American Heart Association Principles on the Accessibility and Affordability of Drugs and Biologics

A Presidential Advisory From the American Heart Association

ABSTRACT: Net US spending on pharmaceuticals reached $309.5 billion in 2015, an 8.5% increase from the year before, and is expected to reach between $370 and $400 billion by 2020. These current and projected levels have raised serious concerns by policy makers, providers, payers, and patient groups that they are unsustainable and threaten the affordability of and accessibility to much-needed therapies for patients. Two trends related to drugs/biologics and generic drugs/biosimilars underlie this overall increase in spending. First, the market entry prices of innovator pharmaceutical products, or brand drugs and biologics, are at levels that some assessments consider unaffordable to the healthcare system. Second, prices for some established generic drugs such as digoxin and captopril have seen sharp and rapid increases. As an evidence-based patient advocacy organization dedicated to improving the cardiovascular health of all Americans, the American Heart Association has a unique role in advocating for treatments, including medicines that are available, affordable, and accessible to patients. This advisory serves to lay out a set of principles that will guide association engagement in pursuit of this goal.

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Net US spending on pharmaceuticals reached $309.5 billion in 2015, an 8.5% increase from the year before, and is expected to reach between $370 and $400 billion by 2020.[1] These current and projected levels have raised serious concerns by policy makers, providers, payers, and patient groups that they are unsustainable and threaten the affordability of and accessibility to much-needed therapies for patients. As an evidence-based patient advocacy organization dedicated to improving the cardiovascular health of all Americans, the American Heart Association (AHA) has a unique role in advocating for treatments, including medicines that are available, affordable, and accessible to patients. This advisory serves to lay out a set of principles that will guide association engagement in pursuit of this goal.

BACKGROUND

First, it is important to lay out a set of definitions. According to the US Food and Drug Administration (FDA), a drug product is an active ingredient intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, combined with ≥1 other ingredients in a dose form (eg, tablet, capsule, or solution). A brand drug, or innovator product, is one that is marketed under a proprietary, trademark-protected name.[2] Generic drugs are products that

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are the same as a brand name drug in dose, safety, strength, delivery, quality, performance, and intended use and have been demonstrated to have substitutability, or "therapeutic equivalence," of brand drugs. Because the molecular structures of drugs are known, a generic drug can be produced and tested to contain the identical amounts of the same active ingredients as the brand name product. Drug products evaluated as therapeutically equivalent can be expected to have equal effect and no difference when substituted for the brand name product.[3] Generic drugs can be marketed only after the brand loses patent exclusivity.

Biological agents can be composed of sugars, proteins, nucleic acids, or complex combinations of these substances, or they may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources, human, animal, or microorganism, and may be produced by biotechnology methods and other cutting-edge technologies. Biological products tend to be heat sensitive and susceptible to microbial contamination, thereby requiring sterile processes to be applied from initial manufacturing steps. Biosimilars are therapies with an active ingredient considered by the FDA to be highly similar to a reference biologic, such that there are no clinically meaningful differences in terms of safety, purity, and potency. Like generic drugs, they can be marketed only after the reference biologic loses patent exclusivity.[3]

Two trends related to drugs/biologics and generic drugs/biosimilars are converging to create a situation that requires serious consideration by all healthcare stakeholders. First, the market entry prices of innovator pharmaceutical products, or brand drugs and biologics, are at levels that some assessments consider unaffordable to the healthcare system.[4] The approval of 2 proprotein convertase subtilisin/kexin type 9 inhibitors for hypercholesterolemia, alirocumab and evolocumab, and another drug for heart failure, sacubitril/valsartan, has focused attention on the price of specialty therapies for cardiovascular disease, although innovator drugs for other disease states such as cancer have similar price tags.[5] Second, prices for some established generic drugs such as digoxin and captopril have seen sharp, rapid increases. For example, between 2013 and 2014, the prices for digoxin and captopril increased 894% and 129%, respectively.[6] Although both trends affect the cost of medicines, the factors responsible for each are separate and require independent examination.

