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AdvaMed
Advanced Medical Technology Association

August 17, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA- 2015-D-1580: "*Patient Preference Information – Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and* De Novo *Requests, and Inclusion in Device Labeling; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders."*

Dear Sir or Madam:

The Advanced Medical Technology Association ("AdvaMed") is pleased to provide comments on FDA's draft guidance "*Patient Preference Information – Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and* De Novo *Requests, and Inclusion in Device Labeling; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders."*

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatment. Our members range from the smallest to the largest medical technology innovators.

We commend CDRH for its leadership in incorporating patient perspective into regulatory decision-making and for collaborating with external stakeholders and organizations in the development of this draft guidance. Overall, we found the document informative, but would benefit from it being less repetitive and more concise.

It should be noted that the Medical Device Innovation Consortium Patient Centered Benefit-Risk project team is developing a systematic literature review regarding how to most effectively communicate benefits and risks of medical procedures to patients and physicians, and will particularly consider situations in which patient preference information plays an important role in product approval. It may also include a pilot study on whether a product label message developed based on these considerations would result in satisfactory levels of

knowledge, risk beliefs, and intentions consistent with preference concordant decision making.[1]

In the Federal Register Notice announcing the availability of this draft guidance, FDA requested feedback on five questions, several of which address inclusion of patient preference in device labeling, and in Section VII of the draft guidance, FDA states "When FDA considers patient preference studies in its consideration of a premarket application, such studies generally should be described in the labeling." We do not necessarily agree with this statement. Not all patient preference information (PPI) used to support regulatory decision-making should be described in the labeling. Very few preference studies have been done thus far, so it is not clear what impact, if any, including PPI in the labeling would have. More research is required on effective communication of this information to patients (see discussion on MDIC efforts above). Further, providing all types of PPI in product labeling may introduce an additional threshold of data in product labeling that is not currently standard practice. For example, today, information used to support clinical trial design typically is not included in product labeling. However, if patient preference data are used to substantiate "minimum clinically meaningful benefit," this would be more comparable to data that are currently provided in the clinical section of the device labeling. For these reasons, including a labeling discussion in draft guidance may be premature.

Nonetheless, publishing the patient preference information in professional or patient labeling should consider the following:

- The primary value of patient preference information seems to be as input to the risk-benefit evaluation of the regulatory decision. Individual patients already have preferences, and the benefit of giving patients data about what others think is not clear. When FDA determines that risks outweigh benefits for subgroups (based on the PPI of those subgroups), then FDA is able to approve the device for use in the subgroups that were more accepting of risks in light of probable benefits. Therefore, such data is already considered in the scoping of the indications for use of the product.
- Patient preference information may bias the patient and physician and encourage them to undergo (or forego) a treatment that they would have chosen differently when given the information in the form of benefit-risk (in the absence of patient preference information). It may be more appropriate to require labeling to adequately discuss risks and benefits so that the patient can make their own unbiased decision.
- Patient preference studies represent a snapshot in time. As treatments change and treatment alternatives are added, patient preference data may become quickly outdated in product labeling and require manufacturers to conduct ongoing patient preference studies that may be unduly burdensome if there is no compelling benefit to include this information in the labeling.

[1] See: http://mdic.org/wp-content/uploads/2013/05/PCBR-RFP-final.pdf.

As noted above, it may not always be helpful for patients to be provided with patient preference information. However, clinical risks and benefits should be clearly outlined in labeling so patients, along with their physicians through the patient counseling process, can make the decision without being biased by the opinions of other patients. All physicians should be discussing risks and benefits of device use with their patients. This should not change when a manufacturer has conducted research to determine patient preferences. If patient preference information shows that there is a significant number of patients who judge the risks of a treatment to be acceptable in light of the probable benefits, then transparently disclosing the risks and benefits in labeling should be sufficient for patients to be empowered to make their own risk/benefit determination.

