SMG 9120

FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM DIRECTIVES

BUSINESS PRACTICES AND AGREEMENTS

INTERCENTER COORDINATION OF CROSS-LABELING ACTIVITIES FOR APPROVED DRUGS/BIOLOGICS AND IN VITRO DIAGNOSTICS

Effective Date: 04/19/2013

1. PURPOSE AND SCOPE

This staff manual guide (SMG) provides procedures for FDA staff when a Center is considering or carrying out changes to an already approved drug/biologic product labeling to include an in vitro diagnostic (IVD) test recommendation or requirement, or when an IVD is submitted for clearance or approval with an intended use that could affect an approved drug/biologic product's use in practice.

This SMG is applicable to IVD products and drugs or biological products. Under this SMG, labeling changes of relevance are those that have the potential to impact products reviewed in more than one Center within the Agency.

This SMG does not apply to pre-market review processes for drug/biologic products co-developed with a companion diagnostic.

2. BACKGROUND

IVD tests can provide useful information to guide the selection, dosing, therapeutic monitoring, and/or toxicity management of a drug/biologic. As new

biological, chemical or genetic markers of potential diagnostic value are identified, sponsors may approach the Agency with a request to market an IVD that may alter the clinical use (e.g., indications, dose selection, etc.) of one or more drugs/biologics. Alternatively, a drug/biologic product sponsor may make a request to reference the utility of an IVD (e.g., for a genetic biomarker) in the labeling of a drug/biologic, or the FDA may itself determine that such an IVD is important for the appropriate use of the drug/biologic, and will request/require that the drug/biologic product sponsor change their labeling to include a recommendation or requirement for an IVD test.

When a submission for a labeling update for a drug/biologic or IVD is received (or is internally generated to cross-reference an IVD and a drug/biologic product through labeling) it is important that all affected Centers participate in the review. Typically, this interaction will take the form of a consultation in which each Center evaluates the request in the context of the product component that they normally regulate (e.g., CDRH, or in some cases CBER, is typically responsible for the IVD component, while CDER or CBER is typically responsible for the drug or biologic).

This SMG was generated to help ensure that all Centers engage their counterparts in the review process for products cross-referenced through labeling using established intercenter consult and collaboration procedures rather than ad hoc processes that are unique to the individual Centers.

This process SMG also acknowledges that intercenter reviews for IVD or drug/biologic labeling updates may, on occasion, require a mechanism to address differences in scientific opinion or regulatory interpretation that involve staff from more than one Center. In these rare cases, informal (and formal if needed) dispute resolution should proceed in accordance with SMG 9010.2 Cross-Center Dispute Resolution at the FDA. Differences of scientific opinion are expected to be resolved in a manner that limits delays in regulatory action.

3. GENERAL OVERVIEW

When a labeling change that may impact the use/claims of a product (e.g., drug, biologic, or IVD) regulated by another Center is contemplated or submitted for review, the Center in receipt of the submission will notify the other affected Center(s) as soon as the link is identified. For the purposes of this SMG, the default intercenter review model will be the consultative review (see Definitions). If both Centers determine that the IVD is **required** for patient selection or dosing decisions (i.e., the IVD constitutes a companion diagnostic), collaborative reviews are expected (see Definitions).

Centers will establish a plan for ongoing communication, with milestones and statutory timelines for the respective submissions clearly identified. A point of

contact for each Center's review team will be identified and the subsequent reviews will be conducted in a coordinated fashion.

4. DEFINITIONS

Consultative Review

Review activity in which reviewer(s) in one Center requests advice from reviewer(s) in another Center on a specific question or issue raised in the review of a submission. The consultative review will be used to assist the requesting Center in making appropriate regulatory/scientific decisions. This is the default review type for the purposes of this SMG.

Collaborative Review

Review activity in which reviewers in two or more Centers each have primary review responsibility and decision-making authority, generally for a defined portion of a submission or in the case of two applications (e.g., labeling supplement and related IVD application), for a specified component. Regulatory and scientific decisions will be made by the management of each Center for that portion of the review assigned to it. Collaborative reviews are performed when the IVD constitutes a companion diagnostic.

Companion diagnostic

An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents of the therapeutic product.

