Points to Consider for Marketing of Computerized Surgical Systems in the U.S.

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Introduction

- A computer assisted surgical device is defined as an operating room system that combines software and electromechanical sub-systems to transmit inputs from a surgeon to the surgical instruments at the operative site. The device requires direct and real-time surgeon input for device operation.
- Computer assisted surgical devices have been classified as Class II 21 CFR 876.1500 for endoscopic instruments and accessories.
- Manufacturer who intends to market a computer assisted surgical device in the United States should submit a 510(k) application to the US Food and Drug Administration.
- This presentation discuss the content to such an application.
- This presentation does not discuss applications for robotic devices.

Content in a 510(k) Application

- Clear statements of the device Intended Use and Indication for Use.
- Detailed description of the device including hardware, software or firmware.
- Draft Operator Manual.
- Comparison to predicate device (s).
- Identification of patient contact materials used in device constructions and biocompatibility testing.
- Sterilization requirements and validation of sterility.
- Conformance to FDA recognized standards.
- Functional validation of the device.
- Clinical validation of the device when required.

Intended Use of the Device

- Clear statement of the intended use of the device.
- The intended use of the device states what the technology does. This is usually a general statement and is not necessarily patient population-specific. It may or may not be identical to the Indications for Use statement.
- Compare your intended use statement to your predicate devices. Differences in intended use statements needs to be addressed.

Indication for Use

- The indication for use describes what the technology is supposed to do for the identified population. *It is critical that the indication for use be clinically appropriate for the population and for the device*

Device Description and Labeling

- Detailed description of all device components, device functions, safety features.
- Software documents in accordance to FDA guidance for software in a medical device.
- Draft of the operator manual
- Description of training program

Comparison to Predicate Devices

- In addition to the comparison of Intended Use and Indication for Use statements,
- Technological comparison
- Functional comparison
- Material comparison

Basic Test Report Requirement

- Biocompatibility test for new patient contact materials if required
- Sterility validation
- Electrical safety testing per IEC 60601-1
- EMC testing per IEC 60601-1-2
- Other testing (e.g., MR safety)

Functional Validation

- Hardware performance testing.
- Software verification and validation.
- Tasks performance validation using bench models and/or animal models.
  - Tools and end effectors positioning and movement
  - Suturing
  - Grasping
  - Dissection

Clinical Validation

- Clinical trial objectives
- Clinical trial design
- Statistical analysis methods
- Patient protection measures

Actual Case

Investigational Device

Objective

- To demonstrate Investigational Device instruments to be equivalent in safety and effectiveness to standard laparoscopic equipment (control) in performance of general laparoscopic tasks including grasping, cutting, blunt and sharp dissection, approximation, ligation, electro-cautery and suturing.

Design

To provide valid scientific data that would allow reasonable clinical assessment of device safety and effectiveness, independent of regulatory path to market:

- Prospective,
- Concurrent controlled: conventional laparoscopic instruments,
- Multi-investigator: four,
- Single - masked: patient
- Randomized: pre-operatively after inclusion / exclusion criteria met and informed consent signed.
- Follow-up: 30 days

Procedures

- Laparoscopic cholecystectomy (LC): well-established, widely practiced, usually straightforward, excisional procedure.

- Laparoscopic Nissen Fundoplication (LNF): technically more challenging, reconstructive procedure.

Sample Size

Determined upon consideration of:

- Literature reported complication rates,
- Literature reported cohort sizes,
- Sample size needed for learning curve assessment,
- Sample size needed for clinically reasonable assessment of safety and effectiveness,
- Sample size determination per statistical calculation.

n = 50 patients / device type / procedure

Endpoints

- Conversion rate: conversion of ID instruments to conventional tools or of control to open technique.
    - Patient anatomy / pathology
    - Software / hardware failure
    - Surgeon / surgical team position on learning curve
- Procedure duration: skin incision to skin closure
- Post-operative hospital stay: days
- Other measures of safety, e.g.: estimated blood loss, bile leak (LC), dysphagia (LNF).
- DeMeester score at 30 days (LNF).
- Quality of Life: Psychological Well Being Score at 30 days.

Target Population

- Otherwise healthy, adult patients with gall bladder disease or gastro-esophageal reflux disease (GERD) confirmed per protocol, who were expected to benefit from non-emergent laparoscopic cholecystectomy or laparoscopic Nissen fundoplication and willing to participate in clinical study.

