

Licensed Immunohematology Products and Associated Instrumentation

Part 1

Kimberly Bigler MLS(ASCP)^{CM}SBB

Division of Blood Components and Devices

Office of Blood Research and Review

CBER

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Outline

- Licensed Immunohematology Reagents
- Bundling
- Submission Organization Best Practices
- Chemistry Manufacturing and Controls (CMC)
- Product Testing
- CBER Lot Release



Licensed Immunochemistry Reagents



Licensed Immunohematology Reagents



- Licensed immunohematology reagents:
 - Blood Grouping Reagents (BGR)
 - Reagent Red Blood Cells (RRBC)
 - Anti-Human Globulin (AHG)

- Current Test Methods:
 - Slide and Test Tube Method (Traditional Reagents)
 - Column agglutination (gel technology)
 - Microplate
 - Solid phase adherence

Bundling

Bundling

- *“Guidance for Industry and FDA Staff: Bundling Multiple Devices or Multiple Indications in a Single Submission”* dated June 22, 2007
- Bundling in Guidance refers to:
 - Inclusion of multiple devices or multiple indications for use for a device in a single premarket submission from the same manufacturer
- Bundling is appropriate for:
 - Multiple individual premarket device submissions that include same indications for use and clinical or analytical data
 - Devices that present similar scientific and regulatory issues that can be efficiently addressed during one review



Companion Submissions

- Submissions from different manufacturers on related products
- Each product is reviewed separately on its own timeline
- One submission can't be approved or cleared independently from the others
 - Example: Company A has a BLA for new Anti-D antigen typing test and Company B has a 510(k) for the instrument. The 510(k) review is completed in 90 days but placed on AI Hold until BLA review is completed



Bundling: Appropriately Bundled

- Examples of appropriately bundled submissions:
 - Reagents and instruments used together as a test system (same manufacturer)
 - New Anti-K antigen typing test added to a instrument
 - Reagent BLA bundled with instrument 510(k)
 - Blood grouping reagents (Anti-D, Anti-K, Anti-Jka, etc.)
 - Similar manufacturing and clinical data
 - De-linking one submission in bundle
 - A change that affects more than one previously cleared device (same manufacturer)
 - Adding a new antigen typing test to five different instruments

Bundling: Not Appropriately Bundled



- Not appropriate for bundled submissions:
 - For Further Manufacturing Use (FFMU) submissions (no user fee) with final product submission
 - Submissions are companion and are tracked and reviewed together
 - Company A (manufacturer of new reagent) 1 BLA and Company B with two 510(k)s (instrument manufacturer)
 - BLA and 510(k) submissions can not be bundled however, they are companion submissions
 - Company B may bundle two 510(k)s together
 - BGR, AHG, RRBCs submissions
 - Different manufacturing, specimen types, intended uses and clinical data



Bundling: General Information

- Each submission must be complete and be its own record
 - Perform all performance testing data for each reagent specificity in the bundle
- The submissions bundled should be specified in the cover letter and FDA forms should be included for each product in the application
 - Submit on same day
- The Guidance states total review time and user fee applied to the bundle is according to the submission type with the higher user fee and longer review time



Submission Organization Best Practices



Recommendations for Submission Organization



- Hyperlinked Table of Contents
- Searchable PDFs
- Large file separation into subfiles
 - Performance Testing should be separated into subsections
 - Each reagent in a bundled submissions should have its own batch record
- Submit draft labeling as word documents
- Cover Letter for companion submissions should cross reference each other



