ROPES & GRAY

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Re: Draft Guidance for Industry: "Regulatory Considerations for Prescription Drug Use-Related Software" (Docket No. FDA-2023-D-2482)

The Medical Information Working Group ("MIWG") appreciates the opportunity to provide the United States Food & Drug Administration ("FDA") with comments on the draft guidance for industry, "Regulatory Considerations for Prescription Drug Use-Related Software" ("PDURS Draft Guidance" or "Draft Guidance"). 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 a risk-based regulatory approach to the digital health space that fosters innovation and provides clarity to medical product manufacturers. The PDURS Draft Guidance raises a number of issues related to manufacturer communications on which we have previously engaged with the agency. We write specifically to address the following aspects of the PDURS draft guidance that are relevant to our group's focus:

1. The commentary and definitions addressing the scope of "labeling";
2. The classification of the end-user output of certain PDURS software functions as FDA-required labeling; and
3. The First Amendment implications presented by the PDURS Draft Guidance.

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

I. The PDURS Draft Guidance Sets Forth an Overbroad Interpretation of the Definition of "Labeling" That Is Inconsistent with Supreme Court Precedent and Other Applicable Authorities

A. The Draft Guidance is Inconsistent with the Supreme Court's Interpretation of the Term "Labeling"

The PDURS Draft Guidance asserts that all software output disseminated by or on behalf of a drug sponsor that "supplements, explains, or is otherwise textually related to one or more of the sponsor's drug products" constitutes labeling subject to FDA's regulatory oversight. 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 Draft Guidance 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, explain, or are otherwise textually related to the article."[2] It also explicitly acknowledges that the Court in *Kordel* also "considered" whether the drug product and the materials relating to the drug product were part of an integrated distribution program.[3] Yet the PDURS Draft Guidance fails to mention that *Kordel* also addressed whether the drug product and materials relating to the drug product had a common origin and common destination. Further, it fails to recognize that *both* of these additional factors serve to meaningfully limit what constitutes "labeling" and are not mere "considerations."

Moreover, the broad language of "otherwise textually related to the article," is found nowhere in *Kordel*. Instead, the Supreme Court in *Kordel* explained, "One article or thing is accompanied by another when it supplements or explains it, in the manner that a committee report of the Congress accompanies a bill. No physical attachment one to the other is necessary. It is the textual relationship that is significant."[4] Considered in context, *Kordel* does not stand for the proposition that *any* textual relationship is sufficient to render content labeling, but rather that materials need not be physically attached to the product to be considered labeling, so long as there is a textual relationship between the material and the product that would rise to the level of "supplement[ing] or explain[ing] it, in the manner that a committee report . . . accompanies a bill."

FDA's overreach on this point is significant. A standard that broadly would consider anything "otherwise textually related" to a sponsor's drug to be labeling could bring within FDA's regulatory authority anything that merely mentions the name of a sponsor's drug. Arguably, such a standard would even render content that does not mention the sponsor's drug but is "textually related" in some way, such as by describing the disease state for which the sponsor's drug is indicated, to be labeling. Such disease-state focused software, like other

[2] FDA, Guidance for Industry: Regulatory Considerations for Prescription Drug Use-Related Software (Draft), footnote 7 (Sept. 2023) [*hereinafter* "PDURS Draft Guidance"].
[3] *Id.*
[4] 335 U.S. 345, 350 (1948).

disease-focused communications by drug sponsors, is not within FDA's authority to regulate as labeling.[5]

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] Beyond that, the Court emphasized that *all* of the following criteria were relevant to supporting a finding that the literature at issue there was labeling:

- "[T]he drugs and the literature had a common origin and a common destination."
- "The literature was used in the sale of the drugs."
- "It explained their uses."
- "Nowhere else was the purchaser advised how to use them."
- "It constituted an essential supplement to the label attached to the package."[8]

It was only based on this totality that the Court concluded: "Thus, the products and the literature were interdependent.... [T]hey were parts of an integrated distribution program."

