Perspective

Brain–computer interface devices for patients with paralysis and amputation: a meeting report

K Bowsher 1, E F Civillico 2, J Coburn 2, J Collinger 3, J L Contreras-Vidal 4, T Denison 5, J Donoghue 6, J French 7, N Getzoff 8, L R Hochberg 9, M Hoffmann 10, J Judy 16, N Kleitman 17, G Knaack 2, V Krauthamer 2, K Ludwig 12, 13, M Moynahan 14, J J Pancrazio 15, P H Peckham 16, C Pena 1, V Pinto 1, T Ryan 7, D Saha 1, H Scharen 1, S Shermer 1, K Skodacek 1, P Takmakov 2, D Tyler 16, S Vasudevan 2, K Wachrathit 13, D Weber 18, C G Welle 2 and M Ye 2

1 US FDA, Center for Devices and Radiological Health, Office of Device Evaluation, Silver Spring, MD, USA
2 US FDA, Center for Devices and Radiological Health, Office of Science and Engineering Labs, Silver Spring, MD, USA
3 Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA, USA
4 Electrical and Computer Engineering, University of Houston, Houston, TX, USA
5 Medtronic, Inc. Minneapolis, MN, USA
6 School of Engineering, Brown Institute for Brain Science, Brown University, Providence, RI, USA
7 Neurotech Network Tampa, FL 33623, USA
8 Center for Neurorestoration and Neurotechnology, Rehabilitation R&D Service, Department of Veterans Affairs Medical Center, Providence, RI, USA
9 College of Engineering, Nanoscience Institute for Medical & Engineering Technologies, University of Florida, Gainesville, FL, USA
10 Craig H. Neilsen Foundation, Encino, CA, USA
11 NIH National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA
12 Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA
13 Institute for Functional Restoration, Case Western Reserve University, Cleveland, OH, USA
14 Bioengineering, University of Texas, Dallas, TX, USA
15 School of Engineering, Case Western Reserve University, Cleveland, OH, USA
16 Advanced Arm Dynamics Redono Beach, CA 90277, USA
17 Defense Advanced Research Projects Agency, Biological Technologies Office, Arlington, VA, USA

Abstract

Objective. The Food and Drug Administration’s (FDA) Center for Devices and Radiological Health (CDRH) believes it is important to help stakeholders (e.g., manufacturers, health-care professionals, patients, patient advocates, academia, and other government agencies) navigate the regulatory landscape for medical devices. For innovative devices involving brain–computer interfaces, this is particularly important. Approach. Towards this goal, on 21 November, 2014, CDRH held an open public workshop on its White Oak, MD campus with the aim of fostering an open discussion on the scientific and clinical considerations associated with the development of brain–computer interface (BCI) devices, defined for the purposes of this workshop as neuromuscular devices that interface with the central or peripheral nervous system to restore lost motor or sensory capabilities. Main results. This paper summarizes the presentations and discussions from that workshop. Significance. CDRH plans to use this information to develop regulatory considerations that will promote innovation while maintaining appropriate patient protections. FDA plans to build on advances in regulatory science and input provided in this workshop to develop guidance that provides recommendations for premarket submissions for BCI devices. These proceedings will be a resource for the BCI community during the development of medical devices for consumers.

Keywords: brain–computer interface, neuroprosthetic, regulation, translation, medical device
1. Introduction

Investigational studies of brain–computer interface (BCI) devices have demonstrated both potential utility for patients as well as challenges in translating scientific knowledge to clinical benefit. Specifically, moving BCI devices from the laboratory to US patients could potentially be impeded by gaps in scientific and clinical knowledge, questions concerning long-term effectiveness, reliability and safety, and the need for transparency in the regulatory and marketing pathways. To ensure that public health receives maximum benefits from advances in BCI devices, these gaps must be addressed by robust discussion, sharing of new advances, and clear explanations of the relevant regulations and their application. The Food and Drug Administration’s (FDA) Center for Devices and Radiological Health (CDRH) believes that all stakeholders (e.g., manufacturers, health-care professionals, patients, patient advocates, academia, payers, and other government agencies) should be a part of this necessary ongoing conversation. To that end, the Agency held an open public workshop on its White Oak, Maryland campus on 21 November, 2014 with the aim of fostering an open discussion on the challenges associated with the development of BCI devices and obtaining public feedback on scientific, clinical, and regulatory considerations associated with BCI devices for patients with paralysis or amputation. This paper summarizes the presentations and discussions from that workshop. CDRH plans to use this information to develop recommendations for BCI devices with the aim of promoting rapid clinical translation of innovation while maintaining appropriate patient protections. FDA plans to build on advances in regulatory science and the input provided in this workshop to develop guidance that provides recommendations for premarket submissions for BCI devices.

