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CDRH: 510(k)s AND SCIENCE IN REGULATORY DECISION-MAKING

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	<p>device. The recommendation was based on information provided by the FDA and on the Panel members' personal knowledge of, and experience with, contraceptive methods of birth control, including barrier-type contraceptives. Additionally, the Panel believed that general controls and special controls would not provide a reasonable assurance of the safety and effectiveness of the devices. The FDA has not received any new data to affect the classification. The FDA agreed and continues to agree with the Panel's recommendation. The Agency notes that the device has fallen into disuse and that the published data are not adequate to demonstrate the safety and effectiveness of the device.</p>	
<p>Transilluminator for breast evaluation (21 CFR 892.1990)</p>		
<p>A transilluminator, also known as a diaphanoscope or light scanner, is an electrically-powered device that uses low intensity emissions of visible light and near-infrared radiation (approximately 700 to 1050 nanometres), transmitted through the breast, to visualise translucent tissue for the diagnosis of cancer, other conditions, diseases or abnormalities.</p>	<p>Class III classification was recommended by the Obstetrics and Gynaecology Devices Panel. The Panel concluded that there were no published studies or clinical data demonstrating the safety and effectiveness of the device. The Panel indicated that the device presents a potential unreasonable risk of illness or injury to the patient if the clinician relies on the device and that although the device's illumination level, wavelength and image quality can be controlled through tests and specifications, insufficient evidence exists to determine that special controls can be established to provide a reasonable assurance of the safety and effectiveness of the device for its intended use. The FDA has not received any new data to affect the classification. The FDA agreed and continues to agree with the Panel's recommendation. The Agency notes that the device has fallen into disuse and that the published data are not adequate to demonstrate the safety and effectiveness of the device.</p>	<ul style="list-style-type: none"> • missed or delayed diagnosis • electrical shock • optical radiation <p><i>Abbreviations:</i> 21 CFR = Title 21 of the Code of Federal Regulations PMA = pre-market approval application FDA = Food and Drug Administration</p>

CDRH: 510(k)s and Science in Regulatory Decision-Making

The Food and Drug Administration (FDA) has released for public comment¹ a two-volume set of documents entitled *Center for Devices and Radiological Health [CDRH] Preliminary Internal Evaluations*, which is comprised of the preliminary reports of two internal committees: the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making. Volume I is entitled *510(k) Working Group Preliminary Report and Recommendations*. Volume II is entitled *Task Force on the Utilization of Science in Regulatory Decision Making - Preliminary Report and Recommendations*. The FDA has solicited public feedback on the recommendations discussed in these reports, including the feasibility of implementation and potential alternatives. Once the Agency has assessed the public's input, and other necessary reviews have been completed, it will announce which improvements it will implement, as well as projected timelines for implementation. On 6 October 2010, the FDA unveiled a report² that provides examples of the

Agency's current activities in regulatory science with consideration of how such advancements can help deliver safer and more innovative products in seven different public health areas through its Regulatory Science Initiative.

510(k) Working Group Preliminary Report & Recommendations³

The Working Group Report outlined the group's findings regarding observed deficiencies in the pre-market notification (510(k)) process and set forth preliminary recommendations for improving the process. Although the Working Group recommended that the current regulatory scheme be left largely intact, many of the proposed recommendations could have significant implications for the future development and clearance of devices through the 510(k) pathway. Some of the more significant recommendations include:

- further defining key terms used to determine 'substantial equivalence';
- establishing a new subclass of medical devices (denoted as Class IIb) that generally require a greater amount of data and information for 510(k) clearance, including clinical data;
- seeking authority for the FDA to evaluate potential off-label uses of a device when considering clearance of a device;
- limiting the use of more than one predicate in a 510(k) notification and potentially disallowing 'split predicates';
- modifying the *de novo* classification process to encourage greater use of that process;
- revising the circumstances under which device modifications require a new 510(k) submission; *and*
- establishing a process to rescind 510(k) clearances.

Some of these recommendations could be implemented by the FDA immediately, while others would require statutory changes.

A summary of the significant observations and recommendations included in the Working Group report are provided below.