With regard to how FDA should report PPI if only a subset of patients in a patient preference study were willing to accept certain risks in order to achieve probable benefits, we note that FDA is required to determine whether PMA applications provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors. This standard is not likely achieved if only a subset of patients is willing to accept risks to achieve probable benefits. Therefore, in such cases, when the data show that only a subset of a population are willing to accept such risks, FDA should narrow the indication statement to include the subset that is willing to accept the risks to achieve the probable benefits or include the appropriate information in the benefit and risk section. Therefore, any PPI to substantiate and support the indication statement would already be considered in the product labeling under the indications or in the benefits and risks sections of the product labeling.

For instance, in section VIII of the guidance, FDA provides hypothetical examples of when PPI would be used. In each of these examples, PPI data were used to support regulatory decision-making and further shaped the indications or benefits and risks identified in the product labeling. Therefore, the data were already considered and adjusted in the product labeling.

FDA also inquired how PPI should be presented to ensure that patients receive and understand this information. It may be more helpful to ask, "How should sponsors and the FDA ensure that patients receive and understand the risks and benefits associated with medical device treatments?" When given the accurate risk-benefit information in a form that is understandable by the patient, the patient has the ability to choose based on their own preference. FDA has announced a public workshop (FDA-2000-D-0067) to discuss such issues associated with the development and use of medical device patient labeling including content, testing, use, access, human factors, emerging media formats, and promotion and advertising. It would seem that the primary goal of addressing such issues would be to ensure patients are receiving and understanding the risks and benefits associated with medical device treatments.

Our specific comments on the document are provided in Attachment 1.

Respectfully submitted,

/s/

Sharon A. Segal, Ph.D.
Vice President
Technology and Regulatory Affairs

Attachment

ADVAMED COMMENTS
Patient Preference Information – Submission, Review in PMAs, HDE Applications, and* De Novo *Requests, and Inclusion in Device Labeling;
Draft Guidance for Industry and Food and Drug Administration Staff

Line(s) No. – Line or lines numbers of the guidance
Change – Proposed change to the guidance
Reason – Reason/Rationale for proposed change

	Line(s) No.	Change	Reason
1.	2,41,75-76, 81,2249-269	Add the word "Voluntary" to the title of the guidance. "Patient Preference Information – Voluntary Submission…"	We appreciate that the guidance makes it clear that submission of these type of data is voluntary. For extra emphasis on this important point, consider adding it to the title.
2.	33	Add a brief definition for "risk tolerance" as used in CDRH's report. For example: "In the 2012 guidance and this guidance, risk tolerance is defined as the degree to which a patient would accept greater probability or severity of a harm in exchange for a given benefit." and reference the MDIC Patient-Centered Benefit-Risk Framework report.	"Tolerance for risk" is ambiguous, given the use of the term "risk tolerance" in the Decision Analysis literature (see MDIC's Patient-Centered Benefit-Risk Framework report, section 2). In Decision Analysis, the term refers to how uncertainty impacts an individual's decision, regardless of whether the uncertainty is of a benefit or a harm. The guidance is using the term to refer to the probability or severity of a harm that a patient would consider preferentially equivalent to a specified benefit.
3.	41-42	Revise to read as follows: "to encourage submission of patient preference information, if available, by sponsors or other stakeholders for the purpose of transparency and to aid decision making, in certain circumstances"	If high quality data are available, then they should be shared publically in the appropriate context. This is to ensure that the overall conclusion about the benefit-risk profile of a product is transparent and reproducible. The collection of patient preference data may be considered voluntary, but the submission of such data and its use in conjunction with benefit-risk evaluation should be encouraged.
4.	42	Delete "in certain circumstances" or reference a section of the guidance that describes these circumstances	Reader is left confused as to what circumstances apply
5.	64-66	Revise to read as follows: "This draft guidance also provides recommendations on how patient preference information ~~should~~may be incorporated into device labeling for patients and health care professionals."	For the reasons provided above, patient preference data should not necessarily be incorporated into device labeling.

