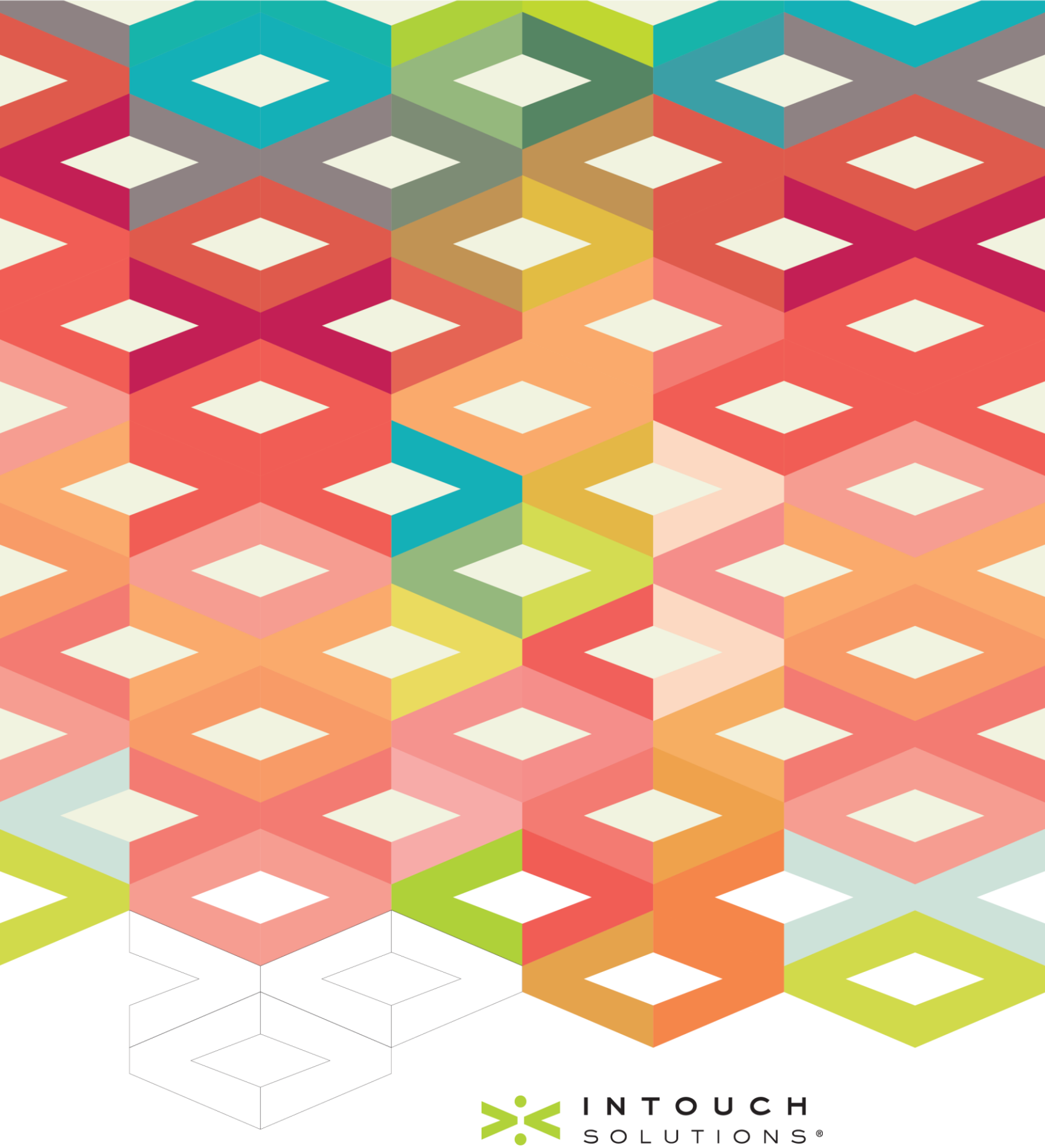

INTOUCH SOLUTIONS®

POV: COMMUNICATING BEYOND THE LABEL: THE IMPACT OF RECENT FDA GUIDELINES

JANUARY 2017

COMMUNICATING BEYOND THE LABEL: THE IMPACT OF RECENT FDA GUIDELINES

EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) has released two important draft guidance documents related to communications about prescription drugs[1]:

1. ***Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers***
2. ***Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers***

Combined with a separate **memorandum** on the FDA's position regarding off-label communications and the First Amendment, these documents represent a significant opportunity for marketers of prescription drugs to revisit existing practices and resolve some outstanding questions, especially regarding providing information to payors prior to receiving FDA approval.

