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November 20, 2017

Re: Content of Risk Information in the Major Statement in Prescription Drug Direct-to-Consumer Broadcast Advertisements; Establishment of a Public Docket; Request for Information and Comments (Docket No. FDA–2017–N–2936)

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, and Public Citizen’s Health Research Group submit these comments in response to the Food and Drug Administration’s (FDA’s) request for information titled “Content of Risk Information in the Major Statement in Prescription Drug Direct-to-Consumer Broadcast Advertisements.”¹ We submit the following comments and recommendations for the FDA:

- (1) We believe that the study commissioned by the FDA, the results of which the agency is using as a primary justification for its potential proposal to decrease the amount of risk information required to be disclosed in prescription drug direct-to-consumer (DTC) broadcast ads, is fundamentally incomplete and flawed and does not address more important factors already known to affect the comprehension and recall of risk information disclosed in DTC broadcast ads.
- (2) Since the current, narrow request for information is inextricably linked to the broader issue of FDA regulation of DTC broadcast advertising, we urge that the FDA take the following actions:
 - (a) As mandated by the Food and Drug Administration Amendments Act of 2007 (FDAAA), issue a legally binding final rule that amends the regulations governing DTC advertisements for prescription drugs (21 C.F.R. 202.1) to require that the disclosure of risk information in the major statement of DTC broadcast ads be clear, conspicuous, and neutral. Such regulatory changes should adhere to the following:
 - (i) Maintain current FDA requirements regarding which risks must be disclosed in DTC broadcast ads. In particular, the FDA should continue to require “a brief summary of all necessary information related to side effects and contraindications,” which may include certain important non-severe, non-serious, and non-actionable risks, while also requiring that severe, serious, or actionable risks be disclosed more prominently;
 - (ii) Expand the scope of drug reactions to be included within the definition of “serious” risks, as explained in more detail below;

¹ 82 FR 39598.

- (iii) Require all risk information to be presented simultaneously in both audio and visual formats; and
 - (iv) Ban the use of distracting imagery and sounds during the disclosure of risk information, as we believe that **any such** simultaneous, distracting stimuli reduce retention of risk information.
- (b) Heighten enforcement of existing regulations governing DTC ads, including issuing far more warning and notice of violation letters to pharmaceutical manufacturers for violative ads (broadcast or otherwise) and, for the first time ever, begin issuing civil monetary penalties to such manufacturers.

Below is a more detailed explanation of our comments.

A. Background

1. Existing FDA regulations for DTC prescription drug advertisements

Section 502(n) of the Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §352(n)) requires that sponsors who advertise prescription human drugs, including biological products, disclose in advertisements certain information about the advertised product's uses and risks. For prescription drugs and biologics, section 502(n) requires advertisements to contain "a true statement" of certain information including "information in brief summary relating to side effects, contraindications, and effectiveness" as required by regulations issued by the FDA.

Current FDA regulations regarding prescription-drug advertisements include the following provision at 21 C.F.R. §202.1(e):

- (e) True statement of information in brief summary relating to side effects, contraindications, and effectiveness:

(1) *When required.* All advertisements for any prescription drug... shall present a true statement of information in brief summary relating to side effects, contraindications... and effectiveness. **Advertisements broadcast through media such as radio, television, or telephone communications systems** shall include information relating to the major side effects and contraindications of the advertised drugs **in the audio or audio and visual parts of the presentation** and unless adequate provision is made for dissemination of the approved or permitted package labeling in connection with the broadcast presentation **shall contain a brief summary of all necessary information related to side effects and contraindications.** [Bolded emphasis added; italics in original]

The above disclosure required for DTC broadcast ads is known as the "major statement."

2. 2007 FDAAA required final improved FDA regulations for DTC broadcast prescription drug ads by 2010

Section 901(d)(3)(A) of FDAAA (Public Law 110-85), which was enacted on September 27, 2007,² amended section 502(n) of the FDCA to require that the major statement relating to side effects and contraindications in DTC broadcast ads for prescription drugs be presented in a “**clear, conspicuous, and neutral manner**” [emphasis added]. Section 901(d)(3)(A) of FDAAA required that the FDA promulgate regulations implementing the requirements of Section 901(d)(3)(A) of FDAAA within 30 months.

On March 29, 2010, the FDA issued a notice of proposed rulemaking (NPRM) (docket No. FDA-2009-N-0582; RIN 0910-AG27) that would have implemented the requirements of Section 901(d)(3)(A) of FDAAA.³ The NPRM proposed that 21 C.F.R. 202.1(e) be revised to read as follows:

(e) True statement of information in brief summary relating to side effects, contraindications, and effectiveness:

(1) *When required.* All advertisements for any prescription drug... must present a true **statement of information in brief summary relating to side effects, contraindications... and effectiveness.**

(i) *Broadcast advertisements.* Advertisements broadcast through media such as radio, television, or telephone communications systems must include information relating to the **major side effects and contraindications (“major statement”)** of the advertised drugs in the audio or audio and visual parts of the presentation and, unless adequate provision is made for dissemination of the approved or permitted package labeling in connection with the broadcast presentation, **must contain a brief summary of all necessary information related to side effects and contraindications.**

(ii) *Clear, conspicuous, and neutral manner.* Advertisements for prescription drugs intended for use by humans presented directly to consumers in television or radio format must present the major statement in a clear, conspicuous, and neutral manner. A major statement is clear, conspicuous, and neutral if:

(A) Information is presented in language that is readily understandable by consumers;

(B) Audio information is understandable in terms of the volume, articulation, and pacing used;

(C) Textual information is placed appropriately and is presented against a contrasting background for sufficient duration and in a size and style of font that allows the information to be read easily; and

(D) **The advertisement does not include distracting representations (including statements, text, images, or sounds or any combination thereof) that detract from the communication of the major statement.**

[Bolded emphasis added; italics in original]

² Food and Drug Administration. Food and Drug Administration Amendments Act (FDAAA) of 2007. <https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcaact/foodanddrugadministrationamendmentsactof2007/default.htm>. Accessed November 7, 2017.

