

# Workshop Materials



## **Discussion Paper: “Neurodiagnostic Devices Intended to Assess Cognitive Function”**



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## Table of Contents

<b>I.</b>	<b>Introduction</b> .....	<b>3</b>
<b>II.</b>	<b>Regulatory Considerations for Neurodiagnostic Devices Intended to Assess Cognitive Function</b> .....	<b>4</b>
<b>III.</b>	<b>Submitting Public Comments</b> .....	<b>11</b>
<b>IV.</b>	<b>Appendix A: A Backgrounder on Medical Device Regulation</b> .....	<b>12</b>
	A. Medical Device Classification .....	12
	B. Marketing Applications .....	12
	C. Investigational Device Exemptions (IDEs) .....	12
	D. Benefit-Risk Evaluation.....	13
	E. Medical Device Master Files (MAFs) .....	14
<b>V.</b>	<b>Appendix B: FDA Guidance Documents</b> .....	<b>16</b>
<b>VI.</b>	<b>Appendix C: Glossary of Acronyms and Abbreviations</b> .....	<b>18</b>

## **I. Introduction**

The FDA is releasing this discussion paper in preparation for the “Neurodiagnostic Devices Intended to Assess Cognitive Function” public workshop, which will be at FDA’s White Oak Campus in Silver Spring, Maryland on November 19, 2015.

It is important to the FDA to help stakeholders (e.g., manufacturers, health care professionals, patients, consumers, consumer advocates, academia, and other government agencies) navigate the regulatory landscape for medical devices. The agency is holding this workshop to discuss and obtain public feedback on scientific and clinical considerations associated with the regulation of Neurodiagnostic devices (neurodiagnostics) intended to assess cognitive function.

The FDA believes open discussion on scientific and clinical considerations associated with neurodiagnostics will help successfully advance this evolving product area. The information and feedback collected by FDA from the workshop will help further develop an appropriate risk-based strategy and regulatory framework for these devices that will promote advances in the technology while maintaining appropriate user protections. This framework will be supplemented by the future development of FDA guidance for this technology.

For the purposes of this workshop, the FDA defines these products as medical devices intended to assess cognitive function – either generally or as related to a specific condition – through measurement of an individual’s performance on particular cognitive tasks. For example, some devices may measure a user’s response time to a single test involving visual or auditory stimuli, while more complex devices may incorporate multiple tests (e.g., a test battery, or battery of tests) that assess different cognitive domains. Devices may provide clinical interpretation of the measurements and/or provide a comparison of the observed results to a reference database, or to baseline performance (e.g., comparison of performance over time). Clinical diagnostic or therapeutic recommendations may also be provided. Devices that do not rely on traditional neurophysiological measures such as electroencephalography (EEG) are of particular interest and relevance to this workshop, as less traditional recording and measurement technologies potentially carry additional uncertainty due to being less established in the scientific and/or medical device space.

This discussion paper provides background information and questions for workshop attendees to consider in advance, and will help facilitate discussion. While the information and questions provided represent FDA’s focus, we look forward to hearing other considerations and questions at the workshop.

*The information and questions contained in this document are not binding and do not create new requirements or expectations for affected parties, nor is this document meant to convey FDA’s recommended approaches or guidance. Rather the information contained in this document offers background and the basis for discussions at the Public Workshop.*

## **II. Regulatory Considerations for Neurodiagnostic Devices Intended to Assess Cognitive Function**

A balanced consideration of probable benefits and risks is important to FDA as part of its review of safety and effectiveness. The field of neurodiagnostics intended to assess cognitive function can span a range of indications from assessing the mental acuity of a healthy individual to the clinical or medical diagnosis of a condition related to a neurological condition or disorder of a patient. The field of cognitive assessment has been rapidly evolving in parallel with advances in computing technology and the increased availability of portable computing platforms.

The FDA recognizes the importance of supporting medical device innovation and the incorporation of new technologies into cognitive assessment devices, with oversight focused on functionalities which could pose a risk to a patient if the device were to not function as intended.

As we grow our understanding of neurological disorders and conditions that affect cognition, reliable methods of measuring and evaluating cognitive function become increasingly important to the diagnostic evaluation, treatment selection, and treatment evaluation processes. As a starting point, the workshop will consider regulatory issues associated with these devices in the following areas:

- A. Current State of the Evidence;
- B. Perspectives on Regulatory Definitions and Classification; and
- C. Clinical Trial Design Considerations.

