REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1–5, were presented by Russell W.H. Kridel, MD, Chair:

1. CSAPH SUNSET REVIEW OF 2004 HOUSE POLICIES

Reference committee hearing: see report of Reference Committee E.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AND REMAINDER OF REPORT FILED

At its 1984 Interim Meeting, the House of Delegates (HOD) established a sunset mechanism for House policies (Policy G-600.110). Under this mechanism, a policy established by the House ceases to be viable after 10 years unless action is taken by the House to retain it.

The objective of the sunset mechanism is to help ensure that the American Medical Association (AMA) Policy Database is current, coherent, and relevant. By eliminating outmoded, duplicative, and inconsistent policies, the sunset mechanism contributes to the ability of the AMA to communicate and promote its policy positions. It also contributes to the efficiency and effectiveness of House of Delegates deliberations.

At its 2012 Annual Meeting, the House modified Policy G-600.110 to change the process through which the policy sunset review is conducted. The process now includes the following:

(1) As the House of Delegates adopts policies, a maximum ten-year time horizon shall exist. A policy will typically sunset after ten years unless action is taken by the House of Delegates to retain it. Any action of our AMA House that reaffirms or amends an existing policy position shall reset the sunset "clock," making the reaffirmed or amended policy viable for another 10 years. (2) In the implementation and ongoing operation of our AMA policy sunset mechanism, the following procedures shall be followed: (a) Each year, the Speakers shall provide a list of policies that are subject to review under the policy sunset mechanism; (b) Such policies shall be assigned to the appropriate AMA Councils for review; (c) Each AMA council that has been asked to review policies shall develop and submit a report to the House of Delegates identifying policies that are scheduled to sunset. (d) For each policy under review, the reviewing council can recommend one of the following actions: (i) Retain the policy; (ii) Sunset the policy; (iii) Retain part of the policy; or (iv) Reconcile the policy with more recent and like policy; (e) For each recommendation that it makes to retain a policy in any fashion, the reviewing Council shall provide a succinct, but cogent justification. (f) The Speakers shall determine the best way for the House of Delegates to handle the sunset reports. (3) Nothing in this policy shall prohibit a report to the HOD or resolution to sunset a policy earlier than its 10-year horizon if it is no longer relevant, has been superseded by a more current policy, or has been accomplished. (4) The AMA Councils and the House of Delegates should conform to the following guidelines for sunset: (a) when a policy is no longer relevant or necessary; (b) when a policy or directive has been accomplished; or (c) when the policy or directive is part of an established AMA practice that is transparent to the House and codified elsewhere such as the AMA Bylaws or the AMA House of Delegates Reference Manual: Procedures, Policies and Practices. (5) The most recent policy shall be deemed to supersede contradictory past AMA policies. (6) Sunset policies will be retained in the AMA historical archives.

In this report, the Council on Science and Public Health (CSAPH) presents its recommendations on the disposition of the House policies from 2004 that were assigned to it. The CSAPH's recommendations on policies are presented in the Appendix to this report.

RECOMMENDATION

The Council on Science and Public Health recommends that the House of Delegates policies that are listed in the Appendix to this report be acted upon in the manner indicated and the remainder of this report be filed.

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APPENDIX - Recommended Actions on 2004 House Policies and Directives

Policy Number	Title	Recommended Action and Rationale
D-60.985	Children and SSRI Antidepressants	Sunset. Accomplished.
D-95.990	Dextromethorphan Abuse	Sunset. Accomplished. Program in place.
D-105.997	E-Commerce and Unsolicited E-mails	Sunset. Accomplished.
D-115.993	Standardization of Appearance, Concentration, and Packaging of Common Classes of Pharmaceuticals	Sunset. Accomplished.
D-115.994	The Role of Color Coding in Medication Error Reduction	Sunset. Accomplished. Final Rule adopted.
D-120.978	Health Insurance Company Practice of "Brown Bagging"	Sunset. Accomplished.
D-125.994	Impact of Drug Formularies and Therapeutic Interchange on Health Outcomes	Sunset. Accomplished.
D-150.991	Herbal Products and Drug Interactions	Retain in part, and change to AMA Policy reading: Our AMA ~~will (1)~~ supports the Food and Drug Administration's efforts to create a publicly accessible database of adverse event and drug interaction information on dietary supplements. ~~and (2) renew efforts to accomplish the objectives of Policy H-150.954, particularly with respect to the labeling requirements for dietary supplements.~~
D-150.992	Labeling of Nitrite Content of Processed Foods	Sunset. Accomplished.
D-250.994	United Nations Population Fund	Sunset. Funding was restored in 2009.
D-285.976	Management of Chronic Disease	Sunset. Already covered in AMA Policy.
D-440.975	Support Efforts to Educate Health Care Providers and the Public about Meningococcal Disease and Vaccine	Sunset. Accomplished.
D-440.976	Vaccine Safety	Sunset. Accomplished.
D-440.978	Culturally Responsive Dietary and Nutritional Guidelines	Retain in part to read as follows: Our AMA and its Minority Affairs Section~~Consortium~~ will: (1) encourage the United States Department of Agriculture (USDA) ~~Food Guide Pyramid Reassessment Team~~ to include culturally effective guidelines that include listing an array of ethnic staples and use multicultural symbols to depict serving size in their ~~revised~~ Dietary Guidelines for Americans and MyPlate food guide ~~Pyramid~~; (2) seek ways to assist physicians with applying the ~~final~~ USDA Dietary Guidelines for Americans and MyPlate food guide ~~Pyramid~~ in their practices as appropriate; and (3) monitor existing research and identify opportunities where organized medicine can impact issues related to obesity, nutritional and dietary guidelines, racial and ethnic health disparities as well as assist physicians with delivering culturally effective care.
D-450.988	Performance Measures for Evidence-Based Medicine	Retain. Continues to be important activity.
D-460.979	Physicians and Clinical Trials	Retain in part, and change to AMA Policy reading: Our AMA ~~will (1) work with the Pharmaceutical Research and Manufacturers of America, the American Academy of Pharmaceutical Physicians, and all other appropriate organizations to develop guidelines that would eliminate~~ supports elimination of the use of restrictive covenants or clauses that interfere with scientific communication in agreements between pharmaceutical companies or manufacturers of medical instruments, equipment and devices, and physician researchers. ~~and (2) take all appropriate action to protect the rights of physician researchers to present, publish and disseminate data from clinical trials.~~

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Policy Number	Title	Recommended Action and Rationale
D-460.980	Scientific Integrity	Retain in part, and change to AMA Policy reading: Our AMA advocates ~~will insist~~ the federal government should rely on sound medical science in formulating public health policies.
D-480.988	Intravenous Catheters	Sunset. Not necessary.
D-485.999	Unrealistic Expectations from Surgery on Television	Retain in part, and change to AMA Policy reading: Our AMA ~~will~~opposes television programs that minimize the seriousness and risks of surgery and distort patient expectations.
D-490.982	Development of a National Smoking Cessation Quitline Network	Sunset. Accomplished.
H-10.985	Bicycle Helmets and Safety	Sunset. Accomplished.
H-10.992	Preventing Tap Water Scald Burns	Sunset. Regulations in place.
H-15.953	Guidance for Installation and Use of Car Seats	Sunset. Accomplished.
H-15.986	Automatic (i.e., Passive) Restraints to Prevent Injuries and Deaths from Motor Vehicle Accidents	Retain in part. Sunset (1), (2), and (3) – accomplished. Retain (4) and (5) – still relevant.
H-25.994	Increased Liaison, Communication and Educational Efforts with the Elderly	Retain. Still relevant.
H-60.938	Adolescent Sexual Activity	Retain (1) Still relevant. Delete (2) Accomplished.
H-60.939	Proposed Legislative Changes in Head Start Program Administration and Funding	Sunset. Accomplished.
H-60.940	Partner Co-Adoption	Retain in part to read as follows: Our AMA will support legislative and other efforts to allow the adoption of a child by the ~~same-sex partner, or opposite sex~~ non-married partner, who functions as a second parent or co-parent to that child.
H-60.957	First Aid Training for Child Day Care Workers	Sunset. Accomplished.
H-60.996	Missing Children Identification	Retain. Still relevant.
H-75.985	Access to Emergency Contraception	Retain. Still relevant.
H-75.991	Requirements or Incentives by Government for the Use of Long-Acting Contraceptives	Retain. Still relevant.
H-80.996	Scientific Status of Refreshing Recollection by the Use of Hypnosis	Retain. Still relevant.
H-90.983	Assistance of Handicapped Individuals onto Aircraft of Less than Thirty Seats	Sunset. No longer necessary. Airlines have procedures in place to assist handicapped individuals.
H-100.965	Improved Notice of Drug Shortages	Sunset. Covered by current policy H-100.956
H-100.990	Guidelines for Parenteral Anti-Neoplastics	Sunset. Superseded by CDC/NIOSH Guidelines.
H-100.993	Recommendations on Drug Development and Drug Regulation	Sunset. Superseded by Policy H-100.980.
H-115.975	Controlled Vocabulary for Extended Use Drug Formulations	Sunset. Not necessary.
H-120.968	Medication (Drug) Errors in Hospitals	Retain. Still relevant.
H-120.970	Increase in DEA Licensing Fees	Sunset. Superseded by D-100.970.
H-120.975	Certifying Indigent Patients for Pharmaceutical Manufacturers' Free Drug Programs	PhRMA has developed RxAssist for both patients and physicians. Retain in part to read as follows: Our AMA (1) supports ~~compliments~~ the Pharmaceutical Research and Manufacturers of America (PhRMA) ~~on its~~ programs for indigent patients and ~~continues to urge PhRMA and its member companies to develop~~ the development of a universal application process, eligibility criteria and form for all prescription drug patient-assistance programs to facilitate enrollment of patients and physicians. ~~In all the programs providing pharmaceuticals to indigent patients that are provided by pharmaceutical manufacturers, and, at a minimum, all member companies should participate in the enhanced version of PhRMA's web site, www.helpingpatients.org;~~ (2) encourages ~~the~~ PhRMA to provide information to physicians and hospital medical

