 product that can arise due to synthetic/manufacturing processes (process-related impurities [PRIs])  
34 and degradation (degradation-related impurities [DRIs]), or due to factors such as storage  
35 conditions, containers, excipients, or contamination. In addition, impurities can be categorized as  
36 identified or unidentified, volatile or nonvolatile, or organic or inorganic species. Figure 1 provides  
37 a flowchart that details the categories of impurities.<sup>31</sup>

### 38 39 *Nitrosamine Impurities*

40  
41 Unacceptable levels of nitrosamine impurities in some batches of the angiotensin II receptor  
42 blocker (ARB) valsartan were first detected in 2018. Subsequently, impurities were found in other  
43 ARBs, as well as unrelated drugs, including ranitidine, nizatidine, metformin, varenicline, rifampin  
44 and rifapentine.<sup>32-34</sup>

45  
46 Nitrosamines are a group of chemical compounds, some of which can pose a risk to patients and  
47 public health due to their mutagenic properties. They are well known to be present in foods, such as  
48 smoked or grilled meats and fish, and they are also present in mainstream and sidestream air from  
49 combusted tobacco in cigarettes, cigars and pipes. Nitrosamines or their precursors can also be  
50 present in a wide variety of manufactured and natural products. Nitrosamines generally are not  
51 intentionally added to foods or consumer products but are formed from constituents of the foods or

1 products that are either naturally present or added during production. When they are metabolized,  
2 nitrosamines are converted to alkylating agents. Some of these are known to damage DNA and  
3 have been linked to an increased risk of cancer if a patient is exposed to unacceptable levels of the  
4 impurity for an extended period of time.<sup>35</sup>

5  
6 FDA testing found the levels of the nitrosamine N-nitrosodimethylamine (NDMA) increased under  
7 normal storage conditions and increase in samples stored at higher temperatures. FDA testing also  
8 determined that levels of NDMA present in drugs is similar to levels a person is exposed to through  
9 consuming grilled meats. The Agency has established “interim limits” for three nitrosamine  
10 compounds: NDMA, NDEA and NMBA.<sup>36</sup> The FDA also noted that the identification of  
11 nitrosamine impurities in tested drug samples may not reflect an emerging regulatory problem, but  
12 is an evolution of scientific methods that are capable of detecting the impurities at significantly  
13 lower levels than in the past.<sup>37</sup>

14  
15 In numerous updates, the FDA notes that they continue to work with manufacturers to investigate  
16 the source of nitrosamines in drug products and whether they are at a level that may pose risks to  
17 human health. The FDA and manufacturers are testing samples of certain medications that may  
18 contain nitrosamines and will continue to take rapid and appropriate action when needed.<sup>36,38-40</sup>  
19 Additionally, the FDA held a public workshop on nitrosamine impurities to educate about  
20 nitrosamine chemistry and toxicology, on the finding of nitrosamines as impurities in drugs, data  
21 gaps and research needs to address uncertainties in nitrosamine safety assessment, and about how  
22 to prevent or minimize their presence in drugs, as well as to provide a forum for an open discussion  
23 of questions.<sup>41</sup>

24  
25 Manufacturers are held responsible for understanding their manufacturing processes and following  
26 cGMP, which includes identifying and preventing the presence of unacceptable impurities. This  
27 involves developing new predictive approaches, along with using suitable methods to detect and  
28 control these impurities as well as others that may arise when making changes to manufacturing  
29 processes. The FDA issued and then revised an immediately-in-effect Guidance for Industry on the  
30 *Control of Nitrosamine Impurities in Human Drugs* which describes steps manufacturers of active  
31 pharmaceutical ingredients and drug products should take to detect and prevent objectionable  
32 levels of nitrosamine impurities in pharmaceutical products. The Guidance also describes  
33 conditions that may introduce nitrosamine impurities. Material in the Guidance is consistent with  
34 recommendations from the ICH on the assessment and control of mutagenic impurities.<sup>42</sup> USP has  
35 also provided information on the topic and has developed a new general chapter to provide  
36 information useful for ensuring the appropriate control of nitrosamine impurities in drug substances  
37 which becomes official on Dec 1, 2021.<sup>43-45</sup>

