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RE: Docket No. FDA-2008-D-0253

Coalition for Healthcare Communication
Comments on FDA Draft Guidance:
Presenting Risk Information in Prescription Drug and Medical Device Promotion

INTRODUCTION

The Coalition for Healthcare Communication (CHC) is pleased to provide comments on the FDA's draft Guidance on Presenting Risk Information in Prescription Drug and Medical Device Promotion Guidance that was issued May 27, 2009.¹

The Coalition is a not-for-profit organization representing major communications organizations whose members are engaged in medical communications including publishing, continuing medical education, and the dissemination of information on health care products and services. The Coalition's mission is to ensure that medical communications is as robust and open as possible, so as to ensure that health care professionals and patients have open access to important health information. As an active voice on various issues relating to the regulation of medical communications, the Coalition consistently seeks to achieve a common goal with the Food and Drug Administration, the medical community, policy makers, and the American public: to optimize the flow of medical information. To accomplish this goal, health care professionals need to have available current, important scientific information concerning disease, its diagnosis and its treatment so that they can make fully informed decisions concerning patient care

GENERAL COMMENTS

The FDA draft Guidance presents FDA's interpretation of factors to be considered when developing risk disclosures (fair balance) in promotional material. FDA should be commended for utilizing both the legal and social science research literature in examining the basis for principles outlined in the draft Guidance concerning this extremely complex subject. FDA also cites numerous articles from the social science literature to provide both description and support for the factors considered when reviewing promotional material. In theory, this should provide a rock solid basis for promotional review of fair balance. Unfortunately, as noted below, the FDA at times

either misinterprets the legal and social science research principles or applies these principles in an incorrect fashion. This comment points out several of these oversights with the expectation that the FDA will remedy them before adopting final guidance and before applying them in its ongoing oversight of promotion and advertising materials.

FDA is also to be commended in its recognition that the regulation of advertising and promotion is subject to the restrictions contained in the First Amendment of the United States Constitution (Subject Federal Register Notice-Attachment: Statutory and Regulatory Requirements for Labeling and Advertising in the subject Notice). Unfortunately, the broadness of the draft Guidance's discussion and its imposition of numerous additional requirements raises serious questions about the ability of manufacturers to communicate truthful information and raises serious First Amendment issues that are outlined below.

Moreover, the draft Guidance assumes new authority that reaches far beyond both the law and existing regulations. FDA's own definitions or applications (as demonstrated in numerous examples throughout the draft Guidance) seek to establish sweepingly new authority with the potential for arbitrary and capricious application of the regulations. Under this draft Guidance, FDA could potentially justify objecting to any risk disclosure, including the reprinting of the entire package insert. FDA's description of "factors without limits" provides the basis for unfettered regulation and provides the Agency with numerous reasons to object to virtually any advertisement or piece of promotional labeling, regardless of whether it is truthful and meets the statutory test of not being false and misleading.

THE DRAFT OVERLY COMPLICATES ADVERTISING AND PROMOTION

Promotional materials contain two forms of risk disclosures: (1) risk information integrated within the promotional communication, mostly importantly the fair balance requirement and (2) labeling information provided as an attachment to the promotional communication, most importantly the requirements for brief summary in advertising and for full product labeling in so-called promotional labeling. The fair balance requirement for advertising and other promotion materials must not be confused with the "brief summary" or full product labeling. Yet, the draft Guidance does not fully distinguish between these two requirements and therefore implies that the purpose of risk disclosures in advertising and promotional material is to fully inform patients and healthcare professionals of all the risks enumerated in labeling. Such a requirement is inconsistent with current regulations and statutory requirements (21USCA 502 (n)), would overly complicate promotion and advertising, and, most important, would complicate advertising so much as to do more to confuse doctors and patients than to inform them.

Advertising and promotional materials have an important use as a supplement to other sources of information obtained by health care professionals and patients. Physicians and patients receive prescribing and utilization information through a variety of information and educational channels. Brief summary disclosures assure that physicians and patients have direct access to important prescribing or drug utilization

information. For the most part, advertising communications are used to improve awareness, increase interest and/or provide information to prescribers and patients about appropriate use. They are not intended to be the sole information source relied upon for decision making. Thus, in the draft Guidance FDA, in order to be consistent with FDA's statutory authority, FDA should make it clear that regulation of the fair balance requirements are required solely to prevent false and misleading information from being provided to the audience. Moreover, it makes little sense to mandate that fair balance statements should be regulated to be a finite source of information needed to control drug prescribing or utilization decisions.

Prescription drugs and medical devices are unique products in that they require the authorization by licensed physicians or other healthcare professionals prior to use. This reality, known in law as the doctrine of the learned intermediary, is a significant consumer protection. In a recognition that these products can have great benefits if used appropriately, and that they also can have significant risks and hazards if not used properly, federal law and FDA regulations require that information about the products' risks be "fairly balanced" in promotional material. The routine incorporation of such risk information into the core of promotional materials is unique for prescription healthcare products. Other products and services do not have a similar requirement. For example, the government does not require car manufacturers to include in their advertising statistics on how many people are harmed in traffic accidents; it does not require food manufacturers to describe how excess fats and sugars can lead to disease and mortality and it does not require airlines to describe the number of air traffic accidents.