In light of these new guidances, Intouch Solutions recommends that prescription drug manufacturers take the following actions:

- Review existing policies to determine whether they are more restrictive than the FDA's new guidances permit, especially regarding the provision of preapproval information
- Assess existing promotional communications under development and in review to determine whether they are affected by these guidances
- Establish (or revise) policies and procedures to ensure adherence to the FDA's current position
- Evaluate the overall impact of these documents and consider developing and submitting comments to the FDA about them

PAYOR COMMUNICATIONS GUIDANCE

The Payor Communications Guidance for the first time addresses the healthcare economic provision included in the Food and Drug Administration Modernization Act (FDAMA), which was passed in 1997. Among other things, that law enabled prescription drug manufacturers to provide information about the economic consequences of using their products to certain groups of people while meeting a lower standard of evidence than is typically required for promotional claims. Specifically, the law stated that:

"Health care economic information [HCEI] provided to a payor, formulary committee, or other similar entity … [in the course of] carrying out its responsibilities for the selection of drugs … shall not be considered to be false or misleading … if the health care economic information relates to an indication approved … [and] is based on competent and reliable scientific evidence … "[2]

In the 20 years since FDAMA passed, the FDA has provided no guidance about this provision (known as FDAMA 114), which left product manufacturers uncertain about such basic questions as what a "similar entity" might be; how to understand the limitations of "health care economic information;" and what the competent and reliable scientific evidence (CARSE) standard was and whether HCEI was regarded by the agency as promotional and subject to promotional requirements.[3] Just last month, Congress expanded the FDAMA 114 exemption further via the **21st Century Cures Act**.

Acronym Guide	
FDAMA	Food and Drug Administration Modernization Act (law passed in 1997)
FDAMA 114	Section 114 of FDAMA that discusses HCEI
HCEI	Healthcare economic information
CARSE	Competent and reliable scientific evidence

FDA's Payor Communications Guidance answers many of the questions raised by the initial FDAMA 114 provision, as well as the expansion provided in the 21st Century Cures Act. Specifically, this guidance addresses: (a) the type of information that falls under the definition of HCEI that can be communicated; (b) to whom this information can be provided; (c) what it means to be related to an approved indication; (d) how to determine whether the information meets the CARSE standard; (e) what information should be included in an HCEI presentation; and (f) what information can be provided prior to approval.

WHAT IS HCEI?

The FDA elaborates on the lengthy definition provided in the statute by noting that any analysis of the outcomes of treatment, including even comparative analysis that does not rely on a head-to-head clinical trial, could be presented. This is a significant broadening of the types of information that are being explicitly permitted and also seems to be more in line with the requests pharmaceutical companies are receiving from payors. The FDA also describes a wide variety of means for disseminating this information, such as reprints, budget-impact models and modeling software.

HCEI AUDIENCE

Interest in HCEI has expanded significantly since the original FDAMA 114 provision was enacted, and the entities requesting it have evolved rapidly. The Payor Communications Guidance provides greater clarity around the audiences for whom the FDA deems it appropriate to provide this information. In addition to the list provided in law, the FDA clarifies that the appropriate audiences include "drug information centers, technology assessment panels, pharmacy benefit managers, and other multidisciplinary entities that review scientific and technology assessments to make drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis for health care organizations."[9] The key factors in the FDA's elaboration are that the audience has the specialized knowledge required to interpret the HCEI analyses presented to them (i.e., "Expertise in this area is essential to understand and evaluate health care economic analyses and their limitations.") Given this limitation, the FDA's guidance does not address the **provision of HCEI via a consumer-directed website**.

The Payor Communications Guidance provides greater clarity around the audiences for whom the FDA deems it appropriate to provide this information.

RELATED INDICATION LIMITATION

The law explicitly limits the provision of HCEI to a related indication that has received FDA approval. The FDA expands on this to provide 10 examples of types of information that go beyond the approved data provided for the approved indication, but which the FDA would

nonetheless see as being appropriately related to an approved indication for the purposes of this guidance.

1. Duration of Treatment — For example, evaluating the cost of treatment for a chronic condition used beyond the length of the pivotal trial
2. Practice Setting — HCEI impacts in treatment settings other than those in the pivotal trial, such as managed care when the pivotal trial was only conducted in fee-for-service setting
3. Burden of Illness — Evaluating economic impact of things such as lost days of work due to the condition
4. Dosing — Presenting the results of observational studies of actual patient usage that differs from approved labeling
5. Patient Subgroups — Analyses of HCEI in subgroups that were not pre-specified in the pivotal trial
6. Length of Hospital Stay — HCEI analyses of effect of treatment
7. Validated Surrogate Endpoints — For example, HCEI analyses projecting impacts on stroke reduction from treatment with antihypertensives
8. Clinical Outcomes Assessments — HCEI analyses based on patient- or other-reported measures on factors such as productivity or basic activities of daily life
9. Persistence — HCEI analyses may present information on how long patients remain on therapy (for the approved indication(s))
10. Comparisons — HCEI analyses looking at the comparison between different treatments, treatment modalities and even comparing treatment to no treatment