The workshop was attended by a diverse group of participants including basic and clinical researchers (including engineers, neuroscientists, clinicians, and other scientists), manufacturers, patients, patient advocates, representatives of government agencies (including FDA, Defense Advanced Research Projects Agency (DARPA), National Institutes of Health (NIH), Department of Veterans Affairs (VA), Centers for Medicare and Medicaid Services (CMS) and White House Office of Science and Technology Policy), outside regulatory consultants, and the press. The first half of the workshop consisted of brief presentations by federal agency staff, other stakeholders, and experts in the BCI field. The afternoon was spent in breakout sessions covering the following topics: clinical endpoints for use in investigational trials, non-clinical bench testing needs, and research and development and translational issues. The sessions were chaired by experts in the field of BCI technology. In the following sections, we summarize the presentations from government speakers (II), outside experts (III), and breakout sessions (IV).

2. Presentations from US government stakeholders in the BCI Field

2.1. Premarket review of BCI devices—Michael Hoffmann

Michael Hoffmann, Branch Chief of the Physical Medicine and Neurotherapeutic Devices Branch in ODE/DNPMED, summarized the risk-based medical-device classification system and its application in the context of premarket review of BCI devices (Online Slides). The FDA classification system (see 21 CFR 860.7) is based on the potential risk presented by a device for an identified population. An overview of the FDA classification and regulatory processes can be found at: http://fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm. For a Class II (moderate-risk) device to be cleared, it must be demonstrated with valid scientific evidence that the device is substantially equivalent to a legally marketed device (see 21 CFR 807 subpart E and 21 CFR 807.92(a)(3)). For a Class III (high-risk) device to be approved, it must be demonstrated with valid scientific evidence that the benefits of the device outweigh the risks in the identified population. The policies and procedures governing premarket-approval determinations are described in 21 CFR 814. Here we will highlight two mechanisms of particular relevance to
BCI devices: the pre-submission process, also known as the Q-submission process, and the early-feasibility-study (EFS) program.

The CDRH Pre-submission format provides the opportunity for sponsors and investigators to obtain early feedback on topics such as proposed non-clinical and clinical testing and regulatory strategies prior to the submission of an investigational device exemption (IDE) or marketing application (e.g., premarket notification (510(k)), premarket approval application (PMA), humanitarian device exemption (HDE)) [1]. Given that many BCI technologies are in the early stages of development, early interaction with CDRH is strongly encouraged. These interactions often serve to clarify regulations, requirements, and recommendations for sponsors and investigators, and provide an opportunity for CDRH to give feedback on proposed non-clinical and clinical testing and pathways to market.

Also highly relevant to the BCI space is the recently established EFS program, which is intended to facilitate the approval of early feasibility studies under the IDE regulations [2]. EFS studies typically include a small number of subjects for the purposes of early clinical evaluation that may provide proof of principle and initial clinical-safety data. The EFS program employs a risk-based approach that includes identifying risks and risk-mitigation strategies to protect study subjects while allowing valuable clinical information to be gathered about medical devices in early device-development stages.

2.2. Regulatory science and its application to BCI devices—Drs Cristin Welle and Eugene Civillico

Regulatory science is defined as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products [3]. Drs Cristin Welle and Eugene Civillico, investigators in CDRH’s Office of Science and Engineering Laboratories (OSEL), described laboratory research efforts in CDRH that are relevant to BCI devices. OSEL scientists are developing test platforms to evaluate the long-term safety and reliability of implanted neural electrodes and to develop clinical metrics to assess system performance in BCI devices (Online Slides) [4–6]. Current research programs include in vivo and in vitro investigations of biological and material factors that may limit device longevity as well as development of improved clinical-outcome metrics to help provide objective measurements of patient benefits. Valid scientific evidence produced by non-clinical and clinical studies is needed by the FDA to make determinations of safety and effectiveness, and the outcomes from OSEL regulatory science research efforts are incorporated into the regulatory review process to aid in this evaluation, where appropriate. Data are shared with both FDA pre- and post-market review staff and the scientific community, which can help to inform decision making and influence the quality of regulatory device submissions. In addition, results from OSEL research can be incorporated into medical-device standards and/or FDA guidance documents. FDA OSEL researchers also collaborate with outside sources, and the ongoing initiative between DARPA and the FDA described below supports regulatory science by expanding the knowledge base needed for BCI technologies to proceed through the regulatory pathway.

