

REGULATIONS/GUIDANCE RECOMMENDATIONS TO ELIMINATE

FOOD AND DRUG ADMINISTRATION (FDA)

I. Premarket Regulations

- **Notice of Proposed Rulemaking (NPRM) for Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies (21 CFR Part 58)**

The NPRM would amend the GLP regulations for nonclinical laboratory studies to, among other things, impose a rigid quality systems framework. This "one-size-fits-all" approach conflicts with a flexible, common-sense risk-based approach (i.e., focus on "errors that matter") FDA has adopted in other areas (e.g., GMP), is burdensome to implement and has no clear benefit. Current risk-based controls for GLP studies ensure safety by focusing manufacturers on risks that matter.

- **Outdated Testing Requirements (21 CFR 610.2(a), 610.13(b))**
 - 21 CFR. 610.2(a) requires biologic manufacturers to submit samples of each lot to FDA, upon request, prior to distribution. The regulations are outdated as many manufacturers have shifted away from a lot-based system to continuous manufacturing. Additionally, submission of samples to FDA prior to distribution does not reflect a risk-based approach and makes it difficult for manufacturers to efficiently manage the supply chain.
 - 21 CFR 610.13(b) requires pyrogenic rabbit testing of injectable biologics. This method of testing has been replaced by more modern/appropriate endotoxin testing. Modern tests already employed by manufacturers ensure safety of these biological products.

II. Postmarketing Regulations

- **Guidance for Industry, Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)**

This guidance sets forth conditions where FDA will waive its requirements for submission formats to authorize sponsors to use the PBRER format (more commonly used globally). To the extent regulations are modified to authorize use of PBRER without the need for an FDA waiver (as suggested in PhRMA's list of regulations to modify), this guidance should be eliminated.

III. Quality, Manufacturing, and Compliance

- **Draft Guidance (and planned rulemaking), Submission of Quality Metrics Data/Technical Conformance Guide/Technical Specifications Document**

FDA's quality metrics initiative requires manufacturers to collect, analyze, and submit FDA-defined metrics for each product (e.g., number of out-of-specification test results for lot release and long-term stability testing invalidated per number of such tests). FDA's one-size-fits all approach would require significantly burdensome process changes for industry with no clear benefits to the public, FDA, or industry. The draft guidance also diverts resources from new product development and raises concerns about confidentiality of data. Companies already collect internal quality data (in their own format, reviewable by FDA inspectors) to maximize quality manufacturing. FDA should pause efforts to implement the Quality Metrics program and continue dialogue with industry to determine a path forward.

- **Draft Guidance, Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009**

The draft guidance addresses legal issues regarding products currently approved under new drug applications (NDAs) that will be deemed to be licensed under a biologics license application (BLA) in 2020. The draft guidance would eliminate valuable marketing exclusivities for these products on the date of transition (e.g., an innovative product with 2 remaining years of exclusivity would lose this exclusivity and immediately be subject to biosimilar competition). This unprecedented taking presents great concern to innovative companies and threatens the balance between innovation and competition recognized by Congress.

CENTERS FOR MEDICARE AND MEDICAID (CMS)

- **Medicaid: Covered Outpatient Final Rule (the "AMP" rule) ((CMS-2345-FC) Expanding the Medicaid Rebate Requirements to the Territories; 42 C.F.R. § 447.502 (extending definitions of "State" and "United States" to the Territories as of April 1, 2020); Note 81 Fed. Reg. 80003 (Nov. 15, 2016) (Interim final rule delaying extension of the rebate program to the Territories until April 1, 2020))**

The Medicaid rebate program has been operating in the 50 States and the District of Columbia since its start in 1991. This 2016 final rule, which has been delayed to 2020, redefines "State" to include the territories (Puerto Rico, Guam, Northern Mariana Islands, American Samoa, and US Virgin Islands) and extends the rebate program to drugs provided to Medicaid beneficiaries in the Territories. This would require manufacturers to collect data on all their sales in the Territories and take those sales – many of which could be subject to price controls and could trigger new lower best prices – into account in determining Best Price and AMP. This would result in Medicaid rebate liability on Medicaid utilization in the Territories. CMS should rescind the regulatory provisions defining "State"

to include the Territories under the rebate program and revert back to the definition of State used by the Medicaid rebate program since 1991.