However, risk information is routinely included in prescription drug and device advertisements and labeling pieces. The CHC acknowledges that prescription healthcare products are unique and supports the importance of providing fairly balanced risk information to physicians, patients and consumers.

Advertisements and promotional interventions have an important role in increasing awareness of new products, communicating product features (both benefits and risks), and in influencing product selection and choice. However advertisements and promotional labeling are just one of many interventions designed to inform and influence prescription drug and device use. Healthcare professionals and consumers receive information in medical and lay publications, educational programs, from colleagues and through counseling. The law and regulations require that advertising and labeling pieces contain full disclosure of risks by mandating "adequate provision" so that professional and consumers can easily obtain direct access to appropriate full labeling or brief summary disclosures.

In addition to legal and philosophical rationales for distinguishing between fair balance and brief summary/full labeling disclosure requirements, there are basic public health concerns about requiring the duplication of extensive amounts of risk information in fair balance contained in promotional materials. The regulations stipulate that risk information should present a fair balance of risk and benefit disclosure. The inclusion of extensive amounts of risk information can have the result of "overwarning."

By over emphasizing risks, physicians and patients may obtain an inaccurate perception of the product, leading to fear and inappropriate avoidance of the use of necessary and indicated medical products; a negative public health outcome. Such over warning has been recently cited by Avorn and Schneeweiss² in pointing out how warnings regarding the use of third generation oral contraceptives led to widespread noncompliance with the use of these products and a sharp increase in unwanted pregnancies³ (the “pill scare of 1995”). In addition, early evidence indicates that warnings about the use of SSRIs and teen suicidal ideation has paradoxically led to an increase in suicide rates for this population as the warnings have decreased antidepressant use and increased rates of depression and suicide.⁴

SPECIFIC COMMENTS

PURPOSE OF RISK DISCLOSURE

FDA states in the draft Guidance (lines 53-55) that “this information (required in the draft Guidance) helps consumers know whether drugs or devices may be appropriate for them, as well as what to tell their healthcare professional about before taking or using a product.” We are seriously concerned that this expectation on the part of FDA establishes a heavy and inappropriate burden on advertising and other promotional material, and that this will deter rather than facilitate the ability of advertisers to communicate truthful information effectively.

The purpose of risk disclosures in fair balance is to prevent promotional communications from being misleading, not to provide full prescribing information. Indeed, FDA regulations state that the purpose of risk information in an advertisement is to provide sufficient context for overall risk disclosures so that material facts are present that would prevent an advertisement from being false or misleading. But, it is unreasonable to expect that all advertising and promotional material contain enough information for an informed decision as to whether or not a drug should be chosen for use. This can only occur after a health care professional evaluates a specific products in relationship to a particular patient’s needs. These types of decisions require much more information and discussion than could be reasonably included in fair balance disclosures..

Physicians and patients receive prescribing and utilization information through a variety of channels. Brief summary disclosures assure that physicians and patients have adequate access to prescribing or drug utilization information. For the most part, advertising vehicles are used to improve awareness, increase interest, and, for direct to consumer advertising, enable consumers to consider consulting their physician. Advertising is not intended to be the sole information source relied upon for these decisions nor does the research literature support that this is the case⁵. Thus, FDA should make it clear that regulation of the fair balance requirements has been established solely to present a balanced and non-misleading message. It would be counterproductive to try to regulate fair balance statements to such a degree as to have them influence or control drug prescribing or utilization decisions. Moreover, such a requirement would not be

permitted by either the Federal Food, Drug and Cosmetic Act (the Act) or the First Amendment..

This view of the role of advertising is supported by FDA's survey on DTC promotion. The majority of respondents (77%) agreed that DTC advertisements increase awareness of new drugs and most (58%) felt the ads provide enough information to make a decision about whether to discuss the drug with a doctor (not a decision to use or how to use a drug). Many respondents (40%) looked up drug information in a reference book, on the internet (38%) or asked a friend (38%) after seeing a DTC advertisement. Interestingly, FDA cited this survey and stated in the draft Guidance that 60% of patients believed that DTC ads did not provide enough information "about the risks" of a drug. However, FDA misquotes its own survey. The question asked in the FDA survey specifically inquired about the "risks and negative effects of using the drug." Thus, survey respondents were not judging the adequacy of risk information within the ad itself for the purpose using the product; rather, they were judging risk information disclosure for the purpose of asking their doctor for advice. It should be noted that many respondents in the FDA survey (44%) also believed that there was inadequate information about drug benefits in DTC advertisements. This supports the concept that DTC advertisements help consumers formulate ideas and seek greater information rather than serve as a sole and final source of information about whether and how to use prescription drugs and devices.