2.3. Improving patient access though early collaboration—Ken Skodacek

Ken Skodacek, policy analyst with CDRH’s Clinical Trials Program, described efforts by the Medical Device Reimbursement Task Force to improve patient access to innovative devices by fostering knowledge sharing and collaboration between medical device manufacturers, regulators, and payers/providers (Online Slides). For small, early-stage innovators, the medical device development process is often focused primarily on developing and testing the device as well as gathering clinical evidence to support FDA clearance or approval, while selling and distributing the product are concerns addressed later in the development cycle. However, payer/provider organizations make decisions that influence patient access to medical devices, even after the FDA has cleared or approved the device for use in the US. Therefore, the Medical Device Reimbursement Task Force at FDA was formed to streamline the pathway from regulatory clearance or approval to reimbursement.
in order to support patient access to innovative medical devices. Ongoing initiatives like the FDA-CMS (Centers for Medicare and Medicaid Services) Parallel Review program allow for a discussion about the evidentiary needs of CMS, with the goal of shortening the time to national coverage decisions. Manufacturers of innovative devices, such as BCI devices, are encouraged to include payers/providers during pre-submission meetings with FDA to consider what evidence could be gathered to support coverage and payment before pivotal studies are designed and initiated to support regulatory approval. A good first step is to email CDRH-Innovation@fda.hhs.gov to obtain more information.

2.4. DARPA BCI efforts and scientific collaboration with FDA labs—Dr Doug Weber

Dr Douglas Weber, Program Manager in the DARPA Biological Technologies Office (BTO) and Associate Professor of Bioengineering in the Department of Rehabilitation Medicine at the University of Pittsburgh, offered a brief history and synopsis of DARPA’s prior and on-going investments in BCI technologies to restore capabilities lost due to injury on the battlefield (Online Slides). Current BTO programs of particular relevance to BCI technologies and neural interfaces in general include reliable neural-interface technology (RE-NET), hand proprioception and touch interfaces (HAPTIX), electrical prescriptions (ElectRx), restoring active memory, and systems-based neurotechnology for emerging therapies. These efforts have sought to understand and improve the lifespan of neural interfaces (RE-NET), allow transradial amputees to control and sense state of the art prosthetic hands (HAPTIX), and control electrical signaling in peripheral nerves for desired cellular, organ, and immune outcomes to maintain the health status of injured soldiers (ElectRx). These last three programs have sustained, via interagency agreement, collaboration with FDA internal laboratories, led by OSEL’s Division of Biomedical Physics and focused on independent verification and validation of technologies developed in the course of the programs.

3. Presentations from non-governmental stakeholders in the BCI Field

The workshop organizers invited experts from a broad cross-section of the stakeholder community to share perspectives on BCI technology. Presentations can be found in their entirety here.

3.1. State of experimental BCI device technologies—Dr Jose L Contreras-Vidal

Dr Jose L Contreras-Vidal, Director of the Non-invasive Brain–Machine Interface Systems Laboratory in the Department of Electrical and Computer Engineering at the University of Houston, provided an overview of the current state of the most advanced BCI technologies, both cortical and peripheral, invasive and noninvasive, and their regulatory/marketing history in the United States (Online Slides). As a useful framework, he divided BCI systems into three groups and described the state of the art for each group. In this schema, Group 1 contains devices in which control flows in one direction, from a neural, muscular, or movement signal to an external effector such as a robotic limb; Group 2 contains devices in which there is bidirectional flow along this path (i.e., the external effector feeds signals, for example sensor data, back into the neural or muscular systems); finally Group 3 contains devices in which bidirectional-feedback control is contained entirely within the neuromuscular system (i.e., no robotic ‘external’ effector is present).

With respect to Group 1, currently marketed systems include myoelectric prosthetics for those patients with partially or fully amputated or congenitally absent upper extremities. Last year an electromyography-controlled multifunctional upper-extremity neuroprosthesis (marketed as the DEKA Arm System) and the first powered exoskeleton (marketed as the Argo ReWalk) both received regulatory approval under the de novo classification process [7, 8]. At the stage of clinical studies, but not cleared or approved, are systems that make use of signals from implants, either muscular or nerve/brain, or which use signals obtained from
the brain via non-invasive sensors. Dr Contreras-Vidal noted that in many cases the relevant sensors for such systems have been cleared or approved for other uses. With respect to Group 2, there are no cleared or approved systems, but several under clinical study, including both implanted cortical- and nerve-interfacing technologies. Finally, with respect to Group 3, the Freehand System presents an example of an FDA-approved technology, although this device is no longer manufactured and will be discussed at length in a subsequent section of this report. Another approved technology which makes use of some of the same scientific principles as Group 3 devices is the Neuropace Responsive Neurostimulation System, an implanted brain stimulator for epilepsy [9].