Product (21 CFR Part 3, Subpart A, Section 3.2 (l))

A drug (as defined in section 201(g)(1) of the Federal Food, Drug and Cosmetic Act), device (as defined in section 201(h) of the FD & C Act), biological product (as defined in section 351(i) of the Public Health Service Act), or combination product (as defined in 21 CFR Part 3, Subpart A, Section 3.2(e)).

Request Originator

The individual originating the request for the consultative or collaborative review. This person will generally be the regulatory project manager (e.g., in CDER or CBER) or the lead reviewer (e.g., in CDRH's Office of In Vitro

Diagnostics), but may be any individual who conducts or is otherwise responsible for the review of the submission, e.g., branch/lab chief, division director, etc.

5. POLICY

Agency personnel will generally initiate intercenter reviews as defined in this SMG in a manner consistent with that described in SMG 4101 *Intercenter Consultative/Collaborative Review Process*.

6. RESPONSIBILITIES

Both Center review teams will work together to determine if anything other than consultative review is required at the outset of the review process. If the IVD is deemed a companion diagnostic, a collaborative review will be performed (see Appendix 1 for Process Diagram).

Consultative Review:

A. Diagnostic device Center responsibilities

1. *As the originating Center for consults regarding new IVD test claims*. When an IVD submission or request is received that may impact the use/claims of an approved drug or biological product, the diagnostic review Center (CDRH or CBER) will:

    a. Notify the drug or biological product review Center (CDER or CBER), as soon as the therapeutic/IVD link is identified (see Appendix 2 for example) as reasonably expected to affect labeling.

    b. Seek appropriate and timely consults from CDER/CBER review divisions regarding use of IVD with respect to the drug/biologic.

    c. Assure that IVD claims are consistent with current drug/biologic labeling, and with CDER/CBER advice on appropriate intended uses.

2. *As the consulted Center when there is a proposal to update the labeling for an approved drug or biologic to include IVD information*. When there is a proposal to update the labeling of an approved drug or biological product to include diagnostic information, the consulted diagnostics device Center will:

    a. Identify a point of contact for their Center, and form a review team if needed.

b. Provide timely consultative reviews concerning availability and intended use for IVD(s) identified in drug/biologic labeling.

c. Evaluate whether existing FDA-cleared or approved tests for the biomarker of relevance could be appropriate to support the updated drug/biologic product label.

d. Determine appropriate intended uses, performance parameters, and other IVD labeling necessary to support use of an IVD included in drug/biologic product labeling.

e. Determine classification of devices with intended uses specifying use with appropriately labeled drugs/biologics.

f. Review analytical information for IVDs with intended uses specifying use with appropriately labeled drugs/biologics.

g. Provide comments for consideration on drug/biologic safety communications and other public materials about test limitations, use, and any other critical issues that may affect decisions when CDER or CBER determine that an IVD has adequate clinical validity characteristics to support a drug/biologic labeling update.

B. Therapeutic product Center responsibilities

1. *As the originating Center for consults regarding labeling updates for approved drugs/biologics to include diagnostics information*. When a drug or biologic submission is received from a sponsor or labeling changes are initiated internally that may impact the use/claims of a diagnostic, CDER or CBER, as applicable, will:

a. Notify the diagnostic review Center (CDRH or CBER) as soon as the therapeutic/IVD link is identified as reasonably expected to affect labeling.

b. Determine whether the risk/benefit of a particular approved drug/biologic might be improved by including IVD test information in the professional labeling. Products which may require updated labels generally are identified as a result of review of 1) data sources in the public domain (e.g., published literature), 2) regulatory submissions from the manufacturer of the therapeutic product, 3) requests from the public, and/or 4) requests from the manufacturer of an IVD.

c. Communicate to the device Center that inclusion of information about an IVD in a drug/biologic labeling update is being considered

and seek consultation in a timely manner.

d. Evaluate whether inclusion of information about the IVD in the drug/biologic labeling helps prescribers use the product in a safer and/or more effective manner. These determinations are multifactorial, therapeutic-area specific, and are based on the totality of evidence (experimental, mechanistic, observational, etc).

e. Make final assessment of the utility of providing the information to prescribers through labeling revision.

f. Determine the appropriate language to be used in the drug/biologic labeling and other communications to the public (e.g., early communications, healthcare professional sheets).

2. *As the consulted Center for IVD labels that reference approved drugs/biologics*. When a diagnostic's intended use could impact the use of an approved drug/biologic, the consulted drug/biologic review Center will:

a. Identify a point of contact for their Center, and form a review team if needed.

b. Provide thorough, timely consults to the diagnostic device review Center.

c. Determine whether the IVD intended use claim presents the potential for promoting a use not included in the professional labeling for the drug/biologic.

