Public Version

IN THE ARBITRATION UNDER CHAPTER ELEVEN OF THE NAFTA
AND THE ICSID ARBITRATION (ADDITIONAL FACILITY) RULES

APOTEX HOLDINGS INC. AND APOTEX INC.,

Claimants,

– and –

THE GOVERNMENT OF THE UNITED STATES OF AMERICA,

Respondent.

ICSID CASE NO. ARB(AF)/12/1

SUPPLEMENT TO REPLY OF CLAIMANTS APOTEX HOLDINGS INC. AND APOTEX INC.

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In accordance with paragraph 13(h) of the Procedural Order of May 14, 2013,[1] claimants Apotex Holdings Inc. ("Apotex Holdings") and Apotex Inc. ("Apotex-Canada") (collectively, "Apotex") respectfully submit this Supplement to their Reply on the merits and counter-memorial on jurisdiction in support of their claims against respondent United States of America.

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[1] Procedural Order on the Schedule Regarding the Parties' Respective Privilege Logs, Further Submissions and Certifications, para. 13(h) (May 14, 2013) ("Tribunal's decision + 17 calendar days – The Claimants will have the opportunity, if they wish, to supplement their 24 May Reply in order to comment on any documents produced by the United States after April 19, 2013[.]"). The US transmitted after April 19, 2013 a little less than 80% of the total number of pages in its document production.

1. The documents produced by the US after April 19, 2013 further support Apotex's case. Nothing in these documents shows that Apotex's products were unsafe or ineffective. Instead, the contemporaneous record shows that FDA's main concerns as to the company's cGMP compliance were based on a series of misunderstandings not discussed with Apotex. The documents are consistent with a rush to judgment on FDA's part – one that provided Apotex no opportunity to set the record straight before adoption of the Import Alert.

2. In addition, the documents confirm that FDA repeatedly cited Apotex as an example of a tough new enforcement approach announced weeks before the Import Alert was adopted. As it noted at the time, FDA placed Apotex on Import Alert only two weeks after the Signet Inspection, without issuing a warning letter concerning this facility, without notice, without providing Apotex an opportunity to correct the cGMP issues raised by FDA and without taking into consideration the firm's response either to the Etobicoke Warning Letter or the Signet Form 483 before the measure was adopted. Unfortunately, as demonstrated in the Memorial and in the Reply, FDA applied that approach to Apotex but not to its comparators with like – or more serious – cGMP violations. FDA took no enforcement action comparable to the Import Alert against those companies.

3. As observed in the Reply, the present case does not center on whether FDA was correct or incorrect in its findings of cGMP violations.[2] It is not disputed that, as concerns the cGMP findings, Apotex and its comparators are in like circumstances.[3] Nor is the correctness or incorrectness of FDA's findings placed into issue by Apotex's Article 1105 claim, which addresses the process (or absence thereof) by which FDA reached its findings, not their substance. The documents addressed in this Supplement are in many respects peripheral to the legal issues presented by the claims under Articles 1102, 1103 and 1105 of the NAFTA. Nonetheless, the documents do shed some light on the context in which the Import Alert was adopted and for this reason merit some discussion.

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2 *See, e.g.,* Reply, paras. 5-6.

3 *Id.*, paras. 6, 263-64. *See also* US Counter-Memorial paras. 330-31, 334.

I. THE DOCUMENTS IDENTIFY NO RISK TO CONSUMERS POSED BY APOTEX PRODUCTS

4. Apotex's Memorial and Reply observed that the record contained no evidence that Apotex drugs on the US market in fact were unsafe or ineffective.[4]

5. A review of the full set of final FDA determinations produced by the US in disclosure[5] confirms this point: FDA adopted the Import Alert in the absence of evidence of any concrete risk posed by Apotex products to US consumers.

6. Thus, in commenting on an advisory on Apotex for the information of the Secretary of Health and Human Services, senior officials of CDER's Division of Manufacturing and Product Quality (DMPQ), suggested adding the following language:

> At present, the FDA has no evidence that … products currently on the U.S. market are not safe and effective. If the FDA identifies … drugs on the market that pose risks to patient safety, the agency will take appropriate additional regulatory action and immediately notify the public.[6]

7. Similarly, FDA periodically generated a report on the status of pending cases known as the "Sharfstein Report." The report included a field where "Known/suspected injuries" were to be set out for each case. As noted in the Reply, the August 18, 2009 Sharfstein Report stating that CDER intended to recommend adoption of the Import Alert set out absolutely nothing under the heading "Known/suspected injuries."[7]

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4 *See, e.g.,* Memorial, paras. 201-02; Reply, paras. 43-47.

