SIDLEY

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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: Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments (Docket No. FDA-2018-N-3017)

The Medical Information Working Group ("MIWG") submits these comments in response to FDA's November 20, 2018 Federal Register notice (83 Fed. Reg. 58,574) inviting comments on its proposed framework for regulating prescription drug-use-related software ("the PDURS Notice"). The MIWG is a coalition of medical product manufacturers formed to seek clarity in the FDA regulatory scheme regarding the dissemination of truthful, non-misleading information about prescription drugs, biological products, and medical devices, and to improve the regulatory and enforcement environment affecting manufacturer communications regarding those products, including products in development and new uses of marketed products.[1]

The MIWG supports FDA's efforts to develop risk-based regulatory frameworks in the digital health space that both foster innovation and provide clarity to pharmaceutical and medical device manufacturers. As Commissioner Gottlieb has recognized, consumers are increasingly using digital health tools to inform their healthcare decisions, so accordingly, "FDA wants to promote the development of digital technologies that can also help guide the safe and effective use of medicines, to help patients improve their health."[2] We support FDA's stated aim "to pursue a risk-based and least burdensome approach to [prescription drug-use-related software] products to promote beneficial innovation that can promote healthcare goals and advance patient health and safety."[3]

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[1] The members of the MIWG are: Amgen, Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Boehringer Ingelheim Pharms., Inc.; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline, LLC; Johnson & Johnson; Novartis Pharmaceutical Corp.; Pfizer Inc.; and Samumed, LLC. The MIWG's prior submissions to FDA are available at www.miwg.org.

[2] FDA, FDA in Brief: FDA Takes Steps to Advance a New Framework to Promote Development of Digital Tools that Can Inform the Safe and Effective Use of Prescription Drugs (Nov. 19, 2018), *available at* https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm626166.htm.

[3] *Id*.

The PDURS Notice, however, raises a number of issues that are related to manufacturer communications and on which we have previously engaged with the agency. We write specifically to address the following aspects of the proposed PDURS framework that are relevant to our group's mission and to our prior advocacy:

1. The commentary addressing the scope of "labeling" as defined in the statute;
2. The commentary addressing intended use;
3. The proposed approach to involve the Office of Prescription Drug Promotion ("OPDP") and CBER Advertising and Promotional Labeling Branch ("APLB") in providing advisory comments with respect to the output of PDURS; and
4. The First Amendment implications presented by the proposed regulatory framework and by the commentary included in the PDURS Notice.

As described below, we urge FDA to be mindful of these considerations so that the PDURS framework encourages, rather than discourages, valuable communication through digital health tools.

I. The PDURS Notice Sets Forth an Overbroad Interpretation of the Definition of "Labeling" That Is Inconsistent with Supreme Court Precedent and Other Applicable Authorities

The PDURS Notice asserts that all outputs from PDURS, such as screen displays, alerts, reminders, audio messages, vibrations, or sounds, would constitute drug labeling. This assertion relies on an overbroad interpretation of the statutory definition of "labeling" that fails to apply properly the applicable Supreme Court case law and other authorities.

The PDURS Notice cites the Supreme Court's holding in *Kordel v. United States*, 355 U.S. 345 (1948), for the proposition that labeling broadly "include[s] materials that supplement or explain an article."[4] FDA acknowledges that *Kordel* also considered whether the drug product and the materials relating to the drug product had a common origin and common destination and whether they were part of an integrated distribution program.[5] Yet the PDURS Notice fails to recognize that these factors serve to limit what constitutes "labeling" and are not mere "consider[ations]."

As the MIWG has explained in prior submissions to FDA regarding the proper scope of "labeling,"[6] the core holding of *Kordel* was that a manufacturer cannot evade the statutory labeling requirements simply by sending drugs and "literature" in two separate shipments.[7] The Court set forth the following criteria for determining whether information constitutes labeling:

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[4] 83 Fed. Reg. 58574, 58576 (Nov. 20, 2018).
[5] *Id.*
[6] MIWG, White Paper: Systemic, Society, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079, at 42-46 (Oct. 31, 2014); MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, at 13-15 (Sept. 3, 2013).
[7] *See* 335 U.S. 345, 348-351 (1948) ("The question whether the separate shipment of the literature saved the drugs from being misbranded within the meaning of the Act presents the main issue in the case . . . . [W]e conclude that the phrase 'accompanying such article' is not restricted to labels that are on or in the article or package that is transported.").

