

## REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1–2, were presented by Robyn F. Chatman, MD, MPH, Chair:

### **1. IMPROVING SCREENING AND TREATMENT GUIDELINES FOR DOMESTIC VIOLENCE AGAINST LESBIAN, GAY, BISEXUAL, TRANSGENDER, QUEER/QUESTIONING AND OTHER INDIVIDUALS**

*Reference committee hearing: see report of Reference Committee K.*

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS  
REMAINDER OF REPORT FILED**  
*See Policy D-515.980*

#### INTRODUCTION

Policy D-515.980, “Improving Screening and Treatment Guidelines for Domestic Violence Against Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, and Other Individuals,” asks:

That our American Medical Association study recent domestic violence data and the unique issues faced by the LGBTQ population.

#### METHODS

English language reports were selected from searches of the PubMed and Google Scholar databases from January 2008 to June 2018 using the search terms “gay,” “lesbian,” “bisexual,” “transgender,” “queer,” “LGBT,” and “LGBTQ” in conjunction with the terms “intimate partner violence,” “domestic violence,” and “partner abuse.” Additional articles were identified by manual review of the reference lists of pertinent publications. Websites managed by non-profit and advocacy organizations were also reviewed for relevant information.

#### CURRENT AMA POLICY

AMA Policy H-160.991, “Health Care Needs of Lesbian, Gay, Bisexual, Transgender and Queer Populations,” recognizes that the physician’s nonjudgmental recognition of patients’ sexual orientation, sexual behaviors, and gender identities enhances their ability to render optimal patient care.” Furthermore, this policy states that our AMA will collaborate with partner organizations to educate physicians on how individuals who identify as a sexual and/or gender minority (lesbian, gay, bisexual, transgender, queer/questioning individuals) experience intimate partner violence (IPV), and how sexual and gender minorities present with IPV differ from their cisgender, heterosexual peers and the fact they may have unique complicating factors. The AMA will also promote crisis resources for LGBTQ patients that cater to the specific needs of LGBTQ survivors of domestic violence (D-515.980, “Improving Screening and Treatment Guidelines for Domestic Violence Against Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, and Other Individuals”). AMA Policy H-515.965, “Family and Intimate Partner Violence,” broadly addresses the physician’s role in IPV and is not specific to patients of a certain gender or sexual orientation. The AMA encourages physicians to routinely inquire about the IPV histories of their patients and upon identifying patients experiencing abuse or threats from intimates, assess and discuss safety issues, and refer patients to appropriate medical or health care professionals and/or community-based trauma-specific resources as soon as possible.

#### BACKGROUND

IPV describes physical violence, sexual violence, stalking and psychological aggression (including coercive acts) by a current or former intimate partner.<sup>1</sup> Examples of intimate partners include current or former spouses, boyfriends or girlfriends, dating partners, or sexual partners. While IPV can occur between heterosexual or same-sex couples and does not require sexual intimacy, much of the effort to address this public health problem has focused on heterosexual women even though other populations experience IPV at similar rates.

## EPIDEMIOLOGY OF IPV IN THE LGBTQ POPULATION

Little is known about the national prevalence of IPV in the LGBTQ population in the United States.<sup>2</sup> While a number of small-scale studies have examined violence in the LGBTQ population, the research is difficult to interpret and generalize due to the variability of methodologies utilized, which include different measures of IPV and different time frames to which the violence corresponds (i.e., past year, lifetime).<sup>2-5</sup> In addition, researchers have had difficulty recruiting samples that are representative of the LGBTQ population, so the majority of studies have been conducted with small convenience samples.<sup>2-4</sup> A further complication with the research involves the failure to distinguish between sexual activity (behavior) and sexual identity.<sup>3</sup> These factors have resulted in inconsistent findings in terms of victimization rates among these groups.<sup>4,5</sup> For example, a systematic review on IPV in self-identified lesbians found that victimization prevalence in studies ranged between 10 to 51 percent.<sup>3</sup>

In 2010, the Centers for Disease Control and Prevention's (CDC) National Intimate Partner and Sexual Violence Survey (NISVS), provided the first national-level data on the prevalence of intimate partner violence, sexual violence, and stalking among the lesbian, gay, and bisexual (LGB) population by self-reported sexual orientation (transgender individuals were not included in this study).<sup>2</sup> The pattern of results suggests that individuals who self-identify as LGB experience an equal or greater likelihood of experiencing sexual violence, stalking, and intimate partner violence compared with self-identified heterosexuals. The survey found that 61 percent of bisexual women and 44 percent of lesbian women reported experiencing rape, physical violence, and/or stalking within the context of an intimate partner relationship at least once during their lifetime versus 35 percent of heterosexual women.<sup>2</sup> For men, the lifetime prevalence of intimate partner violence was 37 percent for bisexual men, 29 percent for heterosexual men, and 26 percent for gay men.<sup>2</sup>

Limited data is available regarding IPV in transgender and genderqueer people as researchers tend to offer only binary gender identify categories. However, the available evidence suggests these populations are even more vulnerable to LGBTQ-specific IPV tactics.<sup>4</sup> Findings of lifetime IPV among people who are transgender range from 31 percent to 50 percent.<sup>6</sup> One study directly compared the lifetime prevalence of IPV among transgender and cisgender people and found that 31 percent of transgender people and 20 percent of cisgender people had ever experienced IPV or dating violence.<sup>7</sup>

## DISCUSSION

### *Risk Factors*

A number of factors can put LGBTQ individuals at increased risk for IPV victimization and perpetration and many of these risk factors are similar to those among heterosexual individuals.