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Policy Number	Title	Recommended Action and Rationale
		staffs about ~~the~~ member~~s~~ programs ~~of PhRMA~~ that provide pharmaceuticals to indigent patients; (3) ~~(a)~~ urges drug companies~~, through the PhRMA,~~ to ~~accelerate the~~ develop~~ment of~~ user-friendly and culturally sensitive uniform centralized policies and procedures for certifying indigent patients for free or discounted medications. ~~The process should not require physician participation beyond providing the prescription and individual patients, once certified, should be able to obtain medications from the pharmacy of choice; and (b) encourages pharmaceutical manufacturers to expand their already generous free drug programs for the indigent by declining to receive noneducational promotional materials from drug manufacturers and by urging that the funds otherwise spent on such materials be redirected to support expanded free drug programs for the indigent; (4) encourages physicians to facilitate the expansion of free drug programs for the indigent by declining to receive noneducational promotional materials from drug manufacturers and by urging that the funds otherwise spent on such materials be redirected to support expanded free drug programs for the indigent; (5) will continue to meet with the PhRMA to develop more uniform, universally accepted, rapid mechanisms for physicians to request and obtain useful quantities of medications from American pharmaceutical companies for use by indigent patients; and (6)~~ (4) opposes the practice of charging patients to apply for or gain access to pharmaceutical assistance programs.
H-135.957	Moratorium on Methyl Tertiary Butyl Ether Use as an Oxygenated Fuel in Alaska	Sunset. No longer used in significant quantities.
H-135.997	Promoting Environmental Health	Sunset. Superseded by Policy H-135.973.
H-150.949	Healthy Food Options in Hospitals	Retain. Still relevant.
H-150.971	Food Labeling and Advertising	Sunset. Appropriate regulations and policies are in place.
H-150.986	Labeling of Soft Drink Sweeteners	Sunset. Accomplished.
H-155.988	Public Health and Safety Awareness	Retain. Still applicable.
H-170.972	Role of Physicians in Improving Adolescent Health	Retain in part to read as follows: The AMA supports ~~reaffirms its advocacy for~~ programs that encourage teen health and supports the involvement of medical students, residents, and other physicians in educational efforts to enhance teen health.
H-175.994	Chelation Therapy	Sunset. Not necessary.
H-175.995	Hair Analysis – A Potential for Medical Abuse	Retain. Still relevant.
H-200.964	Encouragement of Physician Participation in Project USA	Sunset. Project no longer active.
H-245.981	Vitamin K Prophylaxis in Newborn Infants	Retain in part to read as follows: The AMA supports ~~recommends that state medical societies urge state health departments to amend their health codes to specify that every neonate should receive~~ the intramuscular administration of a single dose of 0.5-1 mg of ~~natural~~ vitamin K1 ~~oxide (phytonadione), preferably parenterally,~~ in neonates at ~~within one hour of~~ birth to prevent vitamin K deficiency bleeding. ~~Dependent hemorrhagic disease and coagulation disorders; and will become a vigilant advocate in a continuing way on the routine use of vitamin K prophylaxis for the newborn.~~
H-260.968	Standardized Drug Testing	Sunset. Guidelines in place.
H-280.962	Dehydration	Retain. Still relevant.
H-365.999	Physician's Role in Returning Patients to Their Jobs	Retain. Still relevant.

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Policy Number	Title	Recommended Action and Rationale
H-370.974	Working Toward an Increased Number of Minorities Registered as Potential Bone Marrow Donors	Retain. Still relevant.
H-430.996	Correctional Health Accreditation Program	Sunset. National Program exists (National Commission on Correctional Healthcare).
H-440.884	Food Allergic Reactions in Schools and Airplanes	Retain. Still relevant.
H-440.919	Toward the Control of E. Coli Infection	Retain. Still relevant.
H-440.920	Endorsement as Guidelines of the "Standards for Pediatric Immunization Practices"	Sunset. Accomplished.
H-440.922	Gambling Can Become Compulsive Behavior	Retain. Still relevant.
H-440.938	Multiple-Drug Resistant Tuberculosis – A Multifaceted Problem	Retain. Still relevant.
H-440.942	State Health Officer Report at Annual Meeting of State Medical Society Meetings	Retain. Still relevant.
H-445.987	Sexually Exploitative Advertising to Physicians	Sunset. Not necessary.
H-460.913	Use of the Anal Pap Smear as a Screening Tool for Anal Dysplasia	Retain. Still relevant.
H-460.914	Influence of Funding Source on Outcome, Validity, and Reliability of Pharmaceutical Research	Sunset. Accomplished. Clinicaltrials.gov has been created and IRBs require registration.
H-460.938	Effects of Electric and Magnetic Fields	Retain. Still relevant.
H-460.940	Support for Federal Funding of Early-Stage Embryo Research	Retain. Still relevant.
H-460.942	Enrollment in Clinical Trials	Sunset. Already mandated.
H-460.988	Need for Continued Use of Animals in Research and Education	Retain. Still relevant.
H-470.981	Protective Headgear for Horseback Riders	Sunset. Fédération Equestre Internationale Helmet Rules in place.
H-480.975	Patents on Medical and Surgical Procedures	Retain. Still relevant.
H-490.912	Tobacco as an Incentive in Behavior Modification Programs	Retain. Still relevant.
H-490.915	Tobacco Use in Prison Populations	Retain. Still relevant.
H-495.979	Evaluation of the Health Hazards of Clove Cigarettes	Retain. Still relevant.
H-495.980	Cigar Smoking	Retain. Still relevant.
H-495.982	Tax-Free Tobacco Products	Retain. Although "Prevent All Cigarette Trafficking Act" became law in 2009, the problem persists.
H-500.974	AMA Sponsorship of World Conferences on Tobacco and Health	Sunset. AMA has not been involved with the Conference for many years.
H-500.975	AMA Corporate Policies on Tobacco	Retain. Still relevant.
H-505.962	Smoking on International Flights	Retain. Still relevant on some international flights.
H-505.963	Support for Federal Interagency Committee on Smoking and Health	Retain in part to read as follows, with change in title "Federal Efforts Related to Smoking Cessation:" Our AMA endorses the use of the ~~following proposals approved by the Federal Interagency Committee on Smoking and Health on February 11, 2003. (1)~~ federally-funded National Tobacco Quitline network and ~~(2) implement an~~ ongoing~~, extensive paid~~ media campaigns to help Americans quit using tobacco. ~~(3) include evidence-based counseling and medications for tobacco cessation in benefits provided to all Federal beneficiaries and in all federally-funded healthcare programs by FY 2005; (4) invest in a research agenda by FY 2005 to improve the access, effectiveness and utilization of tobacco dependence interventions for individuals and populations; (5) invest in clinician education and training by FY 2005 to provide the necessary knowledge, skills, and support systems to help patients quit tobacco use; and (6) establish the Smokers' Health Fund by FY 2005 through revenue generated~~

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Policy Number	Title	Recommended Action and Rationale
		~~through an increase in the Federal Excise Tax on cigarettes by $2.00 per pack and similar increases on other tobacco products, with at least 50 percent of revenue for the Fund being used to implement these proposals.~~
H-505.965	Federal Tobacco Price Supports	Sunset. No longer necessary.

2. GENOMIC-BASED APPROACHES TO THE RISK ASSESSMENT, MANAGEMENT AND PREVENTION OF TYPE 2 DIABETES

Reference committee hearing: see report of Reference Committee E.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AND REMAINDER OF REPORT FILED
See Policy H-440.838.

This report is currently being considered for publication, so the content is not included in the Proceedings at this time.

Members of the American Medical Association may contact hod@ama-assn.org to request a copy, which may not be further distributed.

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RECOMMENDATION

The Council on Science and Public Health recommends that the following recommendation be adopted and the remainder of this report be filed:

> That our American Medical Association encourage continued research into the potential of genomic information to improve risk assessment, management and prevention of type 2 diabetes, and will report back on important advances as appropriate.

Table 1. Relative risk associated with T2D risk factors.[3,9,15]

Risk factor	**Relative risk**
Age (≥45 years)	5-6x
Obesity (BMI≥30)	4-5x
Overweight (BMI≥25, <30)	2-3x
Hypertension	2-3x
Hyperlipidemia	4x
Family history	
One first degree relative or two second-degree relatives	2-3x
Two first degree relatives, or one first-degree and two second-degree relatives	5-6x
Genetic variant carrier	
Heterozygous	1.1-1.4x
Homozygous	Up to 2.4x

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3. NATIONAL DRUG SHORTAGES--UPDATE

Reference committee hearing: see report of Reference Committee E.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTION 522 AND REMAINDER OF REPORT FILED
See Policy H-100.956.

INTRODUCTION

Policy H-100.956, "National Drug Shortages," directs the Council on Science and Public Health (CSAPH) to continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates (HOD) on progress made in addressing drug shortages. This policy directs CSAPH to evaluate the forthcoming report on drug shortages from the Government Accountability Office (GAO) and report back on its findings. This report, entitled "Drug Shortages-Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability," is now available.

Accordingly, this report evaluates the findings of the GAO report and the current status of drug shortages in the United States, as well as other recent developments intended to prevent new drug shortages and resolve existing ones.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from 2013 to April 15, 2014, using the MeSH terms "pharmaceutical preparations," or "generics/economics," in combination with "supply/distribution," and using the text term "drug shortages." Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), GAO, American Society of Health-System Pharmacists (ASHP), the Generic Pharmaceutical Association (GPhA), and the Pharmaceutical and Research Manufacturers of America (PhRMA).

BACKGROUND

The Council has issued four previous reports on drug shortages.[1-4] These reports have identified sources for information on drug shortages, described trends in drug shortages and pertinent federal regulations, described the general causes and contributing factors for drug shortages, summarized various recommendations intended to help prevent or mitigate shortages, and discussed various stakeholder responses, including those of the pharmaceutical industry, Congress and the FDA. Readers are referred to those reports for further information on these topics.

CURRENT DRUG SHORTAGES

In recent years, the FDA has tracked and focused on shortages of "medically necessary" drugs.[*] However, the FDA recently commented that they now "post all drug shortages that the agency verifies."[5] The information supporting the drug shortage list is largely supplied by manufacturers, who are only required to report shortages or potential disruptions in supply to drugs that are "life supporting, life sustaining, or used to treat debilitating health issues." The FDA drug shortage website also now separately classifies current shortages according to therapeutic category, identifies the reason(s) for shortages based on standard terminology required by the Food and Drug Administration Safety and Innovation Act (FDASIA), and provides an estimated shortage duration.[6] The FDA considers a shortage resolved "when the total supply of the drug and any pharmaceutical equivalents is sufficient to meet demand in the market overall."[5] The FDA also maintains an internal database to "track shortages on a daily basis, document the actions taken to prevent and resolve shortages, and monitor the workload" of personnel.[5]

The drug shortage resource center maintained by ASHP in collaboration with the University of Utah Drug Information Service (UUDIS) tracks a broader array of drug and biological product shortages based largely on reports from hospital pharmacists.[7] In some cases shortages are local or regional. UUDIS "broadly defines a

[*] A medically necessary drug product is one that is "used to treat or prevent a serious disease or medical condition for which there is no other alternative drug, available in adequate supply that is judged by medical staff to be an adequate substitute."

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shortage as a supply issue that affects how pharmacies prepare and dispense a product or that influences patient care when prescribers must choose an alternative therapy because of supply issues." UUDIS also applies more conservative criteria than the FDA in determining when to remove a drug from the shortage list, as well as different criteria for determining if a shortage is "critical," (i.e., alternative medicines are not available, shortages affect multiple institutions). In particular, drugs may remain on the UUDIS list until all dosage forms (based on National Drug Codes[†]) have been restored. At any given time, approximately 60% of the shortages reported in the ASHP resource center may be deemed "critical."[5]

Accordingly, the number of shortages reported by the FDA is lower than the number catalogued by UUDIS/ASHP and exhibits a different dynamic over time, but may be more "clinically meaningful" according to the FDA.[8] As of April 1, 2014, the FDA identified a total of 99 drug shortages, a number that is ~25% lower than the situation in April 2013.[5] The number of new shortages for January 1, 2013 through September 30, 2013 was 38, compared with 117 new shortages during 2012. According to ASHP, and similar to the recent trend identified by the FDA, the number of new shortages in 2013 (140) was 45% lower than the number of new shortages in 2011. However the number of existing shortages remains largely unchanged. ASHP identified 230 drug shortages as of April 1, 2014, comparable to the number of existing shortages catalogued as of April 2013.[6] Therefore, although fewer new shortages are occurring, existing shortages are apparently taking longer to be resolved.