Accordingly, the Court also 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 "perform the function of labeling," by supplementing or explaining the product, and otherwise be "interdependent" with the relevant product. FDA regulations similarly explain that "labeling" under section 201(m) of the Federal Food, Drug, and Cosmetic Act ("FDCA") "furnishes or purports to furnish information for use or . . . prescribes, recommends, or suggests a dosage for the use of the drug."[9]

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[5] FDA has long respected the fact that "unbranded" communications—which do not mention a specific product by name—are not subject to FDA regulation, as long as they do not "effectively promote" or "clearly point" to a specific product by other means. *See, e.g.*, Policy Statement on Advertising and Promotion of Unapproved Rx Drug Products (July 22, 1982); DDAL, Update of Pre-Approval Promotion Guidance (Aug. 1985); DDAL, Clarification of FDA Policy on "Institutional," "Corporate" or "Health Message" Advertising Practices (Sept. 1985); DDAL, Reissuance of Pre-Approval Promotion Guidance (Aug. 1986); Institutional/Disease Oriented Advertisements (June 6, 1998); Pre-Approval Promotion Guidance (April 1994); Untitled Letter to GlaxoSmithKline (April 15, 2010); Warning Letter to Ipsen Group – Tercica Inc. (Nov. 3, 2010). This is true even though FDA has not developed contemporary guidance on this topic, despite a commitment to do so in 1997. *See* 62 Fed. Reg. 14912, 14916 (Mar. 28, 1997). The most recent guidance was issued in draft form in 2004, but withdrawn in 2015. *See* FDA, Draft Guidance for Industry "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms, at 1 (Jan. 2004); 80 Fed. Reg. 26059 (May 6, 2015) (withdrawing the draft document, along with 46 other drafts "to improve the efficiency and transparency of the guidance development process"). The withdrawal of this draft guidance, which in any case was non-binding and never finalized, has left industry in limbo on a critical area of manufacturer communications.

[6] MIWG, Comments re: Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments, Docket No. FDA-2018-N-3017, at 2-4 (Jan. 22, 2019); 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.").

[8] *Id.* at 348, 350.

[9] 21 C.F.R. § 201.100(d).

Properly construed, "labeling" does not include any "written, printed, or graphic matter" that merely mentions or implicates in some way a specific product. Consequently, not all PDURS end-user output, as defined in the PDURS Draft Guidance, would automatically qualify as labeling. Yet the PDURS Draft Guidance attempts to treat all such software outputs in the same way, without applying the full *Kordel* criteria in a consistent, disciplined manner. This overbroad conception of labeling is particularly striking in Appendix B of the PDURS Draft Guidance, which explicitly suggests that "mention" of a drug is enough to render a software output labeling. For example, in explaining Example B in Appendix B, the PDURS Draft Guidance states that "the mobile app's output must be submitted on Form FDA 2253 because it mentions the sponsor's drug name (e.g., the insulin product), is drug promotional labeling, and no 510(k) is required for these changes" (emphasis added).[10]

This overbroad interpretation of labeling may ultimately discourage manufacturers from communicating through digital health tools or otherwise developing innovative ways to inform the safe and effective use of their products.

We request that FDA revise its interpretation of labeling in the PDURS Draft Guidance to be more consistent with *Kordel*, including by deleting the language "otherwise textually related to one or more of the sponsor's drug products" from the definition of PDURS. Additionally, we request that FDA explicitly acknowledge that disease-focused software tools disseminated by or on behalf of sponsors are outside the definition of PDURS and are not regulated by FDA as labeling.

B. The Draft Guidance Arguably Treats the Output of Non-PDURS Functions of Multi-Function Software Products as Promotional Labeling, Exceeding FDA's Authority to Regulate Prescription Drug Labeling

The PDURS Draft Guidance fails to distinguish between PDURS and non-PDURS software functions in multi-function software. Although FDA defines the term "software function" in the PDURS Draft Guidance, and the Draft Guidance distinguishes between (1) device-connected and non-device-connected and (2) device and non-device software functions, the Draft Guidance does not address a scenario where software may include both PDURS and non-PDURS functions and how FDA proposes to regulate the output of such software.

The need for such distinction could arise, for example, if the software includes a portal for clinical trial participants where they can upload data for the trial, get information on upcoming site visits, or access other relevant clinical trial information. Because the draft guidance fails to address non-PDURS functions of multi-function software, it is unclear whether FDA considers output from non-PDURS functions to be labeling subject to FDA regulation. As currently defined in the Draft Guidance, the term "end-user output" would arguably include all end-user output of multi-function software, including non-PDURS functions. This is because the Draft Guidance does not limit the term to PDURS "function," instead defining end-user output

[10] PDURS Draft Guidance at 14. The discussion of Example A in Appendix B similarly states, "In addition to the dose calculator, the software output mentions the insulin product. This output is determined to be promotional labeling for the prescription drug." (emphasis added).

broadly to include "any material or content presented to a patient, caregiver, or health care practitioner (end user) by the prescription drug use-related software."[11]