During the workshop, and through an open public docket (available to collect public comments starting August 14, 2015), the dialogue at the workshop and attendee feedback we collect will further inform our development of a regulatory framework for these devices. *As part of the workshop discussion paper, a brief overview of device regulation is also provided (Appendix A).*

### **A. Current State of Scientific Evidence of Neurodiagnostic Devices**

Modern development of cognitive testing saw significant growth in the early- to mid-20th century. Following the invention of various intelligence tests, many researchers and clinicians experimented with the application of similar tests to neurological patients to assess mental capabilities associated with discrete cerebral areas. Today, cognitive assessment is still performed across different specific domains, such as attention and concentration, verbal and non-verbal memory, speech and language function, executive function, and visuospatial function for a variety of uses. An individual's performance in each of these cognitive domains can be affected by complex processes across a number of neuronal structures, and while we still lack a complete understanding of the physiological mechanisms by which each of these processes occurs, cognitive assessment tasks are designed to evaluate the combined function of these processes. For example, the clock-drawing test – a test that was developed to assess visuo-constructive abilities – involves tasking the patient with drawing a circular clock with numbers spaced around the face and hands positioned to a specific time.

Automation and computerization of psychological tests first came to prominence in the 1970s and 1980s. More recent advances in computational technology, mobile/wireless

technology, and the growth of the internet have contributed to a proliferation of computerized cognitive assessments. Some of the potential benefits of computerized cognitive assessments that have contributed to their rise in popularity include a reduction in the variance observed in test administration and scoring, a reduction in rater and evaluator burden (particularly in settings where large numbers of individuals need to be evaluated, such as in sports settings), and an increase in portability, distribution, and availability.

However, computerized tests also have a number of potential limitations. First, these tests tend to be brief and rely on a limited sampling of the individual's cognitive functioning compared to a full neuropsychological evaluation. Second, if not properly validated, computerized tests can be susceptible to poor test-retest reliability performance. Third, while computerized tests could provide an increased level of standardization, the technology itself may introduce other sources of error. For example, there can be significant variability in the accuracy of different computer measurements of response time, variability in the responsiveness and sensitivity of peripherals such as a keyboard or mouse, and differences in monitor refresh rates that can lead to variability in test administration as well as performance. In addition, the immediate availability of a clinical report aiming to simplify the results of the test is vulnerable to misuse by clinicians by inaccurately providing a narrow or singular approach to cognitive assessment that is in actuality complicated by the factors mentioned in this discussion paper. These limitations, as well as the risk of inadequate device performance, may lead to incorrect diagnoses when used in a clinical diagnostic setting. Risks associated with false negative diagnoses include potentially delaying treatment, or exposing the individual to increased risk of repeat injury and potentially death in the specific case of concussion in a sporting or combat environment. Risks associated with false positives include contributing to the development of mental health problems such as depression or anxiety, and administration of inappropriate treatment. As such, proper validation of these devices is important to maximize occurrence of the potential benefits and minimize occurrence of the potential risks.

To validate these neurodiagnostic devices intended to assess cognitive function, traditional non-computerized tests have been studied in combination with computerized tests to assess their equivalence and to help demonstrate the construct validity and psychometric properties of the computerized tests. More specific methods of test validation depend upon the goal or intended use of the measurement made by the device (e.g., is the output intended to be used as a cognitive screen; as a stand-alone assessment of one or more cognitive domains; as a clinical aid in the diagnosis of a specific disease, condition, or disorder; as a stand-alone diagnostic).

#### **FDA's Public Workshop on Seizure Detection, Cognitive Function, and TBI/Concussion Devices held on June 2-3, 2011<sup>1</sup>**

On June 2-3, 2011, the FDA hosted a workshop co-sponsored by three clinical professional societies – Academy of Neurology, American Epilepsy Society, and National Academy of Neuropsychology – to discuss issues related to the validation and labeling of devices used to assess seizures, cognitive function, traumatic brain injury (TBI) and concussion. Over 200 people of various backgrounds attended the meeting, with clinicians, academicians/researchers, industry, and government (FDA, NIH and military) represented.

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<sup>1</sup> <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm237273.htm>

As discussed by attendees during the Computerized Cognitive Assessment breakout sessions of this workshop, computerized cognitive assessment devices are validated by a number of key psychometric indicators: criterion-oriented and construct validity, reliability, measurement precision, estimates of measurement error, etc. In the event that the device provides a clinical interpretation of the individual's measured performance, normative data including a detailed description of conditions under which this data were collected are important to assess the safety and effectiveness of the test and to provide the clinician with valuable information allowing for a proper comparison of test setup, environment, and patient population to ensure proper use of the device.