Outcomes: Pre-Operative (LC, LNF)

Control and investigational device study populations were clinically comparable for:

- Demographics
- Inclusion / exclusion criteria

Outcomes: Intra-Operative (LC)

Laparoscopic Cholecystectomy demonstrated grasping, blunt dissection, cautery dissection, suture tie placement around cystic duct and artery were demonstrated.

- Evaluation of knot integrity was precluded by conventional clip placement on the patient side cystic artery & duct.
- Two investigational device randomized patients were converted to and completed with control due to patient pathology and / or surgical team position on learning curve.

Additional Points to Consider

- Valid Scientific Evidence
- Least Burdensome Concept
- Global Harmonization

"…The Agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective."

21 CFR 860.7 (c) (1)

Valid scientific evidence is evidence from 21CFR 860.7 (c) (2):

- Well controlled investigations
- Partially controlled studies
- Objective trials without matched controls
- Well documented case histories conducted by qualified experts
- Reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use."

21CFR 860.7 (c) (2) continued …

"The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warning and other restrictions, and the extent of experience with its use."

"Isolated case reports, random experience, reports lacking sufficient detail to permit scientific evaluation, and unsubstantial opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable."

21 CFR 860.7 (f) lists principles that have been developed over a period of years and are recognized by the scientific community as the essentials of well-controlled clinical investigation and report of investigations including:

- A clear statement of study objectives
- A method of selection of subjects that provides:
  - Adequate assurance that subjects are suitable for the purpose of the study
  - Diagnostic criteria of the condition to be treated or diagnosed
  - Confirmatory laboratory tests where appropriate
  - Evidence of susceptibility and exposure to the condition against which prophylaxis is desired, in the case of a device to prevent a disease or condition,
  - Assigns subjects to test groups in such a way as to minimize bias,
  - Assures comparability between test groups

Continued:

- An explanation of the methods of observation and recording of results utilized, including the variables measured, quantitation, assessment of any subject's response, and steps taken to minimize any possible bias of subjects and observers.
- A comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be specified and explanation provided of the methods employed to minimize any possible bias of the observers and analysts of the data.
- A summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods utilized."

Least Burdensome Concept

Without changing the standard for pre-market approval or clearance, FDAMA Section 205 amended the FD&C Act to incorporate two references to the “least burdensome” decision threshold: Section 513(a)(3)(D)(ii) and 513(i)(1)(D).

The Least Burdensome Concept is defined as a successful means of addressing a pre-market issue that involves the smallest investment of time, effort, and resources on the part of the submitter and the US FDA. Least Burdensome Concept principles encourage that alternative approaches to all regulatory issues are considered to optimize the time, effort, and cost of reaching resolutions.

Global Harmonization and Use of International Data

- Non-US clinical studies depend on local government regulations.

- Global harmonization encourages efforts to harmonize clinical trials. Specifics of the data set, for example the study population, the conditions of device use as governed by local indications and standards of care, and / or details of clinical trial design and conduct may raise issues in the direct use of non-US clinical data or combinability of US and non-US clinical data to support a US marketing application for a medical device.

- Use of international data in pre - as well as post - marketing evaluation of medical devices presents a potential resource of valid scientific data for regulatory needs.

- Standards for clinical study are being developed by consensus standards organizations e.g., the International Standards Organization (ISO) to ensure wide-spread understanding and form a basis for international clinical trials.
- Issues that may arise in the direct use of clinical data or combinability of clinical data, for example, using US and non-US clinical data to support a US marketing application for a medical device may be due to specifics of the data set and / or details of clinical trial design and conduct. For example, in the case of medical devices indicated for use in arteriosclerotic peripheral vascular disease, issues may include:
  - Study population characteristics
  - Device use profiles
  - Clinical trial conduct

Recommendations

- Clear statement of the Intended Use and Indications for Use of device and compare to predicate devices.
- Clear description of device design and function, compared to predicate devices, and adequate performance data, especially where different from the predicate devices.
- Recognition of potential regional variations in study population characteristics, profiles of device use / standard of care, and details of clinical trial conduct.
- Early collaboration with FDA through established venues such as:
  - Informal telephone discussions
  - Meetings
  - Pre- IDE (Investigational Device Exemption) submissions

References and Points of Contact

Draft Guidance: The Least Burdensome Provisions of the FDA Modernization Act of 1997, Concepts and Principles

http://www.fda.gov/cdrh/ode/guidance/1332.pdf

A Pilot Program to Evaluate a Proposed Globally Harmonized Alternative for Premarket Procedures

http://www.fda.gov/cdrh/ode/guidance/1347.pdf

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