FDA clearance or approval of the systems described above represents important developments for the BCI community. Ongoing clinical trials of cortical and peripheral devices, as well as closed-loop sensor-response or neuromodulatory BCI systems, continue to explore the potential risk and benefit of these technologies for those with lost motor or sensory systems. In addition, these trials improve understanding of both brain function and address translational challenges such as device reliability, patient preferences, and safety. The slides from this presentation, available at the BCI workshop website, contain product codes, clinicaltrials.gov identifier codes, and FDA document-control numbers where applicable for these and many other examples.

3.2. Consumer perspective: understanding the end user—Jennifer French

‘For too long there has been separation of basic science, biomedical engineering, clinical science and the people these disciplines are serving. A key ingredient to understanding the real-life consequences of many neurologic disorders ... is to obtain valuable information from the individuals that are actually living with the disorders every day’ [10]. Ms Jennifer French, Executive Director of the Neurotech Network, addressed the perspective of the end user. The Neurotech Network is a nonprofit organization that focuses on education and advocacy of neurotechnology devices for people with impairments (Online Slides). Ms French, who acquired a C6-7 incomplete spinal cord injury in 1998, is an active user of a neural prosthetic system. She noted that people who use medical devices are ‘patients’ only when under the direct care of a clinician. Once the patient is released from direct clinical care, they then use the devices in their daily lives to do such things as live more independently, engage in activities of daily living, and have rich and active lives. For this reason the terms ‘consumer’ or ‘user’ are more appropriate to describe those using medical technology in this way. BCI developer and regulatory communities need to reach out to the consumer, care-giver and clinical populations, in order to understand what technology exists and what still needs to be developed. Potential users may not think in terms of what a particular technological advance can do for them, but rather what functional restorations are their highest priorities. In order to make devices that will actually be used by the population for whom they are intended, it is imperative to address the priorities of that population [11]. Additional published studies are needed to understand the priorities of the targeted consumer [12, 13], specifically the consumer risk-benefit evaluation, which includes family and the respective support system. Importantly, the weighing of risks and benefits varies even at the level of individuals.

Although engaging the consumer early in the development process may extend the time to market, evidence shows that consumers will quickly discard devices that do not fulfill their personal expectations, even in the face of a clinical professional’s view that the consumers’ needs were met. Once open communication between these populations occurs, potential users will be able to share their vision of how the technology could improve their lives. This will lead to increased public-health impact for BCI systems. Consumers already use these medical devices to perform activities of daily living more completely and more independently. Home and real-world environments are where we learn the most about how these technologies can impact people’s lives. For this reason, consumer access to first- or second-generation of devices is valuable for medical-device development. It is particularly important that human factors/usability challenges and successes be studied in real-world environments, not solely in controlled laboratory settings. As with growing use of medical
devices in the home, it will allay the perception of some who see medical devices as treatment of last resort. To ensure that these devices are considered sooner, education and outreach are required, not just to the potential end user, but also to their friends and caregiver networks.

3.3. **Clinical metrics—Tiffany Ryan**

Tiffany Ryan, National Director for Therapeutic Services at Advanced Arm Dynamics, provided a clinical perspective on the importance of outcome measurements for successful clinical integration of technology into users’ lives. The prosthesis-provider community needs outcome-measures data that are specific both to user populations and to particular functional losses, which derive from changes in physical capabilities or disease-specific processes. Necessary, and sometimes underappreciated, assessments include comparative device performance in actual environments of use, and the user’s perception of the influence any given device has on his/her functioning and quality of life. More specifically, performance assessment should include quality measures such as: appropriate integration of technology to the human body via skilled prosthetic design and fit, skillfulness of use, independence in use, intuitive integration, and device acceptance. Additionally, the effects of psychological and physical transitions secondary to traumatic loss impact the final assessment of technological integration and must be systematically examined. Better outcome metrics will allow quantification of the impact of new technology, which is required to justify its medical necessity to reimbursement sources. In addition to the kinds of measures described above, success requires the advanced clinical skill and experience to validate and deploy them. It is critical that our strategies for understanding the needs of patient populations and quantifying our success in meeting them keep pace with the development of BCI technologies.

3.4. **Translational challenges—Dr Hunter Peckham and Megan Moynahan**

Although BCI systems are currently being developed to address the needs of a variety of patient conditions, these systems present unique challenges for those companies trying to commercialize them. Megan Moynahan of the Institute for Functional Restoration and Dr Hunter Peckham from Case Western Reserve University shared insights from two recent experiences with BCI devices: the experience with the FDA Innovation Pathway 1.0 and the history of the NeuroControl Freehand System (Online Slides). In the case of the former, for the DARPA-funded prosthetic arm system in the CDRH Innovation Pathway 1.0, it was necessary to manage multiple interlocking presubmissions, IDEs, and 510(k)s in order to coordinate the technical and regulatory aspects of multiple sub-systems developed by different entities. The process could be improved for similar systems in the future by the development of standardized interconnects to allow approval of subsystems, or by new regulatory approaches that allow developing companies to obtain safety and efficacy data more easily.

