Title: Stepwise Method to Determine Device Regulatory Status
Date of Last Revision: 05/09/18, 04/23/18, 04/25/17, 12/15/17
Author: Laverne Estanol, M.S., CHRC, CIP, MRQA
Audience: Researchers
Citation: https://escholarship.org/uc/item/7x25x4qt

Worksheet

Stepwise Method to Determine Device Regulatory Status	Device 1	Device 2
1. Medical Device [steps i * & ii]? [If YES to any items below, PROCEED to #2 below] ☐ Medical Device; *Investigational Device [21 CFR 812.3(g) – device is the object of the investigation (safety/effectiveness)]* ☐ IVD [Section III.2, and Appendix I] ☐ MMA [Section V.B, and Section VI.B & VI.C – *recent example Cantab Mobile*] ☐ Software ☐ Wellness device ☐ Real-World Evidence [Section B] * *a device does not have to meet all 3 subparts to the definition of a medical device for it to be considered a medical device*		
2. Clinical Investigation? [If YES to any items below, PROCEED to #2b below] ☐ *Activity/data will be submitted to/held for inspection by the FDA in support of a marketing application [21 CFR 50.1]* ☐ *Clinical Investigation [21 CFR 50.3(c) - any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section [505(i) or] 520(g) of the act [subject to 21 CFR 812], or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit]* ☐ *Use of device to evaluate safety/effectiveness [21 CFR 812.2(a)]* ☐ *Investigation [21 CFR 812.3(h) - determine safety/effectiveness of device]* Examples: i. Study looking at how well the device works in measuring something ii. Study "uses" device to measure something but study will collect limited validity data just to demonstrate that the measurements made by device are reasonably accurate iii. Study collects only feasibility data on a device		
a. NO: [If NOT a clinical investigation, STOP here] Examples: i. physiology study (no data is collected about device): 1. device used to measure physiology 2. use device to elicit a response 3. use device to address a research question 4. use device to measure a clinical outcome ii. used according to label iii. device is not the focus of the study iv. monitor a side effect v. measure treatment progress		

vi. a low-risk device is used only to address a research question, however the device is home-made *[considered a basic physiology activity, but IRB would need to consider case by case]*

vii. off-label [note: the term *off-label* applies only to *medical practice*; refers to physicians using devices and approved drugs in a manner inconsistent with the package insert in order to treat patients]

✓ Level of IRB review is determined by overall study risks

✓ If overall level of risk for study is minimal, determine whether Expedited Category #4 is applicable

b. YES [a clinical investigation]: [Choose ONE category for EACH device: (i) Exempt from IDE, (ii) Abbreviated IDE, (iii) IDE required]

- *[2013 guidance, pages 6-7: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm328855.pdf]*

i. Exempt from IDE [21 CFR 812.2(c)]

Common device exempt categories:

1. A device, other than a transitional device (i.e., an inhaler), in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time
2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
3. A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing:
    a. Is noninvasive [21 CFR 812.3(k)]
    b. Does not require an invasive sampling procedure that presents significant risk
    c. Does not by design or intention introduce energy into a subject
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

Other device exempt categories:

4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. A custom device [21 CFR 812.3(b)], unless the device is being used to determine safety or effectiveness for commercial distribution.

Translation (*in other words*): Approved device being used in accordance with its labeling

✓ *search FDA webpage for 510k or PMA approval notice (the marked indication will be listed)*

Transitional Device: a device regulated as a drug before the device laws were passed [21 CFR 812.3(r)]

Criterion [Exempt from IDE]:

1. Approved device used in accordance with approved labeling

Yes to all items below, and provide supporting documentation:

☐ FDA approved for marketing in the US

☐ Results are not intended to be reported to the FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change device labeling

☐ Used in *accordance with the indications in the approved labeling* and does not involve a new device indication (new population, condition, area of the body, or significant design change)

2. Other Criterion:

Yes to any items below, with confirmation from FDA/FDA guidance:

☐ Testing of an IVD that is noninvasive [21 CFR 812.3(k)], does not require invasive procedure that presents risk, does not introduce energy into a subject, will not be used as a diagnostic w/o confirmation by another medically established procedure/product, and results will not be used to make clinical decisions

