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May 16, 2007

John K. Jenkins, M.D., F.C.C.P.
Director, Office of New Drugs (HFD-20)
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Bldg. 22, Room 6304
10901 New Hampshire Avenue
Silver Spring, MD 20993

Re: Complaint and Request for Correction Pursuant to Federal Data Quality Act
NDA 21-649
Genasense (oblimersen) for advanced melanoma

Dear Dr. Jenkins:

On behalf of our client, Genta Incorporated ("Genta"), Buc & Beardsley[1] submits this complaint and request for correction under the Federal Data Quality Act ("FDQA").[2] Genta is the sponsor of the above-referenced NDA.

This complaint concerns the presentations and statements made by members of the Office of Oncology Drug Products (the "Office") and the Division of Drug Oncology Products (the "Division") at the Oncologic Drug Advisory Committee ("ODAC") on May 3, 2004. As explained in more detail below, the Office and Division applied a flawed statistical model to Genta's data and based on that model, stated the erroneous conclusion that Genta's data did not demonstrate that Genasense significantly improved progression-free survival ("PFS"). Heavily influenced by FDA's position on the issue, the Oncologic Drugs Advisory Committee voted 13 to 3 against approval on the basis of FDA's erroneous statements about Genta's data. Genta thereafter withdrew the application.

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1. Our address and phone number are shown above. Our e-mail addresses are nlb@bucbeardsley.com (Nancy L. Buc) and dlivornese@bucbeardsley.com (Deborah Livornese).

2. Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, Pub. L. No. 106-554 (Appendix C), 114 Stat. 2763A-153 (2000).

The harm done to Genta at ODAC by FDA's use of a flawed statistical model and its insistence that the model rendered invalid the data Genta presented on PFS was seriously damaging. Worse, FDA has continued to perpetuate on its website numerous materials that contain the flawed statistical model, the application of that model to Genta's data on PFS, and the erroneous conclusion that Genasense does not improve PFS compared to the control arm in the clinical trial in question. Recently, as Genta was pursuing its Marketing Authorization Application for Genasense for melanoma at the European Medicines Agency ("EMEA"), it was confronted once again by the thesis that FDA's statistical model invalidated Genta's PFS data. Specifically, the EMEA's 180-day assessment report relied heavily on FDA's analysis.[3] It is because it is so clear that this flawed statistical model, the statement of FDA's conclusions based on it, and FDA's assertion that the model invalidated Genasense's PFS data have already harmed Genasense twice and present a continuing risk so long as they remain on FDA's website without correction, that Genta is filing this complaint and request for correction under the FDQA.

The documents and other communications at issue (collectively, the "Disseminated Information") are:

(1) Division of Oncology Drug Products Briefing Material NDA 21-649 Genasense (oblimersen sodium) for metastatic melanoma ODAC May 3, 2004[4] (pages 21-46 and 51-56), attached hereto as Exhibit B;

(2) Questions to the Committee NDA 21-649 Genasense (oblimersen sodium), prepared for ODAC Meeting May 3, 2004,[5] attached hereto as Exhibit C;

(3) Certain sections of the transcript of ODAC meeting of May 3, 2004 (Dr. Pazdur's Opening Remarks at pages 20-26, FDA's Presentation at pages 69-92, Questions from the Committee at pages 93-125, and the Committee Discussion at pages 152-202),[6] attached hereto as Exhibit D;

(4) Slide Presentation by Division of Oncology Drug Products for Genasense ODAC May 3, 2004[7] (slides 19-42), attached hereto as Exhibit E;

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3. Letter dated March 12, 2007, from Loretta M. Itri, M.D., to EMEA, attached hereto as Exhibit A.

4. Located at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037B1_02_FDA-Genasense.pdf.

5. Located at http://www.fda.gov/ohrms/dockets/ac/04/questions/4037Q1_01_Genasense.doc.

6. Located at http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4037T1.htm.

7. Located at http://www.fda.gov/ohrms/dockets/ac/04/slides/4037S1_02_FDA-Kane-Yang%20_files/frame.htm#slide0105.htm.

(5) Memo from FDA dated April 26, 2004 correcting errata in the FDA Genasense Briefing Document,[8] attached hereto as Exhibit F; and,

(6) Possibly, certain other documents and written communications disseminated by FDA outside the agency, such as to foreign regulatory authorities.[9]

In addition to appearing in the documents listed above, the same information may have been communicated orally by members of the Office and Division to, among others, members of the EMEA and the (Australian) TGA. To the extent the same information is disseminated orally, it is no different from the more enduring forms and is subject to the same standards. If it is not held to the same high standards, then the kind of flawed and inaccurate information the FDQA is meant to subject to scrutiny may be perpetuated free from such scrutiny. In the guidelines adopted by FDA to implement the FDQA, FDA notes that oral presentations in public forums are an example of the variety of media used to disseminate information.[10]

To bring an end to FDA's continuing dissemination of this inaccurate statistical model, its application to Genta's data, and the erroneous conclusion that Genasense did not demonstrate an increase in PFS, Genta requests that FDA take the following corrective actions:

(1) Stop disseminating the materials, including removing them from FDA's website;

(2) Post on FDA's website a notice stating that the previous statistical analysis as reported in the Disseminated Information is flawed and inaccurate, should not have been applied to Genta's data, and reached the erroneous conclusion that Genta's data do not demonstrate PFS; and,

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8. Located at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037B1_02_FDA-Genasense-Errata.pdf.

9. We submitted a request for such documents to FDA pursuant to the Freedom of Information Act, 5 U.S.C. §552, on May 15, 2007. A copy is attached hereto as Exhibit G.