5 *See* Procedural Order on the Parties' Respective Requests for Document Production, paras. 30, 33, 34, 36 (March 29, 2013) (summarizing the US's position that it would only produce final agency documents in the context of specific requests). *See, e.g.,* Respondent's Responses and Objections to Claimants' Requests for Production of Documents, Responses / Objections to Document Request No. 2(n) at 10 (March 1, 2013) ("To the extent that Apotex is requesting any drafts or pre-decisional documents that may or may not exist, the United States objects to the request on the basis of legal impediment or privilege.").

6 **Exhibit C-503**, FDA Internal Email Chain, dated June 22, 2009 at US12397 (proposing that language taken from a document concerning Caraco be used for Apotex). In order to assist the Tribunal in identifying the various actors in documents produced by the US, Apotex submits an organization chart of CDER's DMPQ current as of April 3, 2009. **Exhibit C-489**, Excerpt from FDA PowerPoint Presentation, *Overview of the Division of Manufacturing and Product Quality (DMPQ) – Case Management and Guidance Branch* (April 20-24, 2009), *available at* http://www.fda.gov/Downloads/Drugs/NewsEvents/UCM182558.pdf (last visited on July 18, 2009).

7 Reply, para. 79 & n.109 (citing **Exhibit C-373**, FDA Internal Email Chain, dated August 18, 2009).

8. The US document production included a number of other Sharfstein Reports from the summer and fall of 2009. Tellingly – with one exception – the field "Known/suspected injuries" was always blank for Apotex, while that same field in some reports on other companies set out specific information.[8] The exception was the July 8, 2009 Sharfstein Report, which stated that, as concerns "Known/suspected injuries" for Apotex, there was "[n]one known."[9]

9. Newly disclosed documents confirm that, after the Etobicoke Inspection, CDER requested sampling of Apotex products in March 2009.[10] Samples were taken and products tested but FDA never communicated any negative result to Apotex – presumably because there was none.[11]

10. In the Reply, Apotex set out eight facts demonstrating that FDA's contemporaneous acts conveyed no serious concern over the safety of Apotex's products. These facts ranged from FDA's failure to request Apotex to recall any product on the US market, to FDA's classification of Apotex's limited September 2009 recall as one reflecting only a remote possibility of serious adverse health consequences, to FDA's failure to seize any Apotex products on the US market, among others.[12] The documents produced by the US after April 19, 2013 only confirm the showing in the Reply. The record, in short, does not accord with the US's suggestion that Apotex products posed a threat to US consumers.

II. THE DOCUMENTS SHOW AN FDA RUSH TO JUDGMENT

11. As explained in the Reply, in April and May 2009 (continuing into June), FDA was already contemplating an import alert against Apotex based on a series of mistaken and

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8 *See, e.g.,* **Exhibit C-501**, FDA, Combined Sharfstein Reports, dated June 18, 2009 to October 5, 2009 at US11874 (showing that the field "Known/suspected injuries" was filled for firms other than Apotex).

9 *Id.*, at US12692.

10 **Exhibit C-488**, FDA Internal Email, dated March 31, 2009 (Email from Sally Eberhard to Hidee Molina) ("I will request sampling … and have them analyzed for strength, dissolution and content uniformity based on your findings [for the draft Etobicoke Warning Letter].").

11 *See* Reply, para. 46(f). *See also* Second Expert Report of Sheldon T. Bradshaw and Ron M. Johnson, para. 22(c).

12 Reply, paras. 46-47.

unverified assumptions.[13] Additional documents disclosed by the US confirm that showing and demonstrate that FDA's rush to take action against Apotex resulted in a poorly prepared inspection of Signet, tensions between FDA inspectors and the adoption of the Import Alert without providing Apotex any opportunity to address FDA's stated reasons for taking that measure.

12. As noted in the Reply, on June 8, 2009, Ms. Woodcock, CDER's director, stated the following conclusion to her senior staff:

> Obviously this firm [Apotex] should not be shipping drug [sic] to the US! What are we going to do about it besides WL [warning letter]?[14]

13. Ms. Woodcock's conclusion was based on a set of documents transmitted to her the preceding day by Ms. Deborah Autor, director of CDER's Office of Compliance. That set included a document that Ms. Autor referred to as the "key issues" document.[15] This document, put together in less than 24 hours, was a response to a series of questions concerning Apotex posed by Ms. Autor.[16]

14. The "key issues" document prominently addressed suspicions concerning new drug applications supposedly "withdrawn" by Apotex, incorrect conclusions drawn from a list of rejected batches that Apotex had supplied Etobicoke inspectors and data on adverse drug events.[17] FDA had raised none of these issues with Apotex. The "key issues" document did not reflect any input from Apotex.