## 38 39 POSTMARKET SURVEILLANCE

40  
41 The FDA outlines risk-based best practices for conducting ongoing postmarket safety surveillance  
42 activities for drugs and biological products in the document, “Best Practices in Drug and Biological  
43 Product Postmarket Safety Surveillance for FDA Staff,” which was required under a provision of  
44 the 21st Century Cures Act.<sup>46</sup> The document includes considerations that inform the frequency and  
45 extent of systematic drug and biologic safety monitoring; considerations based on specific product  
46 types and patient populations; safety signal identification based on screening and data mining of  
47 the FDA’s AE reporting system and other data sources, including general practices for the  
48 frequency and extent of screening these data sources, as well as prioritizing identified signals; a  
49 multidisciplinary, comprehensive evaluation of the identified safety signal that integrates the  
50 cumulative data gathered from all available sources; an assessment of the causal association

1 between the identified AE and the product; and an overview of regulatory and other actions that  
 2 can be taken in response to identified safety signals.

3  
 4 *Adverse Event Reporting*

5  
 6 Regulatory authorities are interested in receiving reports of serious and unexpected AEs and ADRs  
 7 on an urgent and priority basis.<sup>47</sup> All reporting by physicians is voluntary and also strongly  
 8 recommended; the FDA gives extra credence to physician reports. The Safety Reporting Portal  
 9 (SRP)<sup>12</sup> streamlines the process of reporting product safety issues to the FDA and the NIH,  
 10 formerly done through FAERS<sup>10,11</sup> and MedWatch<sup>9</sup> Online Voluntary Reporting Form. The SRP  
 11 can be used by manufacturers, health care professionals, researchers, public health officials, and  
 12 patients.<sup>48</sup>

13  
 14 DRUG SUPPLY CHAIN AND SECURITY ACT

15  
 16 The Drug Supply Chain and Security Act (DSCSA) also called “track and trace,” enacted as part of  
 17 the Drug Quality and Security Act of 2013, includes extensive requirements related to supply chain  
 18 participants and regulated products. The law outlines the steps manufacturers, repackagers,  
 19 wholesale distributors, dispensers (i.e., pharmacies), and third-party logistics providers need to take  
 20 to develop an electronic, interoperable system that tracks a drug at the unit-level throughout the  
 21 drug supply chain.<sup>49-51</sup> For the tracking component, each supply chain entity should be able to see a  
 22 valid chain of custody for any product. The tracking component will allow FDA the ability to  
 23 follow the chain of custody of a product back to its point of origin.

24  
 25 DSCSA includes provisions on product identification and verification, data sharing, detection and  
 26 response to suspect any illegitimate products, recordkeeping, and unified licensure standards for  
 27 wholesale distributors and third-party logistics providers. The schedule of milestones has been  
 28 broken down into three phases:

- 29  
 30 • Phase 1: Lot-level traceability and verification of products and transactions (2015)  
 31 • Phase 2: Drug product serialization and enhanced verification of serialized products (2017-  
 32 2020)  
 33 • Phase 3: Unit-level traceability (2023)  
 34

35 Requirements for Phase 1 are thus already in effect. In January 2015, the FDA expected dispensers  
 36 to have established a system for verification and handling of suspect or illegitimate products, and to  
 37 confirm that trading partners (i.e., manufacturers, wholesale distributors) are appropriately  
 38 registered or licensed with the FDA or the appropriate state authority. As of March 2016, the FDA  
 39 began enforcing the requirement. In addition, dispensers must maintain such information for no  
 40 less than 6 years after the date of the transaction. Currently with a product transaction, the ability to  
 41 track and trace the product down to the lot level is possible.

42  
 43 By 2023, electronic package-level tracing information using a product identifier will be required. A  
 44 recent presentation from FDA’s CDER provided updates on implementation of these security  
 45 requirements for enhanced drug distribution security.<sup>52</sup> The stated goals are to implement  
 46 interoperable, electronic tracing of products at the package level by 2023 that will enable secure  
 47 tracing of products at the package level; use product identifiers to verify products at the package  
 48 level; enable prompt response to suspect and illegitimate products when found; and improve  
 49 efficiency of recalls. National standards for licensure for wholesale distributors and third-party  
 50 logistics providers will be established by 2023 as well.