³ 75 FR 15376.

In the preamble of the March 29, 2010, NPRM, the FDA discussed the standards of other federal agencies for “clear and conspicuous” disclosures and highlighted the Federal Trade Commission’s (FTC’s) standards. In particular, the FDA noted a 1970 FTC enforcement statement that set forth the following standards, among others, for determining whether an affirmative disclosure in a television advertisement is “clear and conspicuous”:

- (1) The disclosure should be presented simultaneously in both the audio and video portions of the television commercial (dual modality);
- (2) The video portion of the disclosure should contain letters of a color or shade that readily contrast with the background, and the background should consist of only one color or shade; and
- (3) No other sounds, including music, should occur during the audio portion of the disclosure.

In the preamble of its 2010 NPRM, the FDA also stated that the agency believed that “presenting the major statement in both the audio and visual portions of television ads could enhance the clarity, conspicuousness, and neutrality of this information.” Although the proposed rule did not include such a standard, the FDA asked the public to comment on whether the final rule should include it.

The comment period for the NPRM originally closed on June 28, 2010. In Public Citizen’s June 28, 2010 comments on the proposed rule (copy enclosed), we strongly endorsed requiring that the major statement in DTC broadcast ads be presented in both audio and visual formats.

On January 27, 2012, the FDA reopened Docket No. FDA-2009-N-0582 to allow comment on a study added to the docket entitled “Experimental Evaluation of the Impact of Distraction on Consumer Understanding of Risk and Benefit Information in Direct-to-Consumer Prescription Drug Television Advertisements” (Distraction Study).⁴ This study, dated May 2011, was “designed to investigate some advertising factors that could influence consumers’ understanding of a drug’s risks.” Public Citizen submitted comments dated February 27, 2012 (copy enclosed), in which we noted our belief that although there is strong support in the Distraction Study and elsewhere for the use of superimposed text accompanying the audio presentation of risks in DTC prescription-drug ads on television, the study was so flawed that any conclusions or lack thereof as to the other variables studied would be of negligible value in fashioning a regulation that would adequately protect consumers.

Disturbingly, now more than 10 years after the passage of the FDAAA, the FDA has failed to finalize the rule that was mandated by the law and originally proposed in 2010.

B. Long-standing concerns about allowing DTC ads

Public Citizen does not support any DTC advertising of pharmaceutical products on broadcast media. The United States is one of only two countries in the world that permit it (the other being

⁴ 77 FR 4273

New Zealand), and Public Citizen believes that DTC broadcast ads for prescription drugs have not advanced and may actually harm public health in both countries.⁵

We reiterate here our serious concerns about DTC broadcast ads, primarily because they often supplant the knowledge and judgment of the physician in determining whether a particular drug is most suitable for a particular patient. Although a physician must actually prescribe an advertised prescription drug product, there is ample support for the idea that patient pressure increases the likelihood that a physician will prescribe a particular product, even if another product or even non-pharmacologic treatment might have a superior result. This, coupled with the effect of aggressive marketing targeting physicians, practically ensures that prescriptions will be written without adequate attention to important information relating to risk or alternative treatment options. Direct-to-consumer advertising may thus supplant the knowledge and judgment of the physician in determining whether or not a patient will ultimately use the drug in question.

Acknowledging that DTC broadcast ads will continue in the U.S. for the foreseeable future, we encourage the FDA to implement much stronger requirements for companies to assure that, after viewing such commercials, consumers understand the drugs' risks, benefits, and comparability to other pharmaceutical and non-pharmaceutical interventions. The remainder of our comments, however, will focus on the FDA's recent specific request for information concerning the disclosure of risk information in DTC broadcast ads, as well as the bases for what should be included in the final rule amending 21 C.F.R. 202.1(e), as mandated by FDAAA.

C. The recent FDA-commissioned study did not even attempt to definitively determine the optimal format for disclosure of important risk information (Betts et al, 2017⁶)

In 2014, the FDA published in the *Federal Register* an announcement that it had commissioned a study to evaluate the effectiveness of disclosing serious, actionable, and other risks versus disclosing only serious and actionable risks in DTC ads.⁷ The study, the results of which were published online in August 2017, was designed to answer several questions related to the comprehension and recall of risks disclosed in standard pharmaceutical DTC television ads.⁸ We identified several flaws with the study's methodology that call into question the validity and relevance of the results to patients who view DTC broadcast ads. In addition, the study results with regard to the primary outcome are not meaningful when viewed from the perspective of absolute, rather than relative, differences between study arms, and other results strikingly demonstrate that, regardless of how risk information is presented, recall of key risks is very poor.

⁵ Lurie P. DTC advertising harms patients and should be tightly regulated. *J Law Med Ethics*. 2009;37(3):444-50, 396.

⁶ Betts KR, Boudewyns V, Aikin KJ, et al. Serious and actionable risks, plus disclosure: Investigating an alternative approach for presenting risk information in prescription drug television advertisements. *Res Social Adm Pharm*. 2017 Aug 2. pii: S1551-7411(17)30360-30361.

⁷ 79 FR 9217.

⁸ Betts KR, Boudewyns V, Aikin KJ, et al. Serious and actionable risks, plus disclosure: Investigating an alternative approach for presenting risk information in prescription drug television advertisements. *Res Social Adm Pharm*. 2017 Aug 2. pii: S1551-7411(17)30360-30361.

1. Fundamental flaws of study methodology

First, the study was designed primarily to determine the extent to which patients with self-reported depression, insomnia, or high cholesterol remembered and recognized the most important risks disclosed in an actual DTC television ad. The study compared two different types of major statements disclosing risk information:

- (1) Major statements disclosing all major risks associated with a particular drug as presented in the original ads (unedited-risk-statement ads); and
- (2) Major statements disclosing only the “serious and actionable” risks (abbreviated revised-risk-statement ads).