	Line(s) No.	Change	Reason
6.	87-91	Delete this sentence.	Pharmaceuticals are not within the scope of this document. Biologics may have PMAs or HDEs but the relevance of this statement to biologics with PMAs is unclear. Many of these products are diagnostics. The argument given for why patient preference information may be more practical to obtain for devices than for drugs/biologics is unsupported by evidence and counter to the published application of preference studies in many drug and biologic applications. For example, regardless of whether off-target adverse events happen more with drugs than with devices, preference studies rarely include all benefits and harms a treatment causes. They include the most important ones. If a new adverse event is discovered after a preference study is completed, the prior preference results are still of use for the attributes it did include, and additional preference work can be conducted to include the new adverse event.
7.	93-99	Revise this section to read as follows: "Patient preference information may not be relevant or appropriate for all device types. Furthermore, not all benefit-risk scenarios are "preference-sensitive." Patient decisions regarding treatment options are ~~P~~preference-sensitive ~~benefit-risk scenarios may occur~~ when multiple treatment options exist and there is no option that is clearly superior for all preferences~~,~~or when the evidence supporting one option over others is considerably uncertain or variable, and/or when patients' views about the most important benefits and acceptable risks of a technology differ considerably from those of health care professionals."	Distinguish decisions that are preference-sensitive for patients from decisions that are preference-sensitive for regulators.
8.	106-109	Revise to read as follows: "The Agency encourages sponsors and other stakeholders considering conducting patient preference studies for regulatory or other purposes to FDA to have early interactions and gain alignment with the relevant FDA review division when designing such studies."	The role that patient preference studies conducted by patient groups and academia would have on regulatory decisions during the review of PMAs, HDE applications, and *de novo* requests is unclear. These studies could be published in the literature or in white papers (or similar), and be submitted by sponsors for regulatory purposes. Further, patient preference information may be collected by sponsors for purposes other than regulatory purposes, for example, marketing reasons. In line 64-66, FDA states that "patient preference information should be incorporated into device labeling for patients and health care professionals." In addition to making the suggested change to these lines, FDA should acknowledge in this guidance that some patient preference information is

	Line(s) No.	Change	Reason
			collected for reasons other than for regulatory purposes and not all patient preference information is utilized for regulatory purposes (it could be information used for marketing reasons or early in the design input process) and/or not appropriate for product labeling. Finally, there is little documentation on the CDRH site about how to contact the agency to discuss preference studies. There are also currently very few FDA staff who are ready to have a technical discussion on preference studies. Sponsors will also be reticent to meet with CDRH on this novel topic is there is a sense that such meetings can slow the development timeline.
9.	113 – 139	Would seem appropriate to mention CDER's patient-focused drug development meetings in this background section.	Description/clarification of other Agency activities.
10.	150	Reference #6 should be updated to the published MDIC PCBR Framework report.	The current reference is to an MDIC annual meeting. The full report has now been published.
11.	169-196	In this section "3.2 Why include patient preference information in regulatory decision-making?" suggest adding additional text describing how to avoid the subjective nature of the interpretation of the patient preference results either by sponsors or regulators.	The important notion for getting patient preference information is to gain aggregated evidence at the population level that supports the benefit-risk evaluation. However, if such data are interpreted differently across regulatory reviewers or even sponsors, then it seems to defeat the very basic rationale for collecting such objective data. Of course, when designing such studies, the investigators should try to make sure the measurements are meaningful and the participants in the study are representative of the intended patient population.
12.	180-181	Revise to read as follows: "Evaluations of patient-centric variations in tolerance to risks and perspective on benefits ~~may~~will, in the aggregate, reveal a population-level assessment of patient benefit-risk preference for that device	By definition, the evaluation will reveal a population-level assessment.