Risk factors for IPV victimization include:

racial minority status, lower socioeconomic status, younger age, deaf or hard of hearing, substance use/abuse/dependence, low self-esteem, risky sexual behavior, victim blaming attitudes, lack of power in relationships, attachment anxiety, HIV positive status, child abuse, witnessing IPV as a child, victimization in peer networks, psychological and physical health problems, history of sex work, and history of incarceration.<sup>5</sup>

Risk factors for IPV perpetration include:

interpersonal problems, greater conformity to masculine norms, less secure attachments, greater psychological distress, more substance use/abuse/dependency, high need for control, low socioeconomic status, less education, racial minority status, low self-esteem, more stress, HIV positive status, unprotected sexual intercourse, child abuse, exposure to IPV as a child, disordered personality characteristics, and poor relationship quality.<sup>5</sup>

### *Identity Abuse Tactics*

While some research on the abusive partners' use of physical and psychological abuse may be generalizable across communities, unique aspects to LGBTQ relationships are believed to exist. This includes identity abuse (IA), which are abuse tactics that leverage systematic oppression to harm an individual.<sup>8</sup> IA tactics of IPV leverage heterosexism and cissexism against LGBTQ survivors.<sup>8</sup> These tactics including threatening to disclose a partner's LGBTQ status without their consent. This can result in fear of loss of children, employment, housing, or relationships with family

and friends.<sup>4</sup> Another IA tactic includes undermining, attacking, or denying a partner's identity as an LGBTQ person.<sup>8</sup> Examples include accusing a partner of being straight, questioning their authenticity, or being prevented from expressing their gender identity. Other IA tactics include using slurs or derogatory language regarding the partner's sexual orientation or gender identity and isolating survivors from the LGBTQ community.<sup>8,9</sup> These tactics are also used in threatening partners who seek help.

In examining the prevalence of IA in the LGBTQ community, nearly 17 percent of the sample (n=734) of sexual minority adults reported experiencing at least one form of IA in the last year and 40 percent reported experiencing IA at some point in adulthood.<sup>8</sup> In terms of gender, women (43 percent) experienced significantly more exposure to IA in adulthood than men (24 percent). Transgender or gender non-confirming participants (50 percent) reported higher rates of IA in adulthood than their cisgender counterparts.<sup>8</sup> In terms of sexual orientation, queer-identified participants (49 percent) and bisexual participants (48 percent) had the highest rates of IA in adulthood (nearly 50 percent) compared with their lesbian (35 percent) and gay (26 percent) counterparts.<sup>8</sup>

### *Health Outcomes*

IPV is associated with poor physical and mental health outcomes. For example, in a study (n=817) of men who have sex with men there was a significant relationship between a range of health problems and IPV.<sup>10</sup> Abused men were more likely than non-abused men to report problems such as hypertension, heart disease, obesity, smoking-related illness and, to some extent, sexually transmitted infections.<sup>10</sup> Men in abusive relationships were more likely to report depression or other mental health problems, and to engage in unhealthy behaviors such as substance abuse, combining drugs with sex, or unprotected sex.<sup>10</sup> Another study of LGBT young adults (n=172) found that being a victim of IPV was associated with concurrent sexual risk taking and prospective mental health outcomes, but was not associated with substance abuse.<sup>11</sup>

## BARRIERS TO SEEKING HELP

### *Screening*

The medical community has been criticized for neglecting members of the LGBTQ population in their efforts to respond to the problem of IPV.<sup>12</sup> However, research is lacking on the best practices for identifying LGBTQ survivors of IPV.<sup>13</sup> It is unclear if existing tools are relevant to LGBTQ survivors, though limited research suggests that they are and that changes in wording and additional questions could improve their relevancy.<sup>13</sup>