In order to be able to meaningfully compare these two types of major statements, the presentation of these two different major statements should have been identical, with the only variable consisting of the presence or absence of the risks that were not serious and actionable. However, this study did not undertake such an experiment. Instead, the presentation of the serious and actionable risks differed in other substantial ways between the two study arms, as explained by the study’s authors:⁹

The revised statements began by alerting consumers that the drug can cause “serious reactions” or, in the case of the depression ad, “severe, life-threatening reactions,” whereas the first sentence of the unedited risk statement noted that this drug is not appropriate for some people (e.g., “Crestor is not right for everyone”).

Thus, the revised-risk-statement ads presented the serious and actionable risks with more severe-sounding introductory language than the unedited-risk-statement ads that opened the risk disclosure portion of the ad with a more banal statement that the drug might not be appropriate for all patients. The more severe-sounding language in the revised-risk-statement ads may have contributed to heightened attention to, and recall and recognition of, the serious and actionable risks (as seen in the depression, insomnia, and high-cholesterol groups) and an increased tendency to perceive such risks as severe (as seen in the depression group) among the subjects in the revised-risk-statement arms.

Second, the study is notably flawed for what it chose not to investigate. The study was not designed to sufficiently answer the overarching question of what would be the ideal format and content for risk disclosure in DTC ads that would maximize recall, retention, and comprehension of risk information.

For one, all arms in the study provided only audio disclosure of information about specific risks. This is ironic because in order to maximize the chances that the subjects of the study would pay attention to a disclosure statement about the fact that not all risks were being disclosed (for those subjects assigned to groups exposed to ads with this statement), this disclosure statement itself was always simultaneously provided in both audio and visual formats based on prior studies. To justify their decision to include this disclosure statement in simultaneous visual and audio formats, the authors, in the methods section, cited a 2014 study demonstrating that presenting

⁹ *Ibid.*

risk information in this combined form “produced the highest recall and recognition.”¹⁰ Indeed, the FDA’s own earlier Distraction Study, published in 2011, had demonstrated the superiority of combined visual-audio presentation of risks, with the agency concluding the following:¹¹

In summary, we found strong support for presenting risk information at the same time in text and in audio because doing so improves risk comprehension... This finding is consistent with previous research and with standards maintained by the Federal Trade Commission. Sponsors could help ensure the effective communication of risk information in DTC ads by presenting the spoken risk concepts simultaneously in text. Furthermore, an increase in risk comprehension was *not* associated with any reduction in benefit comprehension. ...

This study made a clear contribution to our understanding of the role of visuals in DTC advertising. The study demonstrated that reinforcing audio-delivered risk information with consistent text during the major statement of an advertisement improves consumers’ risk comprehension and does not impede their comprehension of benefit. The results of this study will be helpful as FDA continues to encourage the truthful and nonmisleading presentation of prescription drug information.

It is not clear why the authors of the Betts et al study on disclosing serious, actionable, and other risks did not realize that including both visual and auditory presentations of the risks actually disclosed (or testing this combined presentation with either visual-only or auditory-only presentations) was warranted. The differences in rates of recall and retention of serious and actionable risks between subjects viewing unedited risk statements and those viewing revised risk statements may have been attenuated had risk information been presented simultaneously in both visual and audio modes.

Another important variable not examined in the Betts et al study was the effect of distracting, positive imagery accompanying the auditory-only presentation of risk information in any of the study arms (see discussion of the Sullivan et al study below).

2. Study results: Over-interpretation of small absolute differences and confirmation that DTC ads do not result in equal appreciation of benefits and risks

The authors of Betts et al study concluded that “[t]he revised risk statement improved overall processing of the television ad, as evidenced by improved risk recall and recognition.”¹² This conclusion, however, is based on very small absolute differences in proportions of recalled and recognized serious and actionable risk information between subjects viewing unedited risk statements and those viewing revised risk statements, as shown in the following table (taken from Table 2 of the FDA-commissioned study):

¹⁰ Wogalter MS, Shaver EF, Kalsher MJ. Effect of presentation modality in direct-to-consumer (DTC) prescription drug television advertisements. *Appl Ergon.* 2014;45(5):1330-1336.

¹¹ Food and Drug Administration. Experimental Evaluation of the Impact of Distraction on Consumer Understanding of Risk and Benefit Information in Direct-to-Consumer Prescription Drug Television Advertisements: Technical Research Report. May 2011. <https://www.regulations.gov/document?D=FDA-2009-N-0582-0040>. Accessed November 3, 2017.

¹² Betts KR, Boudewyns V, Aikin KJ, et al. Serious and actionable risks, plus disclosure: Investigating an alternative approach for presenting risk information in prescription drug television advertisements. *Res Social Adm Pharm.* 2017 Aug 2. pii: S1551-7411(17)30360-30361.

Illness population and variable being measured	Unedited Risk Statement	Revised Risk Statement
Depression		
Proportion of key risks recalled	0.12	0.16
Proportion of key risks correctly recognized	0.68	0.73
Insomnia		
Proportion of key risks recalled	0.20	0.24
Proportion of key risks correctly recognized	0.70	0.75
High Cholesterol		
Proportion of key risks recalled	0.28	0.33
Proportion of key risks correctly recognized	0.72	0.73*

* This difference between the unedited-risk-statement and revised-risk-statement groups was not statistically significant. All other differences between the two groups were statistically significant.

As shown above, the absolute differences in the proportions of both recalled and recognized key (serious and actionable) risks between subjects viewing unedited risk statements and those reviewing revised risk statements were never greater than 5%, regardless of the condition studied. It is reasonable to think that these differences may have been smaller, and would likely have approached statistical insignificance, had the key risks in both the unedited- and revised-risk-statement groups been presented with identical, appropriately severe language (as explained above, only the revised risk statement was introduced with such language) as well as with simultaneous visual risk information.

