Guidance for Industry

Presenting Risk Information in Prescription Drug and Medical Device Promotion

DRAFT GUIDANCE

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May 2009

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance describes factors FDA considers when evaluating advertisements (ads) and promotional labeling for prescription drugs [1] ads for restricted medical devices [2] and promotional labeling for all medical devices for their compliance with the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act) and relevant regulations.[3] This draft guidance discusses factors that are relevant to the disclosure of risk information and provides numerous examples to illustrate FDA's thinking on these factors. This guidance responds to stakeholder requests for specific guidance on how FDA evaluates prescription drug and medical device promotional pieces to determine whether they adequately present risk information. The recommendations contained in this draft guidance apply to promotional materials directed to both consumers and healthcare professionals.

[1] This draft guidance does not address over-the-counter (OTC) drug promotional labeling, which FDA also regulates. FDA encourages all manufacturers to ensure that their promotional labeling is truthful and non-misleading. FDA recognizes that the marketing status of animal drugs may vary, depending upon the intended species. For example, several anthelmintics on the market are available only by prescription for dogs and cats, yet very similar products are available OTC for horses and food animals. OTC drugs intended for food animals, in particular, may carry significant risks that may affect not only the intended food animal, but also other animal species and humans. OTC promotional labeling for animal drugs should convey the serious risks associated with use of the products, especially those affecting the public health.

[2] Devices may become restricted, either by regulation issued under section 520(e) of the Act (21 U.S.C. 360j(e), or by order approving an application for premarket approval (PMA), pursuant to section 515(d)(1)(B)(ii) (21 U.S.C. 360e(d)(1)(B)(ii)).

[3] This draft guidance also does not apply to those *reminder* promotions (labeling or advertising that calls attention to the name of a drug or device but does not include indications, dosage recommendations, or other information) that are exempted by regulation from the requirements under the FD&C Act for the disclosure of risk information. See 21 CFR 200.200, 201.100(f), 201.105(d)(2), 202.1(e)(2)(i), 801.109(d). But see 21 U.S.C. 352(r) (requiring certain risk information in all restricted device advertisements).

Although this draft guidance focuses on the presentation of risk information in prescription drug and medical device promotion, the factors relating to effective communication outlined below are also applicable to the presentation of benefit information in promotion. Indeed, when FDA evaluates promotional pieces for compliance with the Act and relevant regulations, it determines whether claims about both risk and benefit of the product are accurate and non-misleading, and it also looks at whether risks and benefits are presented in a comparably prominent manner. Thus, considerations involving the content and format of benefit information are an inherent part of FDA's evaluation of risk presentations in promotional pieces. FDA recommends that companies take the factors outlined in this document into account when developing both risk and benefit presentations in their promotional pieces, as the public health is best served when risk and effectiveness information about drug and device products is clearly and accurately communicated.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The regulation of prescription drug and medical device promotion to healthcare professionals and consumers is a broad and complex topic.[4] This document addresses one key aspect of this topic – the presentation of risk information. FDA believes it is critically important to disclose risk information in prescription drug and medical device promotion appropriately and effectively to healthcare professionals and consumers.[5] This information helps consumers know whether drugs or devices may be appropriate for them as well as what they should tell their healthcare professionals about before taking or using or while taking or using a product. It also lets consumers know what risks they might experience and what steps they need to take for safety reasons (e.g., no driving) because of taking or using a product. Appropriate risk disclosures help healthcare professionals by giving them some of the information they need to know about the product that will enable them to safely use or prescribe it. Recently published industry guidelines encourage manufacturers to develop prescription medicine promotion that is

[4] Although beyond the scope of this document, the complexity of the topic can be demonstrated by past studies that have shown potential positive and negative effects of direct-to-consumer (DTC) advertising for prescription drugs. For example, FDA research suggests that DTC advertising seems to increase awareness of conditions and treatments, to motivate questions for the healthcare provider, and to help patients ask better questions. Yet this research also suggests that almost half of physicians feel some pressure to prescribe as a result of DTC advertising, and patients and physicians report a belief that these ads overstate the drug product's efficacy and do not present a fair balance of benefit and risk information. For the complete study results, see K. Aikin, J. Swasy & A. Braman, Patient and Physician Attitudes and Behaviors Associated With DTC Promotion of Prescription Drugs – Summary of FDA Survey Research Results, Final Report, November 19, 2004, available at: http://www.fda.gov/cder/ddmac/Final%20Report/FRfinal111904.pdf.

[5] Effectively disclosing risk information also requires a consideration of whether an advertisement or promotional material over warns. For example, a drug advertisement that includes a listing of side effects that are not included in the drug's approved labeling may lead to under-emphasis of the most important and serious risks. FDA takes care to ensure that important risk information is included in the drug's approved labeling, and sponsors have an obligation to update their labeling with appropriate new safety information. 21 CFR 201.57(c)(6); 201.80(e). Nothing in this guidance should be construed as recommending that the sponsor of a drug include in advertising or promotional materials risk information not in the product's approved labeling or appropriate for inclusion in the labeling. See 73 Fed. Reg. 2848, 2851 (January 16, 2008).

"designed to achieve a balanced presentation of both the benefits and the risks associated with the advertised" product.[6]

However, omission or minimization of risk information is the most frequent violation of the regulations cited in advertising and promotion enforcement letters sent to sponsors, and illustrative research in one of the areas this guidance covers, direct-to-consumer prescription drug advertising, has shown that 60 percent of patients believe ads directed at them do not provide enough information about risks, 60 percent of physicians believe that patients have little or no understanding from these ads about what the possible risks and negative effects of the products are, and 72 percent of physicians believe that patients have little or no understanding from these ads about who should not use the product.[7]

FDA is issuing this draft guidance to aid sponsors in effectively communicating risk information in their promotion to both healthcare professionals and consumers. This draft guidance describes how FDA reviews prescription drug and medical device promotional pieces to determine whether they adequately present risk information. The document begins with some background information, including a brief overview of legal requirements and a discussion of policy considerations related to drug and device promotional materials. The draft guidance then describes factors FDA considers when reviewing risk communication in promotional materials. Because the principles within this guidance are based on universal concepts of communication and understanding of risk information, the guidance will address promotion aimed at both lay consumer and healthcare professional audiences.

A. LEGAL OVERVIEW

Under the FD&C Act and FDA's implementing regulations, promotional pieces (such as promotional labeling for drugs and devices and advertisements for prescription drugs and restricted devices) making claims about a product are deemed misleading if they fail to disclose certain information about the product's risks.[8] Generally, to comply with the FD&C Act and FDA's implementing regulations, such promotional pieces:[9]

- Cannot be false or misleading in any particular[10]
- Must reveal material facts about the product being promoted, including facts about the consequences that can result from use of the product as suggested in the promotional piece[11]

[6] PhRMA, PhRMA Guiding Principles Direct to Consumer Advertisements About Prescription Medicines, Principle 11, November 2005, available at: http://www.phrma.org/files/DTCGuidingprinciples.pdf.

[7] K. Aikin, J. Swasy & A. Braman, Patient and Physician Attitudes and Behaviors Associated With DTC Promotion of Prescription Drugs – Summary of FDA Survey Research Results, Final Report, November 19, 2004, available at: http://www.fda.gov/cder/ddmac/Final%20Report/FRfinal111904.pdf.

[8] The relevant statutory provisions and regulations are discussed in more detail in the Attachment to this guidance.

[9] The terms *promotional piece*, *promotional materials*, and *promotional communications* are used in this guidance to refer generally to both advertising and promotional labeling, regardless of format. Promotional materials include, among others, television ads, brochures, booklets, detailing pieces, internet web sites, print ads, exhibits, and sound recordings or radio ads. As noted in the introduction, this guidance applies to all types of promotion for prescription drugs, advertisements for restricted devices and promotional labeling for all devices.