1 Additionally, four guidance documents describing key details of how the FDA plans to secure the  
2 pharmaceutical supply chain were recently released. The documents relate to various aspects of the  
3 “track and trace” system.<sup>53</sup> *Enhanced Drug Distribution Security at the Package Level Under the*  
4 *Drug Supply Chain Security Act* provides recommendations on the system attributes necessary for  
5 enabling the secure tracing of drug product at the package level, defined as the smallest individual  
6 salable unit of drug product for distribution by a manufacturer or repackager.<sup>54</sup> *Definitions of*  
7 *Suspect Product and Illegitimate Product for Verification Obligations Under the Drug Supply*  
8 *Chain Security Act Guidance for Industry* lays out the FDA’s current understanding of terms used  
9 to define “suspect” and “illegitimate” products.<sup>55</sup> *Product Identifiers under the Drug Supply Chain*  
10 *Security Act - Questions and Answers* clarifies information for industry.<sup>56</sup> *Drug Supply Chain*  
11 *Security Act Implementation: Identification of Suspect Product and Notification Guidance for*  
12 *Industry* is intended to aid certain trading partners in identifying a suspect product and specific  
13 scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical  
14 distribution supply chain.<sup>57</sup>

#### 15 16 CURRENT AMA POLICY

17  
18 AMA has several policies on the topic of PV (see appendix for full text). AMA Policy H-100.946,  
19 “Source and Quality of Medications Critical to National Health and Security,” supports studies of  
20 United States dependency on foreign components, legislative and regulatory initiatives to ensure  
21 proper domestic capacity, production, and quality of pharmaceuticals, and encourages the  
22 development and enforcement of standards that make the sources of pharmaceuticals and their  
23 chemical substrates used in the United States transparent to prescribers and the general public.  
24 Policy H-100.969, “Assuring the Safety and Quality of Foreign-Produced Pharmaceuticals,”  
25 addresses the safety and quality of foreign manufactured pharmaceuticals and supports inspection  
26 of all products entering the United States and surveillance inspections of foreign manufacturers.  
27 Policy D-100.977, “Pharmaceutical Quality Control for Foreign Medications,” advocates that the  
28 Congress and the FDA use their authorities to ensure safe imported drugs. Policy H-100.995,  
29 “Support of American Drug Industry,” supports pharmaceutical manufacturing industry efforts to  
30 develop and market pharmaceutical products meeting proper standards of safety and efficacy.  
31 Policy D-125.987, “Biosimilar Product Naming and Labeling,” supports appropriate PV for  
32 biosimilar products.

33  
34 Policies D-100.988, “Tracking and Punishing Distributors of Counterfeit Pharmaceuticals,”  
35 H-100.966, “Tracking and Punishing Distributors of Counterfeit Pharmaceuticals,” and D-100.985,  
36 “Federal Regulation and Computerized Tracking of Pharmaceuticals During Shipping and  
37 Handling from Manufacture Until Ultimately Received by Patient,” support pharmaceutical  
38 tracking systems, identification and eradication of illegal activities in the pharmaceutical industry  
39 and punishment of pharmaceutical counterfeiters. Policy H-120.958, “Supporting Safe Medical  
40 Products as a Priority Public Health Initiative,” supports reporting of adverse events; a coding  
41 system for prescription medicine packaging to improve patient safety; and the need for public  
42 health infrastructure and local consortiums to work on problems related to medical product safety.

43  
44 Policy H-100.956, “National Drug Shortages,” notes several relevant themes including: supporting  
45 the improvement of manufacturing quality systems; requiring drug manufacturers to establish a  
46 plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid  
47 production shortages whenever possible; urging the development of a comprehensive independent  
48 report on the root causes of drug shortages, which includes the number of manufacturers, economic  
49 factors and contracting practices; and urging the FDA to require manufacturers to provide greater  
50 transparency regarding production locations of drugs and to provide more detailed information  
51 regarding the causes and anticipated duration of drug shortages.

1 CONCLUSION

2  
3 The originally referred resolution that initiated this report was in response to the recalls of multiple  
4 drug products because of impurities present in the medications. These impurities were identified by  
5 the FDA and partner testing. The FDA subsequently informed the public about the problem,  
6 continues to investigate the issue, and continues to take corrective action. The source of detected  
7 impurities is linked to manufacturing issues and subsequent inspections revealed systemic  
8 problems of supervision that could have created the conditions for quality issues to arise; corrective  
9 action is underway. Importantly, FDA procedures identified the issue.