New Class IIb

A diverse set of devices is currently subject to the 510(k) requirement, in terms of both technological complexity and potential risk to patients. While lower risk or technologically simple devices may be cleared without the need for new clinical data, complex or higher risk devices typically need more robust 510(k) submissions. According to the Working Group Report, however, the Agency often receives submissions lacking the information required to make a substantial equivalence determination. The Report observed that '[i]t is challenging for CDRH to obtain, in an efficient and predictable manner, the information it needs to make well-supported premarket decisions and assure that each new or modified 510(k) device is substantially equivalent to a valid predicate'. Accordingly, the Report recommended the development of a Class II subset called Class IIb. The purpose of creating this subset would be to identify groups of devices for which more extensive data are typically needed.

The Report indicated that clearance of devices in the Class IIb subset would usually require the submission of clinical and manufacturing information, and in some cases the use of post-market evaluation. With respect to clinical data, the Report noted that 510(k)s are increasingly used to clear complex devices for which the

safety of a modification to a device can be measured only by clinical investigation. It recommended that the creation of a Class IIb subset be used as a vehicle to offer a clearer picture of when clinical data will be needed and what form it should take. On the issue of post-market surveillance, the Report noted that 'it might not be feasible' to conduct a large-scale clinical trial of a device containing novel and complex technologies, and therefore it may be necessary to collect additional data over a longer period of time to better assess safety and effectiveness. Nevertheless, the Report noted that the *Federal Food, Drug & Cosmetic Act* (FFD&C Act) does not provide explicit authority to require post-market studies for most 510(k)-cleared devices.

The Agency suggested that, if implemented, this recommendation 'would not reconfigure the current, three-tiered device classification system established by statute'. Rather, delineating between Class IIa and Class IIb 'would represent only an administrative distinction'.

Clarifying Substantial Equivalence

The Working Group also observed ambiguities regarding key terms that are involved in the substantial equivalence determination. Specifically, the Group identified confusion regarding 'intended use' versus 'indication for use', which the CDRH has used interchangeably in some documents. The Report also observed difficulties applying the 'different technological characteristics' and 'different questions of safety and effectiveness' standards. The Report recommended that the CDRH provide guidance to clarify these terms.

Evaluating Off-Label Uses

The Working Group Report concluded that another issue with the 510(k) process is the possibility that devices sometimes receive 510(k) clearance for an intended use that does not match the device's actual use in practice. The substantial equivalence standard requires the device under review to have the 'same intended use' as the predicate device, but according to section 513(i)(1)(E) of the FFD&C Act, 'any determination by [FDA] of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k)'. The Report observed that, in some cases, the 'true' intended use of the product could raise different questions of safety and effectiveness. Given that the statute limits the FDA from looking beyond the labelling to establish intended use, the Report recommended that the CDRH 'explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E)' of the FFD&C Act.

Disallowing Split Predicates

The Working Group observed that 'CDRH's current practice allows for the use of some types of predicates that may not be appropriate'. In particular, the Working Group took issue with the practice of 'split predicates' - a situation in which the sponsor claims substantial equivalence to the intended use of one predicate and the technological characteristics of another. According to the Report, 'this practice is akin to combining different attributes of two or more devices into a single, nonexistent predicate device that may bear little resemblance to the device under review or to any marketed device'. This practice is different from the concept of multiple predicates, a situation in which a device claims substantial equivalence to several distinct predicate devices. The Report noted that some 510(k) submissions include up to five or more predicates.

According to the Working Group Report, a survey of CDRH staff revealed a division in opinion regarding the acceptability of using split predicates. The Report recommended that the CDRH develop guidance on the use of more than one predicate and clarify the difference between split and multiple predicates. It also recommended that the CDRH consider explicitly disallowing the use of split predicates.

Enhancement of the De Novo Review Process

The Working Group Report observed that the *de novo* review process, as currently implemented, is inefficient and has not been utilised optimally across the Center. The Group recommended that the CDRH encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to the CDRH for devices eligible for *de novo* classification, in lieu of the exhaustive 510(k) review that currently precedes *de novo* classification. The Report also recommended that the CDRH consider establishing a generic set of controls that could serve as baseline special controls for devices classified into Class II through the *de novo* process.