[10] Drugs and devices are misbranded under the Act if their labeling is false or misleading in any particular (21 U.S.C. 352(a)). Similarly, prescription drugs and restricted devices are misbranded if their advertising is false or misleading in any particular (21 U.S.C. 352(n) & (q)(1); 21 CFR 202.1(e)(5)(i)).

and

— Should present information about effectiveness and information about risk in a balanced manner[12]

This draft guidance document describes factors FDA considers when evaluating risk disclosure in prescription drug and medical device promotional materials to determine whether these materials comply with the statutory and regulatory requirements. The draft guidance also makes recommendations about how manufacturers can develop the content and format of promotional communications to comply with these requirements. The examples and recommendations provided are intended to provide guidance and illustrate possible approaches; manufacturers are free to use alternative approaches if these approaches satisfy the requirements of the statute and regulations. Unless otherwise specified in this draft guidance, the principles set forth below apply to all promotional pieces, regardless of the medium used or the target audience.

B. POLICY OVERVIEW

Section III of this guidance highlights several factors, including those related to content and format, that FDA uses to evaluate the risk communication in a promotional piece. We recommend that manufacturers consider these factors when trying to achieve effective risk communication. It is important to emphasize that when FDA evaluates the risk communication in a promotional piece, FDA looks not just at specific risk-related statements, but at the ***net impression*** – i.e., the message communicated by all elements of the piece as a whole. The purpose of the evaluation is to determine whether the piece ***as a whole*** conveys an accurate and non-misleading impression of the benefits and risks of the promoted product. Manufacturers should therefore focus not just on individual claims or presentations, but on the promotional piece as a whole.[13] A promotional communication that conveys a deceptive net impression of the product could be misleading, even if specific individual claims or presentations are not misleading.

FDA's consideration of the net impression of risk information is based on well-developed social science principles supported by decades of scientific research[14] and is consistent with the approach of other agencies and organizations. For example, the Federal Trade Commission (FTC) uses the interpretation of the net impression of the piece to determine whether a promotional piece is likely to mislead a consumer.[15] Pharmaceutical industry members have also conducted social science research showing that, when evaluating a promotional piece, the net impression conveyed by the piece as a whole is an important element to consider, independent of individual statements within the piece.

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[11] 21 U.S.C. 321(n); 21 CFR 1.21 & 202.1(e)(5)(iii).

[12] See 21 CFR 202.1(e)(5)(ii).

[13] Manufacturers should note that, although this guidance focuses on risk disclosures in promotional pieces, any claims in a promotional piece that are misleading, whether risk-related or not, can cause the product being promoted to become misbranded (21 U.S.C. 352(a), (n) & (q)(1); 21 CFR 202.1(e)(5)(i)).

[14] For reviews of this field, see Kimble, G.A. (1985) The psychology of learning enters its second century. In Hammonds, B.L. (Ed.), *Psychology and learning.* Washington, DC: American Psychological Association (pp. 5-47) and Mayer, R.E. (2003) Memory and information processes. In Reynolds, W.M., & Miller, G.E. (Eds.), *Handbook of Psychology: Educational Psychology, 7.* New York: John Wiley & Sons, Inc. (pp. 47-57).

[15] See Federal Trade Commission, FTC Policy Statement on Deception, (Oct. 14, 1983), appended to *FTC v. Cliffdale Associates, Inc., et al.*, 103 F.T.C. 110, 170 (1984) (hereinafter "FTC Policy Statement on Deception" with page references to 103 F.T.C. 110).

Section III of the guidance contains examples of how various aspects of content and format can contribute to a misleading net impression in promotional pieces. The following two examples also illustrate this.

> *Example 1*: A broadcast television ad for a cholesterol-lowering drug contains a factually accurate audio risk statement that discloses the drug's major side effects and contraindications. This audio presentation is accompanied by quick scene changes showing comforting visual images of patients benefiting from the drug. It is also accompanied by loud, upbeat music. In this case, the audio disclosure may not adequately communicate risks because of the accompanying discordant visuals and distracting music.
>
> *Example 2*: A one-page prescription drug ad for an arthritis drug, run in a medical journal, prominently presents the following headline claims in large bolded font and with abundant surrounding white space:
>
> - ***Benefits!*** **DrugX is proven safe and effective for the relief of arthritis pain and stiffness**,
> - ***Difference!*** **DrugX's unique gel formulation is convenient and easy to use**, and
> - ***Reason to Believe!*** **Drug X is the most frequently prescribed arthritis drug in the United States**
>
> The bottom of the page contains an inconspicuous statement in small, non-bolded font and without surrounding white space: "Like all arthritis medications, Drug X has been associated with a risk of [illegible] infection." The emphasis on benefit information in this piece – in terms of the way the information is formatted and framed – overwhelms the risk information and may cause readers to receive an erroneous impression that the drug is safer than it has proven to be, even though the statements themselves may be factually accurate.

Using the factors explained in Part III of this draft guidance, trained professionals at FDA with expertise in areas including communication, drug information, medicine and law, apply these factors and evaluate claims in promotional pieces from the perspective of a reasonable consumer. As FDA has stated,[16] the agency believes that the reasonable consumer standard is the appropriate standard to use in determining whether a claim in the labeling of a dietary supplement or conventional food is misleading. The agency confirms that the reasonable consumer standard will be used to evaluate communications covered by this guidance document. The *reasonable consumer standard* used by FDA in evaluating promotional materials is similar to the FTC standard:

> [W]e examine the practice from the perspective of a consumer acting reasonably in the circumstances. If the representation or practice affects or is directed primarily to a particular group, the Commission examines reasonableness from the perspective of that group.[17]

[16] Guidance for Industry: Qualified Health Claims in the Labeling of Conventional Foods and Dietary Supplements (Dec. 2002) (replaced by Guidance for Industry and FDA: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Food and Human Dietary Supplements (July 2003)); see 70 Fed. Reg. 824 (Jan. 5, 2005) (noting that, although the Guidance for Industry on Qualified Health Claims in Labeling of Conventional Foods and Dietary Supplements (Dec. 2002) "has been 'replaced' by subsequent guidance, the agency has not abandoned the position in the 2002 guidance regarding reasonable consumer standard").

[17] See FTC Policy Statement on Deception at 170.

This standard does not preclude multiple interpretations of a claim, as long as they are reasonable. As the FTC's Policy Statement provides:

> To be considered reasonable, the interpretation or reaction does not have to be the only one. When a seller's representation conveys more than one meaning to reasonable consumers, one of which is false, the seller is liable for the misleading interpretation.[18]

In applying the reasonable consumer standard, FDA, like FTC, takes into account the different levels of expertise of lay consumers and healthcare professionals. Due to their training and experience, healthcare professionals develop a level of knowledge related to scientific concepts and medical conditions and products that lay consumers do not possess. FDA takes this difference in knowledge and experience into account when assessing promotional materials directed at healthcare professionals versus those directed at lay audiences. However, research has shown that experts (in this case, healthcare professionals) are subject to the same cognitive biases and processing limitations as non-experts.[19]

Cognitive science research has demonstrated that all people, regardless of expertise, are only able to think through and process a limited amount of information at one time.[20] However, our ability to process information can be greatly improved by considering and controlling for the factors that affect attention and comprehension. This guidance discusses those factors, how we apply them to our review of promotional materials, and what manufacturers can do to ensure that their materials comply with the regulations.

III. FACTORS CONSIDERED IN THE REVIEW OF RISK COMMUNICATION

FDA relies on a vast scientific body of knowledge regarding human cognition in assessing which factors to consider in evaluating promotional pieces and making regulatory decisions about the presentation of risk information. The following sections highlight factors that FDA considers when determining whether risk information is communicated in a fashion consistent with the regulations.

[18] *Id.* at 177.

[19] Although physicians generally do not believe that they are influenced by advertising, (Spiller & Wymer, 2001), research has shown that physicians are influenced by promotional activities (e.g., advertising: Avorn et al., 1982; sales representatives: Gonul et al., 2001). Avorn, J., Chen, M. & Hartley, R. (1982) Scientific versus commercial sources of influence on the prescribing behavior of physicians. *American Journal of Medicine, 73*, 4-8. Gonul, F.F., Carter, F., Petrova, E., & Srinivasan, K. (2001) Promotion of prescription drugs and its impact on physicians' choice behavior. *Journal of Marketing, 65*, 79-90. Spiller, L.D., & Wymer, W.W. (2001) Physicians' perceptions and uses of commercial drug information sources: An examination of pharmaceutical marketing to physicians. *Health Marketing Quarterly, 19*, 91-106.