10  
11 PV is a continuous process requiring active participation and combined efforts from physicians,  
12 other authorized prescribers, the pharmaceutical industry, government regulators, public health  
13 officials, clinicians, and health care organizations. Informed participation by all in PV processes is  
14 necessary to continually improve drug product safety, maintain drug supply chain integrity, and to  
15 identify safety signals. The AMA already has significant, relevant, and well-written policy related  
16 to PV and drug quality. Therefore, your Council recommends updating two outdated policies and  
17 reaffirmation of several existing polices.

18  
19 RECOMMENDATIONS

20  
21 The Council on Science and Public Health recommends that the following be adopted in lieu of  
22 Resolution 518-A-19 and the remainder of the report be filed:

- 23  
24 1. That Policy D-100.988, "Tracking and Punishing Distributors of Counterfeit Pharmaceuticals"  
25 be amended by addition and deletion to read as follows:

26  
27 Our AMA will support the Food and Drug Administration's efforts to evaluate and facilitate  
28 implementation of effective tracking systems for pharmaceuticals, including all outlined  
29 implementation phases of the Drug Supply Chain and Security Act (DSCSA, Public Law 113-  
30 54) also called "track and trace," which contains extensive requirements and provisions related  
31 to supply chain participants and regulated products. (Modify Current HOD Policy)

- 32  
33 2. That Policy H-120.958, "Supporting Safe Medical Products as a Priority Public Health  
34 Initiative" be amended by addition and deletion to read as follows:

35  
36 Our AMA will: (1) work through the United States Adopted Names (USAN) Council to adopt  
37 methodology to help prevent "look alike-sound alike" errors in giving new drugs generic  
38 names;

39 (2) continue participation in ~~the National Patient Safety Foundation's~~ efforts to advance the  
40 science of safety in the medication use process, including and likewise work with the National  
41 Coordinating Council for Medication Error Reporting and Prevention;

42 (3) support the FDA's Medwatch program by working to improve physicians' and pharmacists'  
43 knowledge and awareness of the program and encouraging proper reporting of adverse events;

44 (4) vigorously work to support the Drug Supply Chain and Security Act (DSCSA, Public Law  
45 113-54), including provisions on product identification and verification, data sharing, detection  
46 and response, and encourage efforts to create and expeditiously implement a national machine-  
47 readable coding system for prescription medicine packaging in an effort to improve patient  
48 safety;

49 (5) participate in and report on the work of the Healthy People ~~2010~~ 2030 initiative in the area  
50 of safe medical products especially as it relates to existing AMA policy; and

- 1 (6) seek opportunities to work collaboratively within the Medicine-Public Health initiative  
2 (H-440.991), with pharmacy associations, and with the Food and Drug Administration (FDA),  
3 National Institutes of Health (NIH), United States Pharmacopoeia (USP) and Centers for  
4 Disease Control and Prevention (CDC) the Agency for ~~Health Care Policy and Research~~  
5 (~~AHCPR~~) Healthcare Research and Quality (AHRQ) and the Centers for Medicare & Medicaid  
6 Services (CMS) to provide information to individual physicians, pharmacists, other clinicians,  
7 and state medical societies on the need for public health infrastructure and local consortiums to  
8 work on problems related to medical product safety. (Modify Current HOD Policy)  
9
- 10 3. That Policy D-100.977, “Pharmaceutical Quality Control for Foreign Medications,” that calls  
11 upon Congress to provide the FDA with the necessary authority and resources to ensure that  
12 imported drugs are safe for American consumers and patients, be reaffirmed. (Reaffirm HOD  
13 Policy)  
14
- 15 4. That Policy D-100.985, “Federal Regulation and Computerized Tracking of Pharmaceuticals  
16 During Shipping and Handling from Manufacture Until Ultimately Received by Patient,”  
17 opposing illegal drug diversion, illegal Internet sales of drugs, illegal importation of drugs, and  
18 drug counterfeiting, be reaffirmed. (Reaffirm HOD Policy)  
19
- 20 5. That Policy D-100.988, “Tracking and Punishing Distributors of Counterfeit Pharmaceuticals,”  
21 supporting the FDA’s efforts to evaluate and facilitate implementation of effective tracking  
22 systems for pharmaceuticals, be reaffirmed. (Reaffirm HOD Policy)  
23
- 24 6. That Policy H-100.946, “Source and Quality of Medications Critical to National Health and  
25 Security,” supporting legislative and regulatory initiatives that help to ensure proper domestic  
26 capacity, production and quality of pharmaceutical and chemical substrates as a matter of  
27 public well-being and national security and encouraging the development and enforcement of  
28 standards that make the sources of pharmaceuticals and their chemical substrates used in the  
29 United States of America transparent to prescribers and the general public, be reaffirmed.  
30 (Reaffirm HOD Policy)  
31
- 32 7. That Policy H-100.969, “Assuring the Safety and Quality of Foreign-Produced  
33 Pharmaceuticals,” supporting the inspection of all foreign manufacturers of pharmaceutical  
34 chemicals and products which are exported to the United States to assure compliance with U.S.  
35 standards, be reaffirmed. (Reaffirm HOD Policy)  
36
- 37 8. That Policy H-100.995, “Support of American Drug Industry,” supporting the American  
38 pharmaceutical manufacturing industry in its efforts to develop and market pharmaceutical  
39 products meeting proper standards of safety and efficacy for the benefit of the American  
40 people, be reaffirmed. (Reaffirm HOD Policy)