Modification Guidance

The Working Group has also recommended that the CDRH explore revising existing guidelines for when changes to a device require a new 510(k) or can be handled through other regulatory mechanisms (e.g. a letter to file or a Special 510(k)). The Report noted that submissions sometimes reference as predicates devices whose modifications the Agency has never reviewed, in some cases requiring the CDRH to assess the safety and efficacy of both the modified predicate device and the device seeking 510(k) clearance. The Report also suggested that the CDRH explore 'the feasibility of requiring each manufacturer to provide regular, periodic updates...listing modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not require a new 510(k)'.

Rescission Authority

The Report recommended that the CDRH consider issuing a regulation defining the grounds and procedures for rescinding a 510(k) clearance. The Report stated that such authority is 'inherent' in the Agency's discretion to reconsider its decisions, and it references the FDA's 2001 proposed rule on the rescission of substantial equivalence decisions. The Report does not discuss how the Agency should handle the practical consequences of a rescission process - for instance, the effect of a rescission on already-cleared 510(k)s that reference the rescinded device as a predicate.

Other Recommendations

Some other notable recommendations include:

- CDRH's decisions regarding the criteria for when a device may be considered a predicate are inconsistent and have led to inappropriate 510(k) clearances. The CDRH should develop guidance to explain when a device will be disqualified as a predicate due to safety or efficacy concerns.
- The CDRH should enhance its support for training and professional development for review staff.
- The CDRH should improve the tools and metrics used to assess the consistency of decision making across the 510(k) programme, and should track the programme's public health impact quantitatively.

- The CDRH should clarify the circumstances under which it will refuse to clear a device due to manufacturing concerns.
- The CDRH should develop a public, easily searchable database that contains 510(k) summaries, photographs, schematics and explanations of how 510(k)s relate to one another.

Observations and Next Steps

The recommendations of the 510(k) Working Group are far reaching and have the potential to impact significantly the development and clearance of devices under the 510(k) pathway. Some of the recommendations have the potential to provide useful improvements to aspects of the 510(k) process. For example, streamlining the *de novo* 510(k) process and bringing additional clarity to the standards and definitions used by the FDA have the potential to provide greater predictability to the 510(k) process. Similarly, developing a public, easily searchable database that contains more information about cleared 510(k)s could provide greater transparency and a better source of information about predicates.

Other recommendations, however, could impose new regulatory barriers that unnecessarily limit the utility of the 510(k) pathway. For example, limiting the use of multiple or split predicates could impose unnecessary burdens. Requiring devices that combine well-established intended uses and known technological characteristics to proceed down the Pre-Market Approval application or *de novo* pathway simply because there is not a single predicate combining these elements could limit the utility of the 510(k) pathway. Similarly, while clarifying the standards used by the FDA has the potential to improve the 510(k) process, if the FDA's guidance is unnecessarily restrictive, it could further inhibit investment and innovation.

Moreover, aspects of the Working Group Report raise questions about the extent to which the FDA could implement the recommendations without new statutory authority. For example, the Working Group's recommendation to create a new Class IIb subset raises a question regarding the Agency's authority to manipulate the current regulatory scheme without seeking Congressional intervention. On the one hand, the FFD&C Act clearly lays out three device classifications, and arguably it does not leave room for the Agency to alter that scheme further. On the other hand, the Class IIa/IIb division could be viewed simply as a way of ordering the types of information it expects to see in a 510(k) submission. A similar question arises with respect to the Agency's authority to rescind a 510(k) device clearance. Other recommendations, such as the ability of the Agency to consider off-label uses of a device when considering a 510(k), clearly require statutory changes.

Utilisation of Science in Regulatory Decision Making

The incorporation of new science into the CDRH's decision making depends on three major elements¹:

- To enhance its science-based decision making generally, the Center must have adequate scientific understanding based on meaningful, high-quality, up-to-date information, analytical and technical expertise, and an operational and organisational infrastructure that supports knowledge development and knowledge sharing.
- To determine the appropriate action(s) to take when faced with new science, including, potentially, deciding to take no immediate action, the Center should apply an approach that provides as much predictability as practical and that is consistent with its authorities.

- When it has decided to take a particular action, the Center should communicate its decision and its rationale promptly and as broadly as permissible.

The Task Force identified several areas for improvement related to each of these elements.