[20] See, e.g., Lavie, N. (2001) Capacity limits in selective attention: Behavioral evidence and implications for neural activity. In Braun, J., Koch, C., et al. (Eds.), *Visual attention and cortical circuits*. Cambridge, MA: The MIT Press (pp. 49-68); Miller, G.A. (1994) The magical number seven, plus or minus two: Some limits on our capacity for processing information. Reprinted in Gutfreund, H., & Toulouse, G. (Eds.), Biology and computation: A physicist's choice. River Edge, NJ: World Scientific Publishing Co. (pp. 207-233); Shapiro, K. (Ed.) (2001) *The limits of attention: Temporal constraints in human information processing*. London: Oxford University Press.

A. GENERAL CONSIDERATIONS

This section explores some important factors that relate to both the content and the format of a promotional piece. FDA will consider the use of language and signals and how information is framed and ordered.

1. Consistent Use of Language Appropriate for Target Audience

Both language used to communicate benefits and language used to communicate risks should be comprehensible to the same audience for a piece to be considered accurate and non-misleading. Thus, promotional materials directed to professionals can reasonably describe benefits and risks in medical language, but promotional materials directed to consumers should convey benefits and risks in language understandable to consumers.[21]

> *Example 3:* A consumer-directed ad for a drug that presents benefit claims in consumer friendly language should mention a risk of "fainting," not "syncope."

With respect to consumer-directed materials, FDA encourages manufacturers to present both benefit and risk information in clear, understandable, and non-technical language for consumer audiences.[22]

2. Use of Signals

Signaling is an important component of information communication.[23] In written materials, *signaling* has been defined as the use of "writing devices designed to emphasize aspects of a text's structure or content without altering the information in the text."[24] Headlines and subheads are examples of commonly used signals.[25] Depending on the circumstance, "accurate information in the text may not remedy a false headline [or signal] because reasonable consumers may only glance at the headline" and skip the

[21] See Root, J., & Stableford, S. (1999) Easy-to-read consumer communications: A missing link in Medicaid managed care. *Journal of Health Politics, Policy, & Law, 24*, 1-26.

[22] Although not a true measure of "understandability," text reading level, often expressed as "grade level," is one way to assess text difficulty. Text that scores at a higher grade level (e.g., 12th grade) is considered more complex than text scoring at a lower grade level (e.g., 8th grade). Several validated reading level measures are available to provide an approximate measure of text complexity. See, e.g., Kincaid, J.P., Fishburne, R., Rogers, R.L., Chissom, B.S. (1975) *Derivation of New Readability Formulas (Automated Reliability Index, Fog Count, and Flesch Reading Ease Formula) for Navy Enlisted Personnel.* Research Branch Report 8-75. Memphis: Naval Air Station; McLaughlin, G.H. (1969) SMOG grading: A new readability formula. *Journal of Reading, 12*, 639-646; Mosenthal, P.B. (1998) A new measure of assessing document complexity: The PMOSE/IKIRSCH document readability formula. *Journal of Adolescent and Adult Literacy*, 41, 620-638. We encourage manufacturers to test text *comprehensibility* as well.

[23] Loman, N.L., & Mayer, R.E. (1983) Signaling techniques that increase the understandability of expository prose. *Journal of Educational Psychology, 75*, 402-412; Meyer, B.J.F. (2003) Text coherence and readability. *Topics in Language Disorders, 23*, 204-224; Spyridakis, J.H., & Standal, T.C. (1987) Signals in expository prose: Effects on reading comprehension. *Reading Research Quarterly, 22*, 285-298.

[24] Lorch, R.F., Lorch, E.P., & Inman, W.E. (1993) Effects of signaling structure on text recall. *Journal of Educational Psychology, 85*, 281-290, p. 281.

[25] Hyona, J., & Lorch, R.F. (2004) Effects of topic headings on text processing: Evidence from adult readers' eye fixation patterns. *Learning and Instruction, 14*, 131-152.

remainder of the text.[26] Signals are also used in broadcast situations, such as when an announcer draws attention to different items of information, when a word on the screen identifies a new topic, or when headlines emphasize some messages but not others.

When reviewing promotional materials, FDA looks to see if the use of signals is consistent across benefit and risk information, so that the materials provide accurate and non-misleading impressions of a drug or device.

> *Example 4:* If a piece contains headlines that signal benefit information, (e.g., "Drug X Provides Highly Effective Control"), some sort of headline should also signal risk information (e.g., "Side Effects for Drug X").

However, the mere presence of similar signals for both benefit and risk information is not necessarily sufficient to make a piece accurate and non-misleading. The content of the signals is also important. Certain headlines may *frame* (see next section) subsequent risk information in ways that emphasize or minimize its importance.

> *Example 5:* The headline "Important Risk Information about Device X" is preferable to "Important Information about Device X" because the former headline indicates what type of information follows. Similarly, "Common Side Effects Seen with Drug X," is preferable to "Other Information about Drug X." Specific and clear signals are preferable because they are more effective than vague or abstract terms.

Presenting risk information without signal, or beginning the presentation of risk information with unrelated information (e.g. presenting risk information in a paragraph that begins with information on indication or dosing) can also minimize the risks of the product and mislead the audience. For example, the headlines in the following example convey additional benefit information, potentially misleading the audience about the overall risk-benefit profile of the product.

> *Example 6:* Placing risk information under headlines such as "Now Approved for Epilepsy" or "Safe Enough for Children Under 5" minimizes the risk information that follows, particularly if individuals only look at the headlines. Instead, headlines preceding risk presentations should signal that a risk presentation follows, for example, "Important Risk Information About Drug X."

In videos, broadcast ads, and other promotional pieces with audio components, a change of announcer or a statement in the audio portion of the piece to signal to the audience that risk information follows can aid effective communication. However, manufacturers should consider comparable voice characteristics, as discussed in Section III.C.2. Risk information may also be signaled graphically or visually. Similar to print pieces, specific and straightforward audio signals are most likely to adequately convey risk information.

3. Framing Risk Information

FDA evaluates how risk information is framed because framing can affect the presentation of risks and benefits in a promotional piece. Framing commonly refers to how a particular piece of information is stated or conveyed, such as by emphasizing either the positive or negative aspects of the information or by presenting the information in vague versus specific terms. Research consistently shows that framing

[26] FTC Policy Statement on Deception at 182.

the same information in different ways can change the way audience members respond to that information.[27] Thus, the way information is phrased can significantly influence the message the audience receives from a promotional piece.

Framing risk information in non-specific terms can undermine the effective communication of that information to the audience. Risk information should be presented in the same terms or with the same degree of specificity as benefit information. For example, if a promotional piece refers to the product by name in presenting efficacy information, it should refer to the product by name in presenting risk information, rather than by referring to the product's device or drug class.

> *Example 7:* If the benefit information refers to the brand name, "Drug X," then "Common side effects associated with Drug X" would be preferable to "Common side effects associated with [the generic name]."

Moreover, within the risk information presentation, phrases such as "*Like all medicines*, Drug X has some side effects," may have the effect of minimizing the risks that follow. Framing risk information in a way that minimizes the severity of a risk event may also cause a promotional piece to be considered false or misleading.

> *Example 8:* If a drug's package insert contains a boxed warning about the risk of life-threatening fevers associated with its use and reports that 55 percent of patients taking the drug experience dizziness, a statement such as "Adverse events associated with drug X include fevers. Some patients experienced dizziness" misleadingly describes the risk profile of the drug by failing to convey the seriousness of the fevers and the frequency of the dizziness. Statements like "Life-threatening fevers have been reported with the use of Drug X" and "More than half of patients taking Drug X experienced dizziness" would convey the seriousness and frequency of the two risks appropriately.

In addition, the risks conveyed in the piece should be framed in a way that accurately reflects their nature.

> *Example 9:* A statement such as "continuation of therapy may necessitate certain monitoring" is too vague for a product that requires monthly blood tests to check for liver damage. This statement fails to convey the risk of liver damage and also misleadingly suggests that routine monitoring may ***not*** be necessary for some patients. A statement like "Monthly blood tests should be performed to check for liver damage" would accurately convey the type of monitoring needed and the risk involved.