**U.S. Preventive Services Task Force (USPSTF).** The USPSTF recommends that clinicians screen women of childbearing age for IPV, such as domestic violence, and provide or refer women who screen positive to intervention services (B recommendation).<sup>14</sup> In making this recommendation, the USPSTF examined the accuracy of available screening tests, the effectiveness of early detection through trials examining interventions, the potential harms of screening and interventions, and the estimated magnitude of the net benefit. The USPSTF, in discussing clinical considerations, recognized that a significant body of evidence is lacking for other populations, especially men. It was noted that research is needed in all areas related to screening and treatment in men, as well as reporting, safety, community linkages and supports, legal ramifications, and cultural aspects.<sup>14</sup> The USPSTF is in the process of updating this recommendation, but the draft statement that has been posted indicates that research gaps still exist. However, the draft recommendation does not specifically note the gaps in research related to the LGBTQ population.<sup>15</sup>

Futures Without Violence has collaborated with a number of organizations to develop materials that are specifically for LGBTQ people. The "Caring Relationships, Healthy You" safety cards and poster are survivor-centered tools that are useful conversation starters for health care providers who are doing universal education around healthy relationships and assessing for IPV.<sup>16</sup>

### *Interventions and Services*

In addition to effective screening tools, more research is needed to determine the interventions that are effective in reducing the harms of IPV in the LGBTQ population. For women of childbearing age, effective interventions include ongoing support services focused on counseling and home visits, those that address multiple risk factors (not just IPV), or include parenting support for new mothers.<sup>15</sup> However, IPV interventions should be culturally relevant, tailored to specific groups, and evaluated within those groups.<sup>17</sup>

There is limited knowledge about LGBTQ IPV in the general community and limited resources are available to support LGBTQ survivors.<sup>9</sup> When LGBTQ individuals attempt to access IPV services their options are often severely limited.<sup>12</sup> When services are provided to LGBTQ IPV survivors, the lack of cultural competency and informed support can re-traumatize the victim.<sup>12</sup> Gaps in services include: limited LGBTQ-friendly health care services, lack of adequate training at agencies around LGBTQ issues, limited medical access, and intake forms that are not LGBTQ friendly.<sup>9</sup> A 2010 study by the National Coalition of Anti-Violence Programs surveyed domestic violence agencies, sexual assault centers, prosecutors' offices, law enforcement agencies, and child victim services (n=648). The survey found that 94 percent of respondents were not serving LGBTQ survivors of IPV.<sup>18</sup> For example, in 2011, more than 60 percent of LGBTQ IPV survivors who sought assistance at a shelter were turned away.<sup>19</sup>

Similar barriers exist in seeking support from law enforcement and the justice system.<sup>4</sup> LGBTQ individuals are hesitant to seek law enforcement assistance and this hesitation is likely due to fear of discrimination or harassment.<sup>4</sup> Furthermore, state laws may not specifically grant protections to LGBTQ survivors. For example, state statutes on protection orders that do not include LGBTQ survivors are often decided on a case-by-case basis and are at the discretion of a judge.<sup>4</sup>

## LEGISLATION

### *Violence Against Women Reauthorization Act of 2013*

The Violence Against Women Act (VAWA) reauthorization of 2013 attempted to address the lack of services for LGBTQ survivors by including a non-discrimination clause. This clause provided that no person in the United States shall, based on actual or perceived race, color, religion, national origin, sex, gender identity, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity funded in whole or in part with funds made available under VAWA and any other program or activity funded in whole or in part with funds appropriated by the Office on Violence Against Women.<sup>20</sup> While there has not been an evaluation on the impact of this clause, it is worth noting that VAWA is up for reauthorization in 2018 and there are concerns this provision may be removed.

## CONCLUSION

The lifetime prevalence of IPV in the LGBTQ community is estimated to be comparable to or higher than that among heterosexual couples. Much of the work that has been done to address the public health problem of IPV has focused on heterosexual women. There is limited information available on the aspects of IPV that are unique to same-sex relationships and the effects on LGBTQ survivors' mental and physical health. Research is also lacking on the best practices for identifying LGBTQ survivors of IPV. It is unclear if existing screening tools are relevant to LGBTQ survivors. In addition to effective screening tools, research is needed to determine the interventions that are effective in reducing the harms of IPV in the LGBTQ population. Furthermore, community resources to support LGBTQ survivors of IPV are limited. While the 2013 reauthorization of VAWA specifically provided for non-discrimination against sexual and gender minorities, the implementation and enforcement of this provision is unclear.

Despite the limited research available on this topic, physicians should be alert to the possibility of IPV among their LGBTQ patients and should familiarize themselves with resources available in their communities for LGBTQ survivors of IPV.

## 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 Policy D-515.980, "Improving Screening and Treatment Guidelines for Domestic Intimate Partner Violence Against Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, and Other Individuals (LGBTQ)" be amended by addition and deletion to read as follows:

Our AMA will: (1) ~~study recent domestic violence data and the unique issues faced by the LGBTQ population; and (2) promote crisis resources for LGBTQ patients that cater to the specific needs of LGBTQ victims survivors of domestic intimate partner (IPV) violence, (2) encourage physicians to familiarize themselves with resources~~

available in their communities for LGBTQ survivors of IPV, (3) advocate for federal funding to support programs and services for survivors of IPV that do not discriminate against underserved communities, including on the basis of sexual orientation and gender identity, and (4) encourage the dissemination of research to educate physicians and the community regarding the prevalence of IPV in the LGBTQ population, the accuracy of screening tools, effectiveness of early detection and interventions, as well as the benefits and harms of screening.