☐ Consumer preference testing of a device if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk

☐ Testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purposes of determining safety or effectiveness and does not put subjects at risk

☐ Custom device [21 CFR 812.3(b)] intended for use by an individual patient and not for the purpose of determining safety or effectiveness

☐ Testing of off-the-shelf (OTS) software [section 3.4] as part of an Exempt IVD

3. Other Criterion:

☐ FDA or sponsor has provided documentation indicating that IDE is not required

✓ Level of IRB review is determined by overall study risks
✓ If overall level of risk for study is minimal, determine whether Expedited Category #1 * is applicable [section VIII.A]
✓ If the FDA has already made an Exempt determination, the agency's determination is final [section IIIC]

* *Circumstances where an IDE application would not be required include those where (i) a NSR device is being reviewed by an IRB under 21 CFR 812.2(b); or (ii) the medical device is cleared/approved for marketing and is being used in accordance with its cleared/approved labeling; or (iii) the research is Exempt from the IDE submission requirements under 21 CFR 812.2(c). Per FDA, some medical devices are Exempt because of their use, but they might not be minimal risk.*

ii. Abbreviated IDE [21 CFR 812.2(b)]

An investigation of a device *other than a significant risk device*, if the device is not a banned device ***[21 CFR 812.2(b)(1)]***

Requires an explanation of why the device is ***not*** *a significant risk device (NSR)* ***[21 CFR 812.2(b)(1)(ii)]***

- Significant Risk (SR) - 21 CFR 812.3(m)

✓ IDE submission to FDA is not required [section III.D.2]
✓ Convened IRB must review the SR/NSR determination; if the FDA has already made a NSR determination, the agency's determination is final [section III.C]
✓ To be eligible for expedited review, device must be NSR and the study presents no more than minimal risk to the subject [21 CFR 56.110] [section VIII.A]
✓ NIH NHGRI IDE and Genomics Research (pdf): 2017 Guidance

iii. IDE Required [21 CFR 812.20(a)]

Any device found to pose a significant risk (SR) [21 CFR 812.3(m)] of harm by the sponsor, by any reviewing IRB, or by the FDA, must have an IDE [IDE application].

✓ IDE submission [section 1] to FDA is required [section III.D.1]

	✓ Convened IRB **must** review the SR/NSR determination; if the FDA has already made a SR determination, the agency's determination is final [section III.C] ✓ NIH NHGRI IDE and Genomics Research (pdf): 2017 Guidance		

Other considerations in device studies:

- Adaptive Trials: do not permit *ad hoc* changes; permits design changes that are pre-specified and planned in advance and are not protocol amendments that require prior IRB review (i.e., complicated devices involving software [MRI, CT scans, laser surgery tools, etc])
- Charging participants for the medical device [21 CFR 50.25(b)(3)]
- Combination Products: required documentation is dependent on the Primary Mode of Action (PMO), drug(IND) and/or biologic (BB-IND)
- Companion diagnostics
- Ensure device has protection for device identifiers and/or human subject identifiers; if device is attached to a laptop/computer, please describe data security plan
- Ensure devices have received inspection/clearance from clinical/biomedical engineering
- HUD [21 CFR 814, Subpart H]: clinical use and/or collection of research data
- IDE Investigator Responsibilities
- Implantable/long-term device: ongoing care, costs, removal of the device and associated costs with the removal of the device
- IVD [21 CFR 809.3(a), 45 CFR 46.116(d)]; IVD studies using de-identified human specimens
- Medical Device FAQs
- NIH NHGRI Device and Genomics Research: 2017 Guidance
- Sham surgeries [PMID:10498497, DOI:10.1056/NEJM199909233411311]: Belmont Report (do no harm), Declaration of Helsinki (rights and interests of individual research subjects take precedence)
- Sponsor-Investigator responsibilities
- Standard regulatory requirements: 21 CFR 56.111, 21 CFR 812.43(a), 21 CFR 50 (Subpart D)
- Types of *In Vitro* Diagnostics
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
- Verify whether devices have a subaward and/or MTA