4. Hierarchy of Risk Information

FDA considers the ordering of risks within a presentation an important factor in determining the risk profile conveyed by a piece, regardless of whether it is directed toward healthcare professionals or

[27] See Armstrong, K., Schwartz, J.S., Fitzgerald, G., Putt, M., & Ubel, P.A. (2002) Effect of framing as gain versus loss on understanding and hypothetical treatment choices: survival and mortality curves. *Medical Decision Making,* 22, 76-83; Dunegan, K.J. (1993) Framing, cognitive modes, and imagery theory: Toward an understanding of a glass half full. *Journal of Applied Psychology, 78,* 491-503; Rothman, A.J., & Salovey, P. (1997) Shaping perceptions to motivate healthy behavior: The role of message framing. *Psychological Bulletin, 121*, 3-19; Smith, S.M., & Petty, R.E. (1996) Message framing and persuasion: A message processing analysis. *Personality and Social Psychology Bulletin, 22*, 257-268; Tversky, A., & Kahneman, D. (1981) The framing of decisions and the psychology of choice. *Science, 211*, 453-458.

consumers. As discussed in Section III.B.2 (below) and reflected in the format of the package insert for prescription drugs and medical devices, risks associated with a specific product are assigned a hierarchy of importance.

Memory research consistently shows that, in an experimental setting, when people process an entire list or text, they are better able to recall items at the beginning and the end than items in the middle.[28] Consequently, in a broadcast ad, where viewers do not have the opportunity to control the speed at which information is presented to help them to process it, the beginning or end, or both, should be reserved for the most important risk information. On the other hand, when reading a print promotional piece under normal circumstances, readers may lose interest toward the end of a lengthy paragraph, and it is not likely that the information at the end will be as well-comprehended as the information at the beginning. If a product's most important risks are located in the middle of a list of less important risks, the important risks may not be effectively communicated. FDA therefore recommends that the most important risk information, including relevant warnings and contraindications, be placed or stated first, especially in print materials. As discussed in Section III.C.1 (below), manufacturers should also note, however, that risk information should not just be presented in one location in a piece, but should, like benefit information, appear as an integral part of the piece.

FDA also considers the order in which risk information is presented to determine whether this ordering suggests that certain risks apply only to certain populations or only under certain conditions when this is not the case.

> *Example 10:* A statement in a broadcast ad that "Patients should not drink alcohol when taking Drug X. Common side effects are drowsiness and nausea" may suggest that these side effects occur only if alcohol is consumed when taking the drug. Instead, the sponsor should consider adding intervening information or changing the order of the presentation so that it is clear the side effects listed are not caused by drinking alcohol while taking the drug.

B. CONSIDERATIONS OF CONTENT

This section discusses how FDA evaluates the content of risk presentations in determining whether a promotional piece is accurate and non-misleading.

1. Quantity

One content factor FDA considers is the amount or quantity of information conveyed by a promotional piece. For example, a 30-second broadcast ad is likely to present less information than a 60-second broadcast ad. As the amount of benefit information conveyed increases, the amount of risk information conveyed should similarly increase.

The quantity of information presented can affect the net impression of the piece. The amount of information presented is one component that, together with choice of words, color, graphics, voiceover, and other aspects of the piece, can affect *cognitive load*, the mental effort required to understand the

[28] See Botvinik, M.M., & Plaut, D.C. (2006) Short-term memory for serial order: A recurrent neural network model. *Psychological Review, 113*, 201-233; Capitani, E.; della Sala, S.; Logie, R.H.; & Spinnier, H. (1992) Recency, primacy, and memory: Reappraising and standardizing the serial position curve. *Cortex, 28*, 315-342; Murdock, B.B. (1962) The serial position effect of free recall. *Journal of Experimental Psychology, 64*, 482-488.

various components of information in the piece.[29] If the benefit information is easily understood and maintained through repetition or other reinforcing techniques, and the risk information is not similarly reinforced, the net impression may not be appropriately balanced.

To ensure comparable benefit and risk presentations, manufacturers should consider the space or time devoted to benefits and risks, the comprehensibility of the language used, and the information provided on benefits and risks. FDA 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.

A promotional piece with several paragraphs of information regarding benefits differs from a piece consisting mainly of one-line benefit claims. The treatment of risk information in each piece should be comparable to the treatment of benefit information, including how it is conveyed.

Promotional pieces do not have to convey an identical number of benefits and risks, and a given drug or device may have few or many risks.[30] FDA considers these factors when determining the comparability of benefits and risks in a piece:

- The number of statements about benefits and risks
- The completeness and depth of detail given about benefits and risks
- The amount of time (in both the audio and visual portions) devoted to benefits and risks in a video, audio, or broadcast communication
- The amount of space devoted to benefits and risks in a print communication
- The use of audio or visual components that enhance or distract from the presentation of risk or benefit information

As stated in the Background and discussed above, FDA evaluates the net impression created by promotional communications. This evaluation includes considering the above factors as well as the differences in the inherent risks associated with various drugs or devices. Simply satisfying one of the above factors (e.g., devoting the same amount of time or space to risk and benefit information) will not necessarily make a promotional piece accurate and non-misleading. Furthermore, certain important risk information should be in all promotional pieces regardless of their length (*see* Section III.B.2 below).

2. Materiality and Comprehensiveness

Generally speaking, *materiality* is determined by the degree to which information is objectively important, relevant, or substantial to the target audience. A promotional piece that omits material information about a product's risks could be considered misleading even if the piece devotes similar space or time to risk and effectiveness presentations.[31]

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[29] See Mayer, R.E., & Moreno, R. (2003) Nine ways to reduce cognitive load in multimedia learning. *Educational Psychologist, 38*, 43-52; Pass, F., Renkl, A., & Sweller, J. (2004) Cognitive load theory: Instructional implications of the interaction between information structures and cognitive architecture. *Instructional Science, 32*, 1-8.

[30] If the drug or device being promoted is associated with a minimal number of risks, and *all* of these risks are conveyed in a format that is comparably prominent to the presentation of benefit information, then the risk presentation in such an ad or promotional labeling piece would be considered accurate, non-misleading and balanced even if the ad presented several more benefit than risk claims.

[31] 21 U.S.C. 321(n); see also 21 CFR 1.21 & 202.1(e)(5)(iii). Please see the Attachment to this document for a full description of the relevant requirements.

Material facts are those that would influence reasonable consumers (or healthcare professionals when they are the intended audience) about a product. Material facts include those that influence such people's understanding of the following:

- The relevant properties of a product
- Whether or not the product is appropriate for them or their patients
- Whether or not they are willing to accept the risks or burdens associated with using or prescribing a product

Some drug and device risks are material regardless of the amount or type of benefit claims in a piece. The most serious risks set forth in a product's labeling are generally material to ***any*** presentation of efficacy. A promotional piece that communicates a product's benefits should similarly communicate the most serious risks involved in using the product. Similarly, the most frequently occurring risks would usually be material to consumers and healthcare professionals in promotion, particularly if a product is only associated with a small number of more serious risks, because of the likelihood that they will affect patients taking the drug or using the device.

- Consideration of Target Audience

FDA considers the target audience of a promotional piece to be critical in determining what risk information is material. FDA evaluates the promotion from the perspective of a reasonable member of the targeted population (e.g., consumers, specific patient populations, healthcare professionals). As is explored in more detail below (e.g., Examples 11 and 13), different information can be material to different audiences. For example, if a piece promoting use of a product in a selected class of patients, risks especially applicable to that selected class of patients are material (see "The Nature of Benefit Claims," below).[32]

Generally speaking, communications directed to healthcare professionals should convey the most critical information they need to know about the product to help them decide whether it is appropriate for their patients and to help enable them to safely use the product or counsel patients on the safe use of the product. Consumer-directed communications should generally convey the following:

- What the drug or device is used for
- Who should or should not take a drug or use a device
- What can be expected from a drug or device
- What patients should ask their healthcare professionals about a drug or device
- What patients should tell their healthcare professionals about before or while taking a drug or using a device

Example 11: A drug's package insert includes a warning for healthcare professionals about dosing adjustments in patients with kidney disease. This information is material for healthcare professionals, both because of the seriousness indicated by its warning status and because of its relevance to safe prescribing. However, although this information is important to the safe use of the drug and should be considered by prescribers, it is not material to consumers, although the reasons for such care in dosing (e.g., the consequences of inappropriate dosing) could be.