Collaborative Review:

A. Diagnostic device review Center will be responsible for evaluating:

1. Analytical validity of the IVD

2. Risk assessment for the IVD

3. IVD intended use and labeling

B. Therapeutic product Center will be responsible for evaluating:

1. Clinical utility of the IVD (includes clinical validity)

2. Safety and efficacy of the drug/biologic when used in association with the IVD

3. Proposed drug/biologic labeling

7. DISPUTE RESOLUTION

In the event that reviewers or teams from two or more Centers cannot reach agreement through an informal process at the review team level on an issue related to the regulation of an IVD and an associated drug or biologic, the parties in disagreement will contact their respective Office Directors for assistance in determining the most appropriate path for resolution. If formal dispute resolution is required to address the issue, the affected Office Directors should contact their respective Ombudsmen for assistance. In the rare event that review jurisdiction is in dispute, the dispute is expected to be resolved by the jurisdiction officers from the respective Centers, with assistance from the Office of Combination Products as needed.

8. PROCEDURES

See Appendix 1 for a schematic of the review process under this SMG.

A. The Center that originates the request for consultative or collaborative review, shall:

1. Identify, via e-mail or telephone, the appropriate review or project management personnel to whom the consult/collaboration review request should be directed.

2. Assign a point of contact for all communications regarding the coordinated review.

3. Send consult/collaborative review requests and goal timelines for the coordinated review to appropriate personnel in consulted Center.

4. Work with the other affected Centers to determine whether anything other than consultative review is warranted (see Definitions).

5. Provide the necessary information to review, or if the necessary information is outside the direct control of the requesting Center, ensure it is readily identifiable and/or available.

6. Establish a plan for ongoing communication between the Centers, including appropriate review timelines, milestones, and deadlines. If no firm deadline is required (e.g., no regulatory submission under active review), set a realistic review deadline that gives the consulting Center as much time as reasonable and possible.

7. Notify the consulted Center personnel of key internal and sponsor meeting (if applicable) dates for which the consult/collaborative Center's presence is required. For collaborative reviews, the consulted Center is expected to be a required participant. For consultative reviews, the consulted Center may be required or optional in terms of attendance. Provide a meeting agenda with topics for discussion clearly identified.

8. Coordinate the intercenter exchange of reviews and any other pertinent regulatory information and decisional documents.

9. Notify consulted Center of the final recommendations/comments to be conveyed to the sponsor (if applicable, e.g., for IVDs or labeling supplements).

10. Document reviews and relevant materials in the Center's document archiving system.

B. The Center receiving the collaboration/consult request shall:

1. Contact the request originator by telephone or e-mail immediately if a collaboration/consult request or any aspect of the request (e.g., due date) is believed to be incomplete, inappropriate, or in error.

2. Assign a point of contact for all communications regarding the coordinated review.

3. Work with the requesting Center to determine whether anything other than consultative review is warranted (see Definitions).

4. Notify the request originator promptly if the review will be delayed, and either negotiate a new due date through the supervisory chains of both Centers, or reassign the request so that the previously established due date can be met.

5. Perform a complete review of those areas specified by the request originator in a timely manner. If the division to which the consult/collaboration request is directed does not have the expertise to address all of the identified issues, make arrangements for the review to be completed by someone with the expertise.

6. Attend and participate in key internal and sponsor meetings (if applicable) as requested by the originating Center.

7. Assure that all consultative and collaborative reviews are in electronic format and include a brief summary of the portion of the submission

which was reviewed, recommendations for action (as necessary) and letter-ready comments and/or any requests for information to be conveyed to the firm.

8. Obtain the appropriate clearances/sign-off per Center/submission requirements and forward the consultative/collaborative review (email is acceptable with a notation indicating that the consulted reviewer's supervisor concurs with the review recommendations) along with the completed consult/collaboration review form and the reviewed submission documentation to the request originator.