	Line(s) No.	Change	Reason
13.	179 – 186	Keep lines 179 – 184 as their own paragraph, possibly adding additional content on the use of population-level preferences. Have lines 184 – 186 be part of the following paragraph that focuses on using preferences on a subgroup level. Describe that subgroups can be either inferred by a probabilistic use of the population-based preferences (essentially a market share calculation) or by explicitly assessing preferences for a subgroup of the sample population.	This paragraph starts by describing the assessment of a population-level preference assessment, and then suddenly switches in the last sentence to a subgroup-based preference assessment, where a probabilistic interpretation of the population-based data is used to infer a subgroup. The population-based assessment would indicate whether benefits exceed risk for the device, thinking of the population as a whole. The calculation of the proportion of a population that would regard benefits as exceeding risks is an important point that should be in a separate paragraph and not confused with the population-based assessment.
14.	193 - 195	The points in the last sentence of this paragraph are extremely important and need extensive explanation and examples. They may be best served by being put in their own section. The two reasons for not approving a device are very distinct and should be described in separate paragraphs/sections. A particular point to address is that the second reason given can be read as contradicting the idea of approving for preference based subgroups, a major theme of the draft guidance overall.	This sentence gives two reasons not to approve a device even if there is a subgroup for which benefits exceed risk. (1) The device would expose patients to an unreasonable or significant risk of illness or injury and (2) the benefits do not outweigh the risks for some definable target population. The first reason needs much more detail. For example, if the unreasonable or significant risk occurs only in the subgroup whose preference indicate they regard benefits as exceeding risk, are the risks no longer unreasonable? Is the concern that the unreasonable risks can occur in all patients, including those whose preferences are such that benefits do not exceed risks? How does this differ from most cases, where by definition, patients whose preferences are such that benefits do not exceed risks would consider the risks unreasonable or significant? The first reason seems extremely important, but it is not clear what exactly is meant or how it is operationalized. The second reason may contradict the prior sentences and can be read to contradict one of the main points of the draft guidance. If there is a group of patients for which benefits exceed risks by virtue of preferences, then there almost always will be a different group of patients for which benefits do not exceed risks by virtue of preferences. As written, no B>R subgroup would get approved because of the existence of a B<R subgroup elsewhere in the population. While it is possible in theory for B~=R for most patients and a subgroup have B>R, this is not the type of result seen in preference studies.
15.	208	Update reference 9 to the MDIC PCBR Framework reports Appendix	Reference currently refers to a BAA deliverable that is not the most current version of the catalog and not easily obtained by readers.
16.	208-209	Revise to read as follows: "~~The majority~~ Many of these studies have used a class of	It may be overstating the case to say that a majority of studies use stated preference/discrete choice experiments. Second edit allows for a greater

	Line(s) No.	Change	Reason
		methods called stated preference or discrete choice . . ."	range of accepted terminology for related methods.
17.	219-221	Include other key reasons that revealed preference methods have limited utility.	There are many other important reasons that revealed preference methods are problematic. These include limited access to treatments, bias due to limited information on the alternatives available or misinformation on those alternatives, bias due to insurance plans limiting or redirecting choices, and the impact of cost of choice.
18.	245 – 247	The idea in this sentence is key and is better placed at the start of the paragraph.	Emphasis.
19.	261	Revise to read: "~~Such circumstances may exist~~ Patient preference information might be valuable for devices with the following attributes.	Linking the scenarios in the previous sentence directly to the device categories in lines 263-268 is not always straightforward. Separating these concepts makes the text clearer.
20.	263 - 268	Add brief explanations for why each circumstance tends to result in preference-sensitive decisions.	It is not obvious for all the examples why these circumstances result in preference-sensitive decisions. Since ideally sponsors will learn to recognize preference-sensitive decisions on their own, it will be very helpful for CDRH to explain the thinking for each example.
21.	279 – 327	For each of the three regulatory activities whose benefit-risk requirements are summarized (PMAs, HDEs, and *De Novo* requests, provide some connection to the use of patient preference information. Alternatively, since these benefit-risk requirements are published elsewhere, perhaps these summaries can be omitted from this guidance.	These paragraphs summarize the benefit-risk requirements for PMAs, HDEs, and *De Novo* Requests; but it is not clear how these requirements connect to the use of patient preference information.
22.	337-338	Revise to read: "During the discovery and ideation phase, qualitative patient preference~~s~~ information may inform device design and/or features."	Acknowledge that qualitative information is sufficient during the discovery and ideation phase.
23.	342 - 343	Provide an explanation for how patient preference information can assist in the non-clinical testing example	It is unclear how patient preference information can assist in the non-clinical testing example
24.	344 - 349	Guidance could also suggest that preference studies also have a role in designing the scoring algorithms for PRO instruments.	Clarification and description of other useful applications.
25.	356 - 359	Add an explanation of how communication of benefit-risk information as described in this bullet is connected to the use of patient preference information.	While the point in this bullet is true, the point is not connected to the use of patient preferences.
26.	365	An additional important application of preference information that can be added is to assess and compare the differences	Preferences may differ.