Brand/Biologic Market

The increase in prices for innovator or brand drugs and biologics is seen by many as symptomatic of underlying problems in the marketplace, in which systemic and policy obstructions impede its ability to function appropriately and contain costs. The pharmaceutical industry cites a development and approval process that is expensive, time-consuming, and susceptible to delays as contributing to the high prices that are necessary to offset these costs.[7] The Tufts Center for the Study of Drug Development estimates that the cost of bringing a new drug to market is $2.6 billion,[8] although the methodology that generated this figure has been questioned.[9,10] Others estimate that it falls between $800 million and $1 billion.[8,11] Manufacturers also point out that the high failure rate during clinical trials for efficacy and safety, estimated at ≈85%, requires them to amortize the costs related to the failed therapies across the prices of new, successful products.[2] In addition, the patent system incents manufacturers to recoup their costs in the short time period before a generic equivalent is developed and contains loopholes that allow manufacturers to extend patent life and maintain high prices,[12] limiting any price control that otherwise might occur on its own.

Additional limitations on the ability of the market to function appropriately come from a lack of clarity about the costs factored into determining the price of a product. Although all retail industries mark up the initial price to cover the costs of the inputs of the product, the lifesaving or health-maintaining nature of drugs and biologics, contend many, calls for an increased level of transparency of all factors that contribute to prices. Without an appreciation for the full range of contributions, one cannot evaluate whether the price set for the product along with an appropriate markup aligns with its inputs and whether the markup added to the price of the product is appropriate.

Once products enter the market, information about negotiated prices and rebates is considered proprietary, constraining the ability for fully informed price negotiations. Analysts point to contracting methods such as best price, which guarantees Medicaid the lowest price offered to any purchaser, as disincentives to offering lower prices to some payers because the manufacturer will be required to offer the same to this very large, public purchaser.[13] Manufacturers point to perverse incentives for middlemen such as pharmacy benefit managers to accept high list prices because their revenue is determined as a share of any rebate they negotiate. They also point out that pharmacy benefit managers do not necessarily pass along savings to patients.[14]

Still others feel that the US position as the only country in the 34-member Organization of Economic Cooperation and Development without some degree of government oversight or regulation of prescription drug pricing is to blame. In turn, manufacturers attempt to recoup the discounts given to other countries by elevating prices in the United States. As a result, the United States spends more than any of the other 12 high-income Organization of Economic Cooperation and Development countries (Australia, Canada, Denmark, France, Germany, Japan, the Netherlands, New

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Zealand, Norway, Sweden, Switzerland, and the United Kingdom) on pharmaceuticals.[15]

Generic/Biosimilar Market

According to the Government Accountability Office, the significant and rapid pace of price increases in the generic market is a result of a lack of competition in that market.[16] The Physician Drug User Fee Act and subsequent reauthorizations have reduced the median approval time for standard and priority review drugs,[17] but backlogs still exist for generic medications.[18] These delays dissuade new entrants to the market and make market entry unattractive or cause manufacturers to consolidate their sales of specific drugs, dampening market competition that may bring prices down. As a result, single manufacturers such as 2 recent high-profile examples, Valeant and Mylan, go unchecked in setting extremely high prices for their products.[16]

Although the first generic drug was approved >100 years ago, the first biosimilar was approved by the FDA in 2015 after an approval pathway was authorized as part of the Affordable Care Act. Since then, 3 other biosimilars have been approved, although none of them treat cardiovascular conditions. Given that biologics representing an estimated $100 billion worth of annual sales are set to lose patent exclusivity in the United States by 2020, it is anticipated that biosimilars will and can offer significant cost savings potential for the system, just as generics did for branded drugs.[19] A Supreme Court decision, *Sandoz v Amgen*,[20] may speed up the time for savings to be realized by holding that biosimilar manufacturers do not need to wait until a biologic receives FDA approval to give the biologic manufacturer the required 180-day notice before the launch of the biosimilar. Analysts point out, however, that without changes to the system by which substitution occurs at pharmacies and increased transparency of rebate agreements between pharmaceutical companies and pharmacy benefit managers, these savings may not be realized.[21]

Compounding the impact of these market factors on drug pricing are population trends that further increase societal drug costs. These include an aging population that requires an increasing number of medications to treat chronic conditions. In addition, although precision medicine could ultimately reduce the overall cost to the system by enabling the targeting of treatments to patients most likely to benefit, investment in and testing of precision medicine diagnostics and treatments will bring additional costs in the short term.