Fiscal Note: Less than \$1000

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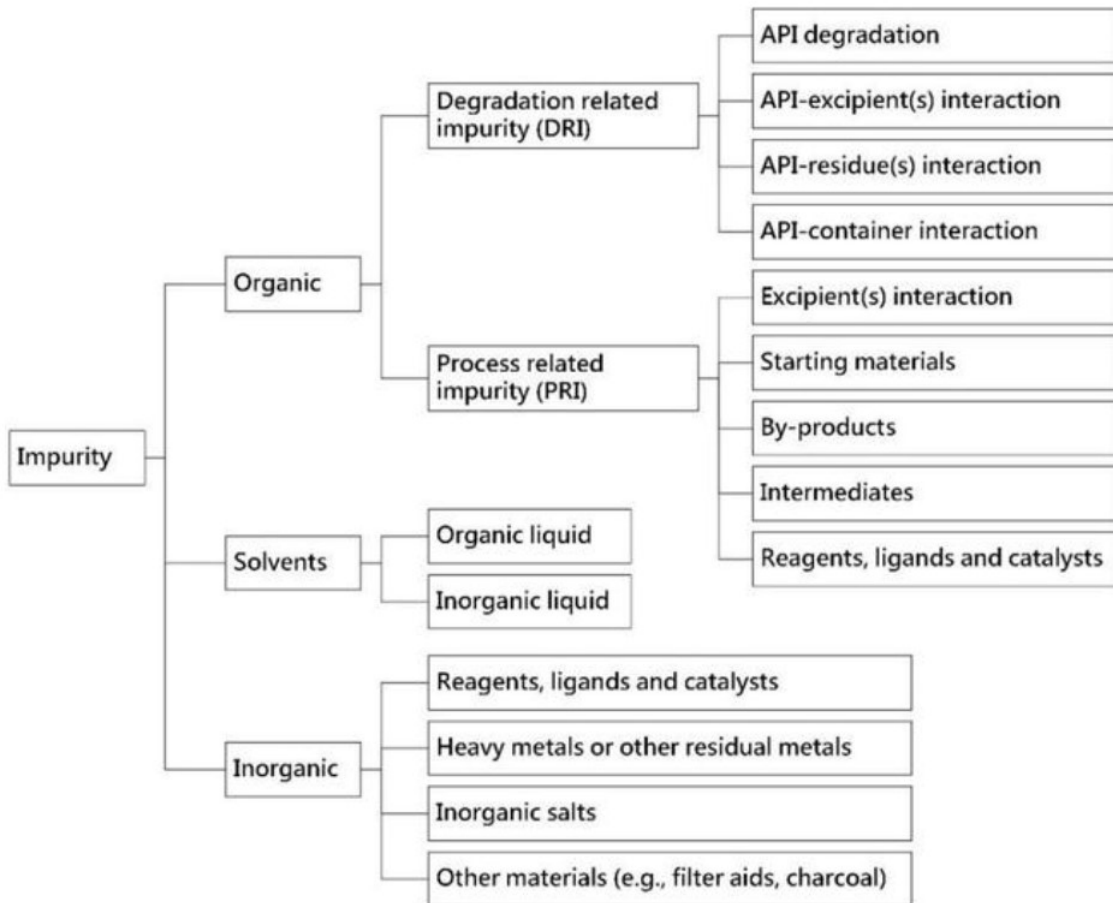
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**Figure 1.** Categorization of impurities from FDA and USP (figure from <sup>31</sup>).