	Line(s) No.	Change	Reason
		in preference between key stakeholders such as patients, caregivers and caretakers.	
27.	373	Use larger type faces in figure	Text in figure is very small and hard to read
28.	373-375	Move or Copy Patient Reported Outcomes mention in the figure.	Although PROs may be collected in the postmarket phase, they are also often collected during the clinical phase of the total product lifecycle. Also, this figure is represented differently than other TPLC diagrams in FDA documentation which represent TPLC as a cyclical process, versus linear.
29.	382-396	Representativeness of the Sample and Generalizability of Results: Add a section on the considerations for the source of the sample; e.g.,"An important consideration is the source of the sample …"	Traditionally, preference surveys have been done with patient panels. However, there are concerns to be considered when using panels for regulatory purposes: (1) ability to always achieve or assess alignment between panel and clinical trial populations (for example, when the trial population must meet a complex biomarker criterion); (2) panel diagnoses are typically self-reported; (3) there is potential bias due to self-selection for membership in panel; (4) there is potential bias due to having an internet-based sample, though this is lessening with time; (5) recall bias if the subjects are using personal experience with an illness for their responses to the survey; (6) limited understanding of the alignment of panel samples between different countries. An alternative is embedding preference studies within the clinical trial; however, there are also concerns with this choice such as : (1) clinical trial inclusion/exclusion criteria often result in a more rigidly-defined population than that which will use the treatment post-approval; (2) patients that choose to enroll in a trial may have biases that are reflected in their preferences; (3) an important harm may not be recognized until after the trial, therefore the preference may be missing an important attribute.
30.	397	It would be tremendously helpful if FDA can provide some guidance about what scale of sample size may be considered adequate or reasonable.	What constitutes a sufficient "sample size" is a challenging question. In most preference studies, the sample sizes may be in the range of several hundreds. As the draft guidance document pointed out, the sample needs to be representative and capture inter-subject variability. Since patient preference studies often lack *a priori* hypothesis testing, adequacy of "sample size" is often judged in an ad-hoc fashion, which is not really helpful from the perspective of scientific design and providing robust evidence. So if FDA can provide some guiding principle, this would be very helpful, although we acknowledge that the guidance may evolve over