GAO REPORT ON DRUG SHORTAGES

FDASIA provided the FDA with new authorities and responsibilities and established new requirements for manufacturers to notify the agency in an effort to prevent or mitigate drug shortages. These modifications to FDASIA and potential ways that the FDA can otherwise act to address drug shortages are summarized in CSAPH Report 2-I-12.[3] The FDA has substantially increased staff resources available for responding to drug shortages and extended this effort to district offices, while strengthening direct lines of communications among staff in the Center for Drug Evaluation and Research's (CDER) Office of Compliance, field investigators, drug shortage staff and individual manufacturers.[9]

FDASIA also mandated that the GAO examine several different aspects of drug shortages. Accordingly, the GAO released a report in February 2014 which reviewed trends in prescription drug shortages, summarized how such shortages may affect patients and providers, further examined potential causes of drug shortages and evaluated progress made by FDA in addressing this serious public health problem. Trend analyses in this report were based on data obtained from UUDIS on prescription drug shortages between January 2007 and June 2013. Information regarding impacts on patients and providers was based on answers from different stakeholders to a series of open ended questions and therefore reflects varying opinions and viewpoints.

In 2012, the number of new shortages captured by UUDIS dropped for the first time since 2006 to 195, a 24% decrease from 2011.[5] The number of new shortages captured by UUDIS continued to decrease throughout 2013, totaling 140 (personal communication, Bona Benjamin, American Society of Health-System Pharmacists). While confirming that generic sterile injectable products remain the most problematic, the GAO report provides some additional perspective. Nearly 1 in 5 drugs that were in short supply since January 2007 have been so on multiple occasions, with the majority of shortages persisting nearly 1 year. GAO also compiled an overlapping dataset of "continuing plus new shortages" that intersect on an annual basis. According to their analysis, total shortages continued to increase from 2007 peaking at 456 in 2012. The combination of ongoing and new shortages stabilized in 2013 actually decreasing somewhat to 428 based on the final total of new shortages reported. The most common therapeutic classes affected by shortages were anti-infective, anesthetic/central nervous system, and cardiovascular drugs, and those used for parenteral/enteral nutrition.

Continuing Implications of Drug Shortages

As described in previous Council reports and re-emphasized in the GAO report as ongoing concerns, drug shortages create many problems adversely affecting clinical practice, healthcare system finances, and patient outcomes. These include delays in or rationing of care, difficulties finding alternative drugs, a higher risk for medication errors, larger pharmacy staffs and drug acquisition costs, increased reliance on pharmacy compounding to meet clinical demands, and diversion of patient care resources. Some institutions may hoard or stockpile drugs that tend to be in short

[†] The NDC is a unique 10-digit, 3-segment number for human drugs in the United States identifying the manufacturer, the product, and the commercial package size.

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supply, thereby exacerbating disruptions being experienced by other practitioners or institutions. Additionally, ongoing drug shortages have prompted more direct examination of ethical issues associated with the rationing of potentially life-saving products, particularly in oncology practice.[10-12] The role and obligations of pharmacy benefit managers to address drug shortages also has been examined.[13]

Consistent with the findings of the GAO report, drug shortages continue to mandate treatment changes in oncology that may affect efficacy and toxicity and increase costs, and significantly impact parenteral and enteral nutrition practices.[14-19] Medication errors and adverse events continue to occur from drug shortages and cause problems for pharmacy and therapeutics committees in hospitals and other health care delivery organizations.[20,21] Disruption in the supply of medication used to prevent rejection of implanted tissues and organs also can significantly influence post-transplant outcomes.[22]

Causes of Drug Shortages

The GAO report confirmed a number of observations made by others and summarized in previous Council reports.[5,23] The most common causes of supply disruptions leading to drug shortages are quality problems coupled with manufacturing delays and limited production capacity (especially in the generic sterile injectable industry), and product discontinuations. These account for more than 80% of drug shortages. Many production facilities are aging and more prone to failures that may trigger FDA enforcement actions, are subject to more frequent and periodic maintenance requirements, or are targets of corporate decisions to remediate and/or upgrade manufacturing facilities. Thus, an overlap may exist between shortages caused by an initial quality issue and those that ultimately reflect a lack of capacity to produce other products on the same production line or at the same facility.[24] The GAO report noted conflicting arguments and opinions about the relative contribution of manufacture-initiated quality reports, the manufacturer's ability to adhere to current good manufacturing practices, and FDA inspections and compliance actions as root causes of supply disruptions that trigger shortages.[5,23,25,26] As previously noted, shortages sometimes are caused by a manufacturer's decision to discontinue production, the unavailability of raw materials, loss of a manufacturing site due to natural disasters, or even increased demand. Discontinuation of products (which accounted for 9% of shortages in 2011) can be driven by profitability concerns, especially when production lines are running at full capacity and new products become available to generic manufacturers because of patent expirations.[24]

While briefly discussing, the GAO report did not provide any additional clarity about economic drivers of drug shortages, other than to confirm that approximately half of the studies examined by the GAO "suggested that the immediate causes of drug shortages, such as quality problems, are driven by an underlying cause that stems from the economics of the generic sterile injectable market." Factors considered under the economic heading included the behavior of group purchasing organizations (GPO), changes in Medicare Part B reimbursement policy, the interplay of manufacturing and purchasing decisions, and whether the manufacturer's reliability or quality attributes could be considered or "rewarded" in the marketplace.[5] Although some attention has been devoted to Medicare Part B reimbursement as a cause of drug shortages, this view has not gained widespread traction[27] as the "trends in shortages of drugs affected by payment reform are similar to the pattern among drugs that should not have been affected by it."[24] Further analysis is precluded because most of the studies considered by the GAO were not specifically identified.

With respect to price competition and quality, one view postulates that the market for generic sterile injectable products does not reward quality and competition is therefore based solely on price.[24] Hospitals and clinics do not differentiate among approved generic equivalents, so manufacturers have little incentive to differentiate themselves. This lack of recognition could contribute to reactive approaches to quality management and/or reduce the incentive to invest in upgrading production facilities or create redundant manufacturing capabilities. However, the GAO noted that most generic drug manufacturers indicated that they "continue to invest in upgrading existing establishments and building new ones." Controversy also exists on whether the contracting practices of GPOs have played a significant underlying role in fostering a more fragile supply chain and causing drug shortages.[5,23,27-29]

The GAO concluded that the FDA could do a better job of "maximizing the agency's ability to use the information at its disposal to address drug shortages." Ultimately, the GAO expressed the belief that the FDA "may be missing an opportunity to identify causes of shortages, risks for shortages, and patterns in events which may be early indicators of shortages." Whether reliable data on shortages submitted by manufacturers and analyzed over time could be used for predictive purposes or in some other proactive manner to better address drug shortages, and how that would be accomplished, is uncertain.

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PROGRESS IN ADDRESSING DRUG SHORTAGES

Recent FDA Actions

As required by FDASIA, and consistent with AMA policy, the FDA developed a drug shortages task force and issued a new strategic plan for addressing drug shortages on October 31, 2013.[26] The FDA also published a proposed rule for public comment on November 4, 2013 to help implement FDASIA's expanded notification requirements[‡] for manufacturers regarding potential disruptions in manufacturing or supply.[30] The proposed rule, which our AMA strongly supported, also extended the notification provision to manufacturers of biologic products.

The FDA's Strategic Plan has two overarching goals: to strengthen the agency's mitigation response and develop long term strategies for prevention of drug shortages.[26] Central to the mitigation strategy are improving communication and efficiency in responding to a notification about disruption in supply, improving database management and use, and clarifying the roles and responsibilities of manufactures and the FDA to improve remediation efforts and establish best practices to avoid or mitigate shortages. Long term strategies focused on developing a risk-based approach to identify early warning signals to prevent supply disruptions, and possible incentives to sustain and/or reward quality in the marketplace. The latter would involve other stakeholders because creating incentives for manufacturing, using manufacturing quality metrics to impact purchasing decisions, investing by industry to increase manufacturing capacity, and providing safeguards to minimize gray market activities are beyond the purview of the FDA.

Preventing Potential Drug Shortages

The GAO concluded that the FDA has continued to prevent more shortages and improved its ability to respond to shortages that occur. The GAO also provided a different perspective on the literal "meaning" of the FDA's reported success in addressing drug shortages. The FDA has publicly reported that it was able to prevent 195 potential shortages in 2011, 282 potential shortages in 2012, and, in a recent report to Congress, 140 potential shortages through September, 2013.[9] Such shortages are product and dosage form specific. If a shortage for the same product or dosage form is averted twice in one year, it is counted as two potential shortages prevented. By focusing on active pharmaceutical ingredients, the GAO concluded that the FDA had prevented 89 shortages in 2011 and 154 potential shortages in 2012.[5]

General agreement exists that the requirement in FDASIA for manufacturers to notify the FDA of a potential disruption in supply (as soon as practicable) has helped the agency to expedite solutions to prevent and/or mitigate drug shortages. A 6- to 12-fold increase in spontaneous reports from manufacturers of potential disruptions in supply has occurred since 2011.[5] See CSAPH Report 8-A-13 for further discussion on various potential expedited solutions, including exercising regulatory flexibility, that the FDA may employ.[4]

From January 1-September 30, 2013, FDA was notified of 202 potential shortage situations by 39 manufacturers.[9] CDER expedited the review of 188 applications (Abbreviated New Drug Applications and Supplements) to prevent or mitigate drug shortages. It also exercised regulatory flexibility and discretion in 76 other instances, affecting 68 products. While these statistics seem significant, it is not clear how many applications and supplements were approved, or over what time frame.

DRUG SHORTAGES SUMMIT

In addition to the GAO report, the findings and recommendations of a multi-stakeholder summit on drug shortages were recently released.[27] The summit was convened by the American Hospital Association, American Society of Anesthesiologists, American Society for Clinical Oncology, Institute for Safe Medication Practices, and American Society of Health-System Pharmacists and intended to evaluate potential long-term solutions to the drug shortage crisis. The AMA was an invited participant. The summit identified 13 potential solutions (see Appendix), most of which "had merit," according to the group, although "those intended to address economic factors required more study."

[‡] FDASIA requires manufactures of drugs that are "life-supporting, life threatening, and intended for use in the prevention or treatment of a debilitating disease or condition," including those used in emergency care or surgery to notify FDA 6 months in advance (or as soon as practicable) if manufacturing is going to be interrupted or discontinued.

