Examination of Documentation Submitted for Marketing Authorization

Manufacturing and Labeling Information Provided to a Regulatory Authority

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U.S. PRESIDENT'S EMERGENCY PLAN FOR AIDS RELIEF

Objective of this Session

To Describe what Manufacturing and Labeling Information is Expected to be Provided to a Regulatory Authority by a Company and why this Information is Important to ensure the "safety and effectiveness" of a Product

“Cover Letter”

Each Submission/File should begin with a “Cover Letter” which includes:

- Name of the company
- Company address, telephone number and contact person (+backup)
- Facility Establishment Identifier (FDA)
- Date facilities ready for inspection

Submitted Information- General Formatting

- Every submission/portfolio should have
- A "Table of Contents"
- All pages are numbered
- Tables/Figures are numbered and appropriately headed
- References are listed

What Information is Requested and for what Purpose?

- Did the Company submit a Detailed Description of the following?
  - The product and its labeling
  - Methods of manufacturing the product
  - Sites where manufactured, packaged, stored
  - Controls to maintain original product design
- Why is this Needed?
  - All Regulators need to determine the developer's ability to design, manufacture or process the product consistently

Description of the Product

What should be Included?

- Appropriate Labeling
- A detailed description of all parts of the product: reagents, platform, software (if applicable)
  - Engineering drawings if applicable
  - Photographs of the product
- Design Control Information

Definition of "Labeling"

"Labeling": Any written, printed, graphic material on any product, on any of its containers or wrappers or on any material accompanying it such as a Package Insert/Instructions for Use/Quick Reference chart etc.

Note: "Electronic Labeling" is also permitted with some exceptions

What are the Basic Requirements for Product Labeling for an *in-vitro* Dx?

Labeling should include:

- Manufacturer, or distributor name and principal place of business
- Product name, both “proprietary” and “common” versions and description
- Intended Use ,Indications for Use and explanation of product including chemical or biological principles
- Interpretation of results
- Warnings, precautions and limitations of product
- Unique Device Identifier (UDI) information

Unique Device Identifier

Should be created and maintained by manufacturers based on global device ID Standards and appear on the label of every product

What should it include?

- Device Identifier- name and address of company and version of product, includes number of tests in kit
- Production Identifiers- lot number, expiration date, date manufactured, storage and handling conditions

Using the CADHIV-1/2 Antibody Assay for Examples

Proprietary Product Name:

CADHIV-1/2 Antibody Assay

Common Product Name:

Human Immunodeficiency Virus Type 1 and Type 2 Antibody Assay

“Intended Use”/Purpose of an *in-vitro* Dx Labeled Product

Includes the Following:

- What is detected?
- Why is it used? To diagnose, screen, monitor a specific disorder, condition or risk factor of interest it is intended to detect, define or differentiate
- Is it a manual or automated test?
- Is it a qualitative or quantitative test?
- What specimen type is required?
- Who are the intended testing population?
- Who is the intended user, trained or untrained?
- Where can the test be performed?

“Intended Use” Example

“*The CADHIV-1/2 antibody assay is an in vitro, visually read, qualitative immunoassay for the simultaneous detection of antibodies to Human Immunodeficiency Virus Type 1 and type 2 (HIV-1 and HIV-2) in human serum, plasma, and capillary (fingerstick) whole blood. It is intended for use as an aid in the diagnosis of infection with HIV-1 and HIV-2.”*

How Does the Product Work?

- "The CADHIV-1/2 Antibody Assay is an immunochromatographic test for the qualitative detection of antibodies to HIV-1 and HIV-2
- The test device is a single use unit that consists of a Sample Well, a Test Zone and a Control Zone
- When a specimen is applied to the Sample Well followed by Run Buffer, it migrates through the Test and Control Zones on the nitrocellulose membrane"

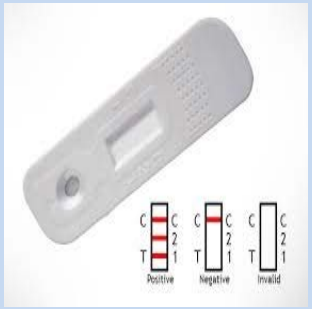
How Does the Product Work?

- “If antibodies to HIV-1 or HIV-2 are present in the specimen, the antibodies bind to recombinant gp41 (HIV-1) and gp36 (HIV-2) antigen colloidal Gold conjugates from the conjugate pad in the Sample Well”

- “The complex migrates through the solid phase by capillary action after addition of Run Buffer until captured by immobilized HIV-1 and HIV-2 synthetic peptide antigens and recombinant gp41 antigen at the test Zone and forms a single pink/red line”

How Does the Product Work?

