Perspectives on In-Vitro Diagnostic Devices Regulated by the Office of Blood Research and Review

Lot Release Strategies

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Release of Lots – Regulatory Testing

- **21 CFR Part 610 Subpart A – General Biological Products Standards**

  No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies

- Upon completion of review of a lot release submission the manufacturer will receive an **Official Release Notification Letter** generated and signed by the delegated CBER authority [Director Division of Manufacturing and Product Quality, Associate Director or Sample Custodian] for the Center Director

- Blood Donor Screening Assays are MDUFA products (devices)

Overview

- The Lot Release Program is designed to provide ongoing monitoring of licensed biological products
- Prior to licensure – in-support testing samples or conformance lots are supplied to evaluate product quality and kit performance
- Post licensure – “Routine Lot Release” requires that sample (kits) and lot release protocols (LRPs) are submitted for evaluation to assure continuing product quality
- Protocols contain manufacturing information, specifications and QC testing data. The content of each LRP is established during the BLA review process
- Samples and LRPs are submitted to the Product Release Branch, Division of Manufacturing and Product Quality, OCBQ that manages the lot release program
  - Samples may be submitted prior to the LRP
  - CBER aims to complete testing and/or LRP review within 30 working days of LRP submission

Unique features of in vitro diagnostic kits that impact Lot Release

- Equipment
  - Equipment to perform tests is unique to each manufacturer
    - Manufacturer usually provides instrument to CBER (firm is responsible for qualification, training and maintenance)
  - Equipment to perform tests is often large
    - Floor space to house instruments is limited at CBER and therefore it may not always be possible to accommodate the equipment
    - Testing of blinded panels by the manufacturer has been developed as an alternative to conducting lot release tests at CBER
    - Blinded panels are provided to the firm; the results are submitted in the LRP
    - CBER compares results of blinded panel from firm with expected results to confirm acceptability of kit performance
- Software
  - During IND and early BLA, manufacturing may not be using final operating software; this can delay testing performed at CBER because final software will need to be in place for release of lots bar-coded for distribution
- Kit design
  - Kits usually consist of the primary reagent kit, accessory kits and confirmatory assay kits
  - Each primary kit lot is submitted together with accessory and confirmatory kits so that testing can be performed, however, only the primary kit lot is released by CBER.
  - The manufacturer is responsible for ensuring the quality of accessory kits and confirmatory assay kits.

Role of DBSQC and DMPQ in Lot release activities

- Role of DBSQC:
  - Test Methods and their validations/qualifications are reviewed
  - The Lot Release Protocol template submitted to the BLA is reviewed and finalized
  - Before BLA approval, equipment to perform lot release testing is identified and if needed, obtained from the manufacturer. Analysts are trained to perform assays.
  - Post licensure, LRPs are reviewed and confirmatory testing performed under ISO 17025 requirements. If blinded panels were used, the results reported in the LRP are compared with the expected results.
  - DBSQC results of LRP review and/or testing are documented in LIMS.

- Role of Product Release Branch, DMPQ:
  - Samples are appropriately stored, logged and tracked in the Lot Release System
  - Testing information is tracked in the quality system database
  - Once all testing and reviews are complete, an Official Release Notification Letter is signed and sent to the manufacturer

In Vitro Diagnostic (IVD) Product Evaluation

- Licensed test kits are evaluated by reviewing
  - Data provided in the LRP
  - Results of tests performed in the DBSQC laboratory or results of blinded panels tested by the manufacturer
- Panels of Reactive (R), Non-reactive (NR) or R/NR sera and RNA/DNA have been developed in DETTD, OBRR for testing HIV-1, HIV-2, HTLV-I/II, HBc, HBsAg, HCV, Chagas (*T. cruzi*), Babesia, WNV, or Zika kits
  - Confirm specificity of test
  - Confirm sensitivity of test
- New products may require development of different panels to test the efficacy of the kit

Lot Release Protocols

LRP format varies by product and manufacturer

Protocols must contain the following information:

- Names of Manufacturer, Product Name and Product Trade Name
- STN and Facility License Number
- Type of container e.g., Final Container [FC]
- Address
- Summary of all test results, e.g., Pass or Fail
- Reason for Submission, e.g., Lot Release
- Signature line for the Authorized Official or delegate, approving the submission
- Lot-specific Product information
    - Results of all release tests
    - If applicable, results of testing CBER panels

There is a process to develop, change or correct an LRP

- Manufacturer submits a LRP template for CBER's review during the original BLA submission
    - CBER will ask for changes if needed during the BLA review
- When manufacturer makes changes that impact information provided in the LRP, a revised LRP is submitted for review together with the supplement
- When LRP is submitted with incorrect information, the manufacturer submits a corrected LRP to the Product Release Branch
- When CBER reviewer(s) identify errors in the submitted LRP, PRB contacts the manufacturer and asks for an explanation or a corrected LRP.

Alternative to Lot Release

- Surveillance is an alternative to Lot Release
- Surveillance is granted to products with an acceptable lot release history and demonstrated control of the manufacturing process
- Manufacturers may submit data in a Prior Approval Supplement to support a request for the product to be placed on Surveillance
- If Surveillance is granted, the manufacturer distributes product lots without prior approval from CBER
- Under Surveillance status, the manufacturer is:
  - Required to continue in-house lot release testing
  - Required to provide information regarding all Lots produced (usually in each Annual Report, but may be requested to submit information more frequently)
  - Required to submit representative lots and/or LRPs at intervals determined by CBER. These lots are subject to CBER confirmatory testing and/or LRP review
- If product performance or manufacturing issues are observed, CBER may direct the return to routine lot release

Sequence

IND

Discuss how assay works
Identify equipment used

BLA

Develop and finalize Lot Release Protocol Template

Blood and Related Products (BRP) Team determines if major equipment can be installed at CBER
Arranges for IQ/OQ/PQ of equipment
Arranges for qualified trainer to provide instruction

After training

BRP Team performs “in support” testing to confirm kit performance and demonstrate QC testing capability
Performs testing and review LRP for any “launch” lots

Post-approval

Manufacturer submits samples of each lot for distribution with completed LRP to Product Release Branch
Manufacturer distributes lots after receipt of notification from CBER

In Summary

- Blood donor *in vitro* test kits are devices regulated through the BLA process
- IVDs are subject to Lot Release, requiring submission of a Lot Release Protocol with product (kit) samples for each lot intended for distribution
- Kits may not be distributed until receipt of an Official Release Notification Letter from CBER
- CBER performs testing of submitted kits and/or reviews results of blinded test panels submitted in the LRP
- All licensed products must demonstrate they are capable of producing accurate results (sensitivity and specificity)
- Changes to manufacturing, testing, facilities or the LRP should be submitted as a PAS, CBE or CBE-30
- Corrections to LRPs should be submitted to the Product Release Branch with the LRP marked as a Corrected Protocol
- Surveillance is an alternative to Lot Release that may be approved upon review of data demonstrating consistent manufacture of product that routinely meets specifications