The above results also serve as further confirmation of the utter failure of DTC broadcast ads to effectively convey fair balance between benefits and risks of a given medication. Subjects in the study demonstrated extremely poor recall of the disclosed risks, regardless of the format of the audio-only disclosure. Subjects viewing the unedited risk statements recalled just 12 to 28 percent of the serious and actionable risks presented, and subjects viewing revised risk statements did not fare much better, with recall rates of 16 to 33 percent. Although the study did not separately assess recall of the disclosed benefits of each advertised medication, it is likely that nearly all subjects recalled the overarching benefit claim, namely that the drug is generally effective for the condition that was the subject of the advertisement. Thus, this study confirms that DTC ads achieve their intended selling purpose for the drugs' manufacturers: clearly and compellingly conveying benefit information, while effectively minimizing the recall of risks.

D. Newest FDA Study Documents that Simultaneous Visual Distraction Impairs Retention of Risk Information (Sullivan et al)

In another even more recent FDA-commissioned study, 300 subjects were randomly assigned to view one of two DTC ads: a "low-distraction" ad or a "high-distraction" ad.¹³ Both ads presented risk information in audio format with superimposed text (combined audio-visual format). The study found that, despite the presence of superimposed text, "...distracting elements during risk presentation drew attention away from the risk text and, in turn, reduced retention of drug risk information." Risk perceptions were not affected by distracting imagery. The authors concluded

¹³ Sullivan HW, Boudewyns V, O'Donoghue A, et al. Attention to and distraction from risk information in prescription drug advertising: An eye-tracking study. *J Public Pol Marketing*. 2017. In Press. doi.org/10.1509/jppm.16.013.

that “...even if dual modality is used to increase consumers’ comprehension of drug risk information, distracting visuals should still be avoided to help consumers focus on key information in the ad.”

These results further call into question the validity and utility of the aforementioned Betts et al study that varied the amount of risk information presented (in audio-only format) to subjects. Had that study removed distracting positive imagery from the sample DTC ads viewed by all subjects, the rates of recall and recognition of key risk information likely would have been higher across all study groups, and the differences between the groups may have decreased.

E. The FDA’s proposed definition of “serious” risks is too narrow

The FDA definitively includes within its definition of serious risks only those reactions “that may result in inpatient hospitalization or prolonged existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.”¹⁴ The FDA equivocated on including other potentially serious reactions within this definition in stating that reactions that do not result in any of the above outcomes but nevertheless “based on appropriate medical judgment...may jeopardize the patient and may require medical or surgical intervention to prevent one of [these] outcomes” *may* (rather than will) also be considered serious risks.

There are many risks that do not result in hospitalization, disability, or incapacity that are nevertheless serious enough to result in medical intervention in the emergency room or outpatient setting, discontinuation of the drug in question, or impairment of patients’ quality of life. In addition, frequent side effects that are associated with non-serious but uncomfortable or distressing symptoms often can lead patients to stop taking their drug without consulting a healthcare provider, which can, in turn, result in serious adverse health outcomes if no other treatment is provided. We therefore believe that all such reactions should be disclosed in DTC broadcast ads.

F. The FDA must promptly finalize the legally mandated regulation, especially given the FDA’s dismal oversight of compliance with prescription drug advertising requirements

It is imperative that the FDA, as mandated by FDAAA, issue a legally binding final rule that amends the regulations governing DTC advertisements for prescription drugs (21 C.F.R. 202.1) to require that the disclosure of risk information in the major statement of DTC broadcast ads be clear, conspicuous, and neutral. Having a binding regulation is especially important given that the FDA’s current oversight of DTC ads is wholly inadequate.

The FDA’s enforcement of violative prescription drug advertisements (both DTC and physician-targeted ads) has declined precipitously over the past two decades. During the most recent three-year period for which full-year data are available (2014-2016), only 30 warning and notice-of-violation letters were issued to pharmaceutical companies for violative DTC and physician-targeted prescription drug ads. This represents a sharp decline from the earliest three-year period for which data are publicly available: from 1997 through 1999, the FDA issued 406 such letters (see Appendix).

¹⁴ 82 FR 39598.

The FDA's dismal record on issuing warning and notice-of-violation letters, even with the weak requirements in the current regulations, heightens the importance of other enforcement avenues. Despite being granted the authority by the FDAAA to issue civil monetary penalties to manufacturers responsible for disseminating violative prescription drug ads,¹⁵ as of November 3, 2017, the FDA has yet to assess any such penalty.¹⁶

G. Our recommendations for what should be included in the final rule

The final rule amending 21 C.F.R. 202.1(e)(1) must include several elements. First, it should modify the existing regulation that outlines the requirements for the "brief summary" of a drug's risks in DTC broadcast ads that gives companies the choice as to whether to present risk information only in audio format or in both audio and visual formats.¹⁷ Unsurprisingly, companies have opted for the less effective audio-only format for disclosing risk information (according to a sample of DTC television ads broadcast in a one-week period in 2003, 98% of the ads that disclosed risks disclosed them only through audio voice-overs with no accompanying text).¹⁸ This regulation should be modified in the final rule to mandate that risks of the advertised drug be presented in *both* audio and visual formats.

Second, the final rule should explicitly ban the use of any distracting, pleasant imagery or sounds during the risk-disclosure portion of DTC broadcast ads.