- “If antibodies to HIV-1 and/or HIV-2 are absent or below the test limit of detection, no pink /red line is formed”
- “A procedural control line containing Immunoglobulin G antigens immobilized on the nitrocellulose membrane is included in the Control Zone and should be a pink/red color for test to be valid”



Reagent Labeling Requirements- What to look for

Materials Provided-

- Information should include: quantity, proportion or concentration of reactive ingredient
- Characteristics of nonreactive ingredients such as buffers, preservatives, stabilizers
- EDTA coated capillary tubes ,lancets, alcohol swipes, specimen transfer device

Storage Conditions-

- Time/temperature, light, humidity, and any other appropriate conditions validated for intended use
- Description of the relevance of a color change to any desiccant included in the package

Reagent Labeling Requirements…

Materials Required and Available as an Accessory to the CADHIV-1/2 Kit

- e.g., HIV-1 and HIV-2 Reactive Controls and a Non-reactive Control that have been validated for use

Materials Required but not Provided

- e.g., Precision pipettes, gloves

Interpretation of Results

- Make sure clear instructions are given in labeling on what is a true Reactive, a true Nonreactive and an Invalid result

- For rapid tests, a simple aid to interpreting results, diagrams /photographs and a Quick Reference laminated card should also be provided

- If a user obtains a "preliminary positive" result, what if any, are the validated, follow-up testing algorithm recommendations that conform with WHO/FDA/other recognized public health authority recommendations?

Warnings, Precautions and Limitations

“Warning” examples

- Follow instructions carefully
- Test units must be stored as per the manufacturers requirements
- Do not use Test Units or kit contents beyond expiration date

Warnings, Precautions and Limitations

"Precaution" examples

- Safety precautions
  - Handle samples, material contacting samples, and kit controls as if capable of transmitting infection
- Handling precautions
  - Do not use any Test units if the foil pouch has been perforated

Warnings, Precautions and Limitations

"Limitations" examples

- "Reactive" results should be confirmed by additional testing
- A "Nonreactive" result does not preclude the possibility of exposure to HIV or infection with HIV

Customer Service Contact

In case of a performance problem with a product there should always be a toll-free telephone number(s) for customer service in the labeling to cover customer complaints

Added Value?

- For the end user could result in identification of a processing /training/storage issue
- For the company it could be an indication of a real product problem that needs to be addressed

Product Manufacturing Section - “Design Controls”

What are “Design Controls” ?

All manufacturers of in-vitro diagnostic products are required to follow “design controls” in the development and manufacturing of their products

These Controls Include:

- Establishing and maintaining plans that describe the design process and define
- Who in a Company is responsible for implementing those controls over both the design and manufacturing of a product intended for commercial distribution
- Include a “design and development plan”

Design and Development Plan

Did Company X provide an adequate Product Design and Development Plan in the Submission that included?

- Design Inputs e.g. “Intended use” of the kit, and intended performance characteristics
- Design Outputs e.g. How does the company evaluate that the product design is adequate?
- Design Review e.g. Company’s plans for formal design reviews during all product development stages

Design and Development Plan

- Design Verification - How did company evaluate that their Design Outputs = Design Inputs in final product?
- Design Transfer - Was a final review planned to confirm product was good enough to transfer to full scale manufacturing?
- Design Changes - Were procedures given and in place for controlling any future product design changes?
- Design History File - Were procedures in place for keeping DHF up to date?

Design and Development Plan

Should also have Included:

- A time chart of product development stages with start/completion dates
- What data and deliverables were needed to justify move to next stage
- Who made these decisions? (senior management)
- Were critical milestones and risk management activities listed?

What other Product Manufacturing Information Should have been Provided?

Quality System Procedures

- A copy of the company's basic quality system procedures including
  - Internal audit procedures
  - Management review procedures
  - Outline of structure of quality system documentation
  - A quality manual

What other Product Manufacturing Information Should have been Provided (cont.)?

Production Flow Diagram

- All production steps and important aspects of production should have been included

Purchasing Controls

- Contract design controls e.g. to ensure quality of outsourced kit components

Production and Process Controls

Documented Inspection, Measuring, Maintenance and Routine Calibration of

- All production and in-process testing equipment

What other Product Manufacturing Information Should have been Provided (cont.)?

Process Validation Procedures and Plans

- Are there examples of these documents?

Acceptance/Rejection Criteria for Incoming Components from Vendor

- Important to show that criteria are being controlled and followed by Company

Final Product Release Criteria

- Critical criteria ensuring a safe and effective product. Are they stringent enough?
- Can you “drive a truck through them”?

Consequences of Inadequate Product Manufacturing Information

What happens when the manufacturing section of a company's submission file is lacking all the appropriate information "*to determine whether the developer has the ability to design, manufacture or process the device consistently*"?

Consequences of Inadequate Product Manufacturing Information

- First - an interactive conversation is held with the Company on identified manufacturing deficiencies
- Then - if no resolution met, a deficiency letter is sent before the formal inspection of the manufacturing sites is scheduled and the deficiencies are communicated to the inspectors
- Note: Frequently a product's approval for commercial use is delayed due to unresolved manufacturing issues, even though the scientific and labeling product review is complete

In Summary ...

In this Presentation we Covered:

- The information that a diagnostic developer should include in the manufacturing and labeling sections of an HIV1/2 diagnostic product submission/file submitted to a Regulatory Authority
- What questions regulatory review staff ask as they review these sections to determine that the product's labeling and manufacture supports its approval and commercialization
- Next step, are its performance and operational characteristics adequate?

Thank You