LEGAL ISSUES – FIRST AMENDMENT CONCERNS

As noted earlier, FDA recognizes the applicability of the First Amendment to its regulation of advertising and promotional labeling. This recognition is based on a series of cases including *Pearson v. Shalala*, 164 F.3rd 650 (D.C.Cir. 1999), *Western States v. Thompson*, 122 S.Ct. 1497 (2002) and *Central Hudson Gas and Electric Corp. v. Public service Comm'n of NY*, 447 U.S, 557 (1980). In *Central Hudson*, the Supreme Court outlined the basic tests, the most important of which is that the government – here the FDA – has the burden of proof to demonstrate the need and effectiveness of any policy or rule that restricts commercial speech that is neither false or misleading. Moreover, advertising content restrictions must be no more restrictive than necessary, and must be avoided if a non-content regulation would suffice.

In our view, the current FDA policy and regulations already strain the limits of commercial speech regulation under the *Central Hudson* test. At the very least, no additional regulations are necessary and appropriate. The draft Guidance would, however, impose extraordinary requirements on the content of commercial speech messages in advertising and promotion. As noted below, taking the draft Guidance literally, a single page advertisement, for example, could conceivably be required to add multiple pages to meet FDA's risk disclosure (fair balance) interpretations and even then, there would be no assurance that FDA's requirements would be met. Manufacturer's advertising and promotional expenses could increase several fold leading to the discouragement of exercising their First Amendment rights to engage in commercial

communications. Certainly, such a result, we submit, would not pass the Supreme Court's test in Hudson.

FDA'S POWER UNDER THE ACT

While the FDA has broad authority to regulate false and misleading information (including the omission of material facts), truthful and non-misleading information cannot be regulated either under the Act. As reflected in the Attachment to the draft Guidance (Statutory and Regulatory Requirements for Labeling and Advertising), we note that FDA's legal authority under the Federal Food, Drug and Cosmetic Act (the Act) is grounded primarily on Sections 21 U.S.C. 352(a), the "false and misleading" provision, and 21 U.S.C. 321 (n), the "material facts" requirement. We question the use of 21 U.S.C. 352 (c), the "conspicuous" requirement that clearly applies only to label and labeling and not advertising. Unfortunately, the draft Guidance would require additional risk discussions even if their absence would not be material, or sufficient to make a promotional discussion false and misleading.

In addition to these statutory and First Amendment concerns, the effort to impose substantive new regulatory requirement through a FDA Guidance without notice and opportunity for a public hearing raises significant due process questions under the Fifth Amendment.

MISGUIDED ADOPTION OF FTC STANDARDS

The FDA draft Guidance adopts long-held FTC standards for the review of advertising and promotional material, stating that FDA relies on the "net impression" of the ad as evaluated by a reasonable consumer. The CHC applauds the FDA effort to adopt this well reviewed and established standard. However, the FDA application discussed in the draft Guidance is cause for major concern. The FTC statement on deception states that, to find an advertisement deceptive, "there must be a representation, omission, or practice that is likely to mislead the consumer." Thus, one would expect that under the FDA's adoption of this principle, the lack of risk information in a prescription drug or device promotional piece must be sufficient to deceive the consumer. Correspondingly, the omission of minor or immaterial risk information, especially in the context of other risk information provided, should not be viewed by FDA as being sufficient to find a promotional piece misleading.

Several of the factors that FDA lists in its review of promotional material are described in an "open-ended" fashion and could lead case by case applications that are arbitrary. The FDA's general principles have no clear limits or measurable standards for application. For example, the FDA states that risk information should be made understandable, comprehensive and specific (framing) but does not provide advice about how understandable, how comprehensive or how specific (how it should be framed, i.e., what is a minimal level is acceptable). Thus, any risk disclosure may be regulated by FDA as inadequate because it does not meet these vague principles with the standards being defined on the spot by FDA reviewers. When presenting such factors, FDA should

provide manufacturers with clearer guidance on what these factors mean. As the FDA well knows, well established First Amendment law requires that laws be clear and understandable, and not so vague as to give the government unlimited enforcement authority.

Historically, the FTC has used the concept of “net impression” to determine whether or not a particular promotional claim is deceptive. Thus, the “net impression” is related to what a typical consumer perceives as the meaning of a specific claim in an advertisement. FDA, however, seeks to apply the net impression concept to the overall perception of a prescription product based on its review of the advertising. This is a totally new and untested application of the concept of net impression. Its application to prescription drug or device risk disclosures establishes new requirements on advertisers, one with uncharted boundaries and seemingly unlimited additional requirements.

While we have no problems in concept with the use of “net impression” as a means to evaluate prescription drug and device advertising for compliance with fair balance requirements, the use of “net impression” needs to be much more fully developed in both principle and via research to be applied in this new fashion. What specific criteria should be used to determine if a “net impression” is false or misleading when applied to the entire fair balance disclosure within advertising? If some risk information is deleted from the body of a promotional piece compared to the package insert (as it must be to provide coherent “fair balance” and not overemphasize risks), what measure or criteria can be used to assess compliance with the draft Guidance? Without answering these or other questions, it is impossible to know how to apply this new concept to the review of prescription drug or device promotional material.