2. Our AMA encourages research on intimate partner violence in the LGBTQ community to include studies on the prevalence, the accuracy of screening tools, effectiveness of early detection and interventions, as well as the benefits and harms of screening.
3. That Policy H-160.991, “Health Care Needs of Lesbian, Gay, Bisexual, Transgender and Queer Populations,” be reaffirmed.

Our AMA will collaborate with our partner organizations to educate physicians regarding: (i) the need for sexual and gender minority individuals to undergo regular cancer and sexually transmitted infection screenings based on anatomy due to their comparable or elevated risk for these conditions; and (ii) the need for comprehensive screening for sexually transmitted diseases in men who have sex with men; (iii) appropriate safe sex techniques to avoid the risk for sexually transmitted diseases; and (iv) that individuals who identify as a sexual and/or gender minority (lesbian, gay, bisexual, transgender, queer/questioning individuals) experience intimate partner violence, and how sexual and gender minorities present with intimate partner violence differs from their cisgender, heterosexual peers and may have unique complicating factors.

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**2. FDA EXPEDITED REVIEW PROGRAMS AND PROCESSES  
(RESOLUTION 201-I-17)**

*Reference committee hearing: see report of Reference Committee K.*

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS  
IN LIEU OF RESOLUTION 201-I-17  
REMAINDER OF REPORT FILED**  
*See Policy H-100.992*

**INTRODUCTION**

Resolution 201-I-17, “Improving FDA Expedited Approval Pathways,” introduced by the Resident and Fellow Section and referred by the House of Delegates asked:

That our American Medical Association work with U.S. Food and Drug Administration (FDA) and other interested stakeholders to design and implement via legislative action (including ensuring appropriate FDA staffing) a process by which drugs which obtain FDA approval via the Fast Track, Accelerated Approval, or Breakthrough Therapy pathways be granted FDA approval on a temporary basis not to exceed 5 years, pending further evidence of safety and efficacy that is at the level set for the standard drug approval process; and,

That our AMA work with the FDA and other interested stakeholders in improving the process by which drugs are selected for the expedited pathway to improve the prevalence of these drugs that are classified as “specialty drugs.”

This report examines expedited FDA drug approval processes in place in the United States, including so-called fast track, accelerated approval, designated breakthrough therapies, and “priority review” for drugs and biologics. Such programs are “intended to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions” (especially when no satisfactory alternative therapies exist), and “be available to patients as soon as it can be concluded that the therapies’ benefits justify the risks.”<sup>1-3</sup> Accordingly, under the current regulatory structure for approval of new chemical entities or new indications (efficacy supplements), the specific drug development program, including eligibility for expedited programs, is determined by the seriousness and prevalence of the disease, availability of existing treatments, and evidence that the drug can offer significant improvement compared with available therapies.

Two specific topics, one referred to in the resolution (specialty drugs) and the other which also impacts the FDA’s review of new drug applications (user fees) are not specifically evaluated in this report. The FDA does not define “specialty drugs” nor is it a term found in regulations or statute. The term specialty drug is generally used for complex, high-cost medications; they are often derived from a living source, characterizing them as biologics. Historically, they have been used to treat serious, chronic conditions such as rare diseases, cancer, rheumatoid arthritis, and multiple sclerosis. In recent years, specialty drugs have targeted more common conditions such as high cholesterol, asthma and hepatitis C, significantly increasing the potential pool of patients that receive them. Specialty drugs are not stocked at most pharmacies, are often injectable medications, and may have unique storage or shipment requirements, such as refrigeration. These medications usually require additional patient education and support beyond traditional dispensing and counseling activities to maintain adherence and ensure patient safety. The growth in specialty drugs has been exponential. In the past four years nearly 100 new specialty drugs were launched, and in the same time there were 80 supplemental approvals establishing new indications for existing products.<sup>4</sup> Based on the number and high degree of success in getting such drugs approved, special attention to these types of drugs, with respect to drug

development, is not warranted. Concerns also have been expressed that the high cost of many specialty drugs is not justified when compared with their clinical benefits. Cost is a variable that is not under the purview of the FDA.

The Prescription Drug User Fee Act (PDUFA), first enacted in 1992, established the current framework by which pharmaceutical manufacturers help fund the FDA by submitting a fee along with their application. Monies derived from so-called “user fees” have been used to expand FDA staffing dedicated to the review of new drug (NDA) and biological license applications (BLA) and efficacy supplements (sNDA); the latter are submitted when sponsors seek approval to add a new indication to prescription drug labeling. A comparable user fee process also is now in place for abbreviated new drug applications (ANDA) that govern generic drug approval. Because user fees support FDA drug reviews in general, and are not an expedited program or process *per se*, the impact of PDUFA review times on drug safety and patient benefits is not further evaluated in this report.