Third, the final rule should be framed in a way that does not present the two choices simply as: (a) maintaining the status quo of disclosing all major risks in audio-only format, with no distinction in the ad's presentation between serious and actionable risks and all other disclosed risks, or (b) eliminating the requirement to disclose all but serious and actionable risks, which would continue to be presented in audio-only format, in the presence of distracting, pleasant imagery or sounds. Rather, the final rule should move beyond this false and unnecessarily narrow dichotomy. It should preserve the requirement to disclose all important risks of a drug in both audio and visual formats, but require that severe, serious, or actionable risks be disclosed in a more prominent and memorable fashion than other risks. In a 2017 study, subjects who viewed prescription drug ads that presented all risks but highlighted the most important risks more prominently (hereafter referred to as "emphasized but complete risk statement") rated the most important risks as severely as subjects that were shown only the most important risks with more minor risks omitted.¹⁹ The authors of that study pointed out that one therefore may not have to sacrifice transparency in order to ensure that the most important risks are understood and remembered (and not "diluted" by presentation of more minor risks) by viewers of DTC ads:

¹⁵ Food and Drug Administration Amendments Act. Section 503B(f)(4). <http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>. Accessed March 11, 2015.

¹⁶ Personal communication, on November 3, 2017, with Jean-Ah Kang of the Food and Drug Administration's Office of Prescription Drug Promotion.

¹⁷ 21 C.F.R. 202.1(e)(1). "Advertisements broadcast through media such as radio, television, or telephone communications systems shall include information relating to the major side effects and contraindications of the advertised drugs in the audio *or* audio and visual parts of the presentation..." [emphasis added].

¹⁸ Macias W, Pashupati K, Lewis LS. A wonderful life or diarrhea and dry mouth? Policy issues of direct-to-consumer drug advertising on television. *Health Commun.* 2007;22(3):241-252.

¹⁹ Sivanathan N, Kakkar H. The unintended consequences of argument dilution in direct-to-consumer drug advertisements. *Nat Hum Behav.* 2017. doi:10.1038/s41562-017-0223-1.

The choice of information architecture employed in [the emphasized but complete risk statement], which affords consumers the ability to compartmentalize and assign appropriate weights to major versus minor side effects, presents one possible avenue by which pharmaceutical companies and regulators may look to attenuate the argument dilution effect while maintaining transparency.

H. Conclusions

We reiterate our opinion that all DTC ads be restricted, due to their deleterious effects on patient care and physician judgment, including increased overprescribing and misinformation on the part of both patients and physicians.

Acknowledging that DTC broadcast ads will continue in the U.S. for the foreseeable future, we urge the FDA to promptly issue a final rule strengthening the existing regulation at 21 C.F.R. 202.1(e) governing risk disclosure in DTC broadcast ads along the lines recommended above.

In addition, we urge the agency to heighten its enforcement of existing regulations governing DTC ads, including issuing far more warning and notice of violation letters to pharmaceutical manufacturers for violative ads (broadcast or otherwise) and, for the first time ever, begin issuing civil monetary penalties to such manufacturers.

Thank you for taking our comments into consideration.

Sincerely,



Sammy Almashat, M.D., M.P.H.
Researcher
Public Citizen's Health Research Group



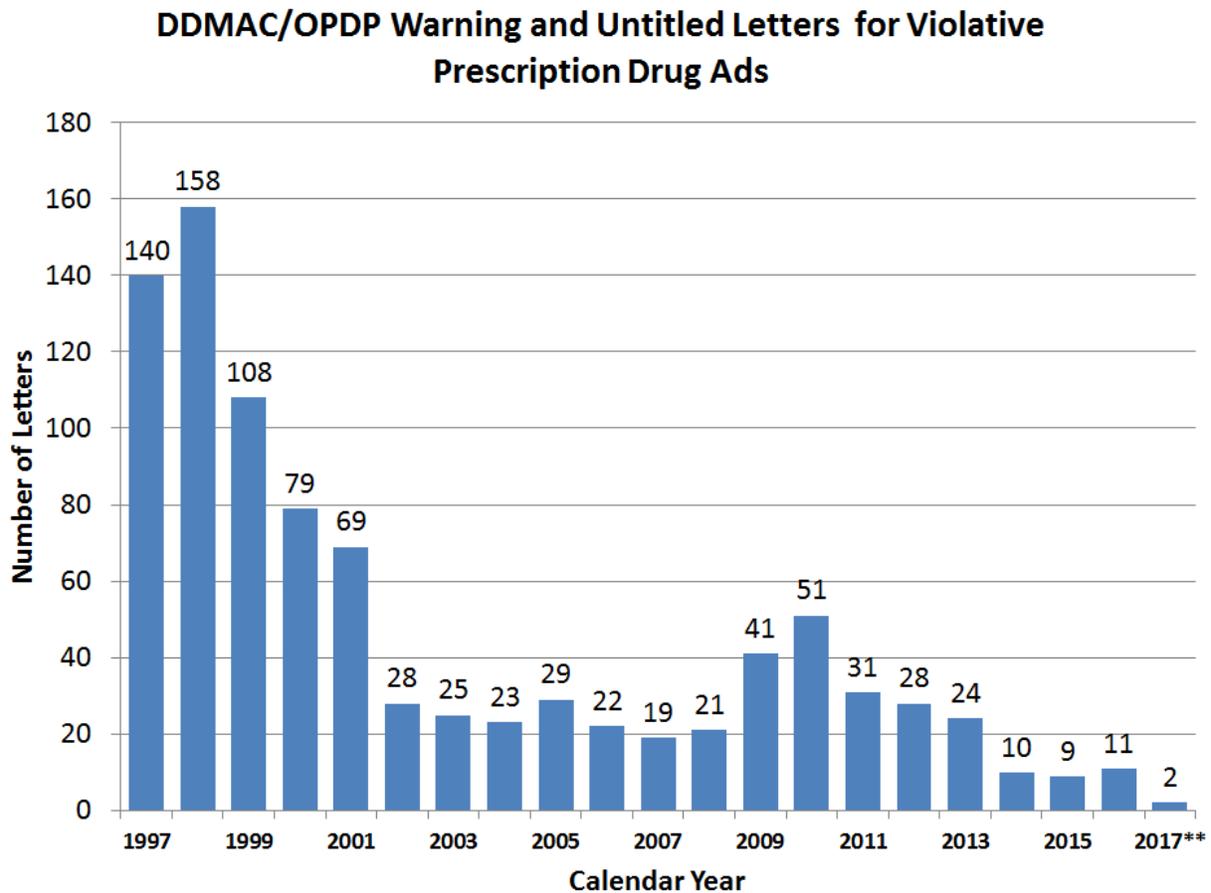
Sidney Wolfe, M.D.
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Enclosures

Appendix. FDA Warning and Untitled Letters to Pharmaceutical Companies Regarding Violative Promotional Materials and Activities



* Includes both direct-to-consumer and physician-targeted advertisements. The Division of Drug Marketing and Communications (DDMAC) was renamed the Office of Prescription Drug Promotion (OPDP) in 2011.