Also discussed were the various patient-related characteristics that could play large roles as confounding factors impacting data. Some of these factors include:

- Key demographic factors known to affect cognitive performance, including age, education, ethnicity, and acculturation
- Lifetime computer use, or computer literacy, or computer phobia
- Primary language with particular emphasis on translation complexities
- Physical ability to interact with the device
- Input errors from the patient
- Sensitivity to environmental factors such as time of day or noise level
- Sensitivity to physiological status such as fatigue

### **Questions for Consideration**

With regard to the current state of scientific evidence, consider the following questions in preparation for the workshop:

1. What additional scientific and clinical clarification is needed to define the cognitive functions being measured, to define how to use these measurements, and to define how interpretation of these measurements vary across neurodiagnostic devices used as
  - a. a cognitive screen?
  - b. a stand-alone assessment of one or more cognitive domains?
  - c. a clinical aid in the diagnosis of a specific disease, condition, or disorder?
  - d. a stand-alone diagnostic test for a specific disease, condition, or disorder?
2. Some of the benefits and risks associated with neurodiagnostic devices intended to assess cognitive function are discussed above. What additional benefits and risks are associated with these devices when assessing cognitive function vs. diagnosis of a specific disease, condition, or disorder? What are the additional benefits and risks when a device is used as a stand-alone diagnostic? How common or prevalent are these benefits and risks? How would these additional benefits and risks be assessed or validated?
3. What factors affect patient and/or clinician preference when these devices are used to diagnosis of a specific disease, condition, or disorder? In 2011, workshop attendees identified a large amount of information to be included in an accompanying cognitive assessment device manual that they considered important for the clinician to properly use the device. Examples include summary validation results, a description of the test setup and use environment, demographic and descriptive information about the patient population, and quantification of precision and reliability. How does this information

affect patient and/or clinician preference? How can this information be best conveyed to positively affect preference and understanding? What additional factors should be considered?

## **B. Perspectives on Regulatory Assessment of Neurodiagnostic Devices Intended to Assess Cognitive Function**

A common understanding between device developers, manufacturers, clinicians, patients, and regulators regarding the definition and regulatory assessment of neurodiagnostic devices intended to assess cognitive function is important to promote device availability, innovation, and safe and effective use as well as focus regulatory oversight on the benefits and risks to public health represented by these devices.

Medical devices are defined in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act, in part, as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease ... or intended to affect the structure or any function of the body of man...” (See Appendix A).

Medical devices are categorized as Class I, II or III according to the level of regulatory control that is needed to provide a reasonable assurance of safety and effectiveness. The class of a particular medical device determines, among other things, the type of premarketing submission/application required for FDA clearance to market (See Appendix A). Lower risk devices are classified as Class I devices and have the lowest level of regulatory oversight. Moderate risk devices are Class II devices and typically require the submission of a premarket notification (510(k)), while Class III devices are the highest risk and require a premarket approval application (PMA). As an example, FDA recently classified Computerized Cognitive Assessment Aids – which are prescription devices that provide an interpretation of a user’s level of cognitive function (e.g., if the user has cognitive impairments) based on their scores on a battery of cognitive tasks – as Class II devices<sup>2</sup>.

FDA’s regulatory paradigm allows oversight tailored to the risks of the device. The Agency has identified certain factors as important in the regulatory assessment of neurodiagnostic devices intended to assess cognitive function including but not limited to:

- Whether the device output, labeling, and/or promotional materials make claims related to the general assessment of cognitive function, or if there are claims made referencing a specific medical disorder or condition. For example, inaccurate measurements made by devices that diagnose a clinical or medical condition may have a greater risk to the patient than cognitive assessment tools that perform a general assessment of cognitive function.
- How these devices compare with paper and pencil tests that have extensive clinical history, validation, and have not been regulated by the FDA. Direct translations of

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<sup>2</sup> [http://www.accessdata.fda.gov/cdrh\\_docs/pdf13/DEN130033.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf13/DEN130033.pdf)

such tests from a paper-based medium to a computer-based medium may not pose as much potential risk as a novel assessment.