Even if a complex system is ultimately approved, the target user population may be too small to support a business. The history of the NeuroControl Freehand System—a neuroprosthetic that provided restored hand function to people with spinal cord injury, and which received premarket approval in 1997 but was only manufactured until 1998—illustrates the difficult situation that users may face when a safe and effective device does not translate to a sustainable business. Following the closure of NeuroControl, users were left with a permanent implant, but were unable to receive revisions to components that failed. Although the Institute for Functional Restoration at CWRU has been able to provide some support for these users; it is nevertheless clear that the developer’s commercial viability has lasting effects on the user experience.
3.5. An industry perspective on the challenges and opportunities of brain–machine interfacing—Dr Tim Denison

Dr Tim Denison, Technical Fellow at Medtronic Neuromodulation, offered an industry perspective. The translation of BCI devices from laboratory to consumers might be accelerated by more explicit consideration of the ‘value’ provided by technology from the perspective of key stakeholders (Online Slides). Drawing from Sasser’s analysis of profit chains, Dr Denison suggested that ‘value’ be defined as a maximization of relevant results and process quality to achieve those results, and a minimization of ‘access cost’ (e.g., accessibility to treatment centers with required expertise) and monetary price [14]. The stakeholders for this value analysis include the intended users, caregivers, clinicians, and the payer/provider infrastructure. Analyzing the translation problem within this context helps focus on key issues of translating new technologies: Do the designers understand the user needs that define a successful result and the economic trade-offs that consumers, payers and providers face when using the new solution? Is the process of calibrating and maintaining system performance feasible for the targeted user group?

The application of BCI technology to existing device architectures could potentially enable smarter future ‘prosthesis’ systems for neural circuits impacted by disease. Several disorders can already be treated effectively by invasive device stimulation therapies; the addition of sensing and algorithm technology might then be seen as an evolutionary expansion of capabilities. If these evolutionary technologies are designed with modularity and extensibility in mind, they are potentially transferable to a broader base of disorders. In addition, this infrastructure might also facilitate novel BCI technologies and applications by providing economic incentives and a mechanism to scale-up for manufacturing. The ultimate potential of BCI technology is still being defined, but creative application of core technologies to consumer needs could enable a positive feedback loop that helps translate technology from the academic lab to the value-conscious user in need of a practical solution.

4. Breakout sessions—workshop-attendee perspectives

The afternoon sessions were designed to evoke robust discussion, using the primarily lecture-based format of the morning session as background. Prior to the workshop, the organizers generated a list of specific questions to help facilitate the discussions. The relationship of the pre-discussion questions to the discussions was in most cases highly variable; nevertheless, the goal of facilitating robust discussions was achieved.

4.1. Clinical use and metrics

The questions for these sessions revolved around appropriate outcome measures for clinical trial design and included concepts such as:

- How outcome measures might vary according to level and type of impairment.
- The impact of comorbid conditions.
- Methods for evaluating usability, retention, and patient satisfaction in addition to traditional functional-performance measures.

The workshop discussions revealed that answers to such granular questions first required consensus on three basic themes, which became the foundation for the dialogue. These themes were (1) objective determination of risks and benefits; (2) assessment of the relative weighting of these risks and benefits by the general and specific user populations; and (3) trial design and outcome measures.

4.1.1. Theme 1—objectively addressing and assessing risk and benefit. All BCI devices may have an element of risk that depends on a variety of device and user attributes. Risks vary based on the design of the device and may include, but are not limited to, loss of
independence, risk of infection, recovery time, change in appearance, interruption of daily routine, psychological factors (e.g., personality change), and increased burden of care. Participants agreed that device developers and clinical researchers should assess risks objectively and in a scientifically rigorous manner. Objective risk assessment allows incorporation of risk-mitigation strategies into device and clinical-trial designs and thus reduce the overall risk to users. Different risk profiles may be best addressed with different outcome measures such as implanted devices versus surface interfaces or pediatric users versus adult users. Additionally, leading-edge BCI devices may have unique risks (e.g., closed-loop operation without clinician or user control), which may require specific prospective methods of assessment.

Despite known risks, the unique potential benefits of BCI systems continue to motivate innovative device development. Participants identified instances of clinical device testing where a device imparted a unique or life-changing benefit to the user that had not been anticipated by designers or clinicians and which sometimes was seen as more salutary than other predicted benefits of the device. For instance, one obvious benefit for a large group of potential users is improved performance of activities of daily living. Other less obvious but still meaningful benefits might include improved psychological well-being and physiological functioning (e.g., improved bladder function). Participants strongly encouraged developers and regulatory agencies to consider these benefits during device development, and collect relevant evidence during the clinical testing process, to allow for a more complete assessment of benefit.