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CONCLUSION

As result of actions taken by the President, Congress, and FDA over the last two and one-half years, manufacturers are notifying the FDA about potential disruptions in supply or shortages earlier than in the past and new shortages are being prevented, and it appears that the agency has improved both its internal communication and communication with manufacturers. Long term shortages, however, persist and continue to impact clinical decision-making and patient care.

The GAO report noted that it "identified multiple potential underlying causes of shortages, all of which were related to the economics of the generic sterile injectable drug market."[5] Although GAO attempted to probe stakeholders' views on the economics of drug shortages, including Medicare Part B reimbursement, no consensus existed. In a footnote to the report in the economic section, the GAO noted that "in subsequent work, we intend to further explore the causes of drug shortages."[5] With only five major companies now producing sterile injectable products, and concurrent remediation efforts in place to upgrade facilities among them, the Generic Pharmaceutical Association's Accelerated Recovery Initiative (see CSAPH Report 8-A-13) also has not made any headway in reducing shortages of generic sterile injectable products.[24] The AMA remains committed to supporting long term solutions to the drug shortage problem. A summary of AMA actions on this issue can be found in Appendix II.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted, and the remainder of the report be filed.

That Policy H-100.956 "National Drug Shortages" be amended by addition and deletion as follows:

1. That our AMA supports the recommendations of the 2010 Drug Shortage Summit convened by the American Society of Health System Pharmacists, American Society of Anesthesiologists, American Society of Clinical Oncology and the Institute for Safe Medication Practices and will work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.

2. Our AMA supports requiring all manufacturers of Food and Drug Administration approved drugs and, including FDA approved drugs with recognized off-label uses, to give the agency advance notice (at least 6 months prior or otherwise as soon as practicable) of anticipated voluntary or involuntary, permanent or temporary, discontinuance of the manufacture or marketing of such a product.

3. Our AMA supports authorizing the Secretary of Health and Human Services 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 supports the creation of a task force to enhance the HHS Secretary's response to preventing and mitigating drug shortages and to create a strategic plan to: (a) enhance interagency coordination; (b) address drug shortage possibilities when initiating regulatory actions (including the removal of unapproved drug products from the market); (c) improve FDA's ability to track and analyze drug shortage data in an effort to develop strategies to better prevent drug shortages (~~c~~d) provide further information on expedited solutions that have worked to prevent or mitigate drug shortages; (e) communicate with stakeholders; and (~~d~~f) consider the impact of drug shortages on research and clinical trials.

5. Our AMA will advocate that the U.S. Food and Drug Administration 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.

6. The Council on Science and Public Health shall continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates on progress made in addressing drug shortages.

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7. 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 Centers for Medicare and Medicaid Services 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. ~~The Council will monitor and evaluate the forthcoming report on drug shortages from the Government Accountability Office and report back on its findings~~.

8. Our AMA urges that procedures be put in place: (1) for the FDA to monitor the availability of Schedule II controlled substances; (2) for the FDA to identify the existence of a shortage that is caused or exacerbated by existing production quotas; and, (3) for expedited DEA review of requests to increase aggregate and individual production quotas for such substances.

9. 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.

10. 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.

11~~0~~. Our AMA will collaborate with medical specialty partners in identifying and supporting legislative remedies to allow for more reasonable and sustainable payment rates for prescription drugs.

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APPENDIX I- Drug Shortages Summit – Recommended Areas for Further Exploration[27]

- Accelerate and streamline Drug Enforcement Administration controlled substance quota approval procedures.
- Consider corporate tax credits and other incentives for manufacturers who maintain robust quality and facility maintenance programs.
- Consider multiple contract awards by group purchasing organizations to ensure alternate suppliers during shortages.
- Encourage collaboration between industry and healthcare stakeholders to develop better methods for demand forecasting.
- Encourage manufacturers to provide single dose medications in smaller volumes to reduce waste.
- Engage payers, including the Centers for Medicare and Medicaid Services, to develop solutions for drug shortages.
- Enhance FDA communication to providers on its mitigation plans and actions, and include more reliable information on when availability will be restored.
- Establish a process for FDA to obtain data that allows the Agency to extend expiry during critical shortages.
- Establish a list of critical drugs similar to the World Health Organization's Model List of Essential Medicines for prioritizing drug shortage resolution efforts.
- Establish traceability of medications to determine patterns of distribution.
- Evaluate the existing Biomedical Advanced Research and Development Authority (BARDA) model for applicability to managing drug shortages.
- Provide FDA with sufficient resources to conduct inspections, process paperwork, and resolve other regulatory issues that contribute to drug shortages.
- Use FDA metrics for manufacturers' quality and reliability to drive purchasing and reimbursement decisions.

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APPENDIX II - Summary of AMA Actions on Drug Shortages

2001: Board of Trustees Report 7-I-01 calls for establishment of an HHS Task Force to explore causes of drug and vaccine shortages and to identify solutions.

2002: The AMA and ASHP convene a special meeting of key FDA officials and representatives of the pharmaceutical industry, drug distributors, GPOs, American Hospital Association, Institute of Medicine, and the Department of Veterans Affairs to examine drug product shortages and potential solutions. A summary is published in November 2002. In the aftermath, ASHP and the University of Utah Drug Information Service develop an electronic drug shortage resource, the precursor to the current ASHP Drug Shortage Resource Center.

2003: The AMA and ASHP met with high ranking FDA and HHS officials to propose an HHS/FDA workshop to include relevant stakeholders in order to prioritize strategies for improving the market dynamics for prescription drugs in order to reduce shortages and improve patient care.

2004: The AMA and ASHP convene a follow-up meeting to discuss next steps. Included in the discussion was draft guidance developed by the Healthcare Distribution Management Association on “Ensuring Product Availability--A Recommended Voluntary Industry Guideline.”

AMA also develops policy and supports view that Congress should require all manufacturers of FDA-approved pharmaceutical products to give the FDA public notice of the anticipated voluntary or involuntary, permanent or temporary, discontinuance of manufacture or marketing of such a product at least six months in advance.

2006: The AMA develops policy and supports the view that the federal government and other key stakeholders should develop and implement strategies that will prevent and better mitigate drug shortages.

2010: Drug Shortage Summit convened by ASHP, ASA, ASCO, and ISMP. The AMA endorses a suite of 19 recommendations to address drug shortages involving regulatory and legislative factors, raw materials and manufacturing, business and market factors, and distribution.

2011-2014
CSAPH Report 2-I-11 developed for the HOD.
CSAPH Report 7-A-12 developed for the HOD.
CSAPH report 2-I-12 developed for the HOD.
CSAPH Report 8-A-13 developed for the HOD.
AMA develops dedicated drug shortage advocacy resource page.

Legislative Activities: Between October 2011 and March 2014, the AMA submitted formal comments on 12 separate occasions on issues related to preventing and mitigating drug shortages including PDUFA reauthorization, the Senate Energy and Commerce Committee, the Senate HELP Committee, and sponsors of specific legislation.

Regulatory Activities: In December 2013 the AMA submitted supportive comments on FDA’s proposed rule that would require manufacturers to notify the agency of a permanent discontinuance or manufacturing interruption of a product that is likely to lead to a meaningful disruption in supply.

In March 2013, the AMA submitted recommendations to the FDA Drug Shortages Task Force on its Strategic Plan, highlighting physician concern and frustration with ongoing shortages, particularly of sterile injectable products. The AMA also indicated its support for the concept of developing a qualified manufacturing partner program; and strongly supported targeted notification of drug shortages to physician medical specialty organizations.

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4. BIOSIMILAR PRODUCT APPROVAL AND MARKETING

Reference committee hearing: see report of Reference Committee E.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS AND REMAINDER OF REPORT FILED
See Policies H-125.980, D-125.987 and D-125.989.

INTRODUCTION

An abbreviated approval pathway established by The Biologics Price Competition and Innovation Act of 2009 (BPCIA) created a two-tiered framework whereby a sponsor may seek Food and Drug Administration (FDA) approval of products under section 351(k) of the Public Health Service Act for so-called "follow-on biologics" (FOB) that are "highly similar" (i.e., biosimilar) to, or further demonstrated to be "interchangeable" with an FDA-licensed biological product whose patent protection has expired.[1,2] The driving force for establishing a science-based abbreviated approval pathway for biosimilars is the recognized benefit, but very high cost, of many biologic products.

The existence of a biosimilar approval pathway raises several questions related to the requirements for approval, drug efficacy and patient safety, potential cost savings, clinical acceptance, substitution practices, naming and pharmacovigilance, and educational gaps for prescribers and policymakers. The Council previously examined several of these issues.[3] Current AMA policy supports the existence of an abbreviated pathway for the approval of biosimilar products which retains appropriate patent protection for innovator companies, but also facilitates the approval of biosimilar products while ensuring patient safety and preserving the authority of physicians to select the specific products their patients receive (Policies H-125.980 and D-125.989).

Policy D-125.988, "Updating AMA Policy on Biosimilars," directs the American Medical Association (AMA) to revisit the topic of biosimilars and study emerging issues that are relevant for such products under the current abbreviated pathway for approval. This report accomplishes that objective and recommends needed changes and updates to relevant AMA policy.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from 2010 to April 1, 2014 using the MeSH terms "biological products/*economics/therapeutic use," "therapeutic equivalency," and "drug approval/*legislation," and the text terms "biosimilar(s)," or "follow-on biologics." Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), the United States Adopted Names (USAN) Council, the World Health Organization (WHO), the Pharmaceutical and Research Manufacturers of America (PhRMA), and the European Medicines Agency (EMA). Additionally, some verbiage in this report is extracted from comments submitted by our AMA in response to an FDA public hearing on the approval pathway for biosimilar and interchangeable biological products held on November 2, 2010, and a recent public workshop held by the Federal Trade Commission (FTC) on the impact of legislative and naming proposals on competition in the, as yet, still emerging U.S. market for biosimilars.[4]

BIOLOGICS IN THE UNITED STATES

Biologics comprise a wide range of products including vaccines, blood and blood components, allergenic extracts and allergen patch tests, recombinant therapeutic proteins, and somatic or human cells/tissue intended for implantation, transplantation, infusion, or transfer into a human recipient.

Depending on the product category, regulation is under the domain of either the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). CBER retains authority over vaccines, allergens, blood and plasma-derived products, human cellular and tissue-based products, antitoxins, venoms, and gene therapy products. Biologic products regulated by CDER include monoclonal antibodies, enzymes, recombinant therapeutic proteins, immunomodulators, and products intended to mobilize, stimulate, decrease or otherwise alter the production of red or white blood cells. Therapeutic biologic products regulated by CDER are the major focus of

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biosimilar development. U.S.-based physicians lack direct experience with biosimilars as no such products have yet emerged from the BPCIA.

