FDA 201--Case Study of a Home Monitoring Device

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Components and accessories

- The following sold separately and made by BuyMore, Inc.
  - ConnectRight™ set top box
  - CareShare™ software for doctor office PCs
- Basic USB cables (various manufacturers),
- Business tools such as cameras, postal meters, scanners, barcode readers, and other USB peripheral devices sold by 4 specific companies that have agreed to make their products compatible
- Medical devices such as blood pressure, glucose meter and scales sold by 3 specific companies that have agreed to make their products compatible

Marketing claims for STB and software

- “Suitable for connecting a wide range of devices to cable Internet, such as sphygmomanometers, glucose meters, scales, cameras, postal meters, scanners, barcode readers, and other USB peripheral devices
- Allows home-based employees to work remotely and stay connected to their companies inexpensively
- Allows people with chronic diseases such as diabetes to stay connected to their caregivers.
  - Doctors can buy software that allows them to sort, read and preserve the data.
  - The software also provides decision support tools to remind the doctors of best practices when making treatment decisions.

More Marketing Claims

- “Remote monitoring with ConnectRight is one of the surest ways to manage your diabetes.”
- “Patients who use ConnectRight stand a better chance of avoiding complications”
- “It’s easy, convenient, reliable and cost effective.”
- Also “helps remote employees increase their efficiency by reducing absenteeism and commute time”

Sales Practices

- BuyMore advertises in *Small Office Productivity Daily*, *Medical Practice Weekly* and *Endocrinologist Quarterly*
- Sales are pretty evenly split between businesses that allow telecommuting and doctor's offices
- As a promotional effort, we are giving the software for free to any doctor in the Endocrinology Society of California Fellows (the senior doctors) who asks over a one month period.
  - This will stimulate use and talk
  - The society will also give us advertising space for free

Adverse event

- A defect in the STB causes the results not to be transmitted.
- The mistake is caught and no injury results.

1. Definition of a Device

Device Definition

Section 201(h) of the Federal Food, Drug, and Cosmetic Act, defines a medical device as:

> "... an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is ... [either]
>
> 2.intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals ... [or]
>
> 3.intended to affect the structure or any function of the body of man or other animals."

Device Definition Distilled

To be a device, boiled down to its essence there are two criteria:

1. A physical, mechanical product is involved and

2. The product is “intended” for a medical use.

Basic Intended Use Framework

Under 21 CFR 801.4, the words “intended uses” …

refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. …

Definitions

- "**Label**" is a:
  - display of written, printed, or graphic matter
  - upon the immediate container of any article....
- "**Labeling**" is:

  all labels and other written, printed, or graphic matter

  (1) upon any article or any of its containers or wrappers, or

  (2) accompanying such article.

Definitions

- "**Accompanying**":
  - Is interpreted liberally to mean more than physical association with the product
    - (*Kordel v. United States*)
  - Extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc., depending how they are used
  - Includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.

Types of Devices

Element of device definition	Finished Stand alone Parent device	Accessory	Component
Definition	A medical device in finished form, ready to use perhaps with accessories, intended for sale to the end user	An article intended for use in or with a finished medical device, intended for use by the end user	An article intended for use in or with a finished medical device, intended for use by a manufacturer
FDA Clearance required?	Yes, unless exempt	Yes, unless exempt	No
GMPs required?	Yes, unless exempt	Yes, unless exempt	No, but quality must be assured to the satisfaction of the finished device manufacturer

Discussion Questions

1. Is the ConnectRight™ STB a medical device?
2. Is the CareShare™ software a medical device?
3. Is the cable a medical device?
4. Is the PC at the doctor's office a medical device?
5. If any of them are medical devices, are they standalone medical devices, accessories or components?

2. Device Classification

Device Classification

Products that are devices are based on intended use

- Class I General Controls
  - With Exemptions
  - Without Exemptions
- Class II General Controls and Special Controls
  - With Exemptions
  - Without Exemptions
- Class III General Controls and Premarket Approval

Device Classifications

868 Anesthesiology
870 Cardiovascular
862 Clinical Chemistry and Clinical Toxicology
872 Dental
874 Ear, Nose, and Throat
876 Gastroenterology and Urology
878 General and Plastic Surgery
880 General Hospital and Personal Use
864 Hematology and Pathology
866 Immunology and Microbiology
882 Neurology
884 Obstetrical and Gynecological
886 Ophthalmic
888 Orthopedic
890 Physical Medicine
892 Radiology

Device Classification Trends

- Trends in device classification process
  - Upclassification
    - Class III products that are allowed to file 510(k)'s to market
      - "call for PMA"
    - Class II products that are 510(k) exempt
  - Pressure on FDA to strengthen device regulatory process
    - Especially for medical devices that are allowed to marketed without gathering any clinical evidence to support safety and efficacy

Discussion Questions

- How is the Connect Right Classified?
- How is the CareShare Classified?