CARSE STANDARD

CARSE (competent and reliable scientific evidence) is required for any HCEI analysis that is presented, and the FDA elaborates on how it understands that standard in the Payor Communications Guidance. Rather than listing specific features an analysis must meet, the FDA indicates that it will regard an analysis to have met the CARSE standard if it is generally accepted as such within the scientific community as indicated by its adoption by third-party, authoritative bodies.

DISCLOSURES

The FDA recommends that companies providing HCEI include certain information to enable the audience to evaluate the presentation. The list of recommendations includes:

1. Study design and methodology
2. Generalizability, especially including any limitations to the ability to project the results of the analysis
3. Limitations (including limitations related to data or the incompleteness thereof), analysis, assumptions, study design, etc.
4. Sensitivity analysis
5. Additional disclosures, including:
    a. A conspicuous and prominent statement of differences from approved indications MUST be presented
    b. FDA-approved indication and labeling
    c. Disclosure of omitted studies or data
    d. Risk information, especially if there is unique or relevant risk information related to the HCEI analysis or use being presented
    e. Financial bias

PREAPPROVAL PRESENTATION OF HCEI

Prior to release of the Payor Communications Guidance, the industry was unclear whether responding to frequent requests from payors for information about products prior to their approval would constitute preapproval promotion. This guidance establishes a safe harbor for such communications. The FDA indicates that it will not consider such communications to the appropriate audience as preapproval promotion, if the communication is limited to:

1. Product information (e.g., drug class, device design)
2. Indication under investigation (e.g., clinical trial endpoint, study design, etc.)
3. Factual presentation of preclinical and clinical trial results (without any characterization of whether these results are promising or imply safety or efficacy)
4. Timeline for FDA review
5. Pricing information
6. Marketing strategies
7. Patient support and other product-related services

When presenting such information, the FDA recommends that firms also indicate clearly:

1. That the product is not yet approved
2. Where the product is in its development (e.g., in Phase III, NDA-submitted, etc.)

In addition, the FDA recommends that companies keep records of such presentations and the information presented so that they can provide follow-up information if the initial communication proves to be outdated, and that the companies then provide the follow-up information (if, for example, the clinical trial results do not meet the study's primary endpoint). And of course, at no point should a company suggest that its product is safe or effective prior to receiving approval from the FDA.

CONSISTENT COMMUNICATIONS GUIDANCE

The second draft guidance released last week addressed the issue of when communications about a product can include additional information that is not in the product's label without violating FDA regulations. Specifically, this includes information that is not explicitly included in a label, but which might nonetheless be considered by the FDA as appropriate because it is consistent with the approved label. The FDA is setting out the standards that companies can use to provide such information without subjecting the company to the charge of misbranding the product. Prior to releasing this guidance and meeting its standards, companies feared that providing such information would be regarded by the FDA as evidence of a new intended use for the product and hence misbranding.

The FDA is setting out the standards that companies can use to provide such information without subjecting the company to the charge of misbranding the product.

The first point to note is that this guidance does not address uses outside of the approved uses for the products. Though such uses might technically be construed as "consistent" with the approved labeling, any communications about unapproved uses are outside of the scope of this guidance.

The First Amendment and Off-Label Information
Although the FDA's guidance about communications consistent with a product's label does not address communications regarding unapproved uses, the FDA released a separate memorandum regarding the First Amendment that set out the current view of the agency on this topic. The memorandum reiterated the agency's traditional view that existing law requires the FDA to place restrictions on the promotion of unapproved uses and the rationale for why the agency believes this is consistent with the Constitution. The FDA is still in the process of reviewing its position on this topic, and the memorandum is not the final step in that review. In the meantime, the agency has provided separate guidances about some forms of communications regarding unapproved uses. 1. *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* 2. *Distributing Scientific and Medical Publications on Unapproved New Uses Recommended Practices*

Instead, this guidance is focused on the difficulty frequently faced by product manufacturers that the product's approved label is, by necessity, limited. Companies have far more information about their products than could possibly be included in the approved label, and quite often the question arises about what (if any) of this information they can share in promotional contexts without being subjected to enforcement for off-label promotion. The FDA provides examples of communications that would and would not be permitted (discussed further below).