Biosimilar Approval Pathway and Product Classification

The BPCIA established an abbreviated approval pathway for biological products that are "highly similar" (i.e., biosimilar) to, or further demonstrated to be "interchangeable" with, an FDA-licensed biological product.[1,2]

Thus, a two-tiered framework was established as follows:

> Biosimilar products are "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and exhibit "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[1] The BPCIA requires that an application for a proposed biosimilar product include information demonstrating that the proposed product is highly similar to the reference product based on analytical, animal, and/or clinical studies, and that the FDA at its discretion can determine what data are necessary to designate such a product as biosimilar.
>
> In order to meet the higher standard of interchangeability, the sponsor must demonstrate that an interchangeable biologic product "produces the same clinical result as the reference product in any given patient" and the "risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product [biosimilar] and the reference product [originator/brand] is not greater than the risk of using the reference product without such alteration or switch." Furthermore, the BPCIA states that "the [interchangeable] biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

EXPERIENCE IN THE EUROPEAN UNION

The European Union (EU) has made substantial progress in developing an FOB market through the EMA.[5] Experience in the EU is limited to biosimilars all having the same International Nonproprietary Name (INN), with products distinguished by unique trade names. In the EU, shared INNs between a biosimilar and the reference biologic product are based on a scientific regulatory assessment that meaningful clinical differences between these products do not exist. Currently, 16 biosimilars are approved for marketing by the EMA (see Appendix).[5] Products include biosimilars for erythropoietin, filgrastim, follitropin, somatropin, and recently, the first biosimilar approved for a monoclonal antibody, infliximab.

With few exceptions, biosimilar products are not interchangeable at the level of the pharmacy in the EU based on regulation. The biosimilar which is dispensed is based on the product which is authorized by the prescriber. Therefore, uptake of biosimilar products at the country level has been uneven based on national payer and/or drug selection policies, although the overall experience has been positive with respect to establishing a viable market for biosimilars. Nevertheless, the practical and clinical implications of the European experience for the U.S. biosimilar market are speculative.

RECENT DEVELOPMENTS

Several developments have occurred since the Council last examined this topic. The FDA issued a guidance for industry on implementing the BPCIA, including scientific and quality considerations for demonstrating biosimilarity to a reference protein product.[6,7] State legislatures have begun amending pharmacy practice acts to regulate substitution practices for biosimilars. Although extremely important, no consensus has emerged on naming conventions for biosimilar products either in the United States or globally. The FTC recently held a workshop to examine how naming conventions and state substitution laws might affect market competition among biosimilars and reference branded products. Additional guidance for industry on biosimilars is expected from the FDA in 2014 on clinical benchmarks for demonstrating biosimilarity and/or interchangeability, and the labeling of biosimilar products.[8]

Accordingly, several issues demand the attention of the physician community. Many require additional analysis and clarification before a long-term state and federal regulatory framework should be adopted. Two of the most relevant issues for physicians and their patients are how naming conventions and state substitution laws may affect product

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uptake, and therefore the development of a competitive, viable, biosimilar market in the United States. Henceforth, for the purpose of clarity, the term "biosimilar" or "interchangeable biosimilar" will be used to reflect the reality of the two-tiered framework in the United States established by the BPCIA for the approval of FOBs. Ultimately, approval of biosimilar products will be a science-based, data-driven process administered by the FDA.

BIOLOGIC PRODUCT ATTRIBUTES—SIMILAR BUT NOT IDENTICAL?

In contrast to small molecule drugs which are typically manufactured via chemical synthesis, biological products are characterized by an increasing array of complexity in structure requiring the use of manufacturing processes typically involving living microorganisms or animal cells. However, serial batches of complex biologics are not "identical," even among originator products. This is a normal feature of the biotechnology processes used to create biologics, subject to analytical control and verification of product attributes within current technical and scientific limitations. Thus, biosimilars cannot be held to an "identical" standard, nor should this verbiage or comparison be used to create mistrust about product integrity. Analytics have improved and evolved to the point where different manufacturers can develop biologic compounds that are highly similar to one another with respect to relevant structural and functional aspects. Nevertheless, because manufacturers of biosimilar products will not have access to the reference product company's proprietary data, cell line, or manufacturing process, some differences in the final product will exist and can be expected.

Comparable Versus Biosimilar─Product Evolution

Manufacturing changes commonly are implemented over the lifecycle of biologic products based on advances in DNA technology, vectors, cell lines, and other processes used in creating biologic products.[9] When manufacturers of existing biologic products change a production element, they must convince the FDA that their new manufacturing process creates a product that is highly similar to the previous version through a "comparability" exercise. That exercise includes analytical comparisons, bioassays, and preclinical animal studies. Sometimes additional clinical data are required, determined by the FDA on a case-by-case basis. Such manufacturing changes constitute a life cycle of product evolution with final product attributes constrained by the analytical and clinical goalposts of "similarity."

Three issues are relevant given these manufacturing realities.

- Different, but highly similar "versions," of an originator biologic may be on the market simultaneously.
- Biosimilar products will be compared with the reference biologic using similar criteria as the comparability exercise. When analytics point to a highly similar substance, clinical trial data will primarily be needed to address residual uncertainties in safety and efficacy.
- If a biosimilar is approved as interchangeable with a reference biologic product, both will likely be subject to manufacturing changes over their life cycle. This creates a potential scenario whereby comparative product attributes may diverge over time, again constrained by the use and applicability of the comparability exercise.

NAMING CONVENTIONS

The BPCIA is silent on the naming of biosimilars. The "intent of Congress was to provide FDA the flexibility to establish a science-based policy for non-proprietary naming of drug substance, and not to encourage FDA to adopt a policy of either identical or differentiated naming."[10]

Background

Our AMA has a unique perspective on this issue because it administers the United States Adopted Names (USAN) Council in collaboration with the American Pharmacists Association and United States Pharmacopeia (USP), with FDA representation.[11] The USAN Council facilitates the identification of pharmaceutical substances in development, and assigns unique nonproprietary names to active pharmaceutical ingredients that are eventually marketed. When a new drug application is acted on by the FDA, the agency assigns an "interim established name," which is used in the product labeling (package insert) approved by the FDA, until an official nonproprietary name is adopted by USP and incorporated into its monographs. The FDA typically adopts the USAN for the interim established name, but has recently used a prefix modifier to create a different name for three distinct biological substances. USP also typically adopts the USAN for their drug substance monograph title, but a different official

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title (nonproprietary name) can be designated by USP for the drug substance or drug product. The FDA retains the statutory authority to establish a different non-proprietary name than that designated by USP, but can do so only through notice and comment rulemaking and has never exercised this authority.

A similar naming process is used by the International Nonproprietary Names (INN) Programme administered by the WHO. The USAN Council and INN Programme engage in a reciprocal process to ensure international harmonization of nonproprietary names (including biologics) among member countries, although certain countries (e.g., Australia, Japan) may take a different approach. Of note, the WHO is currently contemplating a post-hoc unique identifier process for biologics. It is critically important that the FDA issue guidance on the naming of biosimilar products in the United States. Adoption of different naming conventions for biosimilar products could contribute to confusion, bearing in mind that adverse events also are reported to U.S.-based companies from foreign physicians and health care providers.

The USAN or INN identifies the active substance and was designed to be shared among products rather than identify a specific product. Different USANs or INNs denote products with different active ingredients, and the prevailing view until recently has been that they should not be used to differentiate products with the same active ingredient when evidence is available to conclude that no relevant pharmacologic or clinical differences exist.

In the United States, the USAN is important in pharmacovigilance efforts, prescription writing and substitution practices (see below), and for what it infers to the prescriber about the active ingredient in prescription drug products. From this point forward the term INN will be used to refer to nonproprietary names to the extent that it is synonymous with the USAN.

Pharmacovigilance

Pharmacovigilance is extremely important for assuring patient safety and in maintaining brand and product integrity. Two distinct elements comprise pharmacovigilance: (1) an effort to detect a safety signal through adverse event reporting; and (2) attribution of the adverse event to a specific drug substance or active ingredient or, in certain cases, a specific batch or lot number.

The INN is one piece of information that is part of a comprehensive identification system for products including the manufacturer name, batch and lot number, trade name, a National Drug Code (NDC) number in the United States, and within billing systems, the NDC or a unique J-code. Each NDC is a unique 10-digit, 3-segment number which identifies the labeler/manufacturer, specific product, and trade package size. The same INN allows the aggregation of post-marketing surveillance data across branded and related generic products, and facilitates the detection of safety signals associated with a specific active ingredient for simple compounds.

Manufacturers of biologics are concerned, however, about misattribution of adverse events that could harm their brand (or lead to product recalls) when such aggregation occurs based on adverse event reports involving the same INN, and if the specific causative product(s) cannot easily be identified or isolated. This concern is based, to a degree, on the fact that many biologic products are long acting, adverse events related to immunogenicity (including loss of efficacy) may be latent, and manufacturing changes commonly occur over the life cycle of biologic products. As noted above, once a biologic product is approved as interchangeable with a reference product, products that undergo manufacturing changes may theoretically begin to diverge with respect to product characteristics, subject to the “goalposts of similarity” established by the required comparability exercise. Given the natural variability exhibited by biological products, the ability to “disaggregate” adverse event data based on manufacturer has been emphasized as critical to safety surveillance.[9]

The other significant issue is the continuing heavy reliance in the United States on spontaneous adverse event reporting for post-marketing surveillance, and whether that process (as currently constructed) can adequately capture the necessary information for product attribution in the absence of a unique naming identifier for each biosimilar product. Some case studies were offered at the FTC workshop demonstrating high capabilities for specific patient/product identification within a defined pharmaceutical benefit management system (Express Scripts), ePrescribing platform (SureScripts), or when brand names were used in reporting. Other studies showed that reliance on the nonproprietary name as the primary identifier was, in fact, unreliable, and the NDC, despite its highly informative construct, is virtually never included in adverse event reports (and is U.S.-centric in nature).[4,9] The

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surveillance issue is complicated by that fact that biologics are administered in various settings outside of traditional retail pharmacy, mostly in clinics and hospitals, as well as via mail order/self-administration.

STATE SUBSTITUTION LAWS

How State Substitution Laws May Affect the Development of Biosimilar Competition

Although much attention has been devoted to the fact that "biosimilars are not generics," one fundamental similarity exists. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch Waxman Act) has been successful in establishing a regulatory platform leading to a largely seamless, science-based system for generic substitution based on state substitution laws that preserve physician autonomy in product selection, but otherwise allow automatic substitution of drug products that the FDA has deemed to be therapeutically equivalent. This determination of interchangeability of products containing the "same" active ingredient is a regulatory decision based on adequate and credible analytical and clinical data. In a similar fashion, the BPCIA created the framework for a science-based process to establish interchangeability of biosimilar products using a high threshold which, once met, directs that an interchangeable product can be substituted without the intervention of a health care provider (i.e., automatic substitution).

Features of State Biosimilar Substitution Laws

In 2013, 28 biosimilar-related bills were introduced in 18 states. As of April 2014, six states[*] had enacted biosimilar legislation, ten states had rejected/vetoed bills, and nine states had either carried over or introduced new bills. Biosimilar legislation has created new requirements for pharmacists and physicians regarding the potential interchange of biosimilar products including:

- requiring pharmacists to notify patients and/or prescribers when an interchangeable biosimilar is dispensed/substituted. The time period for notification varies (within 24 hours to 10 days); some bills currently contain sunset provisions for prescriber notification requirements (typically 2 years);
- imposing additional record keeping requirements on pharmacists and prescribers for a specified amount of time (up to 5 years in one case); and
- requiring state Boards of Pharmacy to maintain a list of interchangeable biosimilar products.