** 2017 total was taken as listed on the FDA source (below) on November 6, 2017.

Source: Food and Drug Administration. Warning Letters and Notice of Violation Letters to Pharmaceutical Companies.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm>.

Accessed November 6, 2017.



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June 28, 2010

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

Dear Commissioner:

These comments from Public Citizen Health Research Group come in response to Docket No. FDA-2009-N-0582, the FDA Proposed Rule relating to Direct-to-Consumer (DTC) Drug Advertisements, published at 75 FR 15376, March 29, 2010.

It is important to note that well over a decade ago, the FDA considered and even drafted regulations concerning DTC advertising, based on the correct notion that the target audience, consumers, has a very different background in matters pertaining to drug safety and effectiveness than doctors, pharmacists and nurses, the primary intended audience for the then and currently existing advertising regulations. For reasons that were never made clear, these draft regulations never saw the light of day and it would be important to see them in the context of this new, belated rulemaking effort. This disclosure is particularly important since it is highly likely, if not certain, that the scope of the draft rule from the 1990's was far broader than the relatively narrow area of DTC advertising covered by the current proposed rule.

Public Citizen does not support DTC advertising of pharmaceutical products on broadcast media. The United States is one of two countries in the world that permit it (the other being New Zealand), and Public Citizen believes that DTC advertising has not advanced public health in either country. (See Lurie P, DTC Advertising Harms Patients and Should be Tightly Regulated, *J Law Med Ethics* 2009; 37:444-450.)

Given that DTC advertising via broadcast media is permitted in the United States at this time, ostensibly as protected commercial speech, and while reserving our objections thereto, Public Citizen agrees with the general proposition that such advertising should include "major statements" of risk, including side-effects and contraindications in a clear, convincing and neutral manner. This is particularly important as a public safety matter in light of the limited time most physicians have in which to fully advise patients regarding harmful side effects.

Public Citizen suggests that whether a particular advertisement presents risks in a “clear, convincing and neutral” manner should be determined by techniques similar to those used to determine consumer comprehension of benefits.

By requiring that the major statement of risks be presented in a clear, convincing and neutral manner, Congress intended that consumers be given adequate information to comprehend risks equally with the benefits of a particular drug. It therefore seems reasonable to require that the same marketing techniques be used in presenting these risks as are used in presenting the benefits.

To assure that target consumers might equally comprehend risks and benefits of an advertised product, Public Citizen proposes that requests for approval of each proposed “direct to consumer” media advertisement be supported by the results of independent market research organizations. Market research organizations are equipped to carry out empirical testing to determine the extent to which the benefits of advertised products are understood by target consumers. The same techniques should be used to determine the extent to which statements of risk (including side effects and contraindications) are comprehended by the same target group. Applicants should be required to demonstrate that the consumer testing was bias-free in that it was not rigged to inaccurately alter the perceptions and/or comprehension of benefit or risk by the target group.

FDA has specifically requested guidance as to whether the practice of the Federal Trade Commission (FTC) should be adopted in requiring simultaneous video presentation of required audio messages, and as to how the word “neutral” should be interpreted in setting forth information contained in the “major statement” in a “clear, convincing and neutral” manner. The remainder of this comment will focus on these questions.

1. Should the practice of the FTC be adopted to require simultaneous video presentation of required audio messages?

YES. Besides noting the adoption of this practice elsewhere, notably by the FTC, FDA has cited literature supporting the proposition that increased comprehension results when learners can see information as well as hear it and appropriate visuals could direct the attention of the viewer to the simultaneously spoken message.

DTC advertisements currently seen on television frequently distract the viewer from statements of risk with attractive images, often promoting the benefits but having little or nothing to do with the side effects, contraindications and warnings, etc. The current practice of showing distracting benefits images while lists of side effects, contraindications and warnings, etc., are read in either a monotone or a reassuring tone of voice must not continue.

2. Should a broad definition of neutral (as described below) be adopted so that “neutral” would not be a superfluous term?

YES. As noted in the proposed rule, the 2007 Amendments to the Food Drug and Cosmetic act require that the “major statement” in DTC television and radio advertising relating to side effects

and contraindications of an advertised prescription drug intended for humans be presented in a “clear, conspicuous and neutral manner.” FDA has asked for guidance in implementing this Congressional directive of neutrality in presenting information regarding side effects and contraindication, and has indicated that it is not aware of previous standards from other agencies concerning this term. 75 FR 15379 further notes that the terms “clear and conspicuous” have been given extensive interpretations by other agencies but it appears that many of these definitions blur into common definitions of “neutrality.” Therefore, adopting these interpretations alone could render the word “neutral” superfluous.

If “neutral” is to be meaningful, it must encompass features not included in “clear and conspicuous.” We therefore propose a definition of neutrality that would present the advertised product in a “neutral manner” as compared with other pharmacologic or non-pharmacologic approaches to the indications for use, as well as considerations relating to consumer convenience, comfort and cost. Since the desirability of assuming risks (including side effects and contraindications as defined herein) can only be evaluated by comparison with expected benefits, the expected benefits must also be considered in determining “neutrality.”