- How these devices compare with the subset of Mobile Medical Applications (MMAs) to which the FDA does not intend to enforce compliance with regulatory controls<sup>3</sup>. For example, devices that provide and track scores from mind-challenging games or generic “brain age” tests may not introduce as much risk to the user as a device that identifies domains of cognitive impairment or deficiency.
- Whether the device output, labeling, and/or promotional materials only make claims related to general wellness. For example, a device that assesses mental acuity to help understand and maintain good cognitive health may have a lower risk profile, similar to that of the MMA example provided above.
- Whether the device is intended to be used as an adjunct to other diagnostic tools that help the clinician make an informed diagnosis or if the device is intended to be used as a stand-alone diagnostic. Devices that are intended to be used as stand-alone diagnostics carry greater risk associated with misdiagnosis, as there may not be additional adjunctive data for review by the clinician to help mitigate a device error.

### **Questions for Consideration**

With regard to perspectives on the regulatory assessment of neurodiagnostic devices intended to assess cognitive function, consider the following question in preparation for the workshop:

1. Based upon the regulatory risk-based perspectives introduced in the sections above, what key factors should be used to assess the risk associated with neurodiagnostic devices intended to assess cognitive function?

### **C. Clinical Trial Design Considerations for Evaluating Neurodiagnostic Devices Intended to Assess Cognitive Function for Clinical Diagnoses**

Whether or not clinical data from human studies is needed to assess the safety and effectiveness of a neurodiagnostic device intended to assess cognitive function depends on a number of factors, including the proposed clinical indications of the device and whether definitive diagnostic claims pertaining to specific medical diseases or cognitive disorders are being sought. In some cases, non-clinical testing may be sufficient to establish a reasonable assurance of safety and effectiveness.

If clinical data is needed, certain key issues should be carefully considered:

#### **Patient Populations**

Selection of an appropriate study population representative of the intended use population of neurodiagnostic devices intended to assess cognitive function is critical to proper evaluation of their safety and effectiveness. Since cognitive deficits are observed symptoms of a variety of psychological disorders, and the ways in which these deficits manifest themselves vary by disorder, it is important to identify initial and future target populations

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<sup>3</sup> <http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf>

for particular cognitive assessment devices. Different patient populations are likely to have different cognitive impairments and benefit-risk considerations. For example:

- Persons with progressive or degenerative disorders will have impairments that change over time and so a continuous assessment of cognitive function may be appropriate; whereas cognitive deficits due to injury will present following a particular event and so a pre- and post-event assessment of cognitive function may be appropriate.
- The cognitive domains that are impaired in a person with Alzheimer’s disease may differ from those that are impaired in a person with Parkinson’s disease. For example, cognitive deficits associated with memory are more common for Alzheimer’s patients, while cognitive deficits associated with executive function are more common for Parkinson’s patients. As such, the sets of tests applicable to each patient may differ, or the algorithmic combination of results across varying tests may differ, so particular devices may be more suited for one patient population versus another.
- A patient’s tolerance for risk may vary depending on the expected disease progression and potential treatment options available to the patient. These factors directly impact the risks associated with an improper device output or assessment. These factors will play a role in determining what level of device performance (e.g., sensitivity and specificity) adequately demonstrates device safety and effectiveness.

### **Clinical Metrics and Reference Standards**

Clinical metrics or endpoints are important for defining the benefits and risks of medical devices and should ideally be validated for the indicated patient population. One of the main potential benefits of developing computerized cognitive assessment devices is their potential for improved standardization and objectivity. FDA relies on valid scientific evidence in making risk and benefit determinations, including the critical issue of identifying ‘probable risks’ and ‘probable benefits.’ In general, a ‘probable risk’ and a ‘probable benefit’ do not include theoretical risks and benefits, and instead are ones whose existence and characteristics are supported by valid scientific evidence.<sup>4</sup> The following are important factors towards a robust clinical reference standard:

- While in many cases it might be appropriate to use an analogous traditional cognitive assessment tool that tests the same cognitive domain as the clinical comparator, the specific traditional test used should be carefully selected. The methodology by which that traditional test was originally validated may impact the results of the study if it does not appropriately match the intended use environment and population of the computerized cognitive assessment device.
- Clinical diagnostic criteria for specific psychological conditions and cognitive disorders are often complex and contain subjective elements. As such, inter-clinician reliability may be low for certain diagnoses. For example, it may be appropriate to employ methods to mitigate the concerns surrounding inter-clinician

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<sup>4</sup><http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>

reliability, such as utilizing an expert panel of at least three clinicians to review the clinical data and independently provide a diagnosis, with a requirement that the final diagnosis is supported by agreement among at least two out of the three clinicians.