Although there is a lack of consensus as to the importance or magnitude of the contribution of any factor to this pricing trend, there is agreement that no one healthcare stakeholder, nor the system as a whole, can afford it. Recognizing this fact, dialogue has begun about assessing value as a way to match payment and resource allocation decisions to a product's alignment with patient, societal, and system priorities. Different groups have created methodologies to ascertain and quantify this value, and each method attempts to inform the system in a slightly different way. For example, assessments such as the one developed by the Institute for Clinical and Economic Review[22] are used to calculate pricing thresholds above which the value does not justify the price. Others such as the American Society of Clinical Oncology's Value Framework are tools for patients to use in assessing the relative value of treatments, including pharmaceuticals and other therapeutic interventions, taking into consideration clinical benefit, adverse effects, and cost, so that comparisons may be made across different types of treatments (eg, drug versus intervention).[23]

Consumer groups are also involved. The National Health Council's Value Rubric is a tool to evaluate the patient-centeredness of value models and to guide value model developers on the meaningful incorporation of patient engagement throughout their processes.[24] The AHA and American College of Cardiology have contemplated the role of value in their jointly developed clinical practice guidelines, proposing a value classification system with supporting levels of evidence similar to those used for class of clinical recommendation.[25] The AHA has also been involved in an effort led by Faster Cures and Avalere Health to develop a Patient-Perspective Value Framework. It is anticipated that the framework will first be used to develop a shared decision-making tool so that patients and providers may determine the relative value of different treatment regimens on the basis of the individual's specific preferences and values. Later, the groups plan to adapt it to assist public programs in coverage decisions and to aid in condition-specific public analyses.[26]

POTENTIAL SOLUTIONS

Many solutions have been proposed to address rising pharmaceutical costs in both the brand and generic markets. One group of proposals aligns measured value with the prices of the drugs. Indication-based or indication-specific pricing, for example, sets different prices for the various applications of a single product or for distinct patient populations, acknowledging that the use of the drug to treat different ailments may bring more or less benefit to different populations.[27,28] Value-based arrangements, also referred to as outcomes-based contracts, operate similarly, making a pharmaceutical manufacturer's reimbursement contingent on the demonstrated outcomes of a product in a specific, covered population.[29]

Other proposed solutions address the fact that key drivers of cost come from expenses incurred in phase II and III clinical trials by incorporating new evidence along the development and approval continuum. These solutions bring flexibility to these processes such that information can be gathered and incorporated over time. Adaptive clinical trial design or "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects"[30] would decrease the overall cost of the drug approval process by increasing the efficiency and the probability of success of clinical development.[31] Similarly, the use of adaptive licensing of "iterative phases of data gathering" rather than a strictly delineated preapproval and postapproval point for a product would decrease the upfront investment in research and development required of manufacturers to get through the approval process and provide more timely access of products for patients.[32]

New payment arrangements that promote value-based treatment decisions make up another category of proposed solutions. Including drugs in bundled payments that combine the payments for all services or products related to an episode of care incentivizes the efficient use of resources and is suggested as a way to encourage the consideration of a contributed value of a drug to the overall care regimen rather than assigning a price for the product in isolation.