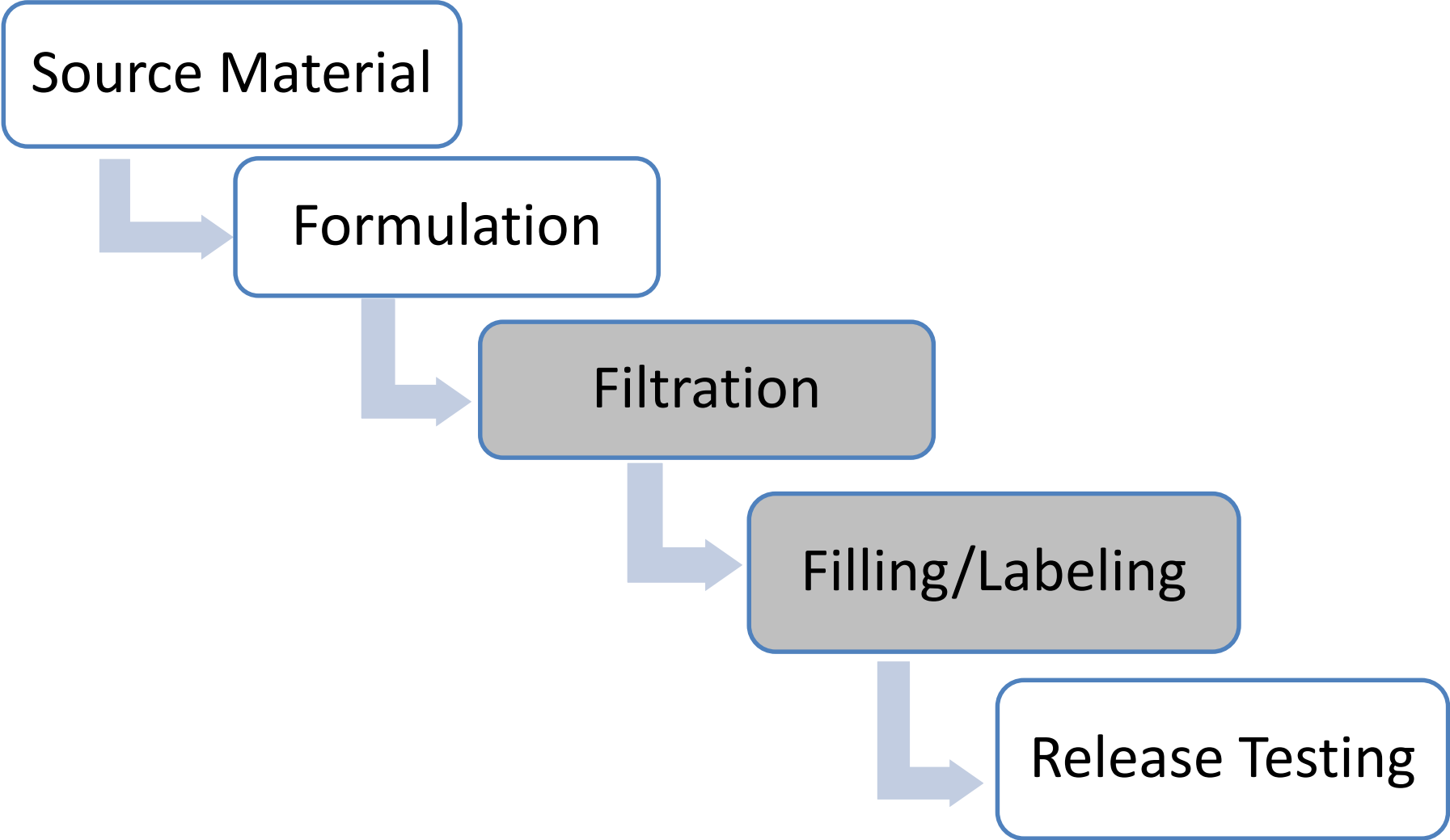
Cooperative Manufacturing Arrangements

- “*Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics*” dated November 2008
- 21 CFR 820.50 Purchase Controls
 - Final Product Manufacturer ultimately responsible for all aspects of product
- Supply and quality agreements should be formalized
 - Describe responsibilities of each manufacturer

Chemistry Manufacturing Controls (CMC)



Chemistry Manufacturing Controls





Source Material – General Considerations

- Active component of BGR/AHG
- Terminology:
 - 21 CFR 820.3(c) defines *component* as any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged and labeled device
 - In Vitro substance, For Further Manufacturing Use (FFMU), or antibody concentrate (supernatant)



Source Material: Monoclonal Antibody



- Master Cell Bank (MCB)
- Working Cell Bank (WCB)
- Inventory records
- Two different storage locations
- When WCBs are depleted, new ones may be created
- If the MCB needs to be re-established, a supplement to the BLA is submitted to CBER



Monoclonal Antibody: Test Methods

- Evaluate for potency and specificity
- Description of the test methods used for potency and specificity
- Red blood cell phenotypes used in potency and specificity testing supports intended use
- If applicable, Certificate of Analysis for cooperative manufacturing arrangements



Source Material: Polyclonal Antibody



- Prepared from human or animal plasma containing antibodies
 - Naturally occurring or produced following sensitization
- 21 CFR 606 (Current Good Manufacturing Practice for Blood and Blood Components)
- 21 CFR 610 (General Biological Product Standards)
- 21 CFR 640 (Additional Standards for Human Blood and Blood Products)
- List the name, address, and US license number for all blood establishments
- Non-US blood establishments provide the establishment's name and address



Polyclonal Antibody: Preparation

- Perform relevant Transfusion-Transmitted Infection (RTTI) testing using one or more licensed, approved or cleared screening tests
 - See 21 CFR 610.40(a) and 610.40(b)
- Data supporting the dating period (bleed date)
- Describe your validated purification method
 - For adsorption or adsorption-elution methods describe all testing parameters, red blood cells etc.
- Red blood cell phenotypes used in potency and specificity testing supports intended use