[32] See 21 CFR 202.1(e)(7)(x).

- Importance of Package Insert

In determining the materiality of the risks associated with a drug or device, FDA refers to the product's package insert. FDA is more likely to consider as important or material a product's most serious or most frequently occurring risks than a product's less serious or less commonly occurring risks.[33] FDA characterizes the risks associated with a specific product along a hierarchy of importance reflected by placement in a risk-related section of the product's package insert – traditionally , the Contraindications, Warnings or Hazards, Precautions, Adverse Reactions or Side Effects sections, as well as the Overdosage, and Drug Abuse and Dependence sections in the case of prescription drugs – and in the use of various means to emphasize certain risks, such as boxed warnings and bolded statements. For labeling that complies with the new formatting requirements in the recently finalized Physician Labeling Rule for prescription drugs,[34] the risk-related sections include Boxed Warning, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Drug Abuse & Dependence, and Overdosage.

For prescription drug physician labeling that follows the new requirements, the risks included in the *Highlights* section of labeling are the most important risks associated with the drug. For other labeling, contraindications and warnings or hazards are considered to contain the most serious and material risk information associated with a drug or device and convey information that must be understood before the product is prescribed or used. Contraindications and boxed warnings are generally considered the most important. Precautions also convey important risk information that can help healthcare professionals and patients use a drug or device more safely. These include ways to avoid adverse effects and information about important differences in individual response and, for drugs, about interactions with other drugs or food. Risks conveyed only in the adverse events or side effects section are generally less serious or less well-documented than those in the preceding three categories. They are often the most commonly experienced risks associated with a product, however, and they therefore may constitute important information for both healthcare professionals and consumers.

- The Nature of Benefit Claims

Promotional pieces should reveal risk information that is material in light of the specific benefit claims made in the piece.

> *Example 12:* If a piece claims convenience because the promoted drug is dosed once-weekly, information about risks directly related to the regimen's convenience is material. Such risk information might include, for example, that inflammatory reactions such as swelling have been reported at the application site for a topical product, or that patients must restrict their activities for some time after taking an oral medication because of a risk of fainting.

[33] As indicated above, the most serious risks set forth in a product's labeling are generally material to any presentation of efficacy. Frequently occurring, less serious risks (e.g., those reflected in Adverse Reactions) can be material, particularly for a product that is not associated with serious risks, but these less serious risks may not be material for a product that has many serious risks that need to be disclosed in promotion, or whose most frequently occurring risks occur at a very low rate. In general, FDA believes that exhaustive lists of minor risks distract from and make it difficult to comprehend and retain information on the more important risks. To this end, we have issued a draft guidance for prescription drugs entitled *Brief Summary Disclosing Risk Information in Consumer-Directed Print Advertisements*, which suggests approaches to communicating less, but better, information in consumer brief summaries. Once finalized, this guidance will represent the Agency's thinking on this topic.

[34] See 71 Fed. Reg. 3922 (Jan. 24, 2006). The rule became effective June 30, 2006.

Similarly, as stated above, for promotional pieces that promote a product's benefits in a selected class of patients, the significant risks applicable to that class of patients are material.[35]

> *Example 13:* If a Web site for a product approved to treat high blood pressure presents information about a product's benefits in postmenopausal women, any risks specific to postmenopausal women are particularly material.

- Accuracy and Comprehensiveness of Risk Information

When it evaluates the content of a promotional piece's risk information, FDA assesses the quality as well as the quantity of the information. Both consumer and professional audiences expect that certain information will be present in promotions for prescription drugs and medical devices. This expectation results from schemas,[36] or mental frameworks, about these promotional pieces that have developed from previous exposures (i.e., preconceived expectations based on past experience). Consumers have preconceived ideas about the amount of scrutiny these ads undergo. Many believe FDA exercises tight regulatory control over the content of these ads and to some extent, believe that all ads have been pre-reviewed prior to airing.[37] As a result, consumers are likely to expect that the most relevant risks have been included in the ad. Because people expect to see risk information, there is no reason for them to imagine that the product has important risks that have been omitted. Instead, the audience is likely to believe that all significant risks are included, especially if some risks are included. This missing risk information can have serious effects: it may cause consumers to fail to inform their healthcare professionals of important considerations, and healthcare professionals to prescribe inappropriately or even dangerously.

> *Example 14:* A product is associated with the rare but serious risk of a heart attack. FDA is likely to consider an ad misleading if it devotes a certain amount of time or space to the presentation of claims about the product's efficacy in treating migraines and then devotes a similar amount of time or space to describing only the frequently occurring, least serious adverse events, or only one of several significant risks.

Even though a similar *quantity* of risk and benefit information may be conveyed, a promotional piece that presents information on the benefits of the product but then communicates only its least serious risks, or an inadequate set of its serious risks, will not have conveyed an accurate understanding of the product's relevant properties.

C. CONSIDERATIONS OF FORMAT

FDA also considers formatting factors when assessing whether a piece is false or misleading. *Format* includes the shape, size, and general layout of all portions of a print promotional piece, as well as the

[35] See 21 CFR 202.1(e)(7)(x).

[36] See Kardash, C.A.M., Royer, J.M., & Greene, B.A. (1988) Effects of schemata on both encoding and retrieval of information from prose. *Journal of Educational Psychology, 80*, 324-329; Smith, E.E., & Swinney, D.A. (1992) The role of schemas in reading text: A real-time examination. *Discourse Processes, 15*, 303-316.

[37] See, e.g., K. Aikin, J. Swasy & A. Braman, Patient and Physician Attitudes and Behaviors Associated With DTC Promotion of Prescription Drugs – Summary of FDA Survey Research Results, Final Report, November 19, 2004, available at: http://www.fda.gov/cder/ddmac/Final%20Report/FRfinal111904.pdf; Prevention Magazine (2004) *5th Annual Survey: Consumer Reaction to DTC Advertising of Prescription Medicines*. Emmaus, PA: Rodale.

general plan of organization, arrangement, and theme in non-print promotional pieces such as videos and broadcast ads.

To process information, a person must first pay attention to it. Several factors contribute to whether people will pay attention to information. These factors also may help or hinder people's understanding of information once it has drawn their attention. When evaluating whether a promotional piece appropriately communicates risk information, FDA considers several formatting factors.[38] Because these factors apply to information processing in general, prescription drug and medical device manufacturers should keep them in mind when developing promotional pieces.

As a general matter, risk and benefit information should be comparably noticeable or conspicuous in promotional pieces, and audiences should be able to read both risk and benefit information with similar ease (e.g., comparably legible and understandable; *see* Section III.A.1 above).[39] Manufacturers should note that any one of the following formatting factors could make a piece false or misleading and that each factor could interact with others to increase this problem or to create a false or misleading impression when there might not be one if a factor were considered in isolation.

1. Print Promotion

The layout of a print promotional piece (generally, its plan, design, or arrangement) influences readers' ability to pay attention to and process specific features of the piece.[40] FDA considers the following selected aspects of the layout of a print promotional piece when assessing the comparable prominence and readability of risk and efficacy information. This is not an exhaustive list; other issues, such as language comprehension and the risk hierarchy, are covered in other sections.

- Overall Location of Risk Information

For a piece to be accurate and non-misleading, risk information should be included in the main part of a piece. If the omission of risk information in any part of a piece makes that part of the piece false or misleading, the problem cannot be corrected simply by including the risk information in a separate part of the piece.[41] To be comparably prominent to benefit information, risk information should generally appear in the same parts of the piece as the benefits.

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[38] See, e.g., 21 CFR 202.1(e)(7)(viii) for a list of implementing factors FDA takes into consideration when evaluating the balance between benefit and risk information in an ad. *See generally* 21 CFR 202.1(e)(6)-(7).