The first consideration for the FDA is a **three-factor test**. A communication must pass all three factors to be considered consistent with the product labeling (and potentially permissible). The three factors are:

1. Does the communication conform with the approved product labeling in the following ways:
    a. Indication?
    b. Intended patient population?
    c. Limitations and directions for handling/use?
    d. Dosing and administration?
2. Does the communication increase the likelihood for harm relative to the approved labeling?
3. Can the FDA-required labeling enable safe use of the product as described in the communication?

The first test for any communication that goes beyond the FDA-approved labeling is to answer all of the questions above. Communications that do not conform with the approved labeling, that would increase the likelihood for harm, or that cannot be used safely via the existing labeling would be construed by the FDA as being inconsistent with the product's label (for the purposes of this guidance) and hence impermissible.

The FDA provides examples of the types of communications that it would consider as consistent with the product label, as defined by this guidance.

- Head-to-head clinical trial results, so long as the clinical trial results compare two on-label uses of the product
- Additional information about the adverse events in the approved labeling
- Onset of action information beyond that contained in the original label
- Information about long-term use beyond that provided in the pivotal trial data (e.g., information about a chronic treatment approved with a 24-week clinical trial about its use over 52 weeks)
- Subgroup information relating to the approved indication (e.g., when a product is approved for male and female patients and the company wants to provide information specifically about the female population in the trial)
- Patient-reported outcomes for the approved indications if the claims are based on adequate and valid measurement tools as outlined in **separate guidance**
- Product convenience claims
- Additional information about a product's mechanism of action beyond what is provided in the product label

The FDA also provides examples of what communications that it does NOT consider consistent with the label:

- Information about a distinct indication for the treatment that is not included in the current label
- Use of a product in a different population from the approved indication
- Use of a product for a different stage or severity of the condition (e.g., discussing use of a product for severe pain when it is only approved for moderate pain)
- Monotherapy use when approved use is solely in combination therapy

- Changing the route of administration from the approved label
- Modifying the strength, dosage or use regiment outside the approved labeling
- Changing the dosage form (e.g., from a capsule to an oral solution)

When communications are consistent with a product's label, the communications should still have appropriate evidentiary support, though the guidance is unclear about exactly what that level of support is. The guidance states that communications should be supported by "scientifically appropriate and statistically sound" data and analyses but doesn't further specify what that means. Because the communication is consistent with the product's label, the FDA indicates that the communication is not automatically false or misleading, but they are open to the possibility that it might be. The FDA states that certain post hoc analyses of pivotal trial data "could improve understanding of a product," but they immediately provide an example where they would see such an analysis as misleading.[4] Caution is warranted in communicating such post hoc analyses given this lack of clarity in the guidance.

The guidance states that communications should be supported by "scientifically appropriate and statistically sound" data and analyses but doesn't further specify what that means.

To ensure that communications are not false or misleading, the FDA recommends always doing the following information in such communications:

- Clearly and prominently disclose the study design, methodology and any material limitations to that analysis
- Present any inconsistent findings or unfavorable findings that would provide context for the communication
- Include the information from the product's label that is relevant to the communication (for example, include clinical trial results on adverse events when discussing postmarketing reports of adverse events)

The FDA notes that this list is not, nor is it intended to be, comprehensive and that companies must still evaluate every communication to ensure that they are not false or misleading and that they meet all the requirements associated with promotional communications in general.

CONCLUSION

In both of these guidances, the FDA is expanding the possibilities for what information companies can provide in areas that have been particularly difficult for them to navigate. While these guidances do not represent a drastic departure from the FDA's previous positions, savvy marketers should be able to provide more valuable information to better inform the decisions of payors (in the case of HCEI) and individual healthcare providers and patients (in the case of communications consistent with the label).

As with all guidance documents, these have been released in draft and are open to comment. As such, companies should thoroughly review the guidances and provide feedback to the FDA about areas where further clarity is needed or where a different position would better serve the public health.

This client advisory was prepared exclusively for Intouch Solutions by PhillyCooke Consulting. PhillyCooke Consulting is not a law firm, and nothing in this advisory should be construed as offering legal advice or counsel.

Author: Dale Cooke

[1] Throughout this POV, the phrase "prescription drugs" is used, but it must be kept in mind that the FDA's position on these issues affects biological products that are regulated as drugs, medical devices, and animal drugs (in some cases).

[2] 21 USC 502(a), as amended by FDAMA.

[3] Though note that FDA Form 2253 has included a category for Formulary Economic and Formulary Kit as categories of material type for several years. The Payor Communications Guidance clearly states that the FDA does regard HCEI analyses as promotional communications subject to all of those requirements.

[4] The specific example pulls individual elements from composite endpoints without being appropriately powered for the individual components.