Overall, the diagnosis of a clinical or medical condition, its clinical manifestation, and the subsequent impact of how it affects the patients who have it, are important factors that FDA considers when characterizing disease and determining benefits and risks of neurodiagnostic medical devices.

### **Statistical Considerations**

The outputs reported by neurodiagnostic devices intended for assessing cognitive function can be grouped into either quantitative results (e.g., numeric values pertaining to specific measurements, or numeric scores pertaining to level of performance in a particular domain, or percentiles showing comparison to a reference database, etc.) or qualitative results (e.g., a statement that cognitive function in a particular domain is either impaired or unimpaired, or a diagnostic indication of presence or absence of a disease, etc.).

Some important statistical considerations to keep in mind when evaluating quantitative device outputs include:

- Whether the computerized cognitive assessment output uses the same type of measurement scale as the chosen comparator.
- Whether the computerized cognitive assessment output operates across the same range of numeric values as the chosen comparator.
- The precision, or repeatability and reproducibility, of the computerized cognitive assessment output measurement.

Some important statistical considerations to keep in mind when evaluating qualitative device outputs include:

- Diagnostic accuracy can be assessed in a number of ways including estimates of sensitivity and specificity pairs, likelihood ratio of positive and negative result pairs, and ROC (Receiver Operating Characteristic) analysis along with confidence intervals.
- Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are two additional methods that can be used to help characterize diagnostic accuracy. PPV quantifies the predictive value of a positive device result and NPV quantifies the predictive value of a negative device result.

For additional information regarding the reporting of results from studies evaluating diagnostic tests where the final result is qualitative (even if the underlying measurement is quantitative) please refer to “Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.”<sup>5</sup>

### **Questions for Consideration**

With regard to clinical trial design considerations, consider the following questions in preparation for the workshop:

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<sup>5</sup> <http://www.fda.gov/RegulatoryInformation/Guidances/ucm071148.htm>

1. Since neurodiagnostics intended to assess cognitive function can be indicated for use in a variety of different patient populations, or to diagnose a multitude of specific neurological conditions, what appropriate comparators are available and how do they differ depending upon the patient population and intended use?
2. What are key factors to consider when determining an appropriate comparator?

### **III. Submitting Public Comments**

Regardless of attendance at the public workshop, if you have information related to this workshop that you wish the FDA to consider, please post your material to Docket Number FDA-2015-N-2711 at <http://www.regulations.gov>. Instructions for posting material can be found at: <http://www.fda.gov/RegulatoryInformation/Dockets/Comments/ucm089193.htm> or in writing to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 (Docket ID: FDA-2015-N-2711). Both individuals and groups may submit materials.

*Please note that the docket will be public, and not appropriate for addressing individual confidential medical device concerns.*

## **IV. Appendix A: A Backgrounder on Medical Device Regulation**

For general information on how to market a medical device please refer to the following FDA website: <http://www.fda.gov/training/cdrhlearn/default.htm>. This is a link to the CDRH web page for multimedia industry education that includes learning modules describing many aspects of medical device and radiation emitting product regulations, covering both premarket and postmarket topics.

Additional resources are provided as follows:

### **A. Medical Device Classification**

There are three classes of devices: Class I (general controls), Class II (special controls), and Class III (premarket approval), with the level of regulatory control increasing from Class I to Class III based on the types of regulatory controls considered necessary to provide reasonable assurance of safety and effectiveness<sup>6</sup>. For more information on device classification please refer to the following FDA website:

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/default.htm>

### **B. Marketing Applications**

Information on the various types of marketing applications can be found on the following FDA websites:

- Premarket Notification (510(k)):  
<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketnotification510k/default.htm>
- Evaluation of Automatic Class III Designation (De Novo Classification Process):  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf>

### **C. Investigational Device Exemptions (IDEs)**

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)<sup>7</sup> establishes a framework for FDA to study medical devices for investigational use. This provides an exemption from certain requirements so that experts qualified by scientific training and experience can investigate their devices' safety and effectiveness. This exemption is known as an Investigational Device Exemption (IDE). In order to study a significant risk device in human subjects, a sponsor (defined here as the person responsible for initiating the investigation) must receive approval of an investigational device exemption (IDE) application prior to beginning the investigation.<sup>8</sup> While most neurodiagnostic devices intended to assess cognitive function are unlikely to pose significant risk, such investigational devices that do require approval of an IDE application would be evaluated by the Division of Neurological and Physical Medicine Devices (DNPMD), one of seven divisions in CDRH's Office of Device Evaluation (ODE).