	Line(s) No.	Change	Reason
			time as we learn more in this area.
31.	407-409	Suggest adding additional text to elaborate on appropriate weighting, particularly if a specific sampling method is used.	The guidance document highlighted an important point that a patient preference study should reflect the preference of patients from the entire spectrum of disease. In some circumstances, this may result in over-sampling certain segments of the disease population to achieve this coverage. Therefore, the preference data should be weighted properly to reflect the actual distribution of the disease population to make sure the preference information is not subject to undue influence from a subset of patients. Again, this part of discussion should be aligned with the expectation of sample size for such studies. Some general guidance would be helpful and may help to develop some standard approach.
32.	411 – 414	Revise to read as follows: "While some study methods can account for preference heterogeneity with sufficient sample size, ~~only a few~~ <u>not all</u> methods <u>can</u> ~~such as~~ ~~discrete choice experiments may~~ effectively identify and quantify preference heterogeneity."	This is not the case. Preference heterogeneity can be characterized by most of the quantitative methods described in the MDIC PCBR Framework provided a survey approach is used.
33.	414-416, 575-587	General comment	We understand that patient preference studies can have value in identifying subjective patient benefits. We are concerned however, that patient preference studies, although optional, could drive limitations that otherwise may not apply to a device. Further, although patient preference studies may be voluntary, a reviewer could request that such a study be done or risk not getting a device approved. The information should be additive and a consideration, but should not drive new limitations.
34.	430-431	Revise to read: "…in situations when the patient may not be able to provide the patient preference perspective <u>or clinical sequelae of the disease had significant impact on families and care givers</u>."	The preference information from care givers for some devastating diseases (e.g., disabling stroke) would be important in evaluating benefit-risk tradeoffs.
35.	455 – 456	Either change the label to "risk differences" or use an NNT example. Ideally switch to risk difference as a much more common representation used in preference studies.	The example shown is a risk difference, not number needed to treat. Preference studies have used risk differences in units of natural frequencies often. We do not recall any examples of NNT/NNH used in preference studies
36.	449 – 456	Align the bullet points with their description, or use separate table for representations of risk for a single treatment and for differences in risk between two treatments.	These bullet points provide representations of risk for a single treatment and differences in risk between two treatments, but they are described as only showing representations of risk.
37.	509	The guidance should specify whether the data handling	Clarification of level of rigor.

	Line(s) No.	Change	Reason
		requirements for preference studies should be at the same level of rigor as for clinical data. Or be clear about this in Lines 567 - 573.	
38.	525	"The sample included more than 500 patients drawn from an online…" It would be critical to elaborate on the sample size (N=500) here. Would that be considered adequate in general for this type of study? Is that a qualitative judgment?	Do we need a vigorous algorithm to determine the sample size of such studies, particularly when *a priori* hypothesis testing is lacking?
39.	539	Specify the professional society whose practices were followed.	Clarification.
40.	567 – 573	Provide details or specific references for the data handling requirements.	Preference studies are rarely done with the data handling requirements used for clinical data. It is not clear from the guidance whether this level is required. This is a much more expensive standard than typical for preference studies and can also add months to the preference study timeline.
41.	568-573	Revise to read as follows: "As with other data submitted for premarket review, efforts should be made to ensure that data integrity and validity are maintained. <u>If collected as a part of a clinical investigation,</u> ~~For example,~~ participating investigators of IDEs are responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device. See 21 CFR 812.140(a)(3). Such case histories may include patient diaries, assessments, electronic patient diaries, and other electronic patient-reported outcome tools (ePRO)."	The text implies that patient preference studies should be governed by the IDE regulation. That may be the case if the preference studies are conducted as a part of the clinical investigation, but if done by surveys or other means, then the collection should be governed by the quality system regulation, in general, specifically in design controls. In any event, if PPI is collected as a clinical study, it should be considered a non-significant risk study.
42.	579-580	Rephrase or expand the following sentence to describe when conditions of approval are warranted: "FDA may determine that conditions of approval are warranted."	It is not clear what "conditions of approval are warranted" means.
43.	Line 588	Either in this section or elsewhere in this guidance document, it would be helpful to elaborate whether patient preference information should be used qualitatively or quantitatively in Benefit-Risk evaluation.	Again, this is a challenging and debatable issue regarding how the preference information should be used, i.e., qualitatively or quantitatively. However, by providing some general guidance, it will increase transparency and consistency regarding how such data will be used in the review process, which may reduce tendency of heavily relying on individual's subjective judgment.