3. Device Clearance and Approvals

510(k) Contents

- Cover Letter
- Premarket Submission Coversheet – FDA Form#3514
  - FDA Summary Documentation
- Administrative Information
  - Date
  - Applicant and/or manufacturer contact info
  - Manufacturing Location
  - FDA Establishment Registration Number
  - Device Name
  - Classification/Product Code/CFR Citation
- Table of Contents
- Truthful and Accurate Statement
  - Certifies that all information is truthful and accurate
- Performance Standards

510(k) Contents, Cont.

- Labeling
  - Package label, instructions for use, package inserts, directions, user manual, promotional materials, advertising, etc.
- Indications for Use Statement
- Substantial Equivalence Comparison Table
  - Comparing new device with predicate device
- Labeling for predicate device
- Device Description
  - Components of device, including accessories provided in kit/pack/tray, etc.
- Performance Data
  - To demonstrate safety and effectiveness
- Biocompatibility
  - Addresses device materials that come in contact with patient

510(k) Contents, Cont.

- 510(k) Summary or Statement
  - Summary – Document available on FDA website after product clearance includes: Submitter's contact information; device name & classification information; Substantial equivalence table; Indications for Use; Device Description
  - Statement – Advising that safety & effectiveness information applicable to product being cleared will be made available by firm upon request
- Software
  - Description and required software details (validation, risk analysis, etc. based on risk)
- Sterility
  - Applicable to devices or components provided as sterile to user

510(k) – de novo

- For devices appropriate for class II where no predicate device exists
  - As name suggests, ‘new’
- Must first receive a ‘non substantially equivalent’ decision from FDA
  - Petition for de novo
  - Must develop special controls for the device as part of the de novo process

510(k) trends

- Review times are up
  - Resources at FDA are limited
- Recent scrutiny on
  - Clinical data
    - FDA's preference is for prospectively gathered, US data
  - Software validation data

Discussion Questions

- What is the appropriate pathway to marketing authorization for ConnectRight and CareShare?
- What are the elements of the submission likely to be of the greatest interest to FDA?

4. Promotional Issues

Topics

1. Fundamental prohibition against misbranding
2. Off Label promotion
3. Special labeling rules
4. Risks in interactions with physicians

Fundamental Prohibition

- The term *misbranded* means:
  - "*False or misleading* in any particular."
    - *False* generally is understood to mean a statement that in any material respect is untrue.
    - *Misleading* is less clear
  - Twin goals of—
    - Safety and effectiveness
    - Preventing economic fraud

Fundamental Prohibition

- Examples of false labeling include:
  - Incorrect, inadequate or incomplete identification
  - Unsubstantiated claims of therapeutic value
  - Substitution of parts or material
  - Inaccuracies concerning condition, state, treatment, size, shape or style

Fundamental Prohibition

- Examples of misleading labeling include:
  - Ambiguity, half-truths, and trade puffery
  - Expressions of opinion or subjective statements
  - Failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion

Fundamental Prohibition

- Examples of other objectionable labeling practices include
  - Deceptive pictorial matter
  - Misleading testimonials
  - Misleading list of parts or components
  - Use of brand or trade names instead of "established names"

Often the surest way to convey misinformation is to tell the strict truth.
Mark Twain

What else is misbranded?

- FDA specifically requires certain information, prominently displayed (unless exempt):
  - Established name of the product
  - Name and place of business of the manufacturer, packer, or distributor
  - Net quantity of contents
  - Adequate directions for use and adequate warnings

Claim Substantiation Generally

- Refers to the evidence needed to support a claim regarding some feature or performance of the device
  - Must support both express and implied claims
  - In labeling, revolves around the FDCA “false and misleading” language
  - In advertising, revolves around the FTC standard requiring a reasonable basis in objective evidence before the claim is made
- Unlike with drugs, there is no explicit FDA guidance yet on device claim substantiation

