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Via Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Food and Drug Administration Safety and Innovation Act Section 907 Report; Request for Comments (Docket No. FDA-2013-N-0745)

These comments are submitted on behalf of the Medical Information Working Group (MIWG) in response to FDA's August 22, 2013, notice (78 FR 52202) announcing the availability of the report, "Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products," issued under Section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA).[1]

The report addresses FDA's dissemination of information to the public about the safety and efficacy of drugs and medical devices in patient subgroups defined by demographic variables. Section 907(a)(2)(A) of FDASIA mandated that the report "address how [FDA] makes available information about differences in safety and effectiveness of medical products according to demographic subgroups, such as sex, age, racial, and ethnic subgroups, to health care providers, researchers, and patients." Section 907(a)(2)(D) required the report to include "[a]n analysis of the extent to which a summary of product safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity is readily available to the public." In its report (p. 59), FDA stated that the agency can communicate demographic subgroup information to the public "using a variety of mechanisms," including product labeling, publicly posted clinical reviews, consumer updates, safety alerts, and label changes.

Although FDA has the ability to communicate with health care providers, researchers, patients, and the general public regarding information on the safety and efficacy of FDA-regulated products in demographic subgroups, manufacturers do not have the same latitude to communicate this highly valuable information because of the lack of clarity in the current regulatory environment.[2]

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[1] The MIWG is a coalition of medical product manufacturers formed to consider issues relating to the federal government's regulation of truthful, non-misleading, scientifically substantiated manufacturer communications about new uses of approved drugs and approved/cleared medical devices. The members of the MIWG are: Allergan, Inc.; Amgen Inc.; Bayer Healthcare Pharmaceuticals Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline LLC; Johnson & Johnson; Novartis Pharmaceutical Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; Purdue Pharma L.P.; and Sanofi US.

[2] These attributes are particularly troubling in light of the Supreme Court's holdings in Sorrell v. IMS Health, Inc., 131 S. Ct. 2653 (2011) (Sorrell) and FCC v. Fox Television Stations, 132 S. Ct. 2307 (2012) (Fox II).

As we explain further below, demographic subgroup information is clinically valuable, and manufacturer communications regarding this information can inform health care professionals and ultimately benefit patients. However, manufacturers face significant risk if they seek to provide the results of demographic subgroup analysis to physicians and other external constituencies. The Department of Justice (DOJ) has sought to criminalize the communication of results of retrospective subgroup analyses.[3] In warning and untitled letters, FDA (through the Office of Prescription Drug Promotion and its predecessor, the Division of Drug Marketing, Advertising, and Communications) has cited manufacturers for presenting the results of retrospective subgroup analysis. That is the case not only where the results of the retrospective analysis were presented in the form of arguably conclusory statements but also where such results were in the form of straightforward, non-promotional presentations that did not prescribe, recommend, or suggest any use of a specific product.

So that manufacturers can provide clinically valuable information regarding the use of drugs in demographic subgroups to health care professionals, we respectfully request that FDA revisit its current approach to manufacturer statements about the safety and efficacy of drugs in demographic subgroups and establish clear rules governing such statements, including particularly those derived from retrospective analyses.

I. Demographic Subgroup Information is Clinically Valuable, As FDA Recognizes, and Manufacturer Communications Regarding This Information Can Inform Health Care Professionals and Guide Patient Care

FDA regulations provide that every new drug application (NDA) must include information about gender, age, and racial subgroups. Under 21 C.F.R. § 314.50(d)(5)(v), "effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups." Section 314.50(d)(5)(vi)(a) provides that the integrated safety summary in the NDA must include "safety data . . . presented by gender, age, and racial subgroups," in addition to additional subgroup data when appropriate. Id.

FDA considers these subgroup analyses and draws clinically relevant conclusions from the data when making approval decisions. Indeed, according to agency guidance, if an NDA submission provides "an inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets[, then] the Agency may refuse to file the application."[4] FDA guidance documents for medical and statistical reviewers further recognize that demographic subgroup analyses may be relied on:

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[3] United States v. Harkonen, 510 Fed. Appx. 633 (9th Cir. 2013) (upholding wire fraud conviction); see also United States v. Harkonen, 2009 U.S. Dist. LEXIS 47255, at *5 (N.D. Cal. June 3, 2009) (explaining details of retrospective subgroup analysis). In its complaint against Pfizer, which resulted in a $2.3 billion settlement in September 2009, the government alleged, in part, that Pfizer had promoted Zyvox off-label, citing claims based on a retrospective subgroup analysis published in the journal CHEST. Fourth Amended Complaint at 14-18, United States v. Pfizer Inc., No. 07-CA-11728 (D. Mass. June 30, 2009).