	Line(s) No.	Change	Reason
44.	590 - 592	The guidance should outline the mechanisms by which sponsors or other stakeholders can discuss preference studies with the FDA – especially for non-sponsor stakeholders who may not know about pre-submission meeting processes. The guidance should also note if there are other/ unique communication mechanisms to have these discussions.	There is little documentation on the CDRH site about how to contact the agency to discuss preference studies. There are also currently very few FDA staff who are ready to have a technical discussion on preference studies. Sponsors may be reticent to meet with CDRH on this novel topic if there is a sense that such meetings can slow the development timeline. Given the novelty of the topic and CDRH's desire to encourage discussions with sponsors on preference studies, CDRH may wish to develop, modify or repurpose a mechanism for sponsor-CDRH discussions specifically for preference studies, at least for the next few years.
45.	633-692	Recommend limiting this section to only those labeling recommendations directly applicable to patient preference information.	Many of these recommendations are general labeling recommendations that are more appropriately included in labeling guidance.
46.	642-648	Revise to read as follows: "For a device for which FDA considers patient preference information in its benefit-risk determination, in addition to the standard elements of labeling (e.g., indications for use, contraindications, benefits, risks, warnings, and user instructions), the labeling ~~should~~ <u>may</u> describe the patient preference study data, including the range of patient preferences and characteristics of patients who considered the device's probable benefits to outweigh its probable risks. ~~It also may be appropriate to include such information in a prominent section of the labeling~~."	For reasons mentioned above, including patient preference information in the labeling should not be a requirement, but an option. If these data are included in labeling, it should not be highlighted or made more prominent, as that is more likely to bias the patient's treatment decision. In clinical practice where we increasingly tend to focus on individualized medicine, one could argue that the actual preference from a particular patient may be more relevant than data from preference studies (albeit informative, similar to consumer report), While including description of patient preference information in the label is informative, it should also make a clear note to healthcare providers that these aggregated data may be more appropriate for judging the overall benefit-risk balance of the product rather than a guiding principle for treating a particular patient.

	Line(s) No.	Change	Reason
47.	650-653	Revise to read as follows: "~~Under certain rare circumstances, a specialized informed consent section may be appropriate to facilitate use in patients who explicitly accept the probable risks in exchange for the probable benefits. In such cases, FDA may include such an informed consent process as a condition of approval~~."	Requiring informed consent for each individual case is problematic. Would the sponsor be required to have records of the completed informed consent documents? Would this be a condition of approval? This would also deter sponsors from collecting PPI, which is mentioned as voluntary in this draft guidance document. Is FDA contemplating that every patient who uses a particular device, which would not be an investigational device, nonetheless would be required to sign an informed consent prior to using such device? Given that this is buried in a draft guidance related to Patient Preference, we assume this would be applicable only to devices for which the patient preference data was critical to the approval. Please clarify or delete.
48.	659-665	General comment.	It is unclear where "study protocols and results of label comprehension or label usability studies" are to be "included" in the labeling. If it is being suggested that Human Factors data on label comprehension is to be included in the physician or patient labeling? If so, that does not seem helpful or appropriate. Does FDA intend to communicate here that this information is to be included in the submission? If FDA adds additional Human Factors testing requirements when PPI is submitted for regulatory decision making, it may deter the use of PPI. In any case, it is outside of current practice to include study protocols in patient or physician labeling as this is confidential, trade secret information; rather, summaries of study protocols are provided. However, sponsors do not include study protocols in product labeling today.
49.		Under section 7.1 "General Labeling Recommendations," FDA states on line 659 of the guidance that "sponsors should also include study protocols and results of any label comprehension or label usability studies that were conducted to demonstrate the target audience understood the risks and benefits of the device."	
50.	667-691	FDA does not acknowledge how to address changing patient preference information over time.	Any patient preference information, even if collected in using robust, scientific methods, only captures benefit/risk tolerance levels identified at a single point in time. As a product is on the market, other confounding factors may come into play that would change benefit/risk tolerance levels of a patient population such as advancing medical technologies and additional treatment options.
51.	678 – 679	Switch order of first two bullets	The nature of the benefits would seem to precede whether patients may receive those benefits.