## **APPENDIX: AMA Policies Related Pharmacovigilance**

### **D-100.977, “Pharmaceutical Quality Control for Foreign Medications”**

Our AMA will call upon Congress to provide the US Food and Drug Administration with the necessary authority and resources to ensure that imported drugs are safe for American consumers and patients. Res. 508, A-08

### **D-100.985, “Federal Regulation and Computerized Tracking of Pharmaceuticals During Shipping and Handling from Manufacture Until Ultimately Received by Patient”**

Our AMA will: (1) continue to actively oppose illegal drug diversion, illegal Internet sales of drugs, illegal importation of drugs, and drug counterfeiting; and (2) work with the Congress, the Food and Drug Administration, the Drug Enforcement Administration, and other federal agencies, the pharmaceutical industry, and other stakeholders to ensure that these illegal activities are minimized. Res. 501, A-04; Reaffirmation I-06; Reaffirmed: BOT Rep. 06, A-16; Reaffirmed: CMS Rep. 01, I-18

### **D-100.988, “Tracking and Punishing Distributors of Counterfeit Pharmaceuticals”**

Our AMA will support the Food and Drug Administration's efforts to evaluate and facilitate implementation of effective tracking systems for pharmaceuticals. Res. 924, I-03 Reaffirmation I-06 Reaffirmed: BOT Rep. 06, A-16

### **D-125.987, “Biosimilar Product Naming and Labeling”**

Our AMA urges the FDA to finalize Guidance on the naming and labeling conventions to be used for biosimilar products, including those that are deemed interchangeable. Any change in current nomenclature rules or standards should be informed by a better and more complete understanding of how such changes, including requiring a unique identifier for biologic USANs would impact prescriber attitudes and patient access, and affect post marketing surveillance. Actions that solely enhance product identification during surveillance but act as barriers to clinical uptake are counterproductive. However, because of unique product attributes, a relatively simple way to identify and track which biosimilar products have been dispensed to individual patients must be established. If unique identifiers for biosimilar USANs are required to support pharmacovigilance, they should be simple and the resulting names should reinforce similarities by using the same root name following standards for nonproprietary names established by the USAN Council. CSAPH Rep. 4, A-14

### **H-100.946, “Source and Quality of Medications Critical to National Health and Security”**

Our AMA: (1) supports studies that identify the extent to which the United States is dependent on foreign supplied pharmaceuticals and chemical substrates; (2) supports legislative and regulatory initiatives that help to ensure proper domestic capacity, production and quality of pharmaceutical and chemical substrates as a matter of public well-being and national security; and (3) encourages the development and enforcement of standards that make the sources of pharmaceuticals and their chemical substrates used in the United States of America transparent to prescribers and the general public. Res. 932, I-19

### **H-100.956, “National Drug Shortages”**

1. Our AMA considers drug shortages to be an urgent public health crisis, and recent shortages have had a dramatic and negative impact on the delivery and safety of appropriate health care to patients. 2. Our AMA supports recommendations that have been developed by multiple stakeholders to improve manufacturing quality systems, identify efficiencies in regulatory review that can mitigate drug shortages, and explore measures designed to drive greater investment in production capacity for products that are in short supply, and will work in a collaborative fashion