## METHODS

English-language reports were selected from a PubMed and Google Scholar search from 1992 to August 2018, using the MeSh terms “\*biomarkers,” “\*surrogate end points,” “drug approval/\*methods/\*statistical outcomes/\*legislation & jurisprudence, \*validation,” “United States Food and Drug Administration,” product surveillance/\*postmarketing” and “government regulation,” combined with the text terms “clinical trials,” “treatment outcome,” “accelerated approval,” “breakthrough therapy,” “priority review,” and “fast track.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet site of the US Food and Drug Administration (FDA).

## CURRENT AMA POLICY

AMA Policy H-100.992, “FDA,” supports the concept that an FDA decision to approve a new drug, to withdraw a drug's approval, or to change the indications for use of a drug must be based on sound scientific and medical evidence derived from controlled trials and/or postmarket incident reports *as provided by statute*. The statute regarding evidentiary standards for drug approval was modified in 1997 permitting FDA to approve a drug product “upon determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.” The evidence should be evaluated by the agency in consultation with its Advisory Committees and expert extramural advisory bodies, and any risk-benefit analysis or relative safety or efficacy judgments should not be grounds for limiting access to or indications for use of a drug unless the weight of the evidence from clinical trials and postmarket reports shows that the drug is unsafe and/or ineffective for its labeled indications.

Policy D-100.978, “FDA Drug Safety Policies,” directs the AMA to monitor and respond, as appropriate, to implementation of the drug safety provisions of the FDA Amendments Act of 2007 (FDAAA; P.L. 110-85). This directive was related primarily to the fact that FDA authorities around Risk Evaluation and Mitigation Strategies were strengthened by the 2007 law.

## DESCRIPTION OF EXPEDITED DRUG AND BIOLOGIC APPROVAL PROCESSES

Regular approval was the only FDA approval pathway until 1992. Largely in response to the HIV/AIDS epidemic in the mid-late 1980s, the FDA institutionalized approaches by which certain drugs, including antiretroviral products at the time, could be initially approved based on less rigorous data, including the use of surrogate endpoints.

### *Accelerated Approval*

Conceptualized in the 1980s, initially implemented in 1992 and further refined in 2012, the accelerated approval pathway for drugs and biologics is described in 21CFR parts 314 (subpart H) and 602 (subpart E) and contained in Section 506(c) of the Food Drug and Cosmetic (FD&C) Act.<sup>5-7</sup> It has been primarily used in settings where the course of the disease is long and an extended period would be required to measure the intended clinical benefit (e.g., decreased mortality from HIV infection, increased overall survival from cancer). Qualifying criteria are a drug that treats a serious condition, generally provides a meaningful advantage over available therapies and demonstrates an effect on a “surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality.” Furthermore, the surrogate endpoint is *reasonably likely* to predict an effect on “some other clinical benefit (i.e., an intermediate clinical endpoint), considering the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.” The accelerated approval designation

requires post-approval testing to verify efficacy and confirm the anticipated risk-benefit profile. From 2000 to 2103, 37 new drugs were granted accelerated approval, or about 10% of new molecular entities (NMEs).<sup>8</sup>

A drug marketed under accelerated approval can be subject to expedited withdrawal if the surrogate endpoint(s) turns out to be faulty. The FDA maintains a list of drugs that have been withdrawn due to safety concerns or lack of efficacy.<sup>9</sup> Many of these products predate 1992. Since 1992 about 25 drugs have been withdrawn from the market, most of which had gone through regular approval. A limited number of drugs marketed under accelerated approval have had their approval for specific indications withdrawn (see below).

**Surrogate Endpoints.** A surrogate is “a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.”<sup>10</sup> Such measures are not intrinsically beneficial to patients, but are relied on to predict the benefits of treatment in the absence of data on patient-relevant final outcomes based on a “reasonably likely” standard. The use of surrogate endpoints allows for clinical trials with reduced sample size and shorter duration, thereby reducing expense and speeding patient access to new therapies. For most drugs marketed under accelerated approval, requiring the endpoint to be overall survival is not practical and may not be ethical.<sup>11</sup>

Approval of a drug based on a surrogate endpoint introduces uncertainty about the drug’s true clinical benefit and this degree of uncertainty must be considered acceptable in order for the new drug or indication to be approved. Different scenarios exist in which a treatment may significantly affect a surrogate marker, but not the clinically significant endpoint. The strength of evidence for validating a surrogate marker is based on: (1) the biological plausibility of the relationship between the surrogate marker and patient outcomes; (2) epidemiologic evidence on the predictive value of the surrogate for the clinical outcome of interest; and (3) clinical trial level data confirming that the response of the surrogate marker to treatment corresponds to the effects of the treatment on the clinical outcome.<sup>12</sup> Optimally, the strength of the surrogate-survival correlation would already be established; however, many surrogate endpoints used during the drug approval process are not validated at the time. To validate all surrogate endpoints ahead of time would require several trials to be conducted on a specific research question, essentially defeating the purpose of the accelerated approval pathway.