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<sup>6</sup> 21 Code of Federal Regulations (CFR) 860.3(c)

<sup>7</sup> 21 U.S.C. § 360j(g)

<sup>8</sup> 21 CFR 812.20

Depending upon the intended use of a particular cognitive assessment device, a clinical investigation designed to collect definitive evidence of safety and effectiveness, typically in a statistically justified number of subjects, may be appropriate. Although it is unlikely that a clinical study designed to evaluate the safety and effectiveness of a neurodiagnostic device intended to assess cognitive function would require approval of an IDE application, we encourage sponsors and investigators to submit a Pre-Submission regarding any planned clinical study for review by DNPMD. This allows for early collaboration between the sponsor and the FDA. Please refer to Appendix B for additional resources regarding FDA's Pre-Submission Program.

**D. Benefit-Risk Evaluation**

In making decisions regarding premarket submissions, the FDA weighs benefits and risks. There are a multitude of factors to consider assessing benefits and risks and some of these are listed in

Table 1 below.<sup>9</sup>

**E. Medical Device Master Files (MAFs)**

Often a sponsor submitting a premarket submission (i.e., an applicant) needs to use another party's product (e.g., ingredient, subassembly, or accessory) or facility in the manufacture of the device. In order that a sound scientific evaluation may be made of the premarket medical device submission, the review of data and other information related to the other party's product, facility, or manufacturing procedures is required. The other party, while willing to allow FDA's confidential review of this information, may not want the applicant to have direct access to the information. To help preserve the trade secrets of the ancillary medical device industry and at the same time facilitate the sound scientific evaluation of medical devices, FDA established the device master file system. Please refer to the following FDA webpage for additional information on device master files:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm>

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<sup>9</sup> Please refer to the FDA guidance documents referenced at the end of this discussion paper for additional information regarding benefit-risk evaluations in premarket submissions.

Table 1 – Factors to Consider when Evaluating Benefits and Risks

<p><b><u>Considerations for Assessing Benefits</u></b></p> <ul style="list-style-type: none"> <li>• Type</li> <li>• Magnitude</li> <li>• Probability of patient experiencing one or more benefit</li> <li>• Duration of effect(s)</li> </ul>	<p><b><u>Considerations for Assessing Risks</u></b></p> <ul style="list-style-type: none"> <li>• Severity, type, number and rates of harmful events associated with the device</li> <li>• Probability of harmful event</li> <li>• Duration of harmful event</li> </ul>
<p style="text-align: center;"><b><u>Additional Benefit-Risk Considerations</u></b></p> <ul style="list-style-type: none"> <li>• Type of submission</li> <li>• Stage of Device Development</li> <li>• Uncertainty</li> <li>• Characterization of Disease</li> <li>• Patient tolerance for risk and perspective on benefit</li> <li>• Availability of alternative treatments</li> <li>• Risk Mitigation</li> </ul>	

## V. Appendix B: FDA Guidance Documents

The following is a list of current FDA guidance documents that may be of interest when developing premarket submissions:

### Benefit-Risk

- “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>

### IDE

- “Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies”  
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>
- “Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff”  
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf>
- “Design Considerations for Pivotal Clinical Investigations for Medical Devices”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf>

### 510(k)

- “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>

### PreSubmission

- “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

### Technical

- “Recognition and Use of Consensus Standards”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077295.pdf>

- “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>
- “Radio Frequency Wireless Technology in Medical Devices - Guidance for Industry and Food and Drug Administration Staff”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077272.pdf>
- “Off-The-Shelf Software Use in Medical Devices”  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf>

### **Developing Guidance Documents**

- “Food and Drug Administration Report on Good Guidance Practices”  
<http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM285124.pdf>

## **VI. Appendix C: Glossary of Acronyms and Abbreviations**

**510(k):** Premarket Notification

**CDRH:** Center for Devices and Radiological Health

**DNPMD:** Division of Neurological and Physical Medicine Devices

**EFS:** Early Feasibility Study

**FDA:** U.S. Food and Drug Administration

**FIH:** First in Human

**IDE:** Investigational Device Exemption

**MAF:** Master File

**MMA:** Mobile Medical Application

**NPV:** Negative Predictive Value

**ODE:** Office of Device Evaluation

**PMA:** Premarket Approval

**PPV:** Positive Predictive Value

**ROC:** Receiver Operative Characteristic

**TBI:** Traumatic Brain Injury