[4] FDA, Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials 2 (Sept. 2005) (if there is "an inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets the Agency may refuse to file the application.").

- to evaluate the evidence of drug safety, by identifying subgroups at particular risk for certain adverse events;

- to evaluate the evidence of drug efficacy, by determining whether there are inconsistencies in treatment effects across relevant subpopulations, especially those subsets where there are special reasons for concern;

- to assess dose-response relationships, and to determine whether dose adjustments are necessary for certain subgroups; and

- to identify hypotheses regarding safety and efficacy in certain subgroups, which would be worth examining in further studies.[5]

Further, FDA has recognized that subgroup analysis performed and evaluated as part of the NDA review may be used to "refine evidence of effectiveness that has already been established," and thereby provide "useful labeling information."[6] FDA has stated that subgroup analysis is required in an NDA "so that the nature of the drug's effectiveness can be as fully defined as possible, and the user of the drug can be given the best possible information on how to use the drug and what results to expect."[7] FDA has stated in guidance that the Clinical Studies section of the labeling should: (1) include the findings of any demographic analyses "that had a reasonable ability to detect subgroup differences"; (2) "note when analyses were not useful because of inadequate sample size"; and (3) present "[c]ompelling results from analyses of other subgroups of established interest . . . with a caution statement, where appropriate, about the inherent risks of unplanned subgroup analyses."[8]

As FDA stated in the Section 907 report, one of its goals is to publicly communicate clinically valuable information regarding the use of a product in demographic subgroups to guide health care professionals in caring for patients. FDA stated:

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[5] CDER, MAPP 6010.4: Good Review Practice: Statistical Review Template 16-17 (July 30, 2012); FDA, Draft Guidance for Industry: Integrated Summary of Effectiveness 7, 8, 9, 10, 11-12 (Aug. 2008); FDA, Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials (Sept. 2005); FDA, Guidance for Industry: Premarketing Risk Assessment 21 (March 2005); FDA, Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review 5 (Feb. 2005); FDA, Guidance for Industry: M4E: The CTD—Efficacy 25 (Aug. 2001); Guideline for Industry: ICH E3 Structure and Content of Clinical Study Reports 22-23 (Jul. 1996); see also 21 C.F.R. § 314.50(d)(5)(v) (requiring that the NDA "identify any modifications of dose or dose interval needed for specific subgroups").

[6] FDA, Draft Guidance for Industry: Integrated Summary of Effectiveness 11-12 (Aug. 2008); see also Guideline for Industry: ICH E3 Structure and Content of Clinical Study Reports 22-23 (Jul. 1996) ("These analyses are not intended to 'salvage' an otherwise nonsupportive study but may . . . be helpful in refining labeling information, patient selection, or dose selection."); FDA, Guideline for the Format and Content of the Clinical and Statistical Sections of an Application 66 (July 1988) (same).

[7] FDA, Guideline for the Format and Content of the Clinical and Statistical Sections of an Application 29 (July 1988).

[8] FDA, Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format 9 (Jan. 2006).

> One of FDA's goals is to make regulatory decisions based on scientific information and to publicly communicate actionable information. That is, when clinically meaningful differences are observed for certain subgroups (e.g., an adverse effect seen more commonly with a certain genetic mutation), this information is included in the product labeling or otherwise publicly released. This information is then used to guide health care professionals in prescribing and monitoring products used by their patients.[9]

Communications by manufacturers regarding the safety and efficacy of their products in demographic subgroups can help further the agency's stated goal of communicating clinically valuable information regarding the use of products in demographic subgroups. Manufacturers are yet another source of this important information for health care professionals. Such communications can help to educate and guide health care professionals as they prescribe and monitor products used by their patients and may ultimately improve patient care.

In sum, FDA policy recognizes the value of demographic subgroup information. The value is not limited to the capacity of such information to inform FDA decision making on an NDA. Demographic subgroup information is also, in FDA's view, useful and even necessary to assure safe and effective use of approved drugs because subgroup analysis can be informative for practitioners. Manufacturer communication of such data can inform practitioners and may ultimately result in better patient care.

II. The Rules Governing Manufacturer Dissemination of Information About Demographic Subgroup Analyses Are Unclear

Although, as noted in the Section 907 report, FDA has broad latitude to communicate subgroup information to the public in connection with the safety and efficacy of drugs and medical devices, the developers and manufacturers of those products are not clearly permitted to communicate demographic subgroup analysis to nearly the same extent.