- "Nowhere else [is] the purchaser advised how to use [the article]."
- "It constitute[s] an essential supplement to the label attached to the package."
- "[I]t supplements or explains [the product], in the manner that a committee report of the Congress accompanies a bill."
- The materials and products are "interdependent; they [are] parts of an integrated distribution program."[8]

The Court made clear that not all "written, printed, or graphic matter" that merely mentions a product qualifies as "labeling." To qualify as "labeling," the "matter" must satisfy the "functional" criteria set forth above, which include the criterion that it constitute an essential supplement to the label. FDA regulations similarly explain that "labeling" under section 201(m) of the Federal Food, Drug, and Cosmetic Act "furnishes or purports to furnish information for use or . . . prescribes, recommends, or suggests a dosage for the use of the drug."[9]

Properly construed, "labeling" does not include any "written, printed, or graphic matter" that merely mentions a specific product. Consequently, all PDURS output, as defined in the PDURS Notice, would not automatically qualify as labeling. Yet the PDURS Notice attempts to treat all software outputs in the same way, without applying the full *Kordel* criteria in a consistent, disciplined manner. For example, FDA suggests that all PDURS output explains how to use a drug, or supplements the use of a drug, without considering the specific information provided by any particular "output." Nor does the preamble consider whether the output is an *essential* supplement to the drug label or whether other materials advise how to use the drug.[10] The PDURS Notice also assumes that "the drug and software are part of an integrated distribution program," without explaining or analyzing the different potential uses of PDURS, the way PDURS may be disseminated, or what an "integrated distribution program" may mean in the digital health context.[11]

This overbroad interpretation of labeling may ultimately discourage pharmaceutical manufacturers from communicating through digital health tools or otherwise developing innovative ways to inform the safe and effective use of their products. As FDA further considers the PDURS framework, the agency should clarify its interpretation of labeling to be more consistent with *Kordel* and eliminate ambiguity that might conflict with FDA's stated aim of promoting innovation.

The PDURS Notice also cites 21 C.F.R. § 202.1(l)(2) as though it functions as a regulatory interpretation of the statutory definition of "labeling." In particular, the notice states: "Promotional labeling can include printed, audio, or visual matter descriptive of a drug that is

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[8] *Id.* at 348, 350.
[9] 21 C.F.R. § 201.100(d).
[10] 83 Fed. Reg. at 58578.
[11] *Id.* Elsewhere the PDURS Notice states that communications that are considered promotional labeling must be submitted to FDA at the time of initial dissemination, "regardless of the content of those communications or the medium used for distribution." *Id*. at 58577. This statement suggests that the determination of whether a communication qualifies as "labeling" does not depend on its content. This stands in direct conflict with *Kordel* and is surely not what FDA intended.

disseminated by or on behalf of a drug's manufacturer, packer, or distributor (21 CFR 202.1(l)(2))." That provision includes an extensive list of categories of "matter" that are "hereby determined to be labeling as defined in section 201(m) of the act."[12] As the government has previously explained in litigation, however, this regulation does not interpret "labeling" but rather operates to exclude the listed categories of "matter" from the statutory definition of "advertising":

> Section 202.1(l)(2) was issued pursuant to 21 U.S.C. § 352(n), which governs prescription drug advertising. By its terms, Section 352(n) excludes "any printed matter which the Secretary determines to be labeling . . . ." Section 202.1(*l*)(2), which lists items that "are hereby determined to be labeling," was issued to implement this exclusion. In keeping with the terms of Section 352(n), its purpose is to limit the domain of the Act's prescription drug advertising requirements, by making clear what kinds of materials are not subject to those requirements. It was never meant to suggest that the items in the list will be regulated as labeling without regard to *Kordel*'s construction of "accompanying," and it has not been applied by FDA in that manner.[13]

The MIWG has previously requested that FDA clarify the scope of "labeling" by issuing new interpretive guidance confirming that "labeling" is defined by 21 C.F.R. § 1.3(a) and 21 U.S.C. § 321(m).[14] Fulfilling that request would bring much-needed clarity to the definition of "labeling" and would inform FDA's authority over PDURS output and in other contexts. We hereby renew our request.

II. The PDURS Notice Inappropriately Suggests That the Intended Use of Software Is Determined by Its Function

The PDURS Notice suggests that intended use may be determined based solely on the function of software, which is inconsistent with applicable law, as the MIWG has previously described in comments submitted to FDA.[15] The PDURS Notice states, for example, that "[w]hether software is a device is determined by [the Center for Devices and Radiological Health ("CDRH")] and may *depend upon the software's functions.*" The PDURS Notice states, further, that software can "meet[] the definition of a device *because of its function*."[16] The preamble also

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[12] The list includes "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints[.]"

[13] Def.'s Reply in Supp. of Mot. to Dismiss or Summ. J. at 22-23, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. Mar. 29, 2010).

[14] *E.g.*, MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, at 15 (Sept. 3, 2013).