[39] See 21 U.S.C. § 352(c).

[40] See Adams, A.S., & Edworthy, J. (1995) Quantifying and predicting the effects of basic text display variables on the perceived urgency of warning labels: Tradeoffs involving font size, border weight, and color. *Ergonomics, 38*, 2221-2237; Brundage, M., Feldman-Stewart, D., Leis, A., Bezjak, A., Degner, L., Velji, K., et al. (2005) Communicating quality of life information to cancer patients: A study of six presentation formats. *Journal of Clinical Oncology*, 23, 6949-6956; Frantz, J.P. (1993) Effect of location and presentation format on attention to and compliance with product warnings and instructions. *Journal of Safety Research, 24*, 131-154; Morrow, D., Leirer, V., Altieri, P. (1995) List formats improve medication instructions for older adults. *Educational Gerontology, 21*, 151-166; Niemela, M., & Saariluoma, P. (2003) Layout attributes and recall. *Behaviour and Information Technology, 22*, 353-363; Wogalter, M.S., & Vigilante, W.J., Jr. (2003) Effects of label format on knowledge acquisition and perceived readability by younger and older adults. *Ergonomics, 46*, 327-344.

[41] See 21 CFR 202.1(e)(3)(i). The prescription drug regulations allow the presentation of risk information in a particular part of a promotional piece to be concise if it is supplemented by a prominent reference on each page to the presence and location of a more complete discussion of such information elsewhere in the piece. *Id.* However,

Complete separation of benefit and risk information (e.g., presenting several pages of benefits before any risks) is one example of a lack of appropriate prominence.[42] FDA will also look to see that risk information is not placed in such a way as to interfere with readers' perceptions of the relative importance or utility of the information.

- Location of Risk Information within a Part of the Promotional Piece

In addition to appearing with or near benefit presentations, risk information should appear as an integral part of the piece, just as benefit information does. For example, a prescription drug ad should not present risks only on a brief summary page.

> *Example 15:* A product's logo and a tagline are often used to signal the end of a piece. Readers may assume that any risk information placed below the logo and tagline is there only for liability purposes or to fulfill a regulatory requirement and is unrelated to the main message, especially if the information is presented in small type or otherwise lacking in emphasis.
>
> *Example 16:* A seven-page sales aid devotes the first six pages to effectiveness claims, which are prominently presented with colorful graphics, abundant white space, and large, colorful headers. Three of these pages also include a footnote referring readers to "Important Information on page 7." The seventh page summarizes some risk information from the PI in single-spaced paragraph format without headers or other presentation elements to emphasize to the reader that it is important risk information. Such a presentation creates problems regarding the adequate presentation of risk. The important risk information about the drug should instead be integrated into the piece and presented with similar prominence to the effectiveness claims.

Similarly, problems can arise when parts of a print promotional piece appear so unrelated that the risks do not look to be part of the piece.

> *Example 17:* Risk information is placed in a thin column along the side of an ad in a different font and color scheme, so that the visuals and benefit information form a complete whole, separate from the risk information. This is not likely to be considered an adequate presentation of risk information.

- Font Size and Style

Font size and type style are format factors that can affect the prominence and readability of information.[43] FDA does not object to a presentation on the basis of minor differences in font size alone, depending on

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although the regulations allow for the "concise" presentation of such information, the nature and importance of this information should be accurately conveyed. For example, if a drug contains a boxed warning with information on the risk of elevations in potassium levels that can lead to life-threatening complications in some patients, a statement in a part of a promotional piece that "Drug X may increase your potassium levels; see Prescribing Information (PI) for more information" is not likely to convey to consumers or healthcare professionals the magnitude (i.e., life-threatening nature) of the risk.

[42] 21 CFR 202.1(e)(3)(i); see also 21 U.S.C. 321(n), 21 CFR 202.1(e)(5)(iii).

[43] Adams, A.S., & Edworthy, J. (1995) Quantifying and predicting the effects of basic text display variables on the perceived urgency of warning labels: Tradeoffs involving font size, border weight, and color. *Ergonomics, 38*, 2221-2237; Arditi, A., & Cho, J. (2005) Serifs and font legibility. *Vision Research, 45*, 2926-2933; Baker, S.

other factors used to achieve emphasis (e.g., bolded lettering, bullets). However, FDA may object to substantial differences in font size or the presentation of risk information in a difficult to read font size, irrespective of the font size of benefit information, because this may seriously reduce the ability to see or comprehend the risk information.

Even with identical risk and benefit font sizes, differences in type styles can render some information easier to read than other information.[44] To be comparably prominent and readable, FDA recommends that risk and benefit information be presented in type styles that are similar in the use of capitalization, serifs, the weight of the type-face, the angle of the letters, the degree of flourishes and scripting, and other typographical factors such as spacing (e.g., leading and kerning).[45]

- Contrast

Contrast between text and background should not highlight the benefit information more than the risk information.

> *Example 18:* If benefit information in a piece is presented in white letters on a black background, risk information should be presented with similar contrast. If the piece presents risk information in a way that would make it difficult to discern (e.g., using white letters on a light gray background or gray letters on a black background), the presentation may be considered false or misleading.

Even if the background is a color designed to attract attention, the contrast influences the prominence of the words once attention has been gained. In fact, printing words in some attention-grabbing colors (e.g., red) may make the words difficult to read.[46] Similarly, the placement of risk information over pictures or

(2006). Provision of effective information. *British Dental Journal, 201*, 100; Sheedy, J.E., Subbaram, M.V., Zimmerman, A.B., & Hayes, J.R. (2005) Text legibility and the letter superiority effect. *Human Factors, 47*, 797-815; Tantillo, J., Di Lorenzo-Aiss, J., & Mathisen, R.E. (1995) Quantifying perceived differences in type styles: An exploratory study. *Psychology and Marketing, 12*, 447-457; Wogalter, M.S., & Vigilante, W.J. (2003) Effects of label format on knowledge acquisition and perceived readability by younger and older adults. *Ergonomics, 46*, 327-344.

[44] English, E. (1944) A study of the readability of four newspaper headline types. *Journalism Quarterly, 21*, 217-229; Mansfield, J.S., Legge, G.E., & Bane, M.C. (1996) Psychophysics of reading. XV: Font effects in normal and low vision. *Investigative Opthamology and Visual Science, 37*, 1492-1501; Sheedy, J.E., Subbaram, M.V., Zimmerman, A.B., & Hayes, J.R. (2005) Text legibility and the letter superiority effect. *Human Factors, 47*, 797-815; Tantillo, J., Di Lorenzo-Aiss, J., & Mathisen, R.E. (1995) Quantifying perceived differences in type styles: An exploratory study. *Psychology and Marketing, 12*, 447-457.

[45] See Arditi, A., & Cho, J. (2005) Serifs and font legibility. *Vision Research*, 45, 2926-2933; Baker, S. (2006) Provision of effective information. *British Dental Journal*, 201, 100; Moriarty, S.E., & Scheiner, E.C. (1984) A study of close-set text type. *Journal of Applied Psychology, 69*, 700-702; Paterson, D.G., & Tinker, M.A. (1947) Influence of leading upon readability of newspaper type. *Journal of Applied Psychology, 31*, 160-163; Smither, J.A., & Braun, C.C. (1994) Readability of prescription drug labels by older and younger adults. *Journal of Clinical Psychology in Medical Settings, 1*, 149-159; Tinker, M.A., & Paterson, D.G. (1946) Effect of line width and leading on readability of newspaper type. *Journalism Quarterly, 23*, 307-309.