9. Document reviews and relevant materials in the Center's document archiving system.

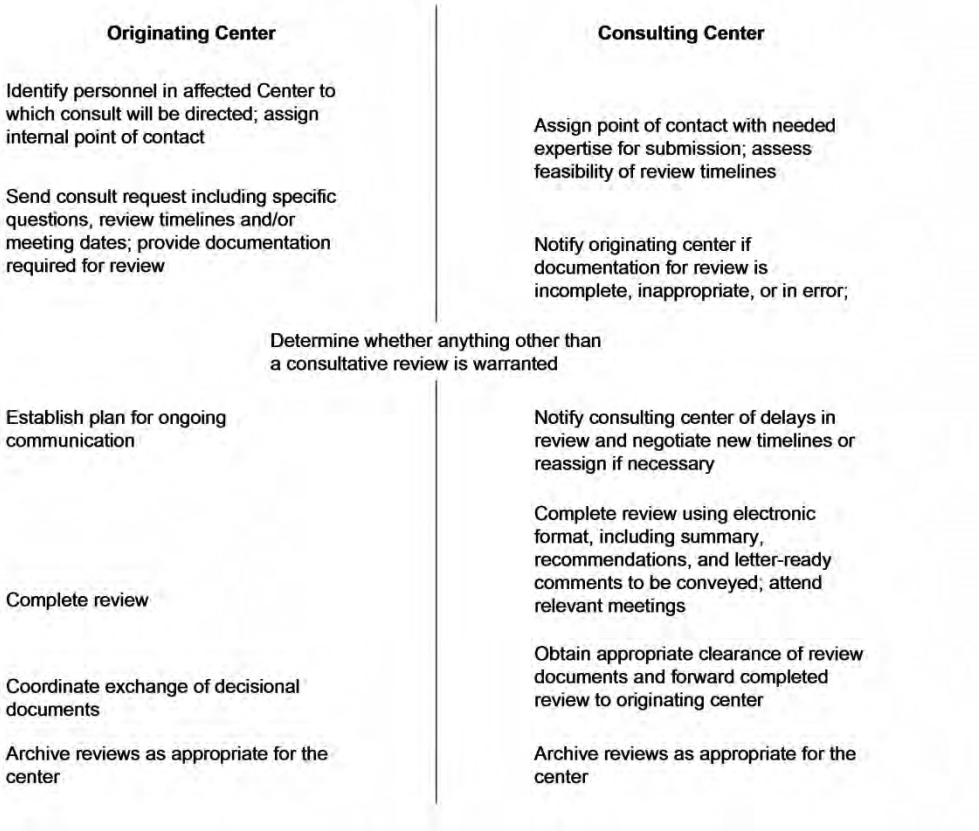
9. EFFECTIVE DATE

The effective date of this guide is April 19, 2013.

10. Document History -- SMG 9120, Intercenter Coordination of Cross-Labeling Activities for Approved Drugs/Biologics and In Vitro Diagnostics

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	04/19/2013	N/a	CDER/OTS/OCP	Janet Woodcock, Director, CDER

Appendix 1: Process Diagram*



*The scope of the review activity under this process SMG is limited to the update of already approved drug/biologic labeling to include new IVD test information or the review of IVD applications whose approval/clearance may affect the use of an approved drug/biologic.

Appendix 2: Examples

Example 1: CDRH receives a 510(k) submission for an N-terminal pro B-type natriuretic peptide (NT-proBNP) seeking a new claim to monitor the effectiveness of an antihypertensive drug. The proposed IVD labeling claims that drug dose adjustments should be made based on NT-proBNP test results. This dosing and effectiveness information is not currently referenced in the drug label. The CDRH review team discusses the submission with their manager and CDRH determines that a consult to the Cardio-Renal review division in CDER should be requested. CDER reviews the clinical data to determine whether the intended use is supported and whether the antihypertensive drug labeling may also need updating. CDER and CDRH work together and resolve any issues quickly and efficiently.

Example 2: CDER hears of new information suggesting that a new kidney injury marker, Kim1, should be used to select the analgesic that is best used for a particular patient. CDER reviewers have obtained clinical trial data supporting this potential new claim. CDER requests a consult from CDRH for the Kim1 test and includes the CDRH consulting reviewer(s) on the drug review team (e.g., on the distribution lists, access to DARTS, etc.). CDRH reviews the information in the clinical trial data on the test, including how the test used during the clinical trial was performed and analytically validated. CDRH also assesses the IVD to determine what risk classification the IVD falls under based on its intended use. CDER reviews the clinical data to determine whether the labeling change is warranted. CDER and CDRH work together and resolve any issues quickly and efficiently.