Scientific Knowledge Base

With regard to CDRH's scientific knowledge base, the Task Force found that it is difficult for Center staff to obtain efficiently and effectively complete information about the risks and benefits of regulated products across the total product lifecycle. This can lead to unnecessary delays and burdens during pre-market review and make it challenging for the Center to identify and respond to post-market trends quickly and appropriately. The Task Force has recommended that the CDRH: take proactive steps to improve the quality of pre-market data, particularly clinical data; address review workload challenges; and develop better data sources, methods and tools for collecting and analysing meaningful post-market information.

In addition, the Task Force found that it is difficult for CDRH staff to share scientific knowledge across the Center, in part due to staffing limitations, and to tap meaningful external scientific expertise in a timely manner. The Task Force therefore recommended that the Center conduct an assessment of its staffing needs to accomplish its mission-critical functions and prepare for anticipated scientific challenges. The Task Force has recommended that the CDRH take steps to improve knowledge management within the Center and make better use of experts outside of the Center, in part by developing a web-based network of external experts, using social media technology.

New Science

With regard to determining the appropriate action(s) to take when faced with new science, the Task Force found that the CDRH has not yet articulated a business process to be followed across the Center for evaluating new scientific information and determining when that information warrants certain types of action, such as a change in pre-market evidentiary expectations. As a starting point for discussion and comment, the Task Force developed a conceptual framework for such a process, comprised of four basic steps:

- detection of new scientific information;
- escalation of that information for broader discussion with others;
- collaborative deliberation about how to respond; *and*
- action commensurate to the circumstance, including, potentially, deciding to take no immediate action.

The Task Force also identified a few key principles that should be considered as the Center puts this framework into practice. Most notably, the Task Force recommended that the CDRH establish a Center Science Council, comprised of experienced employees and managers and under the direction of the Deputy Center Director for Science, to help assure consistency across the Center in responding to new scientific information.

Communication

Finally, the Task Force found that, when new scientific information changes the CDRH's regulatory thinking, it is challenging for the Center to communicate the change and its basis to all affected parties in a meaningful and timely manner. The

Task Force has recommended that, in addition to continuing its ongoing efforts to streamline guidance development, the Center make use of more rapid tools for broad communication on regulatory matters. For example, the CDRH should establish as a standard practice sending open Notice to Industry letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. The CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change. The CDRH would generally issue Notice to Industry letters, if such letters constitute guidance, as 'Level 1 - Immediately in Effect' guidance documents, and would open a public docket in conjunction with their issuance through a notice of availability in the *Federal Register*. Where appropriate, such letters should be followed as quickly as possible by new or revised guidance explaining the Center's new regulatory expectations in greater detail and revising the guidance, where necessary, in response to comments received, so that external constituencies have a fuller understanding of the Center's current regulatory thinking. The Task Force also recommended that the CDRH continue ongoing efforts to increase the transparency of its decision-making processes and rationale, in order to clarify the basis for any action it takes in response to new scientific information.

References

1. *Federal Register*, 2010, **75**(150), 47307 (5 August 2010).
2. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm228482.
3. This section on the 510(k) process has been written by **Ellen Flannery** (email: eflannery@cov.com), **Scott Danzis** (email: sdanzis@cov.com) and **Christopher Pruitt** (email: cpruitt@cov.com) of Covington & Burling LLP, 1201 Pennsylvania Avenue, NW, Washington, DC 20004-2401, USA.

CDRH Inspections Database

The Center for Devices and Radiological Health (CDRH) has announced availability of the CDRH Inspections Database¹. The database provides information about medical device inspections for which CDRH was responsible including details of the firms, types of devices and inspections, and links to warning letters where available. Types of inspections covered include, *inter alia*, foreign inspections, Medical device Reporting (MDR) malfunction issues, labelling and software issues. Clinical trial inspections are not included because information regarding new device development is confidential.

Further details on how to search this database are provided on the Food and Drug Administration (FDA) website as referenced below. The CDRH Inspection Database can be searched at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTPLC/inspect.cfm. For further information on medical device inspections refer to FDA guidance².

References

1. *CDRH Inspections Database*, Food and Drug Administration, 30 September 2010 (www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHTransparency/ucm223770.htm).
2. *Inspection of Medical Device Manufacturers*, FDA Guidance Document (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072753.htm).

CDRH to Enhance Advertising Enforcement Initiatives

The Food and Drug Administration (FDA) Center for Devices and Radiological Health