4.1.2. Theme 2—listen to patients in a scientifically rigorous and knowledgeable way. Assessment of different types of risks and benefits, as discussed in Theme 1 above, is generally performed by clinicians and regulatory bodies; however, it is also critical to understand the user’s view of the relative importance of these factors once they are assessed. User viewpoints should be involved in the regulatory framework.

One issue of critical importance that bears on the patient perspective is informed consent. Discussions revealed a mixed opinion about whether informed consent or labeling could suffice as the only risk-mitigation strategies for participants in a clinical trial or users of a marketed device, respectively. After further discussion, the consensus among the discussants was that these measures were not sufficient as sole methods to mitigate risk. Risks are evaluated very differently in various stages of life; their importance to the user may be underestimated when considered by the user in close proximity to a life-changing event. Accordingly, user-centered benefit/risk assessments should include perspectives from patients throughout the spectrum of time since injury or diagnosis. When assessing and incorporating user risk tolerance in device and trial design, it is important to consider the likely evolution of acceptance and frame of mind over time, which may impact willingness to take on risks. Finally, informed consent is only useful if the principal investigator understands the objective risks posed by the device by means of thorough risk-analysis procedures. This is a precondition of the risk being adequately conveyed to the user for consideration.

4.1.3. Theme 3—trial design/outcome measures. Participants recognized the critical importance of outcome measures that have been validated for specific user populations and impairments. As discussed under Theme 2 above, users may have expectations regarding important device functionality that are completely different from those of device developers. If users are able to identify their own outcome measures (e.g., patient-specific functional scale [10]), then these outcome measures should be weighted and standardized. Assessing the user’s personal tolerance for risk and the outcomes they find most important could then become a key feature of clinical-trial design and the selection of clinical-trial outcome measures.

Due to the myriad of user populations and levels of impairment, determining and validating the appropriate measures for any one device may be challenging, especially on the timeframe imposed by rapidly developing technologies such as BCI. The list of functional outcomes recognized as common data elements for spinal cord injury [15] by NINDS staff/investigators may represent a promising direction. Further, groups were
encouraged to consider the international classification of functioning, disability, and health (ICF) [16] as a framework for developing outcome metrics and assessments for clinical trials. The ICF considers disability and functioning to be a result of the interaction between a health condition and contextual factors such as the environment or other personal factors. Disability can be reduced, or functioning can be increased at multiple levels including at the level of the body part, the whole person, or in terms of participation in society. Outcome metrics should be designed to capture important factors that could impact disability or functioning.

4.1.4. Future directions. Workshop attendees expressed broad support for outcome-metrics research, which should include scientific assessment of patient-oriented risks and benefits as well as impairment-specific and validated functional outcome measures. Additionally, the need for the development of engineering standards and guidance documents was also expressed. Such documents will increase in usefulness as the field matures, and could help to ensure consistency in product development and clinical-trial design. Engagement with medical-device-standards organizations, such as Association for the Advancement of Medical Instrumentation, Institute of Electrical and Electronics Engineers (IEEE), and International Organization for Standardization (ISO), was recommended to help with developing standards for this field.

4.2. Non-clinical device testing

The non-clinical testing discussion session focused on identifying the key test methods to assess the safety and reliability of BCI technologies prior to their use with human subjects. Non-clinical device evaluation can be classified under three broad themes: (1) bench/in vitro testing, (2) animal/in vivo studies and (3) computational/in silico models. Discussions of the currently available methods to establish safety, reliability, and performance covered each of these themes and their application to central and peripheral nervous-system-interfacing technologies. It is critical to understand issues of materials, mechanical forces, and biological effects on device stability. Importantly, these factors may be interdependent.

4.2.1. Bench/in vitro testing. Bench testing for BCI technologies should involve evaluation methods and standards that establish both functional and physical characteristics of a system. These include accelerated lifetime testing, mechanical testing, hermeticity, impedance, and electrical testing. For accelerated lifetime testing, the typical duration of implantation should be considered for characterizing mechanical and electrical durability of the components. It would be helpful if the community were to adopt a goal for device lifetime, and acceptable length of time before device repair/replacement. The standards for more mature technologies, such as pacemakers, could potentially be referenced and adapted to the components and characteristics of BCI technologies. It could be beneficial to develop a comprehensive test platform that could be used to identify weaknesses in the system and ultimately to enhance the reliability and performance of the candidate device.