[46] See Pearson, R., & van Schaik, P. (2003) The effect of spatial layout and link colour in web pages on performance in a visual search task and an interactive search task. *International Journal of Human-Computer Studies, 59*, 327-353; but see Adams, A.S., & Edworthy, J. (1995) Quantifying and predicting the effects of basic text display variables on the perceived urgency of warning labels: Tradeoffs involving font size, border weight, and color. *Ergonomics, 38*, 2221-2237.

other visual elements with multiple colors can cause this information or portions of this information to lack prominence and be difficult to read.[47] Furthermore, a print piece that superimposes risk information over a visual image could compromise the accuracy of the piece as a whole by drawing attention away from the risk information.[48]

- White Space

Background space (often called *white space*) between and around letters can influence the prominence and readability of text.[49] Presenting benefit information in multiple paragraphs with double spaces between each paragraph, while presenting risk information in one block paragraph without spacing or indentation could reduce the comparability of the risk and benefit presentations. Moreover, if a promotional piece uses headings, bullets, and other attention-getting symbols to emphasize product benefits, FDA recommends that it use similar techniques to present product risks.[50]

2. Non-Print Promotion

Some print formatting issues also apply to non-print promotion such as videos, broadcast ads, and similar audio and visual pieces. However, the unique features of non-print media add complexity. As with print, FDA considers factors such as location, proximity, type size, type style, and contrast when evaluating these materials. These factors are especially important with regard to text that is superimposed on other images in videos or broadcast ads (SUPERs) and other visual components, such as graphics, within the scene. In non-print pieces, FDA also evaluates other formatting factors in addition to those described above to determine whether a particular piece is considered false or misleading (e.g., audio components, motion within the visual component, the juxtaposition of visual and audio components, and duration of exposure).

- Textual Elements

Prescription drug broadcast ads must present major product risks in the audio or audio and visual parts of the ad.[51] Thus, broadcast ads and videos often use SUPERs and other text to present risk-related qualifying information. When used to disclose risk, SUPERs can pose particular problems of readability, comprehensibility, and proximity to benefit information. For example, the FTC, which requires that

[47] See, e.g., Hillstrom, A.P., & Chai, Y. (2006) Factors that guide or disrupt attentive visual processing. *Computers in Human Behavior*, 22, 648-656; Petty, R.E., Wells, G.L., & Brock, T.C. (1976) Distraction can enhance or reduce yielding to propaganda: Thought disruption versus effort justification. *Journal of Personality and Social Psychology, 34*, 874-884; Zimbardo, P.G., Snyder, M., Thomas, J., Gold, A., & Gurwitz, S. (1970) Modifying the impact of persuasive communications with external distraction. *Journal of Personality and Social Psychology, 16*, 669-680.

[48] See Shiffrin, R.M., & Schneider, W. (1977) Controlled and automatic human information processing II: Perceptual learning, automatic attending, and a general theory. *Psychological Review, 84*, 127-190.

[49] Adams, A.S., & Edworthy, J. (1995) Quantifying and predicting the effects of basic text display variables on the perceived urgency of warning labels: Tradeoffs involving font size, border weight, and color. *Ergonomics, 38*, 2221-2237; Pracejus, J.W., Olsen, G.D., & O'Guinn, T.C. (2006) How nothing became something: White space, rhetoric, history, and meaning. *Journal of Consumer Research, 33*, 82-90.

[50] See Luckiesh, M., & Moss, F.K. (1940) Boldness as a factor in type-design and typography. *Journal of Applied Psychology, 24*, 170-183.

[51] 21 CFR 202.1(e)(1).

"[q]ualifying disclosures…be legible and understandable," recognizes that, "in many circumstances reasonable consumers do not read the entirety of an ad or are directed away from the importance of the qualifying phrase by acts or statements of the seller."[52] FDA has similar concerns.

FDA assesses the temporal location of SUPERs within a broadcast ad or video when evaluating whether it is false or misleading. If claims must be qualified to avoid misleading the audience, we recommend that the qualifier be vocalized, presented through visual images, or placed in a prominent SUPER that runs ***concurrently*** with the claim.[53] If SUPERs do not appear close enough to the claim or risk information requiring qualification, a misleading impression of the product may result.[54] In addition, if qualifying information is complex and requires more than one line of text, we recommend that manufacturers use other means to convey this information.

Other issues FDA considers important that manufacturers should keep in mind include the following:

- SUPERs, if used, should be reasonably visible to a person under typical viewing conditions.
- All SUPERs should be on screen long enough to allow the audience to read and understand their full content.
- Graphics that distract from the presentation of risk information, including from risk-related SUPERs (e.g., busy scenes, frequent scene changes, vivid and compelling visuals[55] and moving camera angles) can misleadingly minimize the risks of the product being promoted by detracting from the audience's comprehension of the risk presentation.
- Competition from other SUPERs (e.g., presenting a SUPER related to a particular risk while unrelated SUPERs are on the screen) hampers the audience's ability to read and understand the SUPERs and could compromise the communication of risk information and make a piece misleading.[56]
- Factors such as font size, type style, and capitalization can also affect the readability of SUPERs.[57] Words presented in all upper case letters are more difficult to read than words presented in upper and lower case letters.[58]

[52] FTC Policy Statement on Deception at 183.

[53] See 21 CFR 202.1(e)(3)(i).

[54] Manrai, L.A., Manrai, A.K., & Murray, N. (1994) Comprehension of info-aid supers in television advertising for social ideas: Implications for public policy. *Journal of Business Research, 30*, 75-84.

[55] Vivid visual images are those images, pictures or other visual stimuli that are emotionally or cognitively interesting, attention-getting, compelling, provoking, or personal in a sensory, temporal or spatial manger (after Nisbett, R., and Ross, L. (1980) *Human Inference: Strategies and Shortcomings of Social Judgment*. Englewood Cliffs, NJ: Prentice-Hall). Background music can also be distracting (Furnham, A., & Strbac, L. (2002). Music is as distracting as noise: The differential distraction of background music and noise on the cognitive test performance of introverts and extraverts. *Ergonomics, 45*, 203-217).

[56] See, e.g., Mackie, D.M., & Worth, L.T. (1989) Processing deficits and the mediation of positive affect in persuasion. *Journal of Personality and Social Psychology, 57*, 27-40; Manrai, L.A., Manrai, A.K., & Murray, N. (1994) Comprehension of info-aid supers in television advertising for social ideas: Implications for public policy. *Journal of Business Research, 30*, 75-84.

[57] Baker, S. (2006) Provision of effective information. *British Dental Journal*, 201, 100; Manrai, L.A., Manrai, A.K., & Murray, N. (1994) Comprehension of info-aid supers in television advertising for social ideas: Implications for public policy. *Journal of Business Research, 30*, 75-84.

[58] Paterson, D.G., & Tinker, M.A. (1941) Caps vs. lower-case in headlines. *Editor & Publisher, 74*, 51.

- Contrast

Contrast is an important visual factor[59] that FDA considers when evaluating television ads and videos.[60] As in print pieces, risk disclosures presented in SUPERs should be in a font color that reasonably contrasts with the background visuals. Because important non-benefit information is often conveyed by SUPERs, any obstacle to the prominence and readability of this information, and thus to the audience's understanding of SUPERs, may result in a misleading risk presentation.

- Dual Mode Considerations

The interplay of visual and audio components in pieces such as television ads and videos introduces unique factors FDA must consider when evaluating the adequacy of risk disclosure. The issues raised above in Textual Elements about distracting visuals apply not only to the SUPER presentation but also to the audio presentation of risks.[61] If visuals in a broadcast ad distract the audience from the statement of a product's risks, the ad will not, as a whole, convey an accurate impression of the risks of the advertised product. This distraction could be caused by factors including busy scenes, frequent scene changes, moving camera angles, and even inherently compelling, vivid visuals. In addition, the overall tone of the ad or of specific background visuals can affect the comparable prominence of the risks, particularly if the tone is contrary to the risk message.

Example 20: A video or broadcast ad depicts a joyous or exhilarating moment, contains images of people enjoying the benefits of the product, or includes other visually compelling or distracting non-risk related images while major risks are communicated in a voiceover. The inconsistent tone or images may be too distracting for the audience to listen to or process the risks, causing the video or broadcast ad to communicate a false or misleading net impression of the product.

- Audio Considerations

FDA considers several audio-related factors when evaluating pieces such as sound recordings, videos, or broadcast ads, including television, radio, and telephone communications.

— The qualities of speech should be similar across benefit and risk information for these components to be considered comparably prominent.
— A critical speech consideration is *pacing*. If risk information is considerably more difficult to hear and process than benefit information because it is presented at a much faster pace, the piece will not convey an accurate impression of the product.
— Markedly reducing volume or being less articulate when discussing risks compared to benefits may hinder the audience's comprehension of the risks.
— Background music should be comparable in volume and distraction potential during both benefit and risk presentations.