The draft Guidance suggests that, if drug benefits are emphasized to a greater extent than the risk presentation, a reader may “receive an erroneous impression that the drug is safer than it has proven to be” (line 150). Drugs cannot be marketed unless FDA concludes that its benefits outweigh its risks, i.e., that the drug in question is safe and effective when used as directed and that its benefits outweigh any potential risks of its use. Apparently, the FDA draft Guidance is establishing a new standard, that a reader of an advertisement or promotional piece must receive a net impression about the relative safety of a drug that is consistent with research summarized in the labeling.

Most people view advertisements as providing promotional claims and expect that ads for a prescription drug or device emphasize benefits. It unrealistic to expect that a reasonable healthcare consumer would take the view that a prescription drug advertisement’s purpose is to provide complete information about risks. But, the language of the draft guidance posits a “net impression regarding drug safety” test for medical marketing, an entirely new requirement.. According to the draft Guidance, not only must a marketer disclose information about important and material risks, to be compliant with the law it must manage the net impression that a reader has about a drug’s safety – without the benefit of an agreed upon metric for describing that level of risk. - a factor that inherently creates the arbitrary and capricious nature of the draft Guidance.

FDA states that it considers a number of factors to determine comparability of risks and benefits, such as the number of statements about risks and benefits, completeness of depth and detail, and the amount of time or space devoted to communicating risks and benefits. Although FDA states that the number of benefits and risks do not have to be identical, FDA does not provide any guidance for determining what would be an acceptable quantity of risks compared to benefits. Thus, any advertisement that does not contain the same number of words that describe benefits as risks appears susceptible to FDA enforcement action. This is a new requirement that far exceeds current practice where a fair balance of risk information is viewed as acceptable.

The reasonable consumer standard is also described in the FTC statement on deception. FDA states that it will use this standard. Interpreting how a reasonable *healthcare* consumer would interpret a particular advertising claim is difficult without some form of external evidence. In applying the reasonable consumer standard, the FTC frequently relies on copy testing, as well as expert consultants in marketing and consumer behavior. However, to understand the nature and amount of risk disclosure a reasonable healthcare consumer believes is sufficient in an advertisement creates a much more complex problem.

How can a drug or device manufacturer determine what amount of risk disclosure is sufficient from the perspective of a reasonable healthcare consumer? There is no guidance given in the draft Guidance. The reasonable consumer standard is frequently operationalized in terms of a statistical result (i.e., a percentage of consumers in the target audience as measured in a copy test) as opposed to the interpretation of a single individual (i.e., an FDA reviewer). Using an individual reviewer or group of reviewers may be sufficient when evaluating explicit claims to determine whether a particular claim is consistent or inconsistent with the product label. However, determining the adequacy of fair balance requires a much more subjective judgment. Although FDA staff have expertise in their field, it is doubtful that they are experts on communication and cognition of a reasonable healthcare consumer in a multi-cultural society. It would be necessary for FDA to seek academic and other recognized experts in consumer behavior to help shape FDA research that could provide through copy testing sufficient evidence (as is routinely done by the FTC) to reach scientific determinations.

In advertising copy tests used for litigation, for example, results that demonstrate that a certain percentage of the intended audience interprets a specific advertising claim incorrectly, is utilized to demonstrate that the claim is viewed as misleading. Interestingly, in a previous publication, FDA staff and consultants have stated that FDA views false or misleading materials as those where a certain percentage of the population of the target audience is misled.⁶ However, this concept was applied to individual claims. If FDA is to rely on such evidence to determine whether an entire ad is misleading due to the lack of fair balance, then FDA should state in the draft Guidance how a sponsor could determine whether the promotional piece is sufficient or insufficient in its disclosure of risk information. What measurement should be obtained, how could the minimal percentage of a sample that would need to be misled be assessed, and how could such a percentage be computed?

COMMUNICATION THEORY ISSUES-- UNDERSTANDABLE LANGUAGE

FDA states that the language must be appropriate (comprehensible) to the target audience. For health professionals, presumably, technical language consistent with the package insert would be acceptable. However, for consumers, the draft Guidance requires that the information be “clear, understandable and non-technical.” The general concept that a reader should be able to understand the presented risk information is reasonable in principle. However, FDA’s description of how this will be applied is problematic for several reasons.

FDA suggests in footnote 22 that an eighth grade reading level is considered a “lower grade level” but does not make it clear if this is the standard FDA would accept. Even if such a standard is used, it is not clear if such measurement is accurate. Although FDA calls such readability tests as “validated,” the level of validation this draft Guidance views as acceptable is inconsistent with other Guidance FDA has issued on the acceptability of test measures, e.g., the PRO Guidance. Some of the references FDA cites for readability tests are 30 years old or more. They have not been shown to apply to drug information or to advertising material; rather, these tests were validated using text books and other educational material, not advertising material. FDA’s own research shows that the application of readability formula to prescription drug information is invalid⁷. Although we generally disagree with the use of readability tests as sole determinants of appropriateness, the FDA does not provide sufficient guidance on how to use these tests. If FDA would find certain readability tests acceptable as evidence of consumer understandability, FDA should state which test(s) should be used and what grade level is acceptable.