with these and other stakeholders to implement these recommendations in an urgent fashion. 3. Our AMA supports authorizing the Secretary of the U.S. Department of Health and Human Services (DHHS) to expedite facility inspections and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage. 4. Our AMA will advocate that the US Food and Drug Administration (FDA) and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. This plan should include establishing the necessary resiliency and redundancy in manufacturing capability to minimize disruptions of supplies in foreseeable circumstances including the possibility of a disaster affecting a plant. 5. The Council on Science and Public Health shall continue to evaluate the drug shortage issue, including the impact of group purchasing organizations on drug shortages, and report back at least annually to the House of Delegates on progress made in addressing drug shortages. 6. Our AMA urges the development of a comprehensive independent report on the root causes of drug shortages. Such an analysis should consider federal actions, the number of manufacturers, economic factors including federal reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing. In particular, further transparent analysis of economic drivers is warranted. The federal Centers for Medicare & Medicaid Services (CMS) should review and evaluate its 2003 Medicare reimbursement formula of average sales price plus 6% for unintended consequences including serving as a root cause of drug shortages. 7. Our AMA urges regulatory relief designed to improve the availability of prescription drugs by ensuring that such products are not removed from the market due to compliance issues unless such removal is clearly required for significant and obvious safety reasons. 8. Our AMA supports the view that wholesalers should routinely institute an allocation system that attempts to fairly distribute drugs in short supply based on remaining inventory and considering the customer's purchase history. 9. Our AMA will collaborate with medical specialty society partners and other stakeholders in identifying and supporting legislative remedies to allow for more reasonable and sustainable payment rates for prescription drugs. 10. Our AMA urges that during the evaluation of potential mergers and acquisitions involving pharmaceutical manufacturers, the Federal Trade Commission consult with the FDA to determine whether such an activity has the potential to worsen drug shortages. 11. Our AMA urges the FDA to require manufacturers to provide greater transparency regarding production locations of drugs and provide more detailed information regarding the causes and anticipated duration of drug shortages. 12. Our AMA encourages electronic health records (EHR) vendors to make changes to their systems to ease the burden of making drug product changes. 13. Our AMA urges the FDA to evaluate and provide current information regarding the quality of outsourcer compounding facilities. 14. Our AMA urges DHHS and the U.S. Department of Homeland Security (DHS) to examine and consider drug shortages as a national security initiative and include vital drug production sites in the critical infrastructure plan. CSAPH Rep. 2, I-11; Modified: CSAPH Rep. 7, A-12; Modified: CSAPH Rep. 2, I-12; Modified: CSAPH Rep. 8, A-13; Modified in lieu of Res. 912, I-13; Modified: CSAPH Rep. 3, A-14; Modified: CSAPH Rep. 2, I-15; Appended: CSAPH Rep. 04, I-17; Modified: CSAPH Rep. 02, A-18

**H-100.966, “Tracking and Punishing Distributors of Counterfeit Pharmaceuticals”**

Our AMA supports legislation making the production and distribution of counterfeit pharmaceuticals a felony. Res. 924, I-03; Reaffirmation I-06; Reaffirmed: BOT Rep. 06, A-16

**H-100.969, “Assuring the Safety and Quality of Foreign-Produced Pharmaceuticals”**

Our AMA supports: (1) the inspection of all foreign manufacturers of pharmaceutical chemicals and products which are exported to the United States to assure compliance with U.S. standards; and (2) periodic surveillance inspections of all foreign pharmaceutical manufacturers with timely follow-up inspection of all foreign manufacturers that have been identified as having serious

manufacturing deficiencies. Res. 512, A-99 Reaffirmation I-06 Reaffirmation A-08 Reaffirmed:  
Res. 508, A-08 Reaffirmation A-09

**H-100.995, “Support of American Drug Industry”**

Our AMA continues to support the American pharmaceutical manufacturing industry in its efforts to develop and market pharmaceutical products meeting proper standards of safety and efficacy for the benefit of the American people.

Sub. Res. 20, A-74; Reaffirmed: CLRPD Rep. C, A-89; Reaffirmed: Sunset Report, A-00;  
Reaffirmed: CSAPH Rep. 1, A-10

**H-120.958, “Supporting Safe Medical Products as a Priority Public Health Initiative”**

Our AMA will: (1) work through the United States Adopted Names (USAN) Council to adopt methodology to help prevent "look alike-sound alike" errors in giving new drugs generic names; (2) continue participation in the National Patient Safety Foundation's efforts to advance the science of safety in the medication use process and likewise work with the National Coordinating Council for Medication Error Reporting and Prevention;

(3) support the FDA's Medwatch program by working to improve physicians' knowledge and awareness of the program and encouraging proper reporting of adverse events;

(4) vigorously work to support and encourage efforts to create and expeditiously implement a national machine-readable coding system for prescription medicine packaging in an effort to improve patient safety;

(5) participate in and report on the work of the Healthy People 2010 initiative in the area of safe medical products especially as it relates to existing AMA policy; and

(6) seek opportunities to work collaboratively within the Medicine-Public Health initiative (H-440.991) and with the Food and Drug Administration (FDA), National Institutes of Health (NIH), United States Pharmacopoeia (USP) and Centers for Disease Control and Prevention (CDC) the Agency for Health Care Policy and Research (AHCPR) and the Centers for Medicare & Medicaid Services (CMS) to provide information to individual physicians and state medical societies on the need for public health infrastructure and local consortiums to work on problems related to medical product safety.

Res. 416, A-99; Appended: Res. 504, I-01; Reaffirmation A-10