**The Use of Surrogate Endpoints for Drug Approval.** Surrogate endpoints have assumed increasing importance as approximately 40% of pivotal trials constituting the basis for approval of NMEs and/or new indications for existing drugs are based on surrogate endpoints, with a high percentage of these being for oncology drugs.<sup>12,13</sup>

Several studies have been published examining the use of surrogate endpoints and accelerated approval of oncology drugs over the past 25 years.<sup>14-16</sup> Two snapshots covered the periods from 1994-2004 and 2004-2011, with a few others covering different time periods.<sup>16,17</sup> A comprehensive review of oncology drugs approved as NMEs and for new indications via accelerated approval (n=93) was recently published covering the period from the inception of the program (1992) through May 2017 and is the focus of the following discussion.<sup>16</sup>

Twenty-eight percent of accelerated approvals were supported by randomized controlled trials (RCTs), with single arm trials accounting for the remainder; the median patient population for determining efficacy was 143. Seven RCTs used time to progression as the end point and four used disease-free survival; the remainder of both RCTs and single arm trials (87%) used response rate (i.e., tumor burden) as the endpoint. Approximately 55% of the approvals have fulfilled their post- marketing requirements and verified benefit in a median 3.4 years after approval, based on measurement of progression-free survival or time to progression (i.e., disease control) (39%), overall survival (29%), response rate (26%) or disease-free recurrence or progression (6%). Most of the success stories had ongoing confirmatory trials planned and underway at the time of accelerated approval. Forty percent of accelerated approvals are still in the process of completing confirmatory trials and verifying clinical benefit; FDA approval was subsequently withdrawn for five new indications. Most of the unfulfilled commitments represent recent approvals (median time on the market = 18 months), although some outliers exist; eight of such products have been on the market for more than 5 years, mostly in rare patient populations. While one criticism of the accelerated approval pathway is the smaller sample size, review of documentation supporting accelerated approval indicates that the safety database is usually larger, about double the efficacy database.<sup>16</sup> The safety database includes patients “treated with the drug regardless of age, condition, or volunteer status.”<sup>16</sup> If the accelerated approval is for a new indication of an already-approved drug then more expansive safety information and postmarketing data are already available. Only one cancer drug approved under accelerated approval has been withdrawn from the market because of both efficacy and safety issues (gemtuzumab ozogamicin), and this drug was later reapproved for a narrower population.<sup>19</sup>

Several trial-level analyses have “quantified the association between surrogate endpoints and overall survival, with one study finding that nearly 50% of meta-analyses reported correlation between surrogate outcomes and overall survival exceeding 0.7. On average surrogate endpoints are positively correlated with survival.”<sup>20</sup>

#### *Fast Track Designation*

The current fast track designation is defined in section 506(b) of the FD&C, as amended by the 1997 Food and Drug Modernization Act (section 112) and 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) (section 109). This designation was designed to facilitate the development, and expedite the review of drugs to *treat serious conditions and fill an unmet medical need*. Some critics maintain that the term “unmet medical need” has been overused and is too imprecise.<sup>21</sup> This pathway also is available for drugs that have been designated as a qualified infectious disease product. Fast track allows for approval based on preliminary evidence such as Phase 2 clinical studies (rarely Phase 1). A request for fast track designation can be filed with the investigational new drug application (IND) or after, but ideally before the pre-NDA or BLA meeting; the timeline for an FDA decision is within 60 calendar days of receipt of the request.

Actions to expedite development and review include more frequent interactions with the review team to discuss, in part, study design, the extent of safety data required to support approval, dose-response concerns and use of biomarkers, and a “rolling review” where parts of the application can be acted on when they are ready, in sequence. Drugs with fast track designation also could be eligible for *priority review* (see below) if such a request is supported by sufficient data when the NDA, BLA, or efficacy supplement submission is submitted. Fast track designations can be rescinded if qualifying criteria are not met.

From 2000 to 2013, the FDA approved 82 drugs under the fast track designation, or approximately 22% of the NME’s approved during the same time period.<sup>8</sup> More than 60% of the fast track approvals were characterized as specialty drugs by the authors of this study.