In the example used in this section, FDA does not rely on readability tests. Rather, FDA focuses on a single word. It states in the draft Guidance that, for a consumer audience, an advertisement would be misleading if it uses the term “syncope” instead of “fainting.” Medical dictionaries define syncope as:

“...partial or complete loss of consciousness with interruption of awareness of oneself and ones surroundings. When the loss of consciousness is temporary and there is spontaneous recovery, it is referred to as syncope or, in nonmedical quarters, fainting” (<http://www.medterms.com/script/main/art.asp?titlekey=5612>).

Thus, “fainting” captures only temporary loss of consciousness with spontaneous recovery, not the entire concept of syncope. If a manufacturer were to follow the advice in this section of the draft Guidance, FDA could maintain that the use of the terms “fainting” is misleading because the information is “framed” in “non-specific terms” (see line 274). Therefore, FDA should make it clear that for a consumer audience, summary terms are permissible even if they do not fully capture all of the medical issues related to a broad concept. We suggest that some leeway in terms of specificity is necessary to

make terms understandable to a lay audience and that other aspects of the draft Guidance will not be invoked (such as the framing section) when such summarization is used to faithfully represent risk information derived from product labeling. .

Also, there are times when the use of technical terms can be included without making advertising misleading. For example, some drugs cause unique side effects such as progressive multifocal leukoencephalopathy (PML) or thrombotic thrombocytopenic purpura (TTP). These are technical terms that can be included in risk disclosures, even to consumer audiences, without making the advertisement misleading. As long as the terms are described (e.g., a life-threatening condition) we see no value in excluding their disclosure and some benefit to providing key safety information to patients. On the other hand, if these terms are omitted but qualification is included (e.g., the drug may cause a life threatening condition) the advertisement would still be truthful. Thus, there may be multiple ways to present risk information that are both sufficient and truthful.

Unless there is a “net impression” that an advertisement is false or misleading because of the use of technical language, we do not view the use of technical language as offensive and potentially illegal. If a sponsor chooses to quote the physician or patient labeling for certain sections of the fair balance section of an advertisement, we submit that this would not make a promotional message misleading. To view promotion as false or misleading because of the use of a single technical term (when the use of simpler terminology may be perceived by FDA as false or misleading) is extreme and unreasonable.

As a general rule, we can envision using patient labeling for patient advertising and physician labeling for physician advertising. However, if there is no approved patient label and a sponsor uses the actual language from the physician label, FDA is in essence, stating that an advertisement is false and misleading if it uses the approved label language (which by definition cannot be false or misleading).

FDA should make the standard of risk communication clearer. If FDA maintains that it is the “net impression” of drug safety, as opposed to the communication of specific risks (especially minor risks), that are important it should so state. If FDA maintains that the communication of specific risks is important under certain circumstances, FDA should discuss this and provide examples of those circumstances. Exceptions to the “understandability” requirement should be noted in the draft Guidance.

USE OF SIGNALS

FDA states that “signaling is an important component of information communication.” It cites as a definition, “writing devices designed to emphasize aspects of a text’s structure or content without altering the information in the text.” FDA describes the use of headlines and sub-heads in advertising and promotion as examples of signals.

We agree that the information in headlines should not be false or misleading. However, the FDA again uses a “comparability” standard for assessing the degree to which risk information must be conveyed in headlines. For the most part, FDA appears to accept as a headline the “signaling” that a certain section of an advertisement conveys risk information. We find this acceptable. The draft Guidance does not mention how clear or how specific headlines must be. Does a company need to disclose actual risks in a headline if it discloses actual benefits in other headlines? FDA should more fully discuss the scope and limits of this requirement on the specificity of risk disclosure in headlines.

FRAMING

FDA suggests that it will consider how the information is “framed” in reviewing the adequacy of risk disclosures. It defines framing as “how a particular piece of information is stated or conveyed, such as emphasizing either the positive or negative aspects of the information or by presenting the information in vague versus specific terms” (lines 268-269). The draft Guidance cites multiple sources of literature that have investigated “framing effects.” In this literature, framing effects have been more narrowly defined in terms of the phrasing of risk information in terms of gains or losses (e.g., you have a 15% chance of death or an 85% chance of survival).

According to one of the citations used by FDA, information is more understandable when framed as a benefit rather than a risk⁸. Despite this finding, risk communications in advertising are always framed as losses (otherwise they would be perceived as benefits). For example, if a drug advertisement states that there is a low percentage of drowsiness, this would be viewed as benefit communication, not a risk disclosure.

It appears, however, that FDA uses the concept of framing in a much broader fashion than commonly used in the risk communication literature. In essence, when referring to “framing” the draft Guidance states that FDA will focus on how a particular piece of information is “phrased” without making it clear what types of phrases are acceptable or unacceptable. This is overly broad and difficult advice for a drafter of risk disclosures. FDA should make it clearer what type of issues are covered by “framing” and the limits or exceptions to these rules.