Source Material: Reagent Red Blood Cells



- Prepared from human blood meeting donor eligibility criteria
- 21 CFR 630.10 (General Donor Eligibility Requirements)
- 21 CFR 630.15 (Donor Eligibility Requirements specific to Whole Blood, Red Blood Cells and Plasma collected by apheresis)
- Perform RTTIs



Formulation

- Combining all required components
 - Include a narrative summary and a flow chart of the formulation process
- Mixing studies
 - Include data that supports your mixing parameters for the lot volumes you intend to manufacture
- Colorants (BGR/AHG):
 - Property of color should be determined (optimum wavelength)
 - Hue does not interfere with the interpretation of the test result
 - Follow 21 CFR 660.21(b) for BGR Anti-A and Anti-B
 - 21 CFR 660.51(a) AHG (Anti-IgG and Anti-IgG,-C3d polyspecific) may be colored green

In-Process Hold Times

- The maximum time in process and bulk can be held
- Provide the supporting data
- Example: Source material component manufacturer defined a hold time between harvest of monoclonal antibody and clarification
 - Defined maximum hold time as 28 days in submission
 - Provided potency testing during 28 days and stability study performed with maximum 28 day hold time



Date of Manufacture (DOM)

- DOM refers to a time point in the manufacturing process that is used to calculate the product's expiration date
- Clearly identify the DOM in your submission
- BGR DOM defined in 21 CFR 660.21(e) and AHG DOM defined in 21 CFR 660.51(c)
 - Initiate last group of potency tests
 - May choose another DOM
- RRBC DOM defined in 21 CFR 660.34(c)
 - Blood withdrawn from donor



Lot and Sublotting

- Lot defined as material fully processed and mixed in single vessel and filtered
- Alternatives should provide a rationale
- If applicable describe subplot process
 - Sublot numbering convention, test requirements, specification, and lot release testing to ensure that the sublots are identical



Conformance Lots

- Manufacturing process described in BLA should be identical to process used for conformance lots
 - Lock down the manufacturing process- no more changes
- We recommend three lots to validate your performance and manufacturing
 - Provide a summary of the three lots in your submission
- One lot should be manufactured from source material component nearing its expiration date



Conformance Lots 2

- Conformance lots are not required to be in-date at time of submission
- For limited source material one full scale and two pilot scale conformance lots
- In Monoclonal source material components (BGR/AHG) each conformance lot should be manufactured from a separate WCB aliquot (vial)

Product Testing



Product Testing

- Your submission should describe:
 - Test methods
 - Specifications for potency, specificity and other biochemical properties
 - Once approved any changes to specifications require supplement to BLA
 - Include each reagent for a bundled submission
- Summary of the test data for the conformance lots



BGR Product Testing

- BGR should include but are not limited to the following:
 - Potency testing (21 CFR 660.22 and 21 CFR 660.25)
 - Specificity testing (21 CFR 660.26)
 - Avidity testing for slide method (21 CFR 660.26)
 - Test for spontaneous agglutination

BGR Potency Testing

- The potency titer value is the reciprocal of the highest reagent dilution for which the reaction is graded 1+

Reagent	1:1	1:2	1:4	1:8	1:16
Anti-D (investigational reagent)	4+	3+	2+	1+	0
Anti-D (in-house standard or reference)	4+	2+	1+	0	0

BGR Potency Testing (Reference Reagent)

- 21 CFR 660.22
 - If reference reagent available potency titer value at least equal to reference reagent
- Polyclonal Reference Reagents available from FDA with established potency requirements
 - Anti-IgG, Anti-D, Anti-C3d, Anti-C, Anti-A, Anti-E, Anti-B, Anti-c, and Anti-e
 - For release testing only NOT stability studies



BGR Potency Testing (No Reference)

- 21 CFR 660.25
 - Qualified in-house standards are acceptable
- The recommended monoclonal BGR potency titer is at least 1:8
- Follow the test methods in the package insert
 - *Minimum* parameters in package insert
- Red blood cells tested should include cells with heterozygous or diminished expression of the corresponding antigen
 - Example: Fy(a+b+)



BGR Negative Specificity Testing

- Confirm the absence of contaminating antibodies
- Include a positive control
- Follow the methods in the package insert
 - *Maximum* parameters in package insert



BGR Negative Specificity Rule Outs

Rule outs for Monoclonal reagents	A, B, D, C, E, c, e, H, I, K, k, Kp ^b , Js ^b , Fy ^a , Fy ^b , Jk ^a , Jk ^b , Le ^a , Le ^b , P1, M, N, S, s, U, Lu ^b
Rule outs for Polyclonal reagents	A, B, D, C, E, c, e, C ^w , H, I, K, k, Kp ^a , Kp ^b , Js ^b , Fy ^a , Fy ^b , Jk ^a , Jk ^b , Le ^a , Le ^b , P1, M, N, S, s, U, Lu ^a , Lu ^b , Lan, Xg ^a , Do ^a , Do ^b , Yt ^a , Yt ^b , Co ^a , Co ^b , M ^g , Wr ^a , Sd ^a and Vw