10. FDA guidelines at § IV. U.S. Department of Health and Human Services Guidelines for Ensuring the Quality of Information Disseminated to the Public ("HHS guidelines"), Part I.D.4.b. (Sept. 30, 2002). FDA's guidelines are located in Part II.F. of the HHS guidelines. FDA's guidelines also establish methods for making complaints and requests for correction, and describe several offices to which complaints may be directed, including to the agency official who is the supervisor of the employee who made the decision or to the FDA ombudsman. FDA has committed to respond within 60 days. Id. at § VI.B.-C. Because the documents at issue were prepared by the Office of Oncology Drug Products, Genta believes that you are the relevant supervisor.

(3) Issue corrective communications of any other information disseminated by FDA outside of the agency, including to EMEA, TGA, and other foreign regulatory bodies.

The Legal Standard and Its Applicability

The purposes of the FDQA include ensuring the quality of information that federal agencies disseminate and establishing mechanisms to correct information that does not meet these quality standards. FDQA §§ 515(a) and (b)(2). The FDQA directed the Office of Management and Budget ("OMB") to issue guidelines, which each agency must use to prepare its own guidelines addressing methods to accomplish these information quality objectives. OMB's guidelines require that each agency adopt a standard of quality and incorporate information quality criteria, including quality review before information is disseminated, into agency dissemination practices. OMB defines quality to include utility, objectivity, and integrity.[11]

The concept of objectivity, which is most relevant here, is divided into presentation and substance:

- Presentation is explained as "[w]hether information is being presented in an accurate, clear, complete and unbiased manner."[12]

- Substance is defined to mean "a focus on ensuring accurate, reliable, and unbiased information."[13]

The OMB Guidelines and the guidelines adopted by Health and Human Services ("HHS") go on to state that "[O]riginal and supporting data must be subject to commonly accepted scientific. . .and statistical standards."[14] Whether statements are "objective," i.e., accurate, reliable, and unbiased, turns in situations like this on whether they pass muster under "commonly accepted scientific . . . and statistical standards," and whether they are based on "sound analytical techniques."[15] As demonstrated below, FDA's statistical model, its application to Genta's data, and the conclusion that Genta has not demonstrated PFS, all as set forth in the Disseminated Information do not meet those criteria – they are not accurate, reliable, or

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11. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Other Agencies ("OMB guidelines"), 67 Fed Reg. 8452, 8459 (Feb. 22, 2002).

12. Id.

13. Id.

14. Id; and HHS guidelines § D.1.c.2

15. HHS guidelines § D.4.d.

unbiased, do not meet commonly accepted scientific and statistical standards, and did not apply sound analytical techniques.[16] Accordingly, both it and the statements based on it regarding Genta's data lack the objectivity, accuracy, reliability, and lack of bias that the Federal Data Quality Act requires.

The Disseminated Information Is Not Objective

In NDA 21-649 for Genasense for advanced melanoma, Genta presented data from GM301, a controlled trial in which dacarbazine (DTIC) with Genasense was compared to DTIC alone. The primary endpoint in the trial was overall survival, which was not met. Genta's analysis demonstrated that the secondary endpoint of progression free survival was met, however. In the Genasense with DTIC arm, Median PFS was 74 days, in the DTIC arm, Median PFS was 49 days. The p value was 0.0003.

In its presentation, FDA asserted that the difference between the two regimens might have been accounted for by ascertainment bias. While Genta agrees that it is appropriate to investigate whether assessment bias existed in the determination of PFS in clinical trials, it objects strenuously to the lack of objectivity, accuracy, and reliability inherent in the statistical model FDA used to argue that ascertainment bias rather than actual differences in the rates of progression were responsible for Genta's results.

As discussed in the attached document presented to the EMEA,[17] and incorporated herein by reference, FDA's model was deeply flawed in several respects. First, it assumed that all assessments in one group occurred on a given day in the treatment arm and all assessments in the control arm took place 2 days later than that. This assumption simply does not reflect what actually happened in the study, or would be likely to happen in real life. It is no answer to say that it was "just" a model. If a model is based on incorrect assumptions, it models inaccuracy, not accuracy.

Second, FDA's model behaves bizarrely in the sense that the theoretical bias increases as the difference between the two arms in timing of assessment decreases. In other words, the model predicts more ascertainment bias when the difference between the two arms for day of assessment is 2 days than when the difference is 4 days. Even greater bias is "shown" by FDA's model as the difference in assessment times approaches zero. That cannot be correct, and a model that predicts such results cannot be correct, either.

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16. Id.

17. Exhibit A.

Conclusion

The statistical model, its application to the Genta data, and the conclusion that the data do not demonstrate an increase in PFS as set forth in the Disseminated Information are not objective. They are inaccurate, unreliable, scientifically and statistically unsound, biased, and contrary to the requirements of the FDQA. The importance of statistical models and sound conclusions drawn therefrom cannot be overstated, and the effect of FDA's flawed model continues because FDA continues to perpetuate the Disseminated Information. FDA's perpetuating the Disseminated Information is also arbitrary, capricious, and an abuse of discretion in violation of the Administrative Procedure Act. In the interests of sound science and fundamental fairness, the Disseminated Information should be corrected as requested in this complaint. Genta asks that FDA do so, and that it process this request on an expedited basis in order to limit the damage that is being done.

Sincerely,

Nancy L. Buc
Deborah Livornese

cc: Ms. Laurie Lenkel
Office of the Ombudsman (HF-7)

Sheldon Bradshaw, Esq.
Chief Counsel (GCF-1)