Such an approach would exceed FDA's labeling authorities.[12] The output of an independent non-PDURS function, such as a clinical trial portal, would not supplement or explain the product, much less meet the additional criteria described in *Kordel*. Accordingly, we request that FDA clarify that non-PDURS functions of multi-function software are not promotional labeling and therefore need not be submitted to FDA on Form 2253. This could be achieved by modifying the definition of "end-user output" as follows:

> End-user output: Any material or content presented to a patient, caregiver, or health care practitioner (end user) by the prescription drug use-related software functions constitutes the end-user output, and such end-user output constitutes drug labeling. End-user output includes, for example, screen displays created by the software, whether static or dynamic, as well as sounds or audio messages created by the software. The end-user output does not include outputs from non-PDURS software functions of software that includes both PDURS and non-PDURS software functions.

C. The Draft Guidance is Inconsistent with FDA's Prior Interpretation of 21 C.F.R. § 202.1(*l*)(2)

The PDURS Draft Guidance 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 Draft Guidance states: "Promotional labeling can include printed, audio, or visual matter descriptive of a drug that is disseminated by or on behalf of a drug's manufacturer, packer, or distributor (21 CFR 202.1(l)(2))."[13] 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."[14]

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[11] *Id.* at 6.

[12] It would also be inconsistent with FDA's approach to multi-function software products in other contexts. For example, in the device software context, the FDCA addresses multi-function software by specifying that FDA shall not regulate non-device functions of software that also includes device functions, though it may assess the impact that a non-device function has on a device function of the software. FDA has further elaborated on its approach in its guidance for industry and FDA staff, "Multiple Function Device Products: Policy and Considerations" (July 2020), which FDA cites in the PDURS Draft Guidance. The approach of regulating function-by-function for multi-function software products also is one that the FDA endorses in the PDURS Draft Guidance. For example, when addressing inclusion of information in the Prescribing Information for device-connected PDURS, the draft guidance specifies that the Prescribing Information should describe the end-user output of device connected software *functions*. PDURS Draft Guidance at 7. Likewise, in describing when FDA would consider end-user output to be FDA-required labeling rather than promotional labeling, FDA focuses on the specific *function* for which the output is described in the Prescribing Information, not all functions of the PDURS. PDURS Draft Guidance at 7-8 ("If FDA determines the evidence demonstrates a clinically meaningful benefit, the end-user output *associated with the software function* generally would constitute FDA-required labeling, and certain post-approval changes to such output (e.g., end-user output from a mobile app *specific to the software function*) should be reviewed and approved by FDA . . .") (emphasis added).

[13] PDURS Draft Guidance at 4.

[14] 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[.]"

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.[15]

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).[16] 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. For the PDURS Draft Guidance specifically, we request that FDA delete the sentence quoted above that refers to 21 C.F.R. § 202.1(*l*)(2) and that the final guidance refer only to 21 C.F.R. § 1.3(a) and 21 U.S.C. § 321(m) as definitions of "labeling."

II. The PDURS Draft Guidance Treats Certain PDURS Output as FDA-Required Labeling, Which Is Inconsistent With FDA Regulations Governing Labeling and Will Discourage Sponsors From Evaluating and Seeking to Include Information on PDURS in a Drug's Prescribing Information

The PDURS Draft Guidance proposes to treat certain end-user output of PDURS software functions as FDA-required labeling. Specifically, the end-user output of PDURS software functions that are described in the Prescribing Information and either essential to safe and effective use of the drug product *or* for which evidence has been provided to support a clinically meaningful benefit with use of the PDURS, would be regulated by FDA as FDA-required labeling.

This is a change from FDA's 2018 proposed framework for PDURS, which contemplated that a PDURS and its output could be *described in* the FDA-required labeling (*e.g.*, the Prescribing Information), but would not have treated the end-user output of the PDURS itself as FDA-required labeling subject to FDA review and approval. This approach also differs from the PDURS Draft Guidance's treatment of device-connected PDURS functions, which FDA expects

[15] 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).