FTC Factors for Adequate Substantiation

- Type of product
- Type of claim
- Benefits of a truthful claim
- Cost/feasibility of developing substantiation for the claim
- Consequences of a false claim
- Amount of substantiation that experts in the field believe is reasonable

Off-Label Promotion

If an intended use, as shown by the evidence of intent, is for other than the approved indication--

- The lack of approval means the product is “adulterated”
- Inadequate directions for that use in the labeling makes device “misbranded”

Rules Regarding Off Label Communication

- Good Reprint Practices
- Unsolicited Requests
- Contracts for future generations
- Investor Communications
- Websites
- Trade Shows
- Scientific Meetings
- Publication Planning
- Physician Training
- Market Research
- Press Releases

The Risks are Staggering

- OIG continues to investigate off- label promotion
  - Abbott
  - Amgen
  - Boston Scientific
- FCA actions have alleged off-label promotion
  - Cephalon ($425M)
  - Eli Lilly ($1.4B)
  - Pfizer ($2.3 B)
- State AG Investigations of off-label promotion are on the rise

FTC Regulation of Advertising

- FTC has jurisdiction over advertising for a non-restricted device
- FTC applies three requirements
  - Adequate substantiation
  - No deception, from the standpoint of the reasonable consumer
  - Fairness
- Agency influenced by lawyers who focus on consumers and how they are affected

Lanham Act

- Action against a competitor in federal court
- Liability arises from deceptive statements about *either* the competitor's or the company's own product alleged to harm the other party, including:
  - False or misleading claims
  - Unsubstantiated comparative claims
  - Overstatements of efficacy
  - Minimization of risks
- Damages & injunctive relief are available

State Regulation of Advertising

- State Food Drug & Cosmetic Acts
- State consumer protection laws
  - Enforcement by state attorneys general
  - Consumer class actions

Politics gives guys so much power that they tend to behave badly around women. And I hope I never get into that.
Bill Clinton

Risks in Interactions with Physicians

Applicable law

- Federal Anti-kickback statute
- Fraud and Abuse provisions of the Social Security Act (Medicare/Medicaid statute)
- Federal False Claims Act
- State Anti-kickback statutes
- State False Claims Acts
- State statutes requiring disclosure of gifts to prescribers

Risks in Interactions with Physicians

Government enforcement risks arise in the context of:

- Business courtesies
  - Ensure sales personnel follow applicable guidance with respect to gifts, meals and entertainment
- Consulting arrangements
  - Consulting arrangements must be for necessary services pursuant to written agreements in compliance with regulatory requirements
- Research grants
  - Grants should be administered outside marketing function, based on objective criteria
- Educational activities & meetings
  - Sponsored meetings must take place in locations conducive to educational activities, without providing entertainment and with only modest meals and accommodations

Discussion Questions

- What do you need to know to assess the risk?
- Where does the BuyMore have risk?
- What can they do to moderate the risk?

5. Device GMPs

Device GMP's

- **Quality System Regulation (QS) and Good Manufacturing Practices (GMP) - 21 CFR Part 820**
  - The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.