Draft legislation in a few states has included a provision allowing substitution only if biosimilar products have the same INN which would essentially prevent substitution for products with different names even if they were classified as interchangeable by the FDA. This provision may appear to be innocuous because most states already require the same INN for small molecule drugs to enable substitution.

Notification requirements have generally been opposed by a broad coalition of pharmacy groups, the Generic Pharmaceutical Association, pharmaceutical benefit managers, health insurers, and the American Association of Retired Persons, and supported by the companies who already market biologic products, PhRMA, the Biotechnology Industry Organization, as well as some patient advocacy groups. Those opposed to the proliferation of state bills on biosimilars believe this activity is premature because the FDA is still in the process of implementing the pathway for biosimilar approvals and interchangeability standards, no such products are in the U.S. marketplace today, and therefore it is likely that state substitution practices and requirements will vary widely and ultimately create market confusion and uncertainty. Those who support the notification requirement believe it is necessary to ensure adequate pharmacovigilance. Further analysis is needed to determine the impact of notification requirements on prescriber liability and prescribing behavior.

Physician Attitudes Regarding Substitution

<u>Generic Drugs/Generic Substitution</u>. Prescriber knowledge and attitudes about biosimilars will be critical determinants of market dynamics for these products. It is instructive to note, that even after 30 years of generic substitution of bioequivalent, interchangeable A-rated generic products, a segment of physicians do not believe such products are therapeutically equivalent and may prescribe and maintain their patients only on proprietary products, particularly for certain drugs with a narrow therapeutic index. In one recent study, nearly one-quarter of physicians

[*] Florida, North Dakota, Oregon, Utah, Virginia, Indiana

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surveyed expressed negative perceptions about the efficacy of generic drugs, almost 50% reported negative perceptions about the quality of generic medications, and more than one quarter would not use generics as first line medications for themselves or for their family. Physicians older than 55 years of age were more likely to report negative perceptions.[13]

To stem the rising costs of medications, states have implemented varying generic substitution policies. These policies differ in the extent to which pharmacists or patients can influence medication choice. In states where additional requirements are in place for generic substitution (e.g., requiring patient consent prior to generic substitution), substitution rates are reduced up to 25%.[12] Therefore, it seems reasonable to assume that additional recordkeeping or notification requirements may serve as barriers to the uptake of interchangeable biosimilars.

Biosimilars. Limited survey data of U.S. physicians indicate a low level of understanding about: (1) distinctions between generic equivalents of simple organic compounds and biosimilar products; (2) the difference between biosimilars and reference biologics; and (3) the current regulatory approval pathway for biosimilars.[14] Familiarity is more common among practitioners who regularly use biologic products in their practice. The vast majority of U.S. physicians refer to biological medicines by proprietary names in medical records and adverse event reporting.[15]

As expected, physicians want to retain the authority to designate which biologic product is dispensed when choices are available. The AMA strongly supports the view that physician autonomy be preserved in directing which biologic product is dispensed, and that state pharmacy practice acts limit substitution to those biosimilar products determined to be interchangeable by the FDA. The Council believes that physician attitudes about biosimilar products, especially those that may be interchangeable, are poorly characterized at this point. However, based on experiences with simple generic products, a substantial educational effort will be needed to avoid unintended barriers when biosimilar products become available in the United States.

Naming Convention. Some concerns have been raised about how different INNs, or INNs with unique modifiers, for interchangeable biosimilars might affect physician attitudes, and therefore, their potential willingness to prescribe or authorize substitution. These potential concerns can be briefly summarized as follows. Unique or nonidentical INNs may:

- suggest to the prescriber that the active ingredient in products is different;
- create the (false) impression that interchangeable biosimilars have important, clinically relevant, distinguishable effects; and,
- reduce uptake and substitution of interchangeable biosimilar products.

Available survey data to inform how U.S.-based physicians would interpret or view identical or non-identical nonproprietary names of biosimilars, whether interchangeable or not, is sparse, incomplete, and (like all surveys) significantly influenced by the level of understanding, instructions, and the questions themselves. In the absence of more robust information, reliable predictions or recommendations cannot be made on how naming conventions may influence prescriber behavior regarding biosimilar products.

A unique naming convention for biosimilars also has implications for pharmacy practice, drug information systems, and drug standards. As described by the American Society of Health-System Pharmacists, “the current U.S. standard nomenclature for naming clinical drug concepts, the National Library of Medicine’s RxNorm, uses common root names among other things to normalize group products that conceptually are equivalent. This terminology is critical to supporting semantic interoperability among drug terminologies and pharmacy knowledge systems, thereby allowing computer systems to communicate drug-related information efficiently and unambiguously.”[16]

USP’s authority to develop official nonproprietary names for drugs and biologics stems from the adulteration and misbranding provisions of the Food, Drug and Cosmetic Act, which provide that any drug with a name recognized in the USP National Formulary must comply with compendial standards for strength, quality and purity or be deemed adulterated, misbranded, or both. The identity test in the monograph links the applicable USP monograph and its official title to the drug substance or drug product. Thus, any drug substance or drug product that meets the identity test in a monograph must use the compendial name and meet monograph standards for strength, quality and purity. In other words, if USP develops a monograph for a biologic product, any biosimilar product that meets the identity test in this monograph should have the same nonproprietary name according to USP.

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CONCLUSION

Our AMA remains mindful of the unique safety challenges posed by the manufacture of complex biologicals and the corresponding challenges for biosimilars, but is committed to the overall goal of developing policies that recognize physician autonomy, promote patient access, and protect patient safety in a manner that preserves market competition and innovation. This is especially important given the anticipated growth in health care costs associated with biologics and the emergence of biosimilar products in the United States as a market-forming event characterized by substantial uncertainty. Several uncertainties remain with regard to establishing a viable biosimilar market in the United States, including lack of a uniform nomenclature/naming convention, variable state requirements regarding substitution practices that have the potential to serve as barriers to biosimilar uptake, and educational gaps for prescribers. Additional issues exist that are likely to influence competition in the emerging biosimilar market such as the extent to which extrapolation of clinical data is allowed, potential patent/legal challenges, and the potential need for distinctive product labeling for biosimilars, to name a few.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report filed.

1. That Policy H-125.980, "Abbreviated Pathway for Biosimilar Approval," be amended by addition and deletion to read as follows:

   ~~AMA policy is that pharmaceutical companies should be allowed to make biosimilar medications available to physicians and their patients in a reasonable period of time with a reasonably predictable pathway to bring them to market.~~ Our AMA supports ~~will advocate for appropriate~~ FDA ~~Guidance and~~ implementation of the Biologics Price ~~and~~ Competition and Innovation Act of 2009 in a manner that~~: 1) includes a straightforward regulatory process for an abbreviated approval pathway for biosimilars; 2~~1) places appropriate emphasis on ~~the~~ promoting patient access, protecti~~o~~ng ~~of~~ patient safety, and preserving market competition and innovation ~~in both the original branded products and all biosimilar products that are brought to market~~; ~~and 3~~2) includes planning by the FDA and the allocation of sufficient resources to ensure that physicians understand the distinctions between biosimilar products that are considered highly similar, and those that are deemed interchangeable. Focused educational activities must precede and accompany the entry of biosimilars into the U.S. market, both for physicians and patients; 3) includes compiling and maintaining an official compendium of biosimilar products, biologic reference products, and their related interchangeable biosimilars as they are developed and approved for marketing by the FDA.

2. That Policy D-125.989, "Substitution of Biosimilar Medicines and Related Medical Products," be amended by addition and deletion to read as follows:

   Our AMA urges that State Pharmacy Practice Acts and substitution practices for biosimilars in the outpatient arena: (1) ~~mirror the current practices for A-rated generic drugs by~~ preserve~~ing~~ physician autonomy ~~the right of physicians and other prescribers~~ to designate which biologic or biosimilar product is dispensed to their patients; (2) allow substitution when physicians expressly authorize substitution of an interchangeable product; (3) limit the authority of pharmacists to automatically substitute only those biosimilar products that are deemed interchangeable by the FDA.

3. That 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.

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4. That Policy D-125.988, "Updating AMA Policy on Biosimilars," be rescinded.

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APPENDIX - Biosimilars Approved in Europe

Name	Active Substance	Therapeutic Area	Authorization Date
Abseamed	Epoetin alfa	Kidney Failure, Chronic Anemia, Cancer	8/28/07
Binocrit	Epoetin alfa	Kidney Failure, Chronic Anemia	8/28/07
Biograstim	Filgrastim	Hematopoietic Stem Cell Transplantation Neutropenia Cancer	9/15/08
Epoetin alfa Hexal	Epoetin alfa	Kidney Failure, Chronic Anemia Cancer	8/28/07
Filgrastim Hexal	Filgrastim	Neutropenia Cancer Hematopoietic Stem Cell Transplantation	2/6/09
Grastofil	Filgrastim	Neutropenia	10/18/13
Inflectra	Infliximab	Ankylosing spondylitis	9/10/13
Nivestim	Filgrastim	Hematopoietic Stem Cell Transplantation Cancer Neutropenia	6/8/10
Omnitrope	Somatropin	Turner Syndrome Dwarfism, Pituitary Prader-Willi Syndrome	4/12/06
Ovaleap	Follitropin alfa	Anovulation (IVF)	9/27/13
Ratiograstim	Filgrastim	Neutropenia Cancer Hematopoietic Stem Cell Transplantation	9/15/08
Remsima	Infliximab	Akylosing spondylitis, Crohn's disease, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis	9/10/13
Retacrit	Epoetin zeta	Cancer Anemia Kidney Failure, Chronic Blood Transfusion, Autologous	12/18/2007
Silapo	Epoetin zeta	Anemia Blood Transfusion, Autologous Cancer Kidney Failure, Chronic	12/18/2007
Tevagrastim	Filgrastim	Neutropenia Cancer Hematopoietic Stem Cell Transplantation	9/15/2008
Zarzio	Filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	2/6/2009

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5. GUIDELINES FOR MOBILE MEDICAL APPLICATIONS AND DEVICES

Reference committee hearing: see report of Reference Committee E.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTION 514 AND REMAINDER OF REPORT FILED
See Policy D-480.972.

INTRODUCTION

Policy D-480.975, "Guidelines for Mobile Medical Applications and Devices," directs our American Medical Association (AMA) to prepare a report on the appropriate indications, guidelines and certification processes necessary to ensure the efficacy and safety of mobile medical applications and devices developed for smartphones and other personal electronic devices that may be used by physicians, allied health professionals, caregivers and patients.