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[13] Reply, paras. 58-63. *See also* **Exhibit C-491**, FDA Internal Email Chain, dated June 1, 2009 (Email from Carmelo Rosa to Helen Saccone) ("Yes an Import Alert is being worked out as we speak[.]").

[14] Reply, para. 60 (quoting **Exhibit C-359**, FDA Internal Email Chain, dated June 8, 2009 at US7270 (Email from Janet Woodcock to Deborah Autor, dated June 8, 2009)).

[15] **Exhibit C-359**, FDA Internal Email Chain, dated June 8, 2009 at US7270-71 (Email from Deborah Autor to Janet Woodcock, dated June 7, 2009 without attachments).

[16] **Exhibit C-492**, FDA Internal Email Chain, dated June 4, 2009 at US12491 (Email from Joseph Famulare to Edwin Rivera Martinez, dated June 3, 2009) (listing five specific questions to be answered "by tomorrow"); **Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009 (the "key issues" document). In a June 6, 2013 email between arbitration counsel, the US clarified that the "key issues" document referred to in Ms. Autor's June 7, 2009 email was produced at US012479-12482. This document is the same as that produced at US003014-3017 and which was introduced into the record as **Exhibit C-358**.

[17] **Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009 (the "key issues" document) at US3014-16 (conclusions based on rejected batches list), US3016 (adverse events) & US3017 (withdrawal of applications).

15. Unfortunately, the "key issues" document on which Ms. Woodcock's conclusion was based reflected a number of erroneous assumptions.

A. FDA's Suspicions about "Withdrawn" New Drug Applications Were Wrong

16. As shown in the Reply, FDA suspected that Apotex was withdrawing ANDA applications in order to conceal issues with the integrity of application data. However, FDA's concern was based on a misunderstanding. Apotex never withdrew any application; it simply withdrew alternative sites initially listed in some applications in order to expedite the inspection and approval of the same.[18]

17. FDA did not communicate this concern to Apotex, although it colored FDA's view that Apotex's case was a "significant" one meriting enforcement action.[19] Apotex had no opportunity to address FDA's unfounded concern about allegedly withdrawn ANDA applications.

B. FDA Misunderstood Apotex's Batch Rejection System

18. As explained before, at the end of the Etobicoke Inspection, FDA inspectors requested, but did not review, a list of rejected batches.[20] No observation concerning the number of rejected batches was recorded on the Form 483.[21] Apotex accordingly had no opportunity to address this issue in its response to the Etobicoke Form 483.[22] CDER later reviewed the list without the benefit of any explanation by Apotex. It internally concluded that the rejection rate was too high and that this was a significant issue.

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[18] Reply, para. 56.

[19] **Exhibit C-486**, FDA Internal Email Chain, dated March 20, 2009 (Carmelo Rosa noting that "Edwin [Rivera Martinez] was in my office and believes this is a significant case."); *id.* (Email from Hidee Molina to Sally Eberhard) ("[T]he firm states that they are withdrawing 15 ANDAs for not being ready for inspection."). *See also* **Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009 (the "key issues" document) at US3017 ("[T]here has been a pattern of ORA's DFI attempting to schedule inspections for pending applications at certain sites and the company requesting additional time while simultaneously withdrawing numerous applications. DFI reports that of 97 pending generic applications, the firm claimed to be ready to be inspected for around 53 while the remaining 44 will be withdrawn.").

[20] *See* Witness Statement of Edmund Carey, para. 31 ("At the end of the inspection in December 2008, Apotex had provided a list of rejected drug products and in-process materials [from December 2006 to December 2008]."); **Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009 (the "key issues" document) at US3016 ("The investigator did not investigate this further and simply attached the list as Exhibit 7 of the EIR.").

[21] *See* **Exhibit C-34**, Etobicoke Form 483, dated December 19, 2008 (no reference to batch rejection rate or failure to investigate batch failures).

[22] *See* **Exhibit C-37**, Apotex's Response to Etobicoke Form 483, dated January 30, 2009.

19. Joseph Famulare, deputy director of CDER's Office of Compliance, noted the questionable nature of this conclusion in June 2009:

> Part of the complication here is we have uncovered many of the issues here as a result of delving into records here beyond what was uncovered during the inspection.[23]

20. The Etobicoke Warning Letter nonetheless cited a violation based on FDA's reading of the list of rejected batches.[24] In its response to the Warning Letter, Apotex explained that FDA's concern was in significant part based on a misunderstanding of Apotex's batch numbering system.[25] However, CDER did not take the firm's explanations into consideration when it recommended the Import Alert – because at the time it adopted the Import Alert, FDA had not completed its review of Apotex's response to the Etobicoke