BGR Positive Specificity (Reactivity) Testing

- Testing performed to confirm reactivity of each lot
 - Antigen positive cells
- Four different heterozygous red blood cells
 - Example: Four different donors whose phenotype is Fy(a+b+)
- For Anti-A, Anti-B, or Anti-A,B reagents test reactivity with A₁B, A₂B, and also A_x cells if available
- Include a negative control
- Follow the methods in the package insert
 - *Minimum* parameters in package insert

BGR Avidity Testing (for Slide Test Method)



- Confirmation of reactivity
- Red blood cells should be weak heterozygous cells
- Follow the package insert
- Recommend testing undiluted reagent along with 1:2 diluted reagent
- Observe and record the test results at two distinct intervals, halfway and at the end based on the observation time in package insert

Spontaneous Agglutination

- Red blood cells heavily coated with IgG molecules often agglutinate spontaneously with reagents that contain a potentiator
- BGR should be tested for spontaneous agglutination
- Control should be supplied or recommended

RRBC Product Testing

- For RRBC— See 21 CFR 660.33:
 - Phenotyping
 - Group O and each lot of product should be tested for at least the following common antigens: D, C, E, c, e, K, k, Fy^a, Fy^b, Jk^a, Jk^b, Le^a, Le^b, P₁, M, N, S, s
 - Confirm using two or more blood grouping reagents
 - Negative Direct Antiglobulin Test (DAT)
 - Negative antibody screen (including anti-A and Anti-B)
- Describe all other release testing and specifications

AHG Product Testing

- AHG includes but is not limited to the following:
 - Potency tests for determining anti-IgG and anti-complement activity (21 CFR 660.54)
 - Specificity tests (21 CFR Part 660.54)
 - No reactivity with normal red cells
 - No reactivity with enzyme treated cells



AHG Anti-IgG Potency

- To determine Anti-IgG activity
 - Use red blood cells coated with the following dilutions of Anti-D and Anti-Fy^a – 1:2, 1:4, 1:8 etc.
 - Perform serial dilution titrations of Anti-IgG and reference reagent or in-house standard with the coated red blood cells
 - Results Recommendations: Titer endpoint should be equal to reference or in house standard

AHG Anti-Complement Potency

- To determine Anti-Complement activity
 - Use red blood cells coated with complement
 - Prepare serial dilution titrations for the Anti-Complement and reference reagent or in-house standard
 - Result Recommendations:
 - Anti-C₃d should yield 2+ reactions and have a titer endpoint equal to reference or standard
 - Anti-C3b, Anti-C4b, Anti-C4d: the undiluted reagent should yield at least 2+ and the 1:4 should yield 1+

AHG Specificity

- Specificity tests are performed using various sensitized red blood cells
- Appropriate positive or negative reactions
- All controls should yield the appropriate reactions and no hemolysis should be observed
- AHG should not react with normal red blood cell samples
- AHG should not agglutinate enzyme treated red blood cells

Anti-Human Globulin	Sensitized Cells
Anti-IgG,-C3d; Polyspecific Anti-IgG Anti-Complement (e.g., Anti-C3, Anti-C3b, Anti-C3d, Anti-C4)	IgG, C3b, C3d, C4b, C4d
Anti-IgG (heavy chain specific)	IgG, IgA, IgM, C3b, C3d, C4b, C4d



CBER Lot Release



CBER Lot Release

- Submit CBER Lot Release Protocol templates for new products
 - Templates should include testing performed and final specifications
 - The testing on the CBER Lot Release Protocol should be the same as your final release testing
- CBER lot release is not applicable for RRBC final products due to short expiration date
- Surveillance
 - Supplement to BLA

Summary

- Use the Pre-sub program
 - Recommendations might not fit your product
- Quality of the submission lead to a more efficient FDA review
 - Easy to read submissions lead to less questions
- Clearly describe all steps in your manufacturing and testing processes
 - Keep terminology consistent throughout submission
- Follow the test methods listed in your package insert when performing product testing

References

- Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products, December 2017
- Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description for a Biological *In Vitro* Diagnostic Product, March 1999
- Guidance For Industry, Cooperative Manufacturing Arrangements for Licensed Biologics, November 2008
- eCopy Program for Medical Device Submissions- Guidance for Industry and Food and Drug Administration Staff, December 2015
- Code of Federal Regulations, Title 21, Parts 600 – 660, 809.10, 820, and 312



- Thank you for your attention!
- Kimberly Bigler (Kimberly.Bigler@fda.hhs.gov)