#### *Breakthrough Therapy*

Described in Section 506(a) of the FD&C Act, the breakthrough therapy designation was created by the 2012 FDASIA to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy. Qualifying criteria are that a drug is intended to treat a *serious condition* and *preliminary clinical evidence* indicates that the drug may demonstrate “substantial improvement on a clinically significant endpoint over available therapies.” The timeline for FDA response is the same as fast track and priority designations. In contrast to the fast track designation which could include theoretical or non-clinical data, a breakthrough designation requires clinical evidence which is sufficient to demonstrate substantial improvement in safety or effectiveness over available therapies, but additional evidence is still required for final approval. Determining if the “substantial improvement” criterion is met is a matter of judgement, and the evidence that is relied on for approval of drugs with this designation is heterogenous.<sup>22</sup> This designation triggers intensive guidance on the drug development program beginning as early as Phase 1, FDA commitment involving senior FDA managers, a rolling review of the application and eligibility for *priority review* designation.

#### *Priority Review*

This process was established by the 1992 PDUFA to improve the efficiency of NDA reviews for NMEs. A priority review designation can be assigned to applications for drugs “that treat *serious conditions* and provide *significant improvements* in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions *compared to available therapies*.”<sup>3</sup> A priority review designation is assigned at the time of the NDA, BLA or efficacy supplement filing. Priority review can be granted to applications for drugs with fast track or breakthrough therapy designation, or to applications submitted for review under accelerated approval. That decision is based on the information and data available at the time the application is submitted.<sup>1</sup>

The timeline for FDA response is the same as fast track designations with a shorter timeframe for reviewing the application versus standard review cycles (6 months compared with the 10-month target for the latter). From FY 2007 through FY 2016, the (average) median time to application approval was 11.4 months for standard review compared with 7.9 months for priority review.<sup>23</sup>

## CLINICAL TRIAL EVIDENCE AND EXPEDITED REVIEW PROGRAMS

### *A Perspective on New Drug Safety-Related Issues*

One study conducted on postmarket safety outcomes for all NMEs (n=278) approved from 2002-2014 demonstrated that safety updates to the product labeling were the rule rather than the exception.<sup>24</sup> At least one safety update was added to 195 (70.1%) of the products, most commonly between the 2<sup>nd</sup> and 8<sup>th</sup> year after marketing. Safety information was added earlier after marketing for drugs approved with a fast-track designation or under an accelerated approval using a surrogate end point; safety issues also were more likely to arise for drugs with a fast track designation.

### *Evidentiary Standards*

Another perspective on drugs approved via expedited reviews is to examine the strength of evidence accompanying market approvals, which clearly has important implications for patients, physicians, and payers. Concern has been expressed about the potential lack of systematic monitoring for confirmation of effectiveness for drugs that have been approved based on limited evidence, compared with standard approvals.<sup>25</sup>

One recent review of cancer drugs approved from 2006-2016 found that when RCTs were lacking, approved indications were more likely to be based on accelerated approval, receive a breakthrough designation or have a companion diagnostic test. Indications not supported by RCTs had higher odds of post approval safety changes, but not major modifications in indications and dosage, warnings and precautions, boxed warnings, or contraindication sections of the labeling.<sup>26</sup>

Analysis of all drugs approved by the FDA from 2005-2012 revealed that most indications were supported by at least 1 RCT, although more than one-third of indications were approved based on a single pivotal efficacy trial. Substantial variation existed in terms of the comparators and end points, trial duration, number of participants, and completion rates.<sup>12</sup> Surrogate endpoints served as the primary outcome for 91 of 206 (44%) of the approved indications.

From 2005-2014, 295 supplemental NDAs for new indications were submitted. Thirty percent of these were supported by efficacy trials with an active comparator and 32% used a clinical endpoint. Among those expanding the patient population (almost all pediatric), only 11% used an active comparator, with 22% using a clinical endpoint.<sup>27</sup>

## DISCUSSION

Over the years, the FDA has implemented various approaches to expedite the review and approval of new drug and biologic applications, as well as new indications for existing products. Under the current regulatory structure, the specific drug development program, including eligibility for expedited programs, is determined by the seriousness and prevalence (or rarity) of the disease, availability of existing treatments, and evidence that the new drug can offer significant improvement compared with available therapies and/or otherwise address an unmet medical need. Accelerated approval, fast track, priority review, and breakthrough therapy designations have been developed to consider and address these variables. These expedited programs differ and should not be lumped together from a scientific, public health, or policy point of view. Key variables include the requirement for post-approval studies for drugs marketed under accelerated approval, whether a surrogate endpoint that has not been validated is used to support approval, and the need to confirm clinical benefit and the risk-benefit profile for drugs approved based on limited evidence, regardless of their review designation.

It has been argued that the process of approving medications based on more limited evidence, including fewer patients and patient years of exposure, makes the process of reducing healthcare disparities costlier.<sup>28</sup> Earlier drug approval reduces the power of studies to detect difference in risk and benefit in relevant subgroups and could direct the burden of medical uncertainty toward groups of people who are often disadvantaged. It may be advisable for the FDA to encourage that confirmatory trials enable appropriate sub-group analyses that were not possible during initial, lower-powered studies. Accelerating drug approval shifts the burdens of uncertainty away from clinical trial participants (who have undergone informed consent) to others who are exposed to the treatment under different conditions, socializing the costs of uncertainty while pharmaceutical companies profit from new drug development. The relevant question is “whether earlier access to drugs, driven by changes in regulatory policy or growing reliance on surrogate endpoints, benefits or harms patients.”<sup>29</sup>

Confirmatory studies are needed for drugs approved based on limited evidence to avoid exposing patients to potentially unsafe or ineffective therapies. Even the use of uncertain surrogate endpoints is not problematic if confirmatory studies reliably demonstrate meaningful clinical endpoints. A report from the Government Accountability Office, in referring to the FDA's activities in this area, concluded that "the agency needs to clarify the conditions under which it would use its authority to expedite the withdrawal of drugs granted accelerated approval," when confirmatory studies are not conducted in a timely manner or fail to confirm predicted benefits.<sup>30</sup>

Over the past 15 years, most accelerated approvals were for oncologic drugs, and that experience is instructive. The accelerated approval of bevacizumab for breast cancer has been held up as a prime example of harm, because it was approved based on the endpoint of progression-free survival, but eventually this drug was shown to not increase overall survival.<sup>19</sup> However, "clear and convincing evidence" has emerged from phase 2 (and some phase 1) trials leading to marketing approval of new chemical entities within 2-3 years accounting for "advances in treatment for molecular subsets of non-small cell lung cancer, melanoma, chronic leukemia, breast cancer, and acute myeloid leukemia," among others.<sup>19</sup>

Although critics have condemned a lack of "improved survival" as the optimal endpoint for clinical trials, there has been a "steady improvement in U.S. cancer mortality and survival over the past 2 decades."<sup>19</sup> in part because of new treatments, but also better screening and early detection. Nevertheless, more than half of oncologic drugs marketed under accelerated approvals relied on a surrogate endpoint that was chosen in the absence of any formal analysis of the strength of the surrogate-survival connection.<sup>31</sup> This observation reinforces the need for timely determination of the predicted clinical benefit and confirmation of the risk-benefit profile.

Comprehensive evaluation of oncologic drugs marketed under accelerated approval confirms that satisfactory progress has been made on confirmatory trials. By balancing risk, accounting for uncertainty, and operating under a paradigm of regulatory flexibility, existing FDA expedited pathways can ensure early access to, and appropriate use of new drugs and biologics, including specialty drugs. The Institute of Medicine recommended that the FDA should "implement a benefit and risk assessment and management plan that would summarize the FDA's evaluation of drug's risk-benefit profile in a single document and that would be continuously updated" during the life-cycle of the drug on the market.<sup>32,33</sup> While it is important for the agency to retain regulatory flexibility, and mostly positive aspects of expedited programs are apparent, some changes should be made to improve implementation, establish the value of surrogate endpoints, and provide more transparency for physicians and their patients on the level of evidence used for marketing approval.

## RECOMMENDATION

The Council on Science and Public Health recommends that Policy H-100.992 be amended by addition and deletion to read as follows in lieu of Res-201-I-17, and the remainder of the report be filed:

(1) Our AMA ~~reaffirms its~~ supports for the principles that:

- (a) an FDA decision to approve a new drug, to withdraw a drug's approval, or to change the indications for use of a drug must be based on sound scientific and medical evidence derived from controlled trials and/or postmarket incident reports as provided by statute;
- (b) the ~~is~~ evidence for drug approval should be evaluated by the FDA, in consultation with its Advisory Committees and expert extramural advisory bodies, as appropriate;
- (c) expedited programs for drug approval serve the public interest as long as sponsors for drugs that are approved based on surrogate endpoints or limited evidence conduct confirmatory trials in a timely fashion to establish the expected clinical benefit and predicted risk-benefit profile;
- (d) confirmatory trials for drugs approved under accelerated approval should be planned at the time of expedited approval;
- (e) the FDA should pursue having in place a systematic process to ensure that sponsors adhere to their obligations for confirmatory trials;
- (f) any risk-benefit analysis or relative safety or efficacy judgments should not be grounds for limiting access to or indications for use of a drug unless the weight of the evidence from clinical trials and postmarket reports shows that the drug is unsafe and/or ineffective for its labeled indications; and,
- (g) FDA should make the annual summary of drugs approved under expedited programs more readily available and consider adding information on confirmatory clinical trials for such drugs to the drugs trials snapshot.

- (2) The AMA believes that social and economic concerns and disputes *per se* should not be permitted to play a significant part in the FDA's decision-making process in the course of FDA devising either general or product specific drug regulation.
- (3) It is the position of our AMA that the Food and Drug Administration should not permit political considerations or conflicts of interest to overrule scientific evidence in making policy decisions; and our AMA urges the current administration and all future administrations to consider our best and brightest scientists for positions on advisory committees and councils regardless of their political affiliation and voting history.

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