One of the few examples of phrases that FDA would object to depends on the degree of specificity in which risks are phrased. The draft Guidance states that the degree of specificity must be the same for benefits and risks. This is an extremely difficult concept to operationalize. Benefits and risks are not measured on the same scale and are qualitatively different. There are usually many more risks and side effects than benefits noted in labeling and in brief summary as well.

The CHC is particularly concerned that this section of the draft Guidance can be interpreted to mean that FDA will not accept risk summarization as adequate for fair balance disclosure. Summarization is often necessary to convey risks, especially in

patient advertising. Summarization of risk information (e.g., stating that a drug may cause vision problems without delineating the multiple type of problems) should be acceptable as long as it conveys a similar seriousness and likelihood of risk. Clearly, risks in patient labeling are a summarization of risks in physician labeling, which is itself a summarization of risks in the NDA. If summarization is not acceptable, we fear that risk communication will be seriously undermined. Overloading a communication with such specific risk details, as outlined in official labeling, can make the communication of important risks difficult or impossible. Further, research has shown that increasing the amount of information that a consumer must process decreases the quality of decision making⁹

FDA states that certain phrases, such as “like all medicines” (or even “all medications in the same class”) when discussing side effects may minimize risks and therefore, would make a promotional piece false or misleading. We know of no evidence to support this conclusion. If FDA has such data, FDA should publicize these findings. Rather, we believe that this type phrase can help a patient put risks in a proper perspective so that the risks can be understood as a consequence of taking any medicine in the same therapeutic class. To conclude that a promotional piece is false or misleading because it contains such a phrase appears to be highly subjective and would exclude important risk disclosure information.

Still another instance where the Draft Guidance would work against accurate risk disclosure information is when FDA presents an example of a drug that causes 55 percent of the users to have a side effect. FDA suggests that a statement “more than half” of patients have this side effect would be acceptable. We believe that such a statement would be misleading. This statement suggests anywhere between 50 and 100 percent of people would experience this side effect. FDA should use the same rules and standards to judge whether a promotional piece contains too little, or too great, an emphasis on risk information.

Framing effects are a popular source of social science research because researchers find that different ways of presenting information can lead a subset of consumers to reach different decisions regarding willingness to undertake a therapy. However, it is essential to note when investigating framing effects, both positive and negative frames are truthful. There are multiple ways to present truthful risk information. FDA should accept a much greater variety of risk presentations formats and content than suggested in the draft Guidance, as there are many ways to truthfully present the risks of drugs or devices. Further, FDA should focus on how the presentation of risk information impacts whether a communication is truthful or false or misleading, not ultimate decisions on whether or how to use a drug. As stated earlier, advertising and promotion cannot be expected to communicate enough information for the ultimate decision on use to be made.

In general, we view this section as suggesting the need for highly specific risk disclosures that go beyond what is necessary to convey truthful and non-misleading information. FDA does not discuss any limits or exemptions. Almost any risk disclosure

can be objected to for lack of specificity or some aspect of phrasing that FDA may call “framing.” Unless FDA has a clear rationale for why a particular disclosure is misleading, or why in the aggregate, risk disclosures are misleading, this section of the draft Guidance should be seriously curtailed or qualified.

HIERARCHY

FDA considers the order of presentation of risk information an important factor in fair balance risk communication. We generally concur, provided that FDA provides clear guidance on its desired sequence of risks for any given drug. According to FDA, the most important risk information should be presented first. We agree that the order of risk information presentation may be considered a “cue” of the importance of a bit of information. However, most of the research in this section appears to come from studies of short term memory of short series of memorized lists. This is an inappropriate basis for developing policy where long term memory and more complex but meaningful communication is described (not simple lists of words). To use such research to conclude that because a certain bit of risk information is not in a desired order or is not placed in a certain position in a promotional piece is a conceptual leap of enormous magnitude. Risks should appear where they are most relevant to the message.

For the most part, disclosure of risks and the explanation provided about those risks would appear to be much more important than whether these risks are presented first, second, third or so forth in a promotional piece. The example provided by FDA has little to do with the overall order of information in terms of what is perceived as important. Rather the example suggests that people may misinterpret a caution. This misinterpretation may be resolved in a number of ways that have little to do with order. For example, as FDA states, adding intervening information (without changing the order or hierarchy of information) would clarify the miscommunication.

CONTENT CONSIDERATIONS-- QUANTITY OF INFORMATION

The FDA states that the amount of information in an advertisement can affect the cognitive load, which FDA defines as the “mental effort required to understand the various components of information in the piece.” Because of cognitive load limitations, FDA asserts that it will “look to see that promotional communications allot sufficient time and space to convey the important benefits and risks of the product being promoted to ensure that, as a whole, the communication provides an accurate and non-misleading impression of the product” (lines 360-362). The FDA states that it will examine a number of aspects of the piece to determine the comparability of risks and benefits including the number of statements about benefits and risks, completeness of depth and detail, amount of time and space, and use of multimedia communications.

It is unclear how multimedia communications would impact the quantity of risk information in a single piece. If FDA means that FDA will start to examine the risk disclosures in a broad array of promotional pieces for a single product to determine fair

balance within a single communication, this would be a new requirement that cannot not be established through the issuance of a Guidance.