Other proposals, although less explicitly focused on value, also are being considered to address the problems associated with the market for drugs. These include lifting the prohibition on Medicare's ability to negotiate prices and changing the FDA review process to confront backlogs and to address perverse incentives that protections such as exclusivity periods create. The FDA has clarified that review periods will be expedited for generic applications for which there is only 1 manufacturer.[33] Other solutions call for making public the information used to set prices such as the research and development costs and rebates provided to payers.[34] Some proposals would also require advance notification by manufacturers of price increases above a certain threshold. Still others call for caps on out-of-pocket costs for consumers, seeking to focus on immediate affordability concerns with the hope that these caps will eventually force manufacturers to lower the prices of their products.[35]

AHA CONSIDERATIONS

High prices when passed on to patients reduce medication adherence and lead to negative health outcomes.[36] According to a 2015 Kaiser Family Foundation Health Tracking Poll, 24% of respondents who were currently taking a prescription medication reported that they or a family member had not filled a prescription because of cost, and 19% reported that they or a family member had cut pills in half or skipped doses of their medication.[37] In addition, a 2012 literature review found that increased cost sharing by patients decreased medication adherence in 85% of the studies reviewed and adversely affected health outcomes in 76% of the studies.[38] The lack of medication affordability, therefore, threatens to have detrimental effects on patients' health and to limit the association's achievement of its population impact goal. In addition, it risks exacerbating disparities of care by placing many drugs beyond the financial reach of low-income and average-wage families and perpetuating a system of "haves" and "have nots." In this way, access to new therapies, as well as established generics, is based on economic condition. The AHA consistently has advocated for equity and affordability,[39] and it is imperative that the association continue this work as the voice of patients and work toward ensuring equitable access for all.

AHA PRINCIPLES

It is in the best interest of patients that therapeutic innovation continues and high-value products are made available. It is, therefore, critical that solutions are found to address the unsustainable spending that is occurring for drugs and biologics and to develop a process by which resources may be allocated to support medical innovation while ensuring appropriate access to and availability of treatments to patients who have or are at risk of cardiovascular disease and stroke. In light of these considerations, the AHA has developed a set of principles to guide its advocacy and to help frame the ongoing debate in support of patients in addressing rising drug costs and the associated adverse health impacts that consequently occur.

1. Therapeutic advances in cardiovascular and stroke treatment have greatly improved the lives of patients. Patients should have full access to the therapy most appropriate for their disease when used in accordance with current clinical and scientific evidence.
2. Affordable access to these medications is necessary to effectively prevent and treat cardiovascular disease and stroke. Innovative therapies are ineffective if patients cannot afford to buy them.
3. Society has a long-term interest in the discovery and development of new medicines. Policies to address the high cost of new treatments should reward, not stifle, discovery.
4. The regulatory climate must be responsive to drug development. Although consistent attention must be paid to maintaining the safety of approved therapeutics, inspection of and revisions to the regulatory processes may be necessary. These

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could include adjustments to testing requirements such as adaptive clinical trial design or creative approaches in approvals such as adaptive licensing.
5. Value should be defined as the benefit accrued along the entire continuum of care rather than solely the cost and benefit associated with a discrete episode of care or hospital stay. The patient perspective must be incorporated into the determination of overall benefit.
6. Drugs and biologics must be understood as 1 component of a larger healthcare system and one in which an individual's treatment may include pharmaceutical and nonpharmaceutical elements. Savings or costs attributed to 1 component must be considered as part of this larger ecosystem. Therefore, calls for solutions that address only 1 component are less than ideal; a multipronged approach is preferred.
7. Transparency of the process by which prices are set and the contributing costs along the supply chain for medicines is necessary so that all payers may be informed purchasers.
8. Costs of treatment must be readily available for practitioners and patients so that they can make informed treatment decisions. Tools that translate information on pricing and value to make it actionable for decision making must be developed so that providers and patients can work together in selecting care regimens that best align with patient and family preferences and goals.

CONCLUSIONS

Attention to these issues of accessibility and affordability of drugs and biologics is steadily increasing at both the federal and state levels, and legislative and regulatory opportunities for engaging are emerging. As stated, this advisory serves to lay out a set of principles that will guide the association as it advocates on behalf of patients in pursuit of its public health goals. The association recognizes the potential for unintended consequences as the marketplace responds to any changes and will diligently monitor the potential for this in any policy solution it supports or pursues.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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*Modest.

†Significant.

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