- **Medicaid: Requiring Monthly Average Manufacturer Prices (AMPs) (42 C.F.R. § 447.510(d) (requirement to calculate and report monthly AMPs); 42 C.F.R § 447.510(d)(3) (requirement to revise previously-filed monthly AMPs for three years); 42 C.F.R. § 447.510(e) (certification requirements))**

Medicaid rebates are calculated each quarter using a formula based on the AMP for the quarter (generally manufacturer's average price to retail pharmacies and wholesalers) and the Best Price for the quarter (generally the manufacturer's single lowest net price to any commercial customer). Manufacturers must calculate and report these quarterly metrics because they determine rebate payments. But CMS regulations were issued in 2007 to require that manufacturers also calculate and report *monthly* AMPs for all of their drugs: an extra burden that wastes resources because (for all but multiple source drugs) the monthly AMPs have no purpose – CMS has yet to articulate any purpose for these. These monthly AMP filings trigger additional burdens with no purpose: companies must calculate and report the monthly AMPs, report any revision to monthly AMPs for three years after the initial filing, and have top officials (e.g., CEO, CFO) certify to the accuracy of these figures. CMS should undergo notice and comment rulemaking to rescind these needless reporting requirements.

HEALTH-RESOURCE SERVICES ADMINISTRATION (HRSA)/340B Program

- **340B Contract Pharmacy Guidance (HRSA, Notice Regarding 340B Drug Pricing Program Contract Pharmacy Services, 75 Fed. Reg. 10272 (March 5, 2010))**

HRSA's 2010 sub-regulatory guidance permits any 340B covered entity to dispense deeply discounted drugs purchased under the discount program through an unlimited number of unrelated, off-site retail "contract pharmacies" not recognized in the 340B statute. This 2010 policy allowing their unrestricted use has led to sharp growth in the 340B program, and contract pharmacies increase the risk of legal violations by 340B entities, including the risk of illegal diversion of 340B discounted drugs, illegal "duplicate discounts" (where a manufacturer sells a drug at a 340B discount and also is billed for a Medicaid rebate on the same drug). This 2010 contract pharmacy guidance should be rescinded immediately and HRSA should revert back to its pre-2010 policy under which only covered entities lacking an in-house pharmacy could use a contract pharmacy and those entities could only use one contract pharmacy site.

- **340B Final Rule re Ceiling Price/Manufacturer Civil Monetary Penalties/Penny Pricing (HRSA, 340B Drug Pricing Program Ceiling Price and Manufacturer Civil Monetary Penalties Regulation, 82 Fed. Reg. 1210 (Jan. 5, 2017); HRSA Release 2011-2 "Clarification of Penny Pricing" (November 21, 2011); Interim Final Rule Delaying the Effective Date to May 22, 2017, 82 Fed. Reg. 14332 (March 20, 2017))**

This ACA rule imposes a series of burdensome requirements on manufacturers that go well beyond the 340B program's original purpose. It creates two separate sets of burdensome refund requirements and does not permit manufacturers to offset these refunds for prices that were too low. It also fails to permit de minimis exceptions to the refund requirements, forcing manufacturers to provide even nominal refunds that cost more to process than the refund itself. The rule also finalizes a policy that forces certain drugs to be priced at a penny (\$.01) to 340B covered entities, resulting in companies having to essentially give away certain drugs for free under the 340B program. This exacerbates the diversion problem that is already rampant in the program. Finally, the rule fails to provide concrete standards regarding when there is a "knowing and intentional" overcharge of a 340B ceiling price, subjecting manufacturers to unfair civil monetary penalties. The rule contains fundamentally flawed Obama administration policies based on questionable legal authority and should be rescinded. At a minimum, the rule should be further delayed beyond May 22, 2017 to give the new Administration time to review questions of fact, law and policy in the rule and to evaluate how the rule factors into the larger 340B program. Ultimately the Trump Administration should develop new proposals, seek comment on those proposals through a new proposed rule, and issue a sensible final rule that complies with the law and eliminates pointless burdens on manufacturers.