4.2.2. Animal testing/in vivo. While bench testing is appropriate for individual BCI components, animal models may be necessary to fully evaluate the BCI system in biological environment. Animal models are essential to provide information about the safety and reliability of BCI systems (e.g., biocompatibility and mechanical stability of the system during use) that cannot be readily discerned from in vitro studies, but are critical for moving to human trials. However, the choice of animal models, type of measurements, and number of animals needed to establish the safety and reliability are dependent upon the BCI, and may vary depending on device type and indication. While rodent models could be used for biocompatibility or histological evaluations, the choice of animal model for mechanical and chronic implantation testing of the system may also consider the physical and mechanical aspects of the implant site. For example, the consensus from workshop attendees was that larger animal brains are a better platform for evaluating mechanical
stability of cortical devices, due to their similarity to human brains with respect to relative motion of the implanted device. The importance of standardized histological measurements to assess the effects of long-term implantation was also highlighted, along with the importance of incorporating physiological measures of stability that can ascertain the functional properties of local tissue. Although the optimal animal model may be device and/or situation specific, there was a call for greater transparency from regulatory bodies about the types of data that are required from non-clinical animal studies to support clinical work, and the justifications that are needed to support the decisions for non-clinical study protocols.

In addition to mechanical and histological evaluation, motor, sensory and behavioral tests were suggested as outcome measures to assess the safety and effectiveness of the system. The complexity of determining the required number of animals without prior knowledge of effect size for new technologies was briefly described, highlighting the importance of statistical analysis during experimental design. Limitations of animal models include that healthy animals with intact and/or functional limbs may not fully represent the physiology of patients with disease or limb loss, the inability to directly assess sensory perception, and the inability to accurately predict the usability of a system and its effects on certain psychosocial aspects. Given these limitations, in some cases early feasibility studies and staged clinical trials may more effectively address safety and performance questions.

4.2.3. Theme 3—computational modeling/in silico. One of the goals of this workshop was to identify the least burdensome pathway to advance promising BCI technology towards clinical use. A potential method considered was the use of computational modeling. Several workshop participants discussed how their published work describes tests to indicate how a device implanted in the brain may fail [4, 17, 18]. Although much of this research has primarily focused on the electrical properties of device components, investigation of non-electrical failure modes is critical to predict function and reliability, particularly for peripheral-nervous-system interfaces since they are likely to be exposed to mechanical perturbations.

The advantages of computational modeling compared to animal testing were discussed. Computational modeling may be a suitable alternative when no animal model exists that matches human anatomy (e.g., the number of nerve fascicles). Workshop attendees appeared to support information on the electrical fields, thermal fields, multiple electrode contacts, implant locations, as well as other computational models to provide data complementary to clinical testing.

4.2.4. Future directions. The need to establish benchmarks for non-clinical testing that will ultimately help investigators transition into early clinical studies was identified as a key issue. However, guidance that specifically describes the testing parameters for all BCI devices was seen as impractical since testing depends on the site of implantation, the risk associated with the device, the individual patient’s risk/benefit assessment, as well as the implant’s primary function. Instead workshop attendees suggested such a guidance document could be based on risk analysis that would help investigators identify appropriate testing parameters for their proposed application. The guidance would provide information on standards that are currently available for validating software and electronics. Finally, the development of a publicly accessible database of methods and outcomes from previous non-clinical studies is an important goal for the BCI community. Although the FDA cannot disclose proprietary information, the possibility of funding agencies requesting their investigators to share some of this information voluntarily, such as is done for NIH-funded studies, was discussed.

4.3. Translational and regulatory context

Despite increased development and investigational clinical study of BCI devices, successful translation to marketed BCIs for patients has been limited. Various stakeholders have identified challenges to translation including long device development time, high development costs, and small market size, and regulatory considerations. Several specific
challenges were defined, including regulatory review of devices as entire systems, determining the appropriate classification of devices and a lack of standards or standardization across industry.

Many BCI device technologies are inherently modular in nature, with components that may provide sensing, stimulation, processing, and effector output. In current practice, a prosthetist often uses components from various manufacturers to create a customized patient solution. However, increasing technological sophistication of devices, including the use of neural implants, have raised concerns about device modularity and how it should be evaluated in the regulatory review process. CDRH has historically evaluated BCI systems as a single comprehensive device in which the device should be tested as a complete system. Advantages, considerations and potential solutions to the challenge of modularity were discussed.

Workshop attendees expressed difficulty in arriving at consensus taxonomy of modules that should comprise a BCI system. Suggested modules included the BCI-controlled effector (e.g., prosthetic limb, wheelchair, computer, robotic arm, etc), electrode interfaces, connectors, leads, communication protocols, recording electronics, stimulating electronics, power supplies, software algorithms, and surgical methods.