Public Citizen therefore proposes that to present information “neutrally,” DTC advertising should include the following information:

- a. How do the risks of the product compare with the expected benefits of use?
- b. How does the product compare in safety and efficacy with existing products – both under patent and generic – for the same indication?
- c. How does the product compare in safety and efficacy with non-pharmaceutical approaches (including but not limited to lifestyle modification) for the same indication?

Including this information will result in a more neutral presentation by giving consumers a balanced picture of the benefits and risks of the advertised product.

In summary, Public Citizen suggests the following amendments to the proposed rule.

1. To obtain approval of DTC advertising on broadcast media, a party shall present market research demonstrating that information concerning side effects, contraindications and warnings is comprehensible to the target audience, using market research equivalent to that carried out with respect to the benefits of that product.
2. DTC advertising on television and other audio-visual media shall present appropriate visual information about side effects, contraindications and warnings simultaneously with the audio presentation.
3. A broad definition of “neutral” should be adopted to require presentation of other approaches, both pharmacologic and non-pharmacologic, to treating the target condition.

Respectfully submitted,

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Re: FDA-2009-N-0582

February 27, 2012

Dear Commissioner,

These comments from Public Citizen Health Research Group (PCHRG) come in response to Docket No. FDA-2009-N-0582, the FDA Proposed Rule: Reopening of Comment Period on Specific Data relating to Direct to Consumer (DTC) Drug Advertisements, published at 77 FR 4273, January 27, 2012.

The above comment period was reopened to allow comment on a study added to the above docket entitled “Experimental Evaluation of the Impact of Distraction on Consumer Understanding of Risk and Benefit Information in Direct-to-Consumer Prescription Drug Television Advertisements” (Distraction Study). This study, dated May 2011, was “designed to investigate some advertising factors that could influence consumers’ understanding of a drug’s risks.”¹

PCHRG previously submitted comments pertaining to the proposed rule published March 29, 2010.² To the extent these earlier comments speak to matters raised in the Distraction Study, they are incorporated herein.

We reiterate here our serious concerns about DTC advertising, primarily because it often supplants the knowledge and judgment of the physician in determining whether a particular drug is most suitable for a particular patient. If, despite this concern, DTC advertising is allowed, FDA should require far more reassurance than is now the case that after viewing such commercials, consumers would understand the drug’s risks, benefits, and comparability to other pharmaceutical and non-pharmaceutical interventions.

¹ 77 FR 4273(2012), January 27, 2012.

² 75 FR 15376 (2010).

This comment, however, will focus primarily on FDA’s specific request for guidance concerning the Distraction Study and the role that its findings might play in regulating DTC drug advertising on television.

We believe that while there is strong support both in the Distraction Study and elsewhere for the use of superimposed text accompanying DTC drug advertising on television, this study is so flawed that any conclusions or lack thereof as to the other variables studied would be of negligible value in fashioning a regulation that would adequately protect consumers.

The Distraction Study examined six specific issues relating to consumer understanding of risk information. These issues are most conveniently discussed in three groups.

1. The role of superimposed text (SUPERS) on risk comprehension. Does concurrent presentation of risk concepts in both audio and on screen facilitate processing the “major statement”³ of risk information? Our conclusion (based not only upon this poorly designed study but upon a wealth of other evidence and experience) is YES.
2. The role of affective tone in risk comprehension. Does the tone of positive visuals in a television ad such as scenes of patients socializing with family and friends or enjoying recreational activities distract viewers from attending to the major statement? Our conclusion is that the Distraction Study, because of its many limitations upon which we shall expand below, gives no useful guidance and therefore must be disregarded.
3. The effect of inconsistent visuals on risk comprehension. Is information processing improved when similar information, such as visual information relating to risks, is presented concurrently with the audio presentation of the major statement? Conversely, is information processing disrupted when conflicting information, such as visual information relating to benefits, is presented concurrently with the audio presentation of the major statement?

³ The "major statement" is a term that is relevant only to broadcast (TV or radio) ads for prescription drugs. It refers to the presentation of the drug's most important risks. This presentation must be spoken. It also can be included in the video part of TV advertisements. The amount and type of included risk information will vary by drug because different drugs have different risks.

<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm#M>

Here again, our conclusion is that the Distraction Study gives no useful guidance and therefore must be disregarded.

Discussion of the Specific Questions Presented

Question 1 – The role of superimposed text (SUPERS) on risk comprehension.

In its earlier comment, PCHRG strongly urged FDA to follow the practice of the Federal Trade Commission (FTC) in requiring simultaneous on-screen text to accompany video presentations of risk.

The Distraction Study similarly found “strong support” both in the study and, much more importantly, in the literature reviewed, for increased risk comprehension when risk information was presented in text simultaneously with the audio channel. We therefore reiterate our earlier endorsement of following FTC practice of simultaneous on-screen text accompanying audio risk information and urge the FDA to follow this practice as well.

Furthermore, despite the finding of only marginally greater risk comprehension with large SUPERS as opposed to small SUPERS, we would nevertheless support the use of large text, inasmuch as the study did not control for age, visual acuity, and size of television screen normally viewed by subjects. Also, this study involved advertisements viewed on a computer screen, where the consumer is typically seated close up and can easily lean in for a better view. Results cannot be generalized to the context of television advertising, where the consumer is typically seated farther away and cannot adjust themselves as easily.

We also note that in the Distraction Study, both the large SUPER and small SUPER groups viewed text that was easy to read in some contexts: the text read by the small SUPER group took up approximately 7% of the screen, meaning that even in the small SUPER group the text would be .84 inches in height when presented on a 12-inch screen. The text read by the large SUPER group was twice as large.⁴ Also, in both conditions the text was presented on a black banner that filled approximately 1/5 of the screen (21%). Therefore even if FDA decides to permit “small” text in broadcast media, the text should be at least as large as 7% of the screen.

