

**Corporate Regulatory and Quality Science**

April Veoukas
Corporate Regulatory Affairs
D-3QC, AP6C-1
Telephone: (847) 937-8197

100 Abbott Park Road
Abbott Park, Illinois 60064-6091
Facsimile: (847) 938-3106
E-mail: april.veoukas@abbott.com

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Dockets Management Branch (HFA -305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20852

VIA FACSIMILE 301-827-6870

RE: Definition of Primary Mode of Action of a Combination Product
[Docket 2004N-0194]

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA's proposed rule "Definition of Primary Mode of Action of a Combination Product," published in the Federal Register on May 7, 2004 at 69 FR 25527 with an extension of the comment period published at 69 FR 35277 on June 24, 2004. Abbott Laboratories agrees with and supports the comments submitted by the Advanced Medical Technology Association (AdvaMed). Our comments focus on the role of precedent, second-tier assessment, and Intercenter Agreements.

Role of Precedent

We are concerned that the proposed rule creates uncertainty regarding the role of precedent in combination product center assignments and recommend a more definitive statement regarding the role of precedent. The following example illustrates uncertainty created by the proposed rule.

Recent discussions have indicated, that in the pharmacogenomics field, drug and diagnostic products used in conjunction with one another may, under certain circumstances, be considered combination products¹. Presumably an assessment of primary mode of action would be made on a case-by-case basis for each drug and diagnostic pairing.

Applying the proposed primary mode of action rule to a new pharmacogenomic drug and diagnostic pairing, initially one would consider the primary mode of action – that is, the mode of action, which represents "the most important therapeutic action of the

¹ Presentation by Patricia Y. Love, M.D., M.B.A., Associate Director, Office of Combination Products, FDA to Drug Information Association (DIA)/FDA Workshop at page 20 (July 29, 2004)

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combination product."² Here, the modes of action are independent and neither appears subordinate to the other. Thus, the primary mode of action cannot be determined with "reasonable certainty," requiring consideration of the next-tier assessment, assignment to the "agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole."³ As this is a new pharmacogenomic drug and diagnostic pairing, although CDER and CDRH regulate products that raise similar safety and effectiveness with regard to the constituent parts of the product, neither agency component regulates combination products that present similar safety and effectiveness questions with regard to the product as a whole.

Under the second-tier assessment, the Agency proposes to assign the combination product to the "agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product."⁴ Based on the third example of primary mode analysis in the preamble to the proposed rule, it appears one would conclude the most significant safety and effectiveness questions are related to the characterization, manufacturing, and clinical performance of the drug component.⁵ Thus, the paired product would be assigned to CDER because CDER has the most expertise related to these issues.

Here, however, the role of precedent is key. Historically, a therapeutic drug and diagnostic device used in conjunction with one another have been regulated under two separate applications with the diagnostic submission reviewed by CDRH and the *in vivo* therapeutic application reviewed by CDER or CBER. Examples of such pairings include: (1) DakoCytomation EGFR pharmDx™/Cetuximab⁶, (2) DAKO Herceptest/Trastuzumab,⁷ (3) antimicrobial susceptibility test disc/antibiotic, (4) transplant marker/monitoring diagnostic, and (5) anti-rejection drug/monitoring diagnostic. Thus, it appears that these historical jurisdictional decisions would not be considered under the proposed rule. Further, since historically these pairings have not been formally designated as combination products, it appears they would not be considered as precedent under proposed 21 CFR § 3.4(b), as this section contemplates

² 69 FR 25532.

³ *Id.*

⁴ *Id.*

⁵ 69 FR 25530

⁶ See Letter by Steven I. Gutman, M.D., M.B.A., Director, Office In Vitro Diagnostic Device Evaluation and Safety, Center for Devices and Radiological Health to Mr. Ronald F. Lagerquist, DakoCytomation California, Inc. (Feb. 12, 2004), which states, "[t]he Center for Devices and Radiological Health of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the DakoCytomation EGFR pharmDX™...indicated as an aid in identifying colorectal cancer patients eligible for treatment with ERBITUX™ (cetuzimab)." Letter by Karen D. Weiss, M.D., Director, Office of Drug Evaluation VI, Office of New Drugs, Center for Drug Evaluation and Research to ImClone Systems, Incorporated Licensing Cetuximab (Feb. 12, 2004).

⁷ See Letter by Susan Alpert, Ph.D., M.D., Director, Office of Device Evaluation, Center for Devices and Radiological Health to Gretchen M. Murray, Ph.D., RAC, DAKO Corporation (Sept. 25, 1998), which states, "[t]he Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the DAKO Herceptest...indicated as an aid in the assessment of patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered." See Letter by Jay P. Siegel, M.D., FACP, Director, Office Therapeutics Research and Review, Center for Biologics Evaluation and Research to Robert L. Gamick, Ph.D., Genentech, Inc. licensing Trastuzumab (Sept. 25, 1998)



precedent only in terms of "the agency component that regulates other *combination products* that present similar questions of safety and effectiveness" (emphasis added).⁸

Without additional clarification on the role of precedent, we are concerned that each pharmacogenomic diagnostic and therapeutic pairing will be assessed as either two applications both reviewed by either CDER or CBER with CDRH only serving in a consulting role or one application reviewed by one lead center (CDER or CBER).⁹ Given the diagnostic expertise of CDRH, such an approach may unnecessarily complicate the review and approval of pharmacogenomic drug and diagnostic pairings. Thus, we support greater consideration of jurisdictional precedents in informing and guiding decisions of center assignments.

Second-tier Assessment

When one cannot determine with reasonable certainty the primary mode of action and no other combination products present similar questions of safety or effectiveness, FDA, under the second-tier assessment, will assign the combination product to the "agency component with the most expertise to evaluate the *most significant safety and effectiveness questions* presented by the combination product" (emphasis added).¹⁰ Many variables may contribute to a determination of "the most significant safety and effectiveness questions," such as novel technology, drug quantity and route of administration, and U.S. regulatory approval of constituent components. Guidance developed through formal Good Guidance Practices, which addresses factors to be taken into consideration with determining "the most significant safety and effectiveness questions," is recommended.

Intercenter Agreements

The current Intercenter Agreements provide: (1) significant guidance in determining center assignments and (2) a historical basis for jurisdictional assignments. Although Section 204 of the Medical Device User Fee and Modernization Act (MDUFMA) calls upon the Agency to "consult with stakeholders" on the issue of whether "to continue in effect, modify, revise, or eliminate agreement[s]" specific to the assignment of combination products," we note this has not occurred.¹¹ Given the value of the Intercenter Agreements, we recommend FDA confirm in the preamble to the final rule that these documents will remain in effect.

⁸ 69 FR 25532.

⁹ The agency where appropriate may require the approval of a second application, "ordinarily by the lead center." Further, FDA recognizes [in regards to combination products] that requiring the approval of a second agency component would represent the exception rather than the rule 58 FR 53755 (Nov. 21, 1991).

¹⁰ 69 FR 25532.

¹¹ Section 204 of the Medical Device User Fee and Modernization Act, codified at Section 503(g)(4)(F) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 503(g)(4)(F).



Thank you for the opportunity to provide these comments. Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 938-3106.

Sincerely,

A handwritten signature in cursive script that reads 'April Veoukas'.

April Veoukas, J.D.
Associate Director, Regulatory Affairs
Corporate Regulatory and Quality Science
Abbott Laboratories