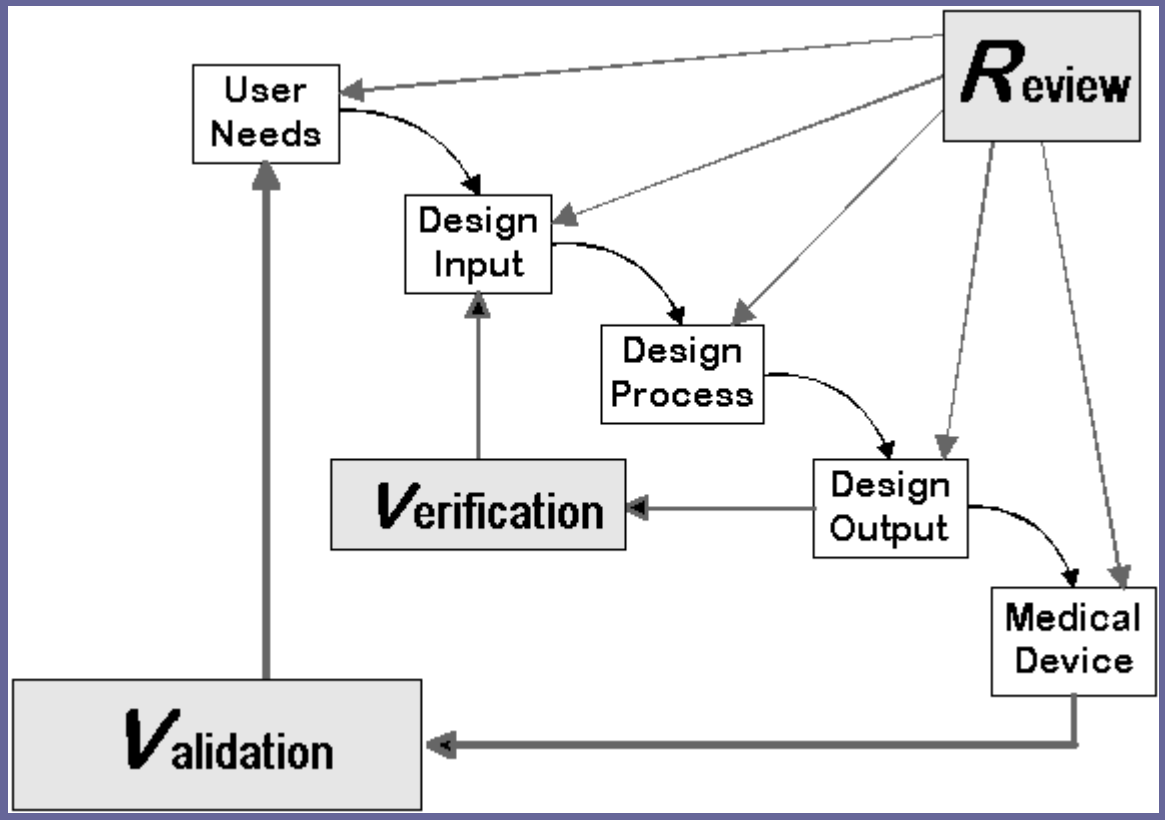
Design Controls

- The quality system regulation includes design controls (21 CFR 820.30) which must complied with during the design and development of the device
  - All Class II, III and some (software controlled) class I devices are subject to design controls
  - Built on a system engineering / requirements delivery model similar to ISO 9001
  - Covers initial requirements development through design transfer (to mfg) and design changes
  - Integral human factors and risk management processes expected
  - Separate guidance for software development

Design Control Elements

- Design Planning
- Design Input
- Design Output
- Design Reviews
- Design Verification
- Design Validation
- Design Transfer
- Design Changes
- Other Controls (risk management, human factors)

FDA Waterfall Model



Design Controls - compliance

- The Design History File (DHF) - objective evidence of Design Controls
- DHF should contain records of compliance with all nine Design Control elements
- DHF should include or reference the Risk Management File if using ISO14971 or other evidence of product risk management activities
- Portions of the DHF (Software records, design trace matrix) are required to be included in 510(k) submissions
- On-going reviews of design changes and assessments of the impact of a change resulting in review, revision and/or repetition of risk management and verification / validation activities are expected as part of on-going GMPs

Design Controls for Software

- Software requirements derived from design input requirements
- Risk control measures – linkages between software and product lableing
- Software verification – whitebox / unit testing and software integration testing
- Software validation – blackbox testing with a human factors (incl labeling) / risk control measure effectiveness emphasis
- Use of IEEE, ISO and ANSI/AAMI software development standards is encouraged
- Risk management for software an FDA focus area
- Design trace matrix ties together requirements with V&V activities and test results

Design Controls for Software-Based Products

- Co-development issues – who has:
  - User needs and design input development responsibilities?
  - Risk management responsibilities?
  - Verification and validation responsibilities?
- Licensing of software
  - Use of Off-the-Shelf (OTS) software
  - Embedded software licenses
  - Service packs and upgrades = design changes!
- All of the above must be defined in the Design and Development Plan and managed post-launch under GMPs

Design Controls – Change Management

- Who controls design changes:
  - During product development?
  - Post-launch
- Who is responsible for and how is the product's configuration (hardware and software) managed?
- How are design change reviews of risk management and verification and validation activities conducted?
- How are software changes controlled and released to manufacturing?

Design Controls for Contract Manufacturing

- Potential co-development issues if CM supports design and development (e.g. prototyping or mfg process equipment development)
- Process development, validation and control per 21CFR820.70 and 820.75
- Design Transfer issues – who has responsibility for:
  - Document control / management
  - Control / management of DHF and RMF
  - Design review and design change management
  - DMR management and DHR creation
  - On-going risk management per ISO14971

Discussion Questions

1. Who is responsible for GMP's for ConnectRight and CareShare?
2. When do design controls 'start'?
3. How will product software be developed and controlled for use in manufacture?
4. What issues do software licensing present?
5. How will product development and manufacturing plans affect design planning and design transfer?
6. Can we 'catch up' our design controls after we submit our 510(k)?