It should be stressed, however, that we support text that is larger than 7% of the screen, given the variety of contexts in which the ads may be viewed.

Questions 2 and 3 – The role of affective tone in risk comprehension and the role of risk reinforcing SUPERS in altering the effect of tonally positive visuals (Question 2) , and the effect of inconsistent visuals on risk comprehension (Question 3).

⁴ Distraction Study, Page 17

The Distraction Study failed to reach any definite conclusions regarding these questions. We submit that this was because the design of this study itself was so flawed that it no valid conclusions could be reached regarding the role of affective tone and inconsistent visuals on risk comprehension. For this reason, we believe that the Distraction Study should play no role whatsoever in shaping the regulation of DTC drug advertising.

Design Flaws in the Distraction Study.

It is likely that the following design flaws resulted in the failure of the Distraction Study to detect any significant effects upon risk comprehension resulting from various forms of distraction.

- A. **The low response rate is questionable.** However random the selections of the initial pool and the distribution of invitations may have been, fewer than 50% of those receiving invitations elected to respond to these invitations. This low response rate could have introduced bias if the characteristics of responders varied between groups. More importantly, the low response rate means that the study results are not generalizable, because it is impossible to determine whether the general population would be more or less distractible than this highly self-selected sample.
- B. **The authors failed to demonstrate that the study was adequately powered.**⁵ This in turn could have led to falsely negative results. This important issue must be raised because of the limited number of participants in each of the numerous subsections of the study.
- C. **The images used in each condition were too highly similar to evoke differing responses.** One set of conditions compared static images of chairs, rocks, and metal arches to static images of a baby with a puppy, a family's hands, and girls jumping with beach balls. The other set of conditions compared bulleted text of risks in front of an exclamation point to bulleted text of benefits in front of a dial. It is not surprising that none of these sets was any more or less distracting than any other. (The study authors admit as much themselves when they point out that their own

⁵ The power of a statistical test is the probability that the test will actually detect an effect if one exists. When a test is under-powered due to a small sample size, the chances increase that the test will fail to pick up a statistically significant difference between groups, even though a difference in fact exists.

manipulation checks failed and therefore “it is not surprising that we did not find substantial differences between these conditions regarding risk comprehension.”)⁶

It remains to be seen whether other techniques might more effectively elucidate the role of distraction in comprehension of risk. For example, actual drug advertisements often include dynamic footage of happy, healthy, and attractive patients “living their lives” while using the product. Using these more dynamic distracting images would have been far more likely to produce evidence of decreased risk comprehension.

- D. The narrow scope of information provided about the fictional drug offered to the study subjects was inconsistent with the “real world” risk profiles of most prescription drugs.** The prescription drug used in this study was a fictional antihypertensive named “Zintria.” Zintria was presented to consumers with a fixed and limited universe of benefits, risks and warnings. Most prescription drugs, including antihypertensives, have much longer rosters of risks and warnings. A thirty- or sixty-second commercial barely has time to cover even the most serious ones, let alone time to compare other products or approaches (including non-pharmacological) for the same condition. Even if there were adequate time, viewers are unlikely to have sufficient background to determine the safety and efficacy as well as the individual appropriateness of a particular drug or other treatment for their particular needs. Therefore, again the study design could not produce results generalizable to real world use of more typical drugs.

Design Flaws in The AMP Study.

In its January 27, 2012 notice, the FDA declined to mention a second study, “A Supplementary Test of Distraction in DTC Advertising Using an Implicit Measure, the Affect Misattribution Procedure” (AMP Study), published by FDA in June 2011. However, the AMP Study was obliquely referenced in the Distraction Study.⁷ While the AMP Study asserted it would “show promise with future refinements”⁸ we note here only that the AMP Study suffered from similar design flaws as the Distraction Study: the same non-distracting images were used, and participation was actually lower due to technical difficulties. Also, the AMP procedure used in

⁶ Distraction Study , Page 31

⁷ Distraction Study, Page 13, citing a “supplementary study using an implicit measure of attitudes called the Attitude Misattribution Procedure (Payne et al, 2005)” discussed in a separate report, the AMP Study, dated June, 2011.

⁸ AMP Study Page 31

the AMP Study was a novel one that has not been subjected to testing. Earlier AMP testing involved only previously-held, strong beliefs, not new associations with made-up products.

FDA Should Not Rely on the Distraction Study in Better Regulating DTC Drug Advertising on Television.

While a physician must actually prescribe an advertised prescription drug product, there is ample support for the role of patient pressure in increasing the likelihood of prescribing a particular product, even though another product or even no product might have a superior result. This, coupled with the effect of aggressive marketing targeting physicians, practically insures that scrip will be written without adequate regard for important information relating to risk or alternative treatment options.

Direct to consumer advertising may thus supplant the knowledge and judgment of the physician in determining whether or not a patient will wind up using the drug in question. This is one of many reasons for carefully regulating direct to consumer advertising of prescription drugs.

However, if there is to be DTC advertising, we would urge that the nostrum "*primum non nocere*" (first do no harm) apply equally to advertisers as to physicians inasmuch as the influence of the advertiser to varying degrees may otherwise supplant the influence of the physician.

The principle of first doing no harm could be operationalized by requiring television advertisements for prescription drugs to include visuals that focus on risks. At the very least television advertisements for prescription drugs should feature simultaneous audio and large-letter, contrasting color, visual presentations of the labeling including adverse effects, warnings, contraindications, FDA safety bulletins, etc.

We would also advocate requiring a discussion of other treatment alternatives, both pharmaceutical and non-pharmaceutical, (including head-to-head safety and efficacy data, where available, and cost considerations).

Such requirements would likely be unacceptable to sponsors, but we urge FDA to exercise its powers to promulgate regulations based on the reality that lay consumers have a vastly different background than the medical professionals who have been the traditional targets of prescription drug advertising.

Sincerely,

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