The rapid rate of technological change in the past decade has led to the proliferation of new terminology and vocabulary that can both clarify or lead to confusion as phrases are coined with limited consensus over meaning and scope. This is true of the current evolving vernacular in the arena of technology and health care. The following terms capture current distinctions and working definitions for mobile applications and devices that are integral to the framework of this report:

Mobile applications (mobile apps). A software application that can be run on a mobile product such as a mobile phone, smartphone, or tablet (with or without wireless connectivity) or a web-based software application run on a server, but meant to be used through a mobile product (such as a smartphone).

Health apps (also referred to as mobile health or mHealth apps). A mobile app that delivers health-related services using a mobile phone, smartphone or tablet. This covers a wide spectrum of functions to support health and fitness, as well as disease management.

Medical apps. A mobile app that meets the definition of a device in the Federal Food, Drug, and Cosmetic Act is considered by the Food and Drug Administration (FDA) to be a medical device, subject to risk-based oversight and regulation (see below). A mobile medical app could be considered a regulated subset of mHealth apps.

Current Guidance and Activity

The FDA released guidance for industry on mobile medical apps in September 2013.[1] Essential elements of this guidance are discussed below. While the FDA will provide oversight on a limited subset of mHealth apps that are also medical apps, most mHealth apps are not medical apps. As a result, there remains an ongoing deliberation among federal agencies and major stakeholders in evaluating and/or establishing the appropriate processes, principles, and entities to assist physicians and patients in understanding the value and reliability of mHealth apps that are not medical apps.

The regulation of mobile health itself is a subset of the much broader array of health information technology (HIT). In addition to the guidance on mobile medical apps, the FDA was required to develop a broader report on HIT. This draft report, developed in consultation with the Office of the National Coordinator for Health Information Technology and the Federal Communications Commission, proposes a strategy and recommendations to develop an appropriate, risk-based regulatory framework for health information technology, including mobile medical applications. The strategy is intended to "promote innovation, protect patient safety, and avoid regulatory duplications." The draft report (named the FDASIA Health IT Report) was released in April 2014.[2] Some of its recommendations and conclusions are relevant to mobile medical apps and also are briefly highlighted below.

Thousands of mHealth apps have been developed for personal use on smartphones and other personal electronic products. Many of these apps provide direct medical advice or instructions, and a smaller proportion can be used to convert smartphones, tablets, etc., into medical devices. A limited number of these mHealth apps have been formally evaluated for their ability to accomplish their intended purpose. Therefore, many questions remain about how

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clinicians should respond to patient inquiries about the use of mHealth apps, and whether to recommend or prescribe mHealth apps.

Relevant AMA policy related to mobile medical apps encourages physicians to become familiar with and capitalize on opportunities to use technology to ensure patient safety in prescribing medications and medical devices (Policy H-450.949). Additionally, the regulation of medical devices should be accomplished in a manner that does not interfere with the patient-physician relationship nor impose regulatory burdens that discourage creativity and innovation in advancing medical device technology (Policy H-480.996). Manufacturers are ultimately responsible for conducting the necessary testing, research and clinical investigation to establish the safety and efficacy of medical devices requiring FDA approval (Policy H-480.972).

Accordingly, this report examines key trends and findings relevant to the developing field of mHealth apps, and how these realities impact the feasibility of our AMA taking a leadership or convening role in this arena.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from 2007 to April 1, 2014 using the search terms “medical,” “mobile,” or “health” in combination with the text term “app*,” as well as “mobile health,” or “mHealth.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the FDA, FCC, and IMS Health.

OVERVIEW OF MOBILE HEALTH APPS

mHealth apps are a solution that leverages the ubiquity of mobile devices to promote access to health care, improve patient self-management, enable electronic interactions between patients and their physicians, and potentially reduce healthcare costs. mHealth apps are one of the fastest growing market spaces with mHealth app revenue expected to grow from $4.5 billion in 2013 to $27 billion in 2017.[3]

Most mHealth apps are designed to assist individuals in their own health and wellness management. Others are targeted to healthcare providers as tools to improve and facilitate the delivery of patient care. Some mHealth apps are designed for doctors themselves to access drug and treatment decision information. With respect to more direct patient care involvement, mHealth apps (a subset of which are devices) are currently involved in a broad array of clinical functions including, for example: 1) applications that use advanced algorithms, logic and/or artificial intelligence to simulate and/or replicate the decision-making process and guidance of expert clinicians; 2) self-monitoring devices created by attaching hardware peripherals to smartphones; 3) remote collection of clinical data; and 4) electronic delivery of clinical advice and motivational messaging to patients.

RELEVANT TRENDS AND ATTITUDES

Smart Phones and mHealth apps. As of May 2013, more than 90% of U.S. adults owned a cell phone of some kind and 56% owned a smartphone, a 21% increase since 2011.[4] Higher income adults and those under age 35 years comprise the largest proportional ownership categories. Fifty-two per cent of smart phone owners have looked up health information on their smart phone, and 19% have at least one app on their smart phone specifically to track and manage a health-related parameter.[5] mHealth apps are the third fastest growing app category for both iOS (Apple) and Android (Google) phones and tablets. As of June 2013, more than 43,000 unique iOS mHealth apps existed based on a search for apps with “health and fitness” or “medical” attributes.[6] With duplication, an estimated 97,000 mHealth applications are available for download across major app stores.[7]

Early Adopters. Among those who already use or plan to use mHealth apps to track their health and fitness, 70% use the app daily. Sixty percent have not shared their progress, achievements or discoveries with their physician, some because they had not thought about it and others because they believed they would “not be taken seriously.”[8] On the other hand, one-third of these early adopters indicated they “would be more likely to use mHealth apps to track their health and fitness if their physicians actually recommended it.”

Physicians. More than 30% of physicians own a tablet, and more than half of them employ them at the point of care.[9] The Department of Veterans Affairs (VA) is implementing the Mobile Health Provider Program intended to leverage the power of mobile technology and transform the way their clinicians and patients interact.[10] A recent poll

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conducted by QuantiaMD to better understand physician perspectives on prescribing mHealth apps found that 37% of physicians have recommended such an app to their patients.[11] A similar percentage is largely unaware of what mHealth apps are available or in the marketplace. Forty-two percent of physicians will not prescribe them because of lack of regulatory oversight or evidence of safety and effectiveness; 21% said they would never recommend them.[11]

Approximately 40% of physicians believe that mobile health technologies have the capacity to reduce the number of office visits, and 88% of physicians would like their patients to monitor health at home. Physicians are not alone, with some 78% of consumers expressing an interest in mobile health solutions.[5] Among consumers with cell phones, some demographics—Latinos, African Americans, women and those between the ages of 18-49 years—are more likely to seek health information online, as are caregivers, those who recently faced a medical crisis, and those who experienced a recent significant change in their physical health.[5]

Pharmaceutical Companies. Pharmaceutical companies are using smartphone technology to facilitate physician recruitment of patients for trials, enable patients to participate in clinical trials regardless of their proximity to a treatment site, and for disease management programs by combining a personalized action plan with digital coaching and wireless monitoring to measure the impact of behavioral interventions.[12] In a related fashion, significant attention has been devoted to facilitating treatment and promoting medication adherence. Hundreds of mHealth apps are intended to improve medication adherence, but an understanding of their actual effectiveness is incomplete.[13]

MEDICAL DEVICE APPROVAL

Current FDA regulations and guidance on medical devices are relevant to the development and appropriate regulation of mHealth apps that, based on their intended use, meet the definition of a device. Although many mHealth apps exist, and many may be medical devices, the FDA will oversee only a small subset of the mHealth apps that are medical devices (mobile medical apps). The FDA's regulation of software as a medical device is based on risk and functionality and not the platform.

Definition of Device. Medical devices are defined as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including any component part, or accessory," that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man," or "intended to affect the structure or any function of the body of man or animals."

The FDA's Center for Devices and Radiological Health is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. Medical devices are classified as Class I, II, and III. Regulatory control increases from Class I to Class III. Most Class I devices are exempt from Premarket Notification 510(k), most Class II devices require Premarket Notification 510(k), and most Class III devices require Premarket Approval.[14]

Device classification depends on the intended use and indication for the device, as well as the level of control necessary to ensure safety and effectiveness. Classification determines the specific regulatory requirements. Basic requirements that manufacturers of medical devices distributed in the United States must comply with are general controls including facility registration, device listing, quality control systems (subject to FDA inspection), as well as labeling and reporting requirements.[14] Incidents in which a device may have caused or contributed to a death or serious injury must be reported to the FDA under the Medical Device Reporting program. In addition, certain malfunctions also must be reported.

The FDA has classified and described more than 1,700 distinct types of devices and organized them into medical specialty "panels" such as cardiovascular devices or ear, nose, and throat devices. For more information on device regulation and requirements one can consult the dedicated FDA webpage on this topic.[14] A description of medical device classification and a link to the Product Classification Database is available at "Classification of Medical Devices."

FDA GUIDANCE ON MOBILE MEDICAL APPLICATIONS

The FDA released final guidance on mobile medical applications on September 24, 2013.[1] This final guidance was preceded by a draft guidance issued August 2013, on Radio Frequency Wireless Technology in Medical Devices.

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The use of wireless technology includes additional regulatory review processes−in particular, the Federal Communications Commission which has a mandatory certification process.

Definition.

According to the FDA guidance, a mobile medical app is a mobile app that meets the definition of device (above) and is intended to either: 1) be used as an accessory to a regulated medical device; or 2) transform a mobile platform into a regulated medical device. The intended use of a mobile app determines whether it meets the definition of a "device."[1]

FDA's authority to regulate a particular mobile medical app stems from which medical device classification (i.e., I, II, or III) the mobile app falls into, which depends upon the potential risk to the user.[9] As noted above, most mobile apps are not medical devices. However, as is the case with traditional medical devices, certain mobile medical apps could pose potential risks to public health, or the risks could be derived from the platform on which the app is run (e.g., attempting to interpret radiologic images on a mobile device screen for the purpose of diagnosis). Therefore, the FDA intends to apply its regulatory authority to only those mobile apps performing medical device functions and whose functionality could pose a risk to patient safety if the app were not to function as intended. The FDA intends to exercise "enforcement discretion," for many other mobile medical apps, meaning that even though they technically meet the definition of a medical device, they possess such a low risk profile that regulation is not necessary to protect patient safety.

As noted in the guidance, selected examples[*] of mobile apps that FDA does not consider to meet the definition of medical device include:

- apps that provide access to medical textbooks, references
- apps that offer training materials for physicians
- apps intended for general patient education.

Some examples of mobile apps for which the FDA intends to exercise enforcement discretion include:

- apps that provide periodic reminders or motivational guidance
- apps that allow patients to track and manually enter symptoms
- apps that use a checklist of common signs and symptoms to provide a list of possible medical conditions with advice on when to consult a healthcare provider.

Some examples of mobile apps and accessories that are the focus of FDA's regulatory oversight include mobile apps that:

- use a sensor or lead connected to a mobile platform to measure and display heart rhythm
- create a stethoscope
- generate controlled tones for audiologic testing
- use an attachment to the mobile platform to measure blood oxygen saturation, alter the function or setting of an infusion pump, or allow remote perinatal monitoring.