[16] *E.g.*, MIWG, Comments re: Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments, Docket No. FDA-2018-N-3017, at 4 (Jan. 22, 2019); MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, at 15 (Sept. 3, 2013).

would be described in the Prescribing Information but for which the end-user output would be considered promotional labeling rather than FDA-required labeling.[17]

The PDURS Draft Guidance does not explain why the end-user output itself would constitute FDA-required labeling, or how FDA could treat it as such under the applicable regulations.[18]

More importantly, the agency's proposed approach is inconsistent with the very regulations that FDA cites in the PDURS Draft Guidance, i.e., 21 C.F.R. §§ 314.50(c)(2), 314.94(a)(8), and 601.2(a). Specifically, 21 C.F.R. § 314.50(c)(2)(i) specifies that applicants should include in a new drug application ("NDA") submission, "[t]he proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the NDA that support the inclusion of each statement in the labeling, and, if the NDA is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter" (emphasis added). The NDA regulations at 21 C.F.R. § 314.50(e)(2) further provide that applicants must submit to the archival copy of the NDA "[c]opies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter)." Through the references to Medication Guides, the label, and the sections of labeling described in 21 C.F.R. § 201.57, which describes the contents of the Prescribing Information, it is clear that § 314.50 contemplates that FDA-required labeling submitted with an NDA includes *only* the Prescribing Information, content within the narrow definition of "label,"[19] and, if applicable, a Medication Guide. It does not contemplate submission of end-user output of related software, which is not a "label" and does not include *any* "section or subsection of the labeling format in § 201.57 of this chapter" nor the requirements for a Medication Guide under Part 208.

Similar to the NDA regulations, FDA's regulations governing submission of a Biologics License Application ("BLA") at 21 C.F.R. § 601.2(a) contemplate that an applicant submitting a BLA must include "specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product." Label, as defined in 21 C.F.R. § 600.3(dd) means "any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper."

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[17] PDURS Draft Guidance at 8-9 ("Notably, in these examples, the prescription drug use-related software relies on data directly transferred from the device constituent part of the combination product. . . . In this situation, the PI (e.g., in the HOW SUPPLIED/STORAGE and HANDLING section) should provide a brief description of the device constituent part and the associated software function(s). . . . The end-user output would be considered promotional labeling and should not be described in the PI (e.g., from the example above regarding tracking inhaler events, the output could be the display of how frequently the inhaler is used).").

[18] We do not object to the requirement that certain PDURS end-user output be described in the Prescribing Information if it is essential to safe and effective use of the drug, which is consistent with the requirement that labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug. 21 C.F.R. § 201.56(a)(1). Our concern is with FDA's proposed treatment of the PDURS end-user output itself as FDA-required labeling.

[19] The FDCA defines "label" more narrowly than "labeling" to mean "a display of written, printed, or graphic matter upon the immediate container of any article." 21 U.S.C. § 321(k).

Thus, like the NDA regulations in Part 314, the BLA regulations also restrict FDA-required labeling to the drug label – i.e., the Prescribing Information and other physically attached labels – and a Medication Guide, if applicable. End-user output of PDURS is not within the scope of FDA-required labeling as defined in 21 C.F.R. § 601.2(a). This conclusion is further supported by FDA's regulations at 21 C.F.R. § 601.12(f)(1), addressing requirements for revising FDA-required labeling. This regulation states, in relevant part, "Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter, and include the information necessary to support the proposed change." Here again, it is clear that FDA's regulations governing FDA-required labeling for biological products contemplate only the Prescribing Information, package label, container label and, if applicable, Medication Guide.

Accordingly, FDA's regulations governing FDA-required labeling do not permit FDA to treat the end-user output of PDURS as FDA-required labeling. Rather, such output, if it fulfills the function of labeling, must be considered promotional labeling.

The implications of this distinction for sponsors are significant. If the end-user output is promotional labeling, it need only be submitted to FDA on Form 2253 at the time of initial dissemination and is not subject to FDA approval. The sponsor would still need to consider if any revisions to the Prescribing Information describing the PDURS software function would be necessary as a result of changes to the end-user output. However, the end-user output itself would not be reviewed and approved by FDA under the regulatory regime applicable to FDA-required labeling, pursuant to which changes to the end-user output could be subject to prior authorization by FDA.[20]

Because FDA's regulations applicable to FDA-required labeling are exacting, treating the end-user output of PDURS software described in a drug's Prescribing Information as FDA-required labeling would discourage drug sponsors from investigating or seeking to include information in the Prescribing Information about PDURS software functions that, while not essential to safe and effective use of the drug, may have a clinically meaningful benefit. Instead, to retain flexibility to make even relatively minor modifications to the PDURS without FDA review or approval, sponsors may prefer to treat the end-user output of the PDURS as promotional labeling and discuss the evidence of its benefits promotionally in accordance with FDA's guidance for industry, "Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers" (2018). This is not the optimal outcome from a public health perspective, as the Prescribing Information can more broadly and effectively convey the benefits of using the PDURS than a promotional campaign.