The FDA analysis suggests that a considerable amount of time and space must be devoted to risk communication in a promotional piece to provide an “accurate and non-misleading impression about the product.” If it is FDA’s intention to use the “number of statements” about benefits compared to risks as criteria for the sufficiency of risk communication, it is establishing a totally new and arbitrary requirement that far exceeds the current standard that a “fair balance” can be achieved by providing a meaningful summary of important risk information.

We contend that the FDA analysis of a quantity factor is seriously flawed and misdirected. The FDA uses much “deeper” criteria for information processing than should be reasonably applied. Again, we underscore that the statutory mandate supports that the purpose of risk disclosures is to prevent promotional material from being false and misleading. Unfortunately, the FDA Draft Guidance goes well beyond such a standard.

The FDA analysis of cognitive load is based on the analysis of teaching material (e.g., text books, multimedia learning). A cited reference for cognitive load theory, Mayer and Marino¹⁰, focuses their discussion of cognitive load theory on what they call “meaningful learning” from multimedia material. They define “meaningful learning as deep understanding of the material, which includes attending to important aspects of the presented material, mentally organizing it into a coherent cognitive structure, and integrating it with relevant existing knowledge.” Further, they state that “meaningful learning requires that the learner engage in substantial cognitive processing during learning.”

Accordingly, it is clear from this discussion that the criteria utilized by FDA for assessing the quantity of risk disclosures are based on learning from textbooks and instructional material, not the review of promotional material. The purpose of risk disclosures in advertising/promotion is not to provide “meaningful learning” but to provide an “impression” of the product and to prevent the message from being misleading. To assure compliance with the statutory standard, FDA’s proposed standard on the quantity of risk disclosures needs to be substantially revised to eliminate any utilization of deep learning of complex instructional texts.

MATERIALITY AND COMPREHENSIVENESS

Under the Act, an advertisement is misleading if it fails to present material facts about a product. In the draft Guidance, FDA states that materiality is “determined by the degree to which information is objectively important, relevant, or substantial to a target audience” (lines 390-391). Material facts are defined by FDA to include the relevant properties of a product, whether the product is appropriate to use and whether patients or prescribers are “willing to accept the risks and burdens” of using or prescribing a product (lines 398-401). This suggests that FDA is using “informed consent” criteria to judge

whether promotional information is sufficient. Again, this far exceeds the law and regulations, establishes a new burden on promotion and asks promotion to accomplish something that is beyond this vehicle's limitations.

Under the section "consideration of target audience," FDA again states that promotional material should convey the most critical information to help health professionals decide whether a product is appropriate. For consumers, the information should convey what the drug or device is for, who should or should not use it, what can be expected from the product and what to discuss with the health care professional.

Here, again, the FDA is basing its assessment of the amount of risk information necessary to disclose in promotion on what is needed for health professionals to prescribe or for patients to decide to use a product. As stated previously, these decisions require a great deal more information than can reasonably be assumed to be contained in advertising material. The FDA requires physician and patient labeling materials (PIs, PPIs and Medication Guides) for the purpose of providing these types of disclosures. Such labeling information is appended to promotional material (or adequate provision is provided to obtain the information) so physicians and patients have ready access to such information. We believe that material facts, when applied to the inclusion of risk information, should entail the most serious and/or most common risks and side effects that are relevant to the promotional message. This information is necessary for physicians and patients to obtain an accurate and non-misleading impression of the product. However, it simply is not feasible to require that risk disclosures within the context of promotional material match the content necessary for product labeling.

NATURE OF BENEFIT CLAIMS

FDA states that certain risk information should be disclosed based on the specific benefit claims being made in the piece. We agree that risk information that is necessary to prevent a specific claim from being misleading should be disclosed. However, in two of the examples provided in this section, FDA goes much further in its discussion of risk disclosure.

In the first example, FDA states that, if a product is promoted as having convenient once-a-week dosing, then the product advertisement should disclose that there may be application site reactions and that the patient has to restrict activities after the injection. These disclosures might be appropriate as a matter of fair balance regardless of the specific claims made. However, these disclosures do not appear to bear any relationship to a convenience claim's being false and misleading, nor are they necessary to prevent a convenience claim from being misleading. Therefore, we disagree with the FDA that a convenience claim would trigger the need to talk about application site reactions or restricted activity. Certainly this information would be available in the brief summary attached to the promotional piece. Using FDA's own analysis within this section, the inclusion of this additional information may distract from the communication of more important risk information by increasing the cognitive load necessary to process more important risk information. The risk disclosures within the advertising should focus

on the most important risks and not add extra information unless that information is necessary to prevent misleading the consumer.

The second example states that if a promotional vehicle (a web site) discusses benefits for a certain class of consumers (post menopausal women) then “any” risks to that class of consumers is material and should be disclosed. Determining that the decision about whether a risk to a certain group of consumers (or consumers in general) is material should be based on the nature of the risk in the context of the other risks disclosed or in reference to the specific promotional claims in order to prevent those claims from being misleading. The concept that “any” risk to a group of consumers should be disclosed goes far beyond risk disclosure envisioned by the law and regulations for the promotional content of advertising or promotional labeling.