	Line(s) No.	Change	Reason
52.	683-684	Revise to read as follows: "~~if they share characteristics with the group of patients who view the benefits as outweighing the risks, and~~"	For the reasons provided above, patient preference data should not necessarily be incorporated into device labeling. This may bias patients to make a treatment decision that they might not otherwise make.
53.	710-712	This may be the place where the guidance document may elaborate about qualitative and quantitative use of such preference data.	While qualitative application of preference data may be viewed as simplistic, which preserves the judgment right for individual reviewers or assessors, it may also be subject to bias inherent to individual subjectivity and variability. There are issues with quantitative approaches, but over time it may enhance consistency and transparency.
54.	716-717	Revise to read as follows: ~~with labeling that contains important information about the patient preference study~~.	Delete because risk/benefit would already be captured in product labeling and presented to individual patients/physicians so that they can decide without being influenced by the risk/benefit opinions of others. Furthermore, in this example, FDA has already reduced the scope of the approved indication to include the patient subgroup that stated that they would accept the risk for the benefits. Providing further information may encourage off-label uses.
55.	741	Revise to read as follows: ~~as well as information from the patient preference study.~~	Delete because risk/benefit should be presented to individual patients/physicians so that they can decide without being influenced by the risk/benefit opinions of others. Furthermore, in this example, FDA has already asked for the labeling information to specify the limited duration of effect. Moreover, how would the product label be adjusted for potential changing patient preferences as other wrinkle treatment options become available?
56.	781-782	Revise to read as follows: ~~along with information from the patient preference study.~~	Delete because risk/benefit should be presented to individual patients/physicians so that they can decide without being influenced by the risk/benefit opinions of others. Furthermore, in this example, FDA has already adjusted the labeling to contain important information regarding the additional risks.
57.	811-812	Revise to read as follows: ~~as well as information about the patient parent preference study~~	Delete because risk/benefit should be presented to individual parents/patients/physicians so that they can decide without being influenced by the risk/benefit opinions of others. Furthermore, as FDA highlights in this example the informed consent process with parents/physician are critical to ensure the parents fully understand the tradeoffs and risks/benefits of this treatment option. While it may seem perfectly reasonable for FDA to consider parent preference data in a consideration of benefit/risk when making a regulatory decision, it may not be appropriate to share this same data with a parent who needs to make such a significant decision and the data could be more coercive than

	Line(s) No.	Change	Reason
			informative. The parent/physician consultation is critical here so the parents truly understand the specific situation their child is in and how the benefits and risks apply to their specific situation.
58.	Appendix A	Patient-centric assessment box should include "Are there data on maximum acceptable risk for each key risk and minimum acceptable benefit for meaningful changes in each key risk?"	The table focuses on maximum risk tolerance. It should also allow for minimum benefit required for a given risk, and repeat that minimum for each key risk or important combinations of risks.
59.	Appendix A	Define "PPI"	Remaining questions in the middle column in the section talk about "the PPI" as if it is an expectable part of every submission. Term PPI should be introduced sooner.
60.	Appendix A	For middle column of disease severity and chronicity - suggest "does the PPI information, *if available*, include …"	You could supply information on disease chronicity and severity without having PPI info.
61.	Appendix A	Disease severity middle column and disease chronicity middle column – remove questions " how does PPI vary across the spectrum"	This is redundant to the last question in the 'patient centric assessment' box on line 828
62.	833	Add additional information on the direct approach.	Direct and indirect approaches are introduced in line 833 but there is no further discussion of direct approaches. See also comment on line 838.
63.	838	Revise to read as follows: "The following issues should be considered when adopting the <u>in</u>direct approach."	According to the description of direct and indirect approaches in lines 833-836, the issues in lines 838-844 appear to pertain to indirect approaches.