[15] *E.g.*, MIWG, Comments on Proposed Partial Delay of Effective Date of "Intended Use" Final Rule, Docket No. FDA-2015-N-2002-2014 (Feb. 5, 2018); MIWG, Comments on Microneedling Draft Guidance, Docket No. FDA-2017-D-4792-0006 (Nov. 14, 2017); MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002-2001 (July 18, 2017); MIWG, PhRMA & BIO, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002-1977 (Feb. 8, 2017).

[16] 83 Fed. Reg. at 58576-77 (emphasis added).

states that software "may contain multiple *functions, some of which may be considered a device*."[17]

On January 16, 2018, FDA delayed the effective date of certain amendments to its existing intended use regulations that would have significantly modified the regulatory definitions by, among other things, incorporating a "totality of the evidence" standard.[18] The delay was issued so that FDA could further consider the substantive issues raised by comments received from the MIWG and other industry stakeholders.[19] The approach to intended use contemplated by the PDURS Notice raises the same issues as the broader intended use rulemaking and improperly preempts the FDA's consideration of the substantive issues raised by comments to that rulemaking.

The PDURS Notice is not the first time FDA has advanced a problematic interpretation of intended use outside of the broader intended use rulemaking. For example, in September 2017, the agency issued *Draft Guidance for Industry and FDA Staff: Regulatory Considerations for Microneedling Devices* ("Draft Guidance on Microneedling"). There, FDA proposed an interpretation of intended use that would permit consideration of a wide variety of evidence, including but not limited to product design and technological characteristics and features,[20] and the MIWG objected to that proposed approach.[21]

The MIWG has previously requested—including in our comments to the Draft Guidance on Microneedling—that FDA abandon the "totality of the evidence standard," refrain from adopting positions on intended use outside of the intended use rulemaking, and revise its regulatory framework to eliminate any suggestion that intended use of a product may be solely determined by its function. We renew our prior requests on intended use and further ask that FDA prevent the publication or adoption of new policies or procedures that preempt the agency's final action on the stayed final rule.

III. The PDURS Notice Proposes an Expansion of FDA's Existing Voluntary Advisory Comment Process That Will Impose Significant Burdens and Discourage Innovation

The PDURS Notice states that, for certain PDURS output that "may increase the potential for harm to health where it provides recommendations that may direct patients to make decisions about their drug or disease that would normally be made in consultation with a healthcare provider," FDA "would recommend" that a sponsor use the OPDP or APLB voluntary advisory comment process before disseminating the PDURS output.[22] The PDURS Notice states that such prior review would assess whether the proposed output is consistent with the FDA-required product labeling and is truthful and non-misleading.[23]

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[17] *Id.* at 58581 (emphasis added).
[18] *See* 82 Fed. Reg. 2193 (Jan. 9, 2017).
[19] *See* 83 Fed. Reg. 2092 (Jan. 16, 2018).
[20] FDA, Draft Guidance for Industry and FDA Staff: Regulatory Considerations for Microneedling Devices, at 7-8 (Sept. 15, 2017).
[21] *E.g.*, MIWG, Comments on Microneedling Draft Guidance, Docket No. FDA-2017-D-4792-0006 (Nov. 14, 2017).
[22] 83 Fed. Reg. at 58580.
[23] *Id.*

As an initial matter, the recommended use of the voluntary advisory comment process is concerning because the process is already over-burdened. The PDURS Notice acknowledges that more than 100,000 promotional pieces are already submitted to OPDP annually[24] and that OPDP is able to review only a fraction of these.[25] The voluntary advisory comment process is not subject to any statutory or regulatory deadlines by which OPDP or APLB must respond, and as a practical matter, companies frequently must wait months to obtain meaningful feedback. OPDP and APLB do not have sufficient resources to provide advisory comments in a timely manner for the submissions it currently receives, and adding to the workload with submissions of PDURS outputs would exacerbate the problem and could have the downstream effect of chilling innovation by pharmaceutical manufacturers and software developers, as well as delaying the launch of new software that could be beneficial to patients.

These constraints aside, OPDP and APLB also lack the resources to consider dynamic software output, which necessarily involves some analysis of the way in which the software functions, or the expertise to evaluate the potential for the PDURS output to increase harm to health of patients. As a practical matter, we expect that OPDP and APLB personnel would routinely require input from the relevant review division and from CDRH, and that such consultations would significantly add to the already-lengthy advisory comment timeline.

The PDURS Notice also proposes that updates be submitted to FDA at the time of initial dissemination whenever a software update "results in changes to the output experienced by the user."[26] Given the expansive definition of "output" proposed in the notice, we anticipate that many software updates could alter the user experience. Taken together with FDA's "recommend[ation]" that PDURS output that "may increase the potential for harm to health" be reviewed through the advisory comment process prior to dissemination, it appears that FDA would expect manufacturers to refrain from implementing any updates to PDURS output before obtaining advisory comments in situations where the updated output "*may* increase the potential for harm to health."