ACCURACY AND COMPREHENSIVENESS

FDA states that consumers and health professionals have certain expectations about the information that will be present in promotional communications. These expectations are based upon “schemas” which are theoretical models for how we store and retain information in memory. We agree that consumers and health professionals have expectations about what information to expect in advertising material. FDA states that this expectation is based upon consumers’ views of the amount of scrutiny that advertisements undergo by FDA and therefore “there is no reason for them to believe that important risks have been omitted” (line 497).

FDA’s analysis is much too parochial. We contend that the primary perception of an advertisement is that it is, indeed, an advertisement. Although consumers may believe that the advertisement is reviewed by FDA, we believe that this in and of itself would lead to the expectation that the ad is truthful and not “false and misleading,” consistent with the statutory standard. We see no evidence that consumers believe that all “significant” risks are disclosed in the body of the ad. This is especially the case because advertising is required to meet the brief summary disclosure requirements which summarize to a much greater extent the “significant” risks of the product. Further, we believe that consumers’ skepticism of advertising claims would lead them to be critical of the claims being made and to be suspect about the full disclosure of risks. This well documented skepticism about advertising would mitigate expectations about full risk disclose^{11, 12}

CONSIDERATIONS OF FORMAT

FDA states that risk information should be comparably “noticeable and conspicuous” to benefit information (line 521). This is consistent with the regulatory requirement that that the risk information be prominent and readable and we agree with this requirement. However, FDA goes further in its analysis. It asserts that the layout (its plan, design or arrangement) should be examined when assessing prominence and readability (lines 537-540).

One aspect of the FDA's analysis focuses on the location of risk information. FDA states that risk information should not only be included in the main part of the advertising material, but that it needs to be integrated into the advertising piece and that "presenting several pages of benefit information before any risks" is an example of lack of appropriate prominence (lines 551-552). FDA cites its own regulation (21CFR 202.1(e)(3)(i) to support this contention.

This is a very narrow interpretation of the regulations. We are quite concerned that FDA will interpret its own draft Guidance much more liberally than the regulations intend.

First, the FDA citations for noticeability are based on literature regarding warning labels, not advertisements. This warning label literature appears to focus on consumers' interpretation and memory for information, not on whether warnings are noticed. It would be more appropriate to cite literature from eye-track research on advertisements. This literature shows that consumers review advertisements using a schema based on expectations. They review the advertising material briefly and then go back to focus on information they believe is new or relevant¹³. As risk information is one of the most important pieces of information desired by consumers reviewing advertising, the risk information will be viewed as a key aspect of the advertising no matter where it is located (as long as it is presented in a fashion comparable to the benefit information).

Second, FDA suggests that risk information should be fully integrated into an advertisement. Examples given by FDA suggest that several pages of benefits before mentioning risks is not acceptable. While we agree that risk information should be viewed as an integral part of the body copy of an advertisement, we are concerned about FDA's concept of "integration." If FDA is suggesting that risk information should be dispersed throughout an advertisement, we have serious reservations.

FDA does not present a compelling argument that risk information must be integrated throughout a piece. We find no reason to believe that the summarization of risk information near the end of an advertisement is insufficient, as long as individual claims are not misleading and the main fair balance disclosure is located in the main body of the ad. Using a schema approach, we would anticipate that people expect an advertisement to present benefits and then discuss risks. Dispersing benefit and risk information throughout an advertisement could lead to confusion, consumer fear or wariness or a lack of understanding of the risk information being presented. Further, in a recent letter to a sponsor, FDA objected to risk information that was presented in two places in an advertisement, stating that the first risk disclosure was incomplete and, therefore, misleading (FDA letter to Amgen regarding Sensipar® (cinacalcet HCl) Tablets, October 27, 2008).

CONCLUSION

The CHC is seriously concerned about the potential of FDA's application of the principles described in this draft Guidance to seriously curtail truthful advertising both

directly (by providing FDA with faulty reasoning to find a truthful advertising piece false or misleading) or indirectly (by discouraging advertisers from presenting otherwise truthful information). To provide a reasonable basis for regulation, the principles described by FDA must be more fully described, limits to their application must be more fully established, and these must be accomplished within the limits of the Act and the First Amendment.. We, therefore, respectfully request that FDA establish further opportunities for the public and the industry to participate in these decisions, including holding a hearing to address these and other comments.

We believe that promotion of prescription drugs and devices is an important component to assuring that health professionals and patients can learn about important new advances in healthcare. Such communications should be truthful and provide a fair balance of risk information. However, the disclosures envisioned by FDA in this draft Guidance present a significant departure from current FDA requirements and appear to impose new substantive regulatory requirements without providing appropriate notice and an opportunity for a full and complete discussion. We believe the FDA should engage in additional rulemaking procedures to explore the principles and the factors discussed in this draft Guidance. As part of such a process, FDA should carefully review and revise these proposed interpretations and requirements to assure that they do not represent new counterproductive burdens on the regulated industry and that they are consistent with current law and regulations.

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