Regulatory provisions applicable to prescription drug advertising acknowledge that a manufacturer can use retrospective analysis. Under 21 C.F.R. § 202.1(e)(7)(iii):

> An advertisement may be false, lacking in fair balance, or otherwise misleading or otherwise violative of section 502(n) of the act if it:
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> * * *
>
> Uses statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.

This provision is significant for two reasons. First, it states that a prescription drug

[9] Section 907 Report at 60 (emphasis in original).

advertisement may be "violative" if it uses retrospective analysis as described in the regulation. Necessarily, then, it is possible to use such analysis under certain circumstances without causing the advertisement to be "violative." Second, it refers to the use of retrospective statistical analyses and techniques for two specific purposes as potentially violating Section 502(n) of the FDCA: (1) to "discover and cite findings not soundly supported by the study"; and (2) "to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations." In other words, retrospective analysis is not categorically deemed even to potentially violate Section 502(n)—it is only in two specific scenarios that use of such analysis "may be . . . violative."

To our knowledge, FDA has not provided guidance to industry setting forth the agency's interpretation of 21 C.F.R. § 202.1(e)(7)(iii). The regulation does not squarely address when it would constitute a violation for a prescription drug advertisement to use retrospective subgroup analysis. Nor does it define key terms, such as "discover and cite findings." If a retrospective subgroup analysis suggests drug effect that is different from that observed in the overall population in the study, it is not clear whether communicating that possibility constitutes a "finding[]" of the type that could cause the advertisement to be "violative." The regulation is particularly hard to interpret because of the other regulatory provisions (discussed above) that appear to provide for the presentation of retrospective subgroup analysis in product labeling according to different standards than those in § 202.1(e)(7)(iii). Additional ambiguity is created by the assertions in the Section 907 report about FDA's ability to communicate subgroup information to the public, which appears to reflect the agency's view that such information is useful to a wide range of stakeholders.

It seems plain that, under the existing regulatory scheme, communications regarding use of a drug in demographic subgroups based on retrospective subgroup analyses are not inherently false or misleading. FDA's regulatory framework, which provides for retrospective subgroup analysis in NDA submission and permits manufacturers to communicate the findings of such analysis in some (inadequately defined) circumstances, reflects the reality that it would be impossible and inappropriate to require manufacturers to conduct studies large enough prospectively to investigate the safety and effectiveness of investigational products in all demographic subgroups.[10] Moreover, this framework recognizes that communications regarding subgroups based on retrospective analyses would be supported by the exact type of information that FDA regulations require in an NDA.[11] FDA relies on this information when performing its own review of drug efficacy and safety and may communicate this information in drug labeling. This is significant because all information in the approved labeling must be "informative and accurate and [not] false or misleading in any particular."[12] By including information based on retrospective subgroup analyses in labeling, FDA recognizes that such information can be truthful and non-misleading.

Questions regarding the appropriate use of subgroup analysis, particularly retrospective analysis, are not likely to become any less important as FDA increasingly focuses on the genetic determinants of response to therapy. Although FDA's Section 907 report focused on subgroups defined according to demographic variables, the lack of clarity extends to

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[10] FDA, Guidance for Industry: E9 Statistical Principles for Clinical Trials 34 (Sept. 1998) (FDA recognizing that "[i]n most cases . . . subgroup or interaction analyses are exploratory . . .").
[11] 21 C.F.R. § 314.50(d)(5)(v) & (vi).
[12] Id. § 201.56(a)(2).

analysis of drug and device performance in subgroups defined by genetic variables.[13] As the report itself acknowledged (pp. 4, 7, 60), "scientific advances in understanding the specific genetic variables underlying disease and response to treatment are increasingly becoming the focus of modern medical product development as we move toward the ultimate goal of tailoring treatments to the individual, or class of individuals, through personalized medicine." Thus, "[a]s we move into the coming decades, [and] FDA's regulatory mission . . . increasingly focus[es] on gathering and understanding information related to . . . genetic and biological influences that affect disease and response to medical products," it will become ever more important to assure clarity in the rules governing manufacturer dissemination of subgroup analysis, which of necessity includes retrospective analysis.

We appreciate the opportunity to comment.

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[13] Section 907 Report at 4, 7 ("[S]cientific advances in understanding the specific genetic variables underlying disease and response to treatment are increasingly becoming the focus of modern medical product development as we move toward the ultimate goal of tailoring treatments to the individual, or class of individuals, through personalized medicine."); see also id. at 60 ("As we move into the coming decades, FDA's regulatory mission will increasingly focus on gathering and understanding information related to [. . .] genetic and biological influences that affect disease and response to medical products (effectiveness and safety).").

Respectfully submitted,

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