According to one analysis of the FDA's medical device database, FDA has approved more than 100 mobile medical apps through 2013.[15] A representative list of mobile medical applications cleared by the FDA since 1997 is available.[16]

FDASIA Health IT Report.

The draft FDASIA Health IT Report proposed three categories of health IT (administrative, health management, medical device) and the creation of a public-private entity termed the Health IT Safety Center. The Center would, among other things, establish a governance structure for the creation of a sustained integrated health IT learning system.[2] This report also directed the FDA to provide greater clarity on several aspects of medical device regulation involving health information technology including: 1) the distinction between wellness and disease-related claims;

[*] A more complete list of examples in each category is available in the FDA guidance.[9]

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2) medical device accessories; 3) medical device clinical decision support software; 4) medical device software modules; and 5) mobile medical apps. Among these aspects, mobile medical apps may directly intersect with clinical decision support software. Also relevant to Policy D-480.975, key priority areas for the Health IT Safety Center include the development of quality management principles and standards and best practices, including promoting interoperability and electronic information sharing between health IT products and across organizational boundaries.

Development of Mobile Medical Apps.

The relevance of the FDA guidance for business development of mobile medical apps can be illustrated by two high profile examples.[17] In February, Biosense Technologies Private Ltd. (based in India) unveiled uChek, a mobile application and companion kit that allows individuals to use their phone cameras to read subtle color differences on urine test strips. Biosense maintained that uChek could potentially inform an individual's risk for more than 25 medical conditions, including diabetes and hepatitis. This mobile app clearly meets the definition of a medical device, and within one month of marketing the device in the United States, the company was notified by the FDA that it needed to seek clearance to market its product. On the other hand, recognizing the need to pursue FDA approval before marketing its device, Scanadu (a mobile technology company based in California) raised more than $1.5 million through the crowdfunding site Indiegogo to support the device application process for its Scout monitor device. The Scout monitor connects wirelessly to a smartphone and is capable of measuring blood pressure, temperature, heart activity, and other vital signs.[17]

AN UNREGULATED MARKET

A major challenge faced by the mobile health market is the quality of mHealth apps and whether their use helps patients or physicians achieve the intended purpose.

The most comprehensive analysis of mHealth apps currently available was conducted by the IMS Institute for Healthcare Informatics.[6] IMS conducted an extensive review of the more than 23,000 iTunes Store mHealth apps. Approximately 70% of these apps were intended for consumers and the remainder for health care professionals. IMS was able to evaluate the health apps based on their ability to inform, provide instruction, and provide reminders or alerts, capture user-entered data, graphically display data, offer clinical guidance, or enable communication with healthcare providers or other patients via social networks. Most efforts in app development have been in the overall wellness category, do little more than provide information, and do not target populations accounting for the greatest contribution to healthcare expenditures, namely older patients with multiple chronic diseases. Fewer than half the apps which provide information also provide instruction, and less than one-third of apps that provide information also track or capture user data. IMS scored the apps based on a proprietary system using twenty-five functional criteria with a maximum possible score of 100. More than 90% of the apps scored at or below 40.

An analysis of 1,500 mHealth apps for purchase by the New England Center for Investigative Reporting found that "both the iTunes and Google Play stores are riddled with health apps that experts say do not work and in some cases could even endanger consumers."[18] One in five made claims to treat or cure medical problems using light, sound, or vibrations emitted from the cell phone for conditions such as acne, seasonal affective disorder, insomnia, and chronic pain. Even high-profile vendors like Epocrates have recently come under scrutiny. Their popular Bugs & Drugs App, specifically designed to assist physicians in identifying the best antimicrobial choice for specific pathogens, has been criticized for significant content errors.[19]

Apps capable of running medical calculations to gauge the severity of a disease or condition, risk stratify, or estimate the likelihood of having a certain condition appear to be more reliable.[20] Also as might be expected, apps for complex medical disorders often fail to measure up. An evaluation of HIV/STD-related apps identified nearly 2000 apps in Apple iTunes and Android Google Play stores. Only 6 of these apps covered all major prevention areas by providing disease information and information on testing or resources, condom use, and safe sex practices.[21]

A systematic review of hundreds of apps focusing on cancer and available for general use by the public from iPhone, Android, Nokia, and Blackberry platforms found evidence was lacking to support their effectiveness in promoting behavior change, monitoring symptoms and physiological indicators of disease, or providing real time supportive interventions, conveniently and at low cost.[22]

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Another systematic review identified more than 100 apps for asthma self-management, nearly half of which provided specific tools.[23] No apps combined reliable, comprehensive information about asthma with supportive tools for self-management. Nearly half the time, apps made unequivocal recommendations about strategies for asthma control or prophylaxis that were unsupported by current evidence-based guidelines.

The ability to record, analyze, share and obtain feedback on self-monitored blood glucose levels would seem to be a potentially valuable aid in the management of diabetes. Analysis of apps available from the Apple App store identified more than 400 diabetes related apps. Most of these did not conform to evidence-based recommendations or addressed only a narrow subset of generally recommended target behaviors.[24]

Based on these types of reviews, a large percentage of available mHealth apps are lacking in overall quality, and only limited advice is available to help guide selection of those that may be more reliable in providing useful guidance and assistance in medical decision-making.

Efficacy in Clinical Practice

Asthma. A systematic review of clinical trials that evaluated the effect of a mobile-phone-based asthma self-management intervention compared with traditional paper-based asthma self-management found insufficient evidence to recommend use of the mobile medical app platform to improve asthma control.[25]

Diabetes. One of the more advanced mobile medical apps for condition management and remote monitoring approved by the FDA is the WellDoc Diabetes Management system, a software-based patient-coaching and provider clinical decision support system.[26] This multimodal tool enables patients to wirelessly upload blood glucose readings and other diabetes-related information, and receive real-time feedback via a health care provider, caregiver or WellDoc research team. In a 1-year cluster-randomized clinical trial, the intervention group's A1c decreased by 1.9% compared with 0.7% in the usual care group. The initial randomized clinical trial of this app demonstrated improvements in outcomes for A1c values, diet, medication adherence, and exercise compared with usual care.[27]

Use of another diabetes app, the DiabetesManager® sponsored by AT&T and Health Care Service Corporation, demonstrated a decrease in hospital admissions and emergency room utilization in Medicaid participants when comparing their data 90 days before the pilot trial to 90 days after enrollment. Participants demonstrated high adoption, sustained engagement and high levels of satisfaction.[28]

Weight Loss. Several randomized controlled trials have been conducted of mHealth apps designed to promote weight loss. Apps were designed to provide information about meal replacement options, deliver reminders or motivational messages at various intervals, and combine self-monitoring of diet, weight, and activity with feedback to and/or from practitioners. Significant improvements were observed in 8 out of 10 studies.[29]

These cited examples represent only a limited sampling of published evidence. However, evidence is emerging that the use of well-designed mHealth apps can make a significant difference in clinical care.

CERTIFICATION AND STANDARDS

A need exists for some process to aid the marketplace in sorting through the vast majority of mobile applications that will not be subject to FDA approval. Some kind of private certification or at least a reputable and trusted evaluation platform for mHealth apps could spur app developers to produce better, more secure products and provide guidance for consumers.[†] What, if any, role might be played by a public/private Health IT Safety Center, as described in the FDASIA Health IT report, is uncertain.

There have been limited efforts to address the problems described above. Happtique, a commercial health app storefront established a certification program that recently certified 16 apps after a technical and content review following published guidelines. However, the program was suspended after questions were raised about flaws in the technical review of 3 of the 16 certified apps. The IMS analysis noted above offered its top ratings of mHealth apps for healthy lifestyles, finding a healthcare professional or facility, self-diagnosing certain conditions, filling prescriptions, and promoting medication adherence.[6] Additionally, IMS identified top mHealth apps for diabetes,

[†] While the FCC currently has a certification process for wireless products, a private certification for mHealth apps would include an evaluation of a broader scope of factors relevant to physicians, patients and those interested in health promotion.

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mental health and behavioral disorders, chronic musculoskeletal pain, oncology, and central nervous system disorders such as epilepsy.

Aetna launched CarePass, a wellness app that pulls data from 20-plus free consumer wellness apps, downloads those that are wanted and tracks health improvement progress.[30] CarePass allows individuals who download multiple apps to display data from those apps in a single normalized dashboard, rather than having to view the data in silos.

iMedicalApps is an independent online medical publication written by a team of physicians and medical students who provide commentary and reviews of mobile medical technology and applications.[31] Reviews and commentary are based on the physicians' and students' own experiences in hospital and clinic settings. Content control is managed by the medical professionals running the site. According to the iMedicalApps website, their publication receives more than 400,000 views monthly.

Among other efforts to bring clarity to the field, the Johns Hopkins School of Public Health has developed a program to grade mobile health evidence based on literature reviews, and Continua Health Alliance is developing a certification program for the interoperability of medical devices. Finally, the Scripps Translational Science Institute has established a digital health program to conduct clinical studies of select mHealth apps.

SUMMARY AND CONCLUSION

Health care reform—with new delivery and payment models—is likely to place increasing emphasis on wellness and self-care as physicians apply themselves to delivering high quality care in the most cost-effective manner, and as incentives for consumers to take accountability for their own health proliferate. According to Ernst and Young, "mobile technology that enables remote monitoring of patients and provides patients with rapid access to clinicians…is expected to play a key role." In a recent Healthcare IT Trends report from AT&T, a shift from stand-alone "unsponsored" apps to meaningful "sponsored" mHealth app solutions supported by insurance companies, healthcare providers, employers, or other institutions will result in higher patient adoption and engagement. In order to improve health outcomes and provide value, systematic evaluation and information on mHealth app functionality, limitations, data integrity, security and privacy is needed from a neutral trusted source. Furthermore, additional important considerations include the:

- extent to which apps support clinical decision-making in a user friendly fashion
- interoperability of mHealth and mobile medical apps with other patient care and technology platforms existing in offices, clinics, and hospitals
- need for peer-review systems, supporting statements of evidence, or certification standards to maintain the quality and credibility of health-focused apps. As with any other clinical intervention, as evidence of clinical usefulness is developed, findings should be published in peer-reviewed journals and be reproducible.

Given the complexity and sheer volume of mHealth apps, and in light of the rapidly evolving policy and market considerations, our AMA should continue to engage with relevant stakeholders to identify guiding principles for promoting a vibrant, useful and trustworthy mHealth app market, and to identify appropriate opportunities for AMA involvement.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed.

1. That our American Medical Association (AMA) monitor market developments in mobile health, including the development and uptake of mHealth apps, in order to identify developing consensus that provides opportunities for AMA involvement.

2. That our AMA continue to engage with stakeholders to identify relevant guiding principles to promote a vibrant, useful and trustworthy mHealth market.

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3. That our AMA make an effort to educate physicians on mHealth apps that can be used to facilitate patient communication, advice, and clinical decision support, as well as resources that can assist physicians in becoming familiar with mHealth apps that are clinically useful and evidence-based.

4. That Policy D-480.975, "Guidelines for Mobile Medical Applications and Devices," be rescinded.

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