The MIWG has long advocated that FDA implement a meaningful voluntary advisory opinion process that allows manufacturers to obtain timely, binding advice from the agency with respect to proposed communication initiatives.[27] Such an advisory opinion process would enable companies to seek comments on the legality of contemplated business practices, rather than comments on specific advertisements or promotional pieces as permitted under the framework that currently exists at FDA.[28] Such advisory opinions, which would be available to the public,

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[24] In FY 2018, OPDP received a total of 107,108 promotional materials from 60,841 Form 2253 submissions. Office of Prescription Drug Promotion (OPDP) FDA-Track Metrics, https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm614663.htm (last updated Oct. 25, 2018).
[25] 83 Fed. Reg. at 58577.
[26] *Id.* at 58579.
[27] *See* MIWG, Comments on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, Docket No. FDA-2016-N-1149, at 20-27 (Apr. 19, 2017); MIWG, Comments to the FDA Transparency Task Force, Docket No. FDA-2009-N-0247 (Apr. 15, 2010).
[28] *Compare* 21 C.F.R. § 10.85 (contemplating FDA advisory opinions on "matter[s] of general applicability") *with* 21 C.F.R. § 202.1(j)(4) (providing for advisory comment process for prescription drug advertisements).

would provide manufacturers and others with additional insight on the agency's application of the law in the context of a rapidly-evolving area like digital health that may not be addressed by existing regulations and guidance documents. We believe that implementing such an advisory opinion process would be preferable to putting additional strain on the existing advisory comment process.

IV. The PDURS Notice Presents Significant First Amendment Issues and Threatens to Chill Protected Speech

The PDURS Notice explains that "promotional labeling is generally any labeling other than FDA-required labeling that is devised for promotion of the product" and "may have *other functions in addition to promotion*."[29] We are concerned that the italicized language could be interpreted to mean that any written, printed, or graphic matter that mentions or effectively identifies a specific product, even if it includes non-promotional content, is labeling.

Such an interpretation would implicate the First Amendment and could chill manufacturer communications. The statement in the PDURS Notice is addressing a scenario in which manufacturer speech has both promotional (i.e., commercial) and non-promotional (e.g., scientific or educational) characteristics. The Supreme Court has stated that, where commercial speech is "inextricably intertwined" with fully protected non-commercial speech (e.g., scientific expression), it will not "parcel out the speech, applying one test to one phrase and another test to another phrase" and will instead "apply [the] test for fully protected expression" to the entirety of the speech.[30] The PDURS Notice does not consider the higher level of constitutional scrutiny that a court may apply to such "mixed" speech.

Additionally, the recommendation that manufacturers submit certain PDURS output for OPDP or APLB advisory comments (*see* Section III above) could, in practice, amount to a prior restraint on manufacturer speech. Rather than providing generally applicable, meaningful guidance to help manufacturers determine whether and when PDURS output is consistent with the FDA-required labeling, is truthful and non-misleading, and otherwise satisfies FDA requirements, the agency instead proposes that manufacturers seek individualized feedback—and encounter lengthy delays—prior to making PDURS output available to prescribers and patients whenever FDA believes such output "may" increase the potential for harm. Because of the significant delays involved in obtaining advisory comments, this approach would have First Amendment implications; if implemented, it could also result in delays in the development and launch of new software products that enable valuable communications to health care professionals and patients. To the extent that FDA, in refining its regulatory approach to PDURS, continues to believe that the advisory comment process is an appropriate way for manufacturers to seek agency feedback, it is critical that the process remain voluntary and that the agency not expect or specifically recommend that any manufacturer obtain such feedback prior to dissemination of the PDURS.

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[29] 83 Fed. Reg. at 58576.
[30] *Riley v. Nat'l Fed'n of the Blind of N.C.*, 487 U.S. 781, 795-96 (1988).

V. Conclusion

The MIWG appreciates and supports FDA's proposal to apply existing authorities in a risk-based manner that fosters innovation and the use of digital health technologies with prescription drugs. However, the MIWG is concerned by assertions in the PDURS Notice that would potentially stretch FDA's authority beyond its permissible boundaries and impose significant burdens on industry. We therefore request that the agency:

1. Clarify the scope of "labeling" by issuing new interpretive guidance confirming that "labeling" is defined by 21 C.F.R. § 1.3(a) and 21 U.S.C. § 321(m);

2. Refrain from adopting positions on intended use outside the intended use rulemaking, abandon the "totality of the evidence" approach to intended use, and prevent the publication or adoption of new policies or procedures that preempt the agency's final action on the stayed final rule;

3. Implement an advisory opinion process; and

4. Make clear that use of the OPDP or APLB advisory comments process for PDURS is voluntary, rather than expected or recommended.

Thank you for the opportunity to comment.

Respectfully submitted,

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