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[20] *See* 21 C.F.R. § 314.70. *See also* Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments, 83 Fed. Reg. 58,574, 58,576 (Nov. 20, 2018) ("For prescription drugs and biological products, FDA-required labeling is the labeling, drafted by the manufacturer, that is reviewed and approved by FDA as part of a new drug application (NDA), an abbreviated new drug application (ANDA), or a biologics license application (BLA), including supplemental applications (21 CFR 314.50(c)(2), 314.94(a)(8), and 601.2(a)). It includes the information that is essential for a provider to make an informed decision about the risks and benefits of prescribing the drug for a patient and the information needed to safely and effectively use the drug. Most changes to such drug labeling require review and approval by FDA.") (emphasis added).

To the extent that FDA proposes to treat PDURS end-user output as FDA-required labeling because it is concerned that changes to the output could render the Prescribing Information inaccurate or incomplete, this concern is already addressed by FDA's regulations at 21 C.F.R. 314.70. Even if the PDURS output were *not* treated as FDA-required labeling, the sponsor would need to assess if changes to the PDURS output require changes to the Prescribing Information and to update the Prescribing Information accordingly. Indeed, this is already how FDA intends to handle device-connected PDURS functions under the PDURS Draft Guidance.

In light of these considerations, we request that FDA revise the PDURS Draft Guidance to treat the end-user output of PDURS software functions as promotional labeling, regardless of whether the PDURS is described in the drug's Prescribing Information.

III. The PDURS Draft Guidance Presents Significant First Amendment Issues and Threatens to Chill Protected Speech

The PDURS Draft Guidance raises significant issues under the First Amendment and will chill protected speech. For example, in addition to the statutory issues described in Section I above, FDA's assertion that all software output disseminated by or on behalf of a drug sponsor that "supplements, explains, or is otherwise textually related to one or more of the sponsor's drug products" constitutes labeling subject to FDA's regulatory oversight is problematic from a First Amendment perspective. In particular, we are concerned that such a broad definition of labeling to include anything merely "textually related" to a drug 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. Similarly, a policy by which FDA would consider non-PDURS functions of multi-function software products to be promotional labeling would also implicate First Amendment concerns and chill manufacturer communications to the detriment of patient health.

In each of these scenarios, the software would involve manufacturer speech that has both promotional/PDURS (i.e., commercial) and non-promotional/ non-PDURS (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. [21] To the extent that FDA intends to treat non-promotional or non-PDURS software functions as promotional labeling, the PDURS Draft Guidance does not consider the higher level of constitutional scrutiny that a court may apply to such "mixed" speech.

Conclusion

The MIWG appreciates FDA's efforts to provide risk-based guidance addressing PDURS. However, the MIWG is concerned by assertions in the PDURS Draft Guidance that would potentially stretch FDA's authority to regulate prescription drug labeling beyond its

[21] *Riley v. Nat'l Fed'n of the Blind of N.C.*, 487 U.S. 781, 795-96 (1988).

permissible boundaries and impose significant burdens on industry. We therefore request that the agency:

1. Revise the definition of PDURS in the PDURS Draft Guidance to be more consistent with *Kordel*, including by deleting the language "otherwise textually related to one or more of the sponsor's drug products" from the definition ***[See Comments Section I.A]***;

2. Explicitly acknowledge that disease focused software tools disseminated by or on behalf of sponsors are outside the definition of PDURS and are not regulated by FDA as labeling ***[See Comments Section I.A]***;

3. Clarify that the end-user output of non-PDURS software functions in multi-function software with at least one PDURS software function is not "labeling" and need not be submitted to FDA on Form 2253 ***[See Comments Section I.B]***;

4. Revise the PDURS Guidance to delete the sentence, "Promotional labeling can include printed, audio, or visual matter descriptive of a drug that is disseminated by or on behalf of a drug's manufacturer, packer, or distributor (21 CFR 202.1(l)(2))." Instead, the PDURS Draft Guidance should refer only to 21 C.F.R. § 1.3(a) and 21 U.S.C. § 321(m) as definitions of "labeling" ***[See Comments Section I.C]***;

5. 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) ***[See Comments Section I.C]***; and

6. Revise the draft guidance to treat end-user output of PDURS software functions described in a drug's Prescribing Information as promotional labeling rather than FDA-required labeling. ***[See Comments Section II]***

Thank you for the opportunity to comment.

Respectfully submitted,

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