6. Device Registration and Listing

Device Registration and Listing

- Owners or operators involved in the production and distribution of medical devices intended for use in the US are required to register annually with the FDA.
- Most are required to list the devices that they make and to describe activities that are performed on those devices.
  - Linked to submissions (510(k), for example)
- All registration and listing information must be submitted electronically.

Device Registration and Listing

- Examples of who must register and list
  - Manufacturers
  - Manufacturers of custom medical devices
  - Contract Manufacturers who distribute product to end user
  - Specification Developers
  - Contract sterilizers
  - Foreign Manufacturers
    - if products are intended for use in the US

Device Registration and Listing

- Examples of who need not register or list
  - Manufacturers of devices being investigated under an IDE
  - Contract manufacturers of components or subassemblies
  - Contract sterilizer who doesn't distribute final device to end users

Device Registration and Listing

- Timing
  - Must submit information within 30 days of commercial distribution
  - Annual updates
    - A new device introduced to market
    - Removal of device from market
    - Change to a previously listed device

Discussion Questions

- Is BuyMore electronics required to register as a device manufacturer?
  - When?
- If so, how would they list the ConnectRight and CareShare?

7. Postmarket Reporting Obligations

Adverse Events – what to report

- Manufacturers must report all **MDR reportable events** to FDA on Form FDA 3500A.
  - Each manufacturer shall review and evaluate all **complaints** (see definition) to determine whether the complaint represents an event which is required to be reported to FDA. A separate Form 3500A is required for each device involved in a reportable event. For example, if a manufacturer receives a report from a user facility which indicates that more than one of the manufacturer's devices may have been involved in a reportable event, a separate report for each device is required. A report is required when a manufacturer **becomes aware** (see definition) of information that reasonably suggests that one of their marketed devices has or may have caused or contributed to a death, serious injury, or has malfunctioned and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Reportable Events – serious injuries

- **Serious injury/(Serious illness)** [§803.3(aa)(1)] is an injury or illness that:
- is life threatening, even if temporary in nature;
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Malfunctions – what's reportable

- A **malfunction** [§803.3(m)] is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. A malfunction should be considered reportable if any one of the following is true:
- the chance of a death or serious injury occurring as a result of a recurrence of the malfunction is **not** remote;
- the consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury;
- it causes the device to fail to perform its essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness which could cause or contribute to a death or serious injury, or other significant adverse device experiences. The essential function of a device refers not only to the device's labeled use, but for any use widely prescribed within the practice of medicine;
- it involves an implant malfunction that would be likely to cause or contribute to death or serious injury, regardless of how the device is used;

Malfunctions – what's reportable, continued

- the device is considered life-supporting or life-sustaining, and thus essential to maintaining human life; or
- the manufacturer takes or would be required to take action under section 518 or 519(f) of the FD&C Act as a result of the malfunction of the device or other similar devices.
- Reporters do not need to assess the likelihood that a malfunction will recur. The regulation presumes that the malfunction will recur. Furthermore, FDA believes that once a malfunction has caused or contributed to a death or serious injury, a presumption that the malfunction is likely to cause or contribute to a death or serious injury has been established. This presumption will continue until the malfunction has caused or contributed to no further deaths or serious injuries for two years, or the manufacturer can show, through valid data, that the likelihood of another death or serious injury as a result of the malfunction is remote.
- Malfunctions are **not** reportable if they are not likely to result in a death, serious injury or other significant adverse event experience.
- A malfunction which is or can be corrected during routine service or device maintenance **must be reported** if the recurrence of the malfunction is likely to cause or contribute to a death or serious injury if it were to recur.

Closed-Loop QS Elements

- Failure analysis of units returned from the field
  - Feedback to manufacturing
  - Feedback to product developers
  - Risk assessments for field failures part of post-launch risk management system
  - Design changes driven by field failure information
- Tied to CAPA system
- Tied to field action / recall system

Discussion Questions

- Defect in the modem causes the results not to be transmitted. The mistake is caught and no injury results
  - What should BuyMore do with this information
    - Is an MDR report required?
    - Who has responsibility for failure analysis?
    - Who has responsibility for CAPA?
    - When would a recall be considered?