[59] Mitzner, T.L., & Rogers, W.A. (2006) Reading in the dark: Effects of age and contrast on reading speed and comprehension. *Human Factors*, 48, 229-240.

[60] Seibert, W.F., Kasten, D.F., & Potter, J.R. (1959) A study of factors influencing the legibility of televised characters. *Journal of the Society of Motion Picture & Television Engineers, 68*, 467-472.

[61] See, e.g, Regan, D.T., & Cheng, J.B. (1973) Distraction and attitude change: A resolution. *Journal of Experimental Social Psychology, 9*, 138-147.

IV. CONCLUSION

The FDA's regulation of prescription drug and medical device promotion to healthcare professionals and consumers is a broad and complex topic. A vast scientific body of knowledge is available regarding human cognition, and FDA relies on this knowledge when evaluating promotional pieces and making regulatory decisions about the presentation of benefit and risk information. The Agency hopes that by discussing the most relevant factors and by providing specific examples, manufacturers will gain a better understanding of what they should consider as they develop the content and format of their promotional communications.

It is important to re-emphasize that, in addition to specific risk-related claims, FDA also considers the net impression conveyed by all the elements of a piece. For this reason, manufacturers should focus not just on individual claims or presentations, but on the messages conveyed by the promotional piece as a whole.

ATTACHMENT: STATUTORY AND REGULATORY REQUIREMENTS FOR LABELING AND ADVERTISING

FDA regulates the manufacture, sale, and distribution of drugs and devices in the United States under the authority of the Federal Food, Drug, and Cosmetic Act (the Act). This authority includes oversight of labeling for all drugs and devices and of advertising for prescription drugs and restricted devices. 21 U.S.C. 352(a), (n), (q), & (r). In regulating the labeling and advertising of drugs and devices, FDA attends to the First Amendment.

The Act defines label to mean "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." 21 U.S.C. 321(k). According to FDA regulations (21 CFR 1.3(b)): "Label means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity." The Act defines labeling to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. 321(m). Similarly, FDA regulations (21 CFR 1.3(a)) provide that labeling includes "all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce."

According to *Kordel v. United States*, 335 U.S. 345, 350 (1948), the language "accompanying such article" in the "labeling" definition includes materials that supplement or explain an article, "in the manner that a committee report of the Congress accompanies a bill. No physical attachment one to the other is necessary. It is the textual relationship that is significant." FDA's prescription drug advertising regulations (21 CFR 202.1(l)(2)) thus provide as examples of labeling a wide variety of written, printed, or graphic matter that bears a textual relationship with a product.

FDA generally recognizes two types of labeling for drugs and devices: FDA-required labeling and promotional labeling. Much FDA-required labeling is subject to FDA review and approval. For example, after drafting by the manufacturer, required labeling is reviewed and approved by FDA as part of the new drug application (NDA), new animal drug application (NADA), biologics license application (BLA) or premarket approval application (PMA) review (21 CFR 314.50(c)(2), 514.1(b)(3), 601.2(a), and 814.20(b)(10)).

For devices that are not subject to premarket approval, but instead are subject to premarket notification requirements or are exempt from premarket review, there is no agency review or approval of labeling, but such devices remain subject to all of the requirements of applicable labeling regulations, including those for adequate directions for use. For a prescription drug or prescription device to be exempted from the Act's requirement of adequate directions for use (21 U.S.C. 352(f)(1)), its FDA-required labeling must contain, among other information, information addressing product hazards and other risk information, as specified in FDA regulations.[62]

Promotional labeling is generally any labeling other than the FDA-required labeling that is devised for promotion of the product. Promotional labeling may include items such as "brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar

[62] 21 CFR 201.100(d)(1), (3), 201.105(c)(1), & 801.109(d).

pieces of printed, audio, or visual matter . . . ."[63] The Act specifies that a drug or device shall be deemed to be misbranded if its labeling is false or misleading in any particular. 21 U.S.C. 352(a). The Act further specifies that labeling or advertising may be considered misleading if it fails to reveal material facts about the product being promoted, including facts about the consequences that can result from use of the product as suggested in a promotional piece. 21 U.S.C. 321(n). In addition, the Act specifies that a drug or device will be deemed to be misbranded if any word, statement, or other information required under the Act to appear on the label or labeling is not "prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use." 21 U.S.C. 352(c).

Advertising[64] for prescription drugs and restricted devices is also subject to requirements under the Act for the disclosure of risk and other information. Under section 502(n) of the Act (21 U.S.C. 352(n)) and FDA's implementing regulations (21 CFR Part 202), an ad for a prescription drug must include, in addition to the product's established name and quantitative composition, a "true statement" of information in brief summary "relating to side effects, contraindications and effectiveness" of the product with respect to the use or uses that the message promotes.[65] Advertisements for restricted devices must include "a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications . . . ." 21 U.S.C. 352(r)(2). For prescription drug advertisements, FDA's implementing regulations specify that, among other things, the statutory requirement of a "true statement" is not satisfied if an ad for a prescription drug product is false or misleading with respect to side effects, contraindications or effectiveness or if it fails to reveal material facts about "consequences that may result from the use of the drug as recommended or suggested in the advertisement." 21 CFR 202.1(e)(5). Similarly, the Act also specifies that restricted device advertisements must not be false or misleading (21 U.S.C. 352(q)(1)) and must reveal facts that are material about the product being advertised, including facts about the consequences that can result from use of the product as suggested in an ad. 21 U.S.C. 321(n).

The prescription drug regulations also specify that ads must present a fair balance between information relating to risks and benefits, which is achieved when the treatment of risk and benefit information in a promotional piece is comparably thorough and complete throughout the piece. 21 CFR 202.1(e)(5)(ii). These regulations also provide illustrations of the factors FDA considers in determining whether promotional pieces comply with the above requirements relating to risk disclosure. Specifically, these regulations identify twenty types of advertising communications that FDA considers "false, lacking in fair balance, or otherwise misleading." 21 CFR 202.1(e)(6). These include, for example, representations or suggestions that a drug is more effective or safer than has been demonstrated by substantial evidence or substantial clinical experience, the use of pictures or graphics in a way that is misleading, and the presentation of risk information "by means of a general term for a group" rather than disclosing specific

[63] See, e.g., 21 CFR 202.1(l)(2).

[64] The act does not define "advertising" or "advertisement." According to FDA regulations (21 CFR 202.1(l)(1)), "Advertisements subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems."

[65] According to 21 CFR 202.1(e)(3)(iii), the information in brief summary relating to side effects and contraindications must disclose "*each specific side effect and contraindication* (which include side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc. . . .) contained in required, approved, or permitted labeling for the advertised drug dosage form(s)" (emphasis added).

risks. 21 CFR 202.1(e)(6)(i), (xviii), & (xx). Representing or suggesting that a drug product is "safer than has been demonstrated by substantial evidence or substantial clinical experience" means obscuring or failing to include the most serious risk information set forth in the drug's FDA-approved labeling, and does not refer to a failure to include risk information that is not set forth in the drug's FDA-approved labeling.

In addition, these regulations identify thirteen additional types of advertising communications that "may be false, lacking in fair balance, or otherwise misleading." 21 CFR 202.1(e)(7). These include, for example, advertising communications that fail to "present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug." 21 CFR 202.1(e)(7)(viii).

Although the regulations discussed above were promulgated in the context of prescription drug advertising, the guidance they provide on what FDA considers false or misleading in promotion has broader applicability. For example, promotional pieces that fail to present a balanced view of the risks and benefits of a product are generally considered to be false or misleading and also generally fail to reveal material facts about the product being promoted. Because both labeling pieces for drugs and devices, and advertising pieces for prescription drugs and restricted devices, are considered to misbrand a product if they are false or misleading or fail to reveal material facts,[66] drug and device manufacturers should take into account the guidance provided by these regulations when developing promotional labeling and advertising pieces for their products.

[66] 21 U.S.C. 352(a), (n), (q)(1) & 321(n); 21 CFR 202.1(e)(5).