The advantages that a module-based regulatory review might bring to industry stakeholders might include reduced development time and cost, reduced time to market, increased competitive landscape by allowing the entry of small companies into the market and increased ease of product upgrades. A module-based review process was discussed as a potential way to address issues regarding device classification, specifically when one component of a system is of higher risk, rendering the entire system a Class III device. Workshop attendees discussed that a modular approach may enable different modules to potentially have different classifications, which would allow for a reduced clinical and non-clinical testing burden for the manufacturers of lower-risk modules. Device Master Files may be used as a tool to allow one manufacturer to reference pertinent information from the manufacturer of a related component. Patients may also receive benefit from increased and more rapid access to advanced components, customization for individuals, and accessibility to upgrades.

A number of considerations were discussed as challenges to the implementation of modularity. The most pressing challenge is how to ensure that the complete system operates safely and effectively when individual modules are connected together, especially in a world of increasing system complexity. This typically requires testing of the system as a whole, which could be burdensome and costly for the individual module manufacturers, especially if their module is to be used with multiple system configurations. An additional concern is defining the responsibility for device failure, and appropriate protocols for failure analysis. Finally, some device manufacturers might not find a compelling business case for modularity, and would prefer to manufacture an integrated system. Workshop attendees suggested that the field may not be ready to consider modularity, as many devices are still in early development, and modularity might be better considered after key components have first been approved in a complete device system so that components can be built to those standards.

Standardization is one potential solution to the issues of modularity, as it would enable components to be individually improved and then tested fully to meet the well-defined specifications that the community has articulated to ensure adequate performance of the system. This would avoid the need to test the whole system or various configurations of systems separately, and the associated time and resource investments. Although standardization was primarily discussed in the context of device hardware, algorithms for data processing could also be standardized. For instance, workshop attendees proposed that there could be a test data set of neural data that each manufacturer could use to test their processing modules. Precedent for this approach may be found in the pacemakers and orthopedic implant device fields. It is important to consider that that implementing standardization too early could potentially stifle innovation if the standard is too restrictive. Likewise, it is unclear who should lead a standardization effort (e.g., FDA, academia,
industry, etc) and which organizations should be involved (e.g., ASTM, ISO, IEEE). One potential solution would be the formation of a consortium to handle issues of standardization and device modularity.

5. Roadmap forward

CDRH plans to use the early input from individuals or groups at this workshop to develop recommendations that will promote innovation while maintaining appropriate patient protections. FDA plans to build on advances in regulatory science and the input provided in this workshop to develop guidance that provides recommendations for premarket submissions for BCI devices. Note that for the purposes of the workshop, we have defined BCI devices as neuroprostheses that interface with the central or peripheral nervous system to restore lost motor or sensory capabilities.

In addition, all stakeholders should be aware of CDRH’s newer mechanisms for facilitating innovative product development for unmet public health needs:

- The expedited-access program (EAP) [19] facilitates the development and expedites the review of breakthrough technologies. As part of this program, FDA intends to provide, as resources permit, more interactive communications and more interactive review of IDEs, PMA applications, and de novo requests. In addition, the FDA intends to work interactively with the sponsor to create a data-development plan specific to the device, which should outline all data the sponsor intends to collect in support of device approval. Requests for EAP designation were accepted beginning 15 April 2015.
- The early feasibility study program [2] allows CDRH to work with sponsors to ensure appropriate patient safety and to acquire crucial clinical data early in the product-development cycle. BCI devices at their current stage of development are likely to be candidates for EFS.
- The medical device development tool draft guidance [20] provides a mechanism for new outcome measures (clinical outcome assessments) to be qualified as medical device development tools. This would ensure their acceptance as valid assessments within the defined context of use. Tools can be proprietary, licensed, or publicly available once they are qualified.
- The ‘Leapfrog’ guidance is a new mechanism by which CDRH can share initial thoughts regarding the content of pre-market submissions for emerging technologies to speed development and approval of future submissions.
- The FDA-CMS parallel-review pilot program provides a mechanism by which sponsors may voluntarily invite to the table representatives from the CMS, with the goal of obtaining feedback on evidentiary requirements pertinent to national coverage decisions [21]. Sponsors may email parallel-review@fda.hhs.gov to become part of this pilot program.

Although the FDA alone may help address some medical device hurdles in moving to market (such as enabling earlier feedback to Sponsors and Investigators about the regulatory pathways available), several other hurdles identified by the community will require the involvement of all stakeholders. Past meetings have been helpful in shaping the discussion in preparation for this workshop, such as the 2013 Clinical Brain Neural Machine Interface Workshop (http://bmiconference.org/). Workshop attendees further recommended that the BCI community continue to meet regularly to collaborate and share experiences to help address current and future impediments to advancing the field.

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