PATENT AND TRADEMARK OFFICE (PTO)

- **Regulation on Amendment of the Patent in Post-Grant Proceedings (37 CFR 42.121 (IPR Proceedings); 37 CFR 42.221 (PGR Proceedings))**

The regulations provide unwarranted limitations on the ability of patent owners to amend patent claims during Patent Trial and Appeal Board (PTAB) proceedings, including both inter partes review (IPR) and post-grant review (PGR) proceedings. The regulations should be repealed, and the PTAB should directly apply 35 U.S.C. § 316(d)/ 35 U.S.C. § 326(d), which provide patent owners an opportunity to move to amend patent claims in IPR/PGR proceedings.

Potential Administrative Actions:

Fostering an environment that enables industry to advance innovative, safe, effective, and affordable treatments and cures to the patients who need them as quickly as possible.

- Encourage Use of 21st Century Tools for Drug Evaluation, Review and Approval: Examples include:
 - Broader use of biomarkers to speed medical product evaluation and shorten product development timelines.
 - Wider acceptance of new approaches to clinical trial design and statistical methods that could reduce the cost and time to bring a new medicine to market.
 - Greater use of real-world evidence could allow information other than that derived from traditional studies to aid regulatory decision-making.
 - (Reference: PhRMA <http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf>)
- Improve Predictability for Payers and Dissemination of Evidence: Provide medical product information to payers either before approval because payers often set premiums and formularies 18 months in advance or be able to provide off label safety and efficacy information not included in the product's labeling. (Reference: PhRMA <http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf>)
- Explore administrative actions to encourage greater uptake of biosimilar and interchangeable biosimilars.
- Explore ways FDA can better utilize current regulatory pathways including 505(b)(2) and 505(j) to better rationalize awards of exclusivity.
 - https://www.washingtonpost.com/news/wonk/wp/2017/02/10/an-old-drug-gets-a-new-price-to-fight-a-rare-disease-89000-a-year/?utm_term=.30950c545473
- Reconsider FDA's Unapproved Drug Initiative.
 - <http://www.latimes.com/business/hiltzik/la-fi-mh-the-little-known-fda-program-20150923-column.html>
- Implement the FDA commitments outlined in the PDUFA VI, MDUFA IV, GDUFA II, and BSUFA II commitment letters to Congress. (Source: HHS/FDA)

Rationalizing Reimbursement Policy

- Consider administrative modifications to streamline the Open Payments program in an effort to reduce drug and device manufacturers' burden from reporting and validating data.
 - References:
 - American Medical Association, June 2016 - *Statement on Newly Released Open Payments Data*
 - Bloomberg Bureau of National Affairs (BNA), 2015 - *As Second Open Payments Release Date Nears, Industry Feels Increased Burdens*
- Explore ways to clarify or modify regulations, or pursue future rulemaking as appropriate, to enable manufacturers to voluntarily enter into value-based purchasing arrangements.

Potential Legislative Ideas for Discussion:

Fostering an environment that enables industry to advance innovative, safe, effective and affordable treatments and cures to the patients who need them as quickly as possible.

- **REMS and access to brand samples:** Removing barriers that delay generic and biosimilar market entry.
 - *Ensure access to brand samples for generic development:* Recent proposals, including bipartisan bills in Congress, are intended to improve generic developer access to brand drugs for product testing.
 - The Fair Access for Safe and Timely (FAST) Generics Act would require brand companies to sell their products, including REMS drugs, to generic developers without restriction.
 - Rep. Marino introduced HR 2212 Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act on April 27, 2017, similar to a Senate version introduced last year by Senators Leahy, Grassley, Klobuchar and Lee would allow generic developers to sue brand companies in federal court to obtain samples of REMS drugs as well as drugs subject to manufacturer-imposed limited distribution networks.
 - *Separate Risk Evaluation and Mitigation Strategies (REMS):* HR 2212 Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act would give FDA the flexibility to allow separate REMS.
- **FDA reforms to speed review of complex generics**
 - *Expand allowable evidence to support review of complex generics:* Give FDA the flexibility to rely on a broader complement of data for review of complex generic drugs in addition to bioequivalence and bioavailability data when necessary for approval.
 - *Expand threshold for generic approval:* Give FDA the authority to allow generic copies to have minor differences, to account for small variations between brand drug and proposed generic or biosimilar, such as patient retraining.
 - Reference: Dr. Gottlieb (<http://www.aei.org/publication/epipen-shows-a-path-to-solve-the-bigger-drug-pricing-challenge/>)

Generic Competition

Problem: Address bad actors and improve generic competition

Over the past few years, rapidly rising prices for some older medicines have garnered the attention of policymakers, media and patients. In multiple instances, decades old medicines suddenly increased in price. Generally, the price of a medicine drops when patent protection ends and a generic copy enters the market. However, in recent instances the opposite has occurred: prices for older, off-patent medicines have increased, rather than decreased. This is happening even though there are no regulatory or patent exclusivities prohibiting entry of a competitor. For example, in the well-publicized case of Turing Pharmaceuticals' drug Daraprim, a small market size and well publicized, ongoing review delays at the FDA created economic and regulatory disincentives for competition. As a result, Turing was able to dramatically increase the price of the product, knowing the barriers to entry for competition were steep.

Solution: Incentivize entry of a first generic

New regulatory and economic incentives are needed to inject greater competition and lower costs into the market in circumstances where no patent or regulatory barriers stand in the way. Incentivizing the entry of a first generic competitor when 1) there is only one manufacturer of a product, 2) the drug treats a small patient population and 3) there are no regulatory or patent exclusivities, can improve competition and lower costs.

The following incentive policy options could be pursued legislatively for medicines that lack competition due to the fact pattern described above. An asterisk is used to indicate policies which could also be implemented administratively without legislation:

Expedite review of the generic drug application and inspection of the generic manufacturing facility:* This policy would allow for speedier generic entry and quicker recouping of investment by expediting FDA's review of the generic drug application and the inspection of the manufacturing facility. Earlier market entry serves as an incentive to the generic manufacturer versus other market entrants as it provides additional time to gain market share.

Waive existing application and facility fees: This policy would reduce hurdles for generic manufacturers to compete with older medicines by waiving the application user fee for a generic drug application and facility fees. Waiving such fees would reduce a financial obstacle cited by generic firms in bringing generics to market quickly.

Create a priority review voucher for future generic drug approval: This policy would provide generic manufacturers with a transferable priority review voucher for any future generic drug application upon approval of a generic drug to treat a small patient population for which there are no other competitors and no patent or regulatory exclusivities. The transferable voucher serves as an incentive to spur the introduction of new generic drugs that otherwise would not attract interest from companies due to the cost of development and lack of market opportunities.

Create 180-day exclusivity period for the first eligible generic application: This policy would create a 180-day exclusivity period to incentivize timely entry of additional competition (in situations where there are no patents). Currently, the first generic patent challenger to reach the market is allowed to market their generic for 180 days without facing additional generic competition. This proposal would provide similar exclusivity for the first successful eligible generic application (as regulatory and patent exclusivity would not be a barrier), providing the generic applicant additional predictability regarding the potential to earn a return on investment. This policy could also be expanded to a second eligible generic application where applicants would share an exclusivity period.

Develop FDA technical assistance program:* This policy would establish a formal FDA technical assistance program to help ensure eligible generic manufacturers develop quality drug applications and are prepared to meet good manufacturing practices. This program could help ensure generic manufacturers meet the criteria for application quality and receive additional needed support in developing manufacturing plans that will meet good manufacturing practices and avoid costly manufacturing issues.

Publish list of qualified contract manufacturers:* This policy would establish a published list on FDA's website of generic contract manufacturers who could provide manufacturing capacity if needed. This can help in instances where a generic company lacks the resources or ability to dedicate manufacturing capacity to a new product as well as helps manufacturers avert a potential drug shortage. Generic manufacturers must consider their technical ability to manufacture generic versions of branded products, and for complex products they may not have sufficient resources to produce technically challenging products. The public posting and regular updating of a list of voluntary contract manufacturers to address manufacturing hurdles would help address this challenge.

Create a tax credit to support generic manufacturing investments: This policy would implement a tax credit to support generic manufacturing investment offsetting tax liability for generic manufacturers. Modeled on existing research tax credits, this tax credit of up to 50 percent would apply for relevant research and development, manufacturing, and distribution related expenses. If the manufacturer discontinues production of the particular generic, the manufacturer would no longer be eligible for the tax credit.

Outcome: Through these reforms, policymakers will increase competition in areas of unmet patient need. These proposals would prevent aggressive price gouging by unscrupulous companies that acquire off-patent drugs that have been widely used for decades, for which there is no generic competitor. Research consistently demonstrates that increasing competition would increase patient access to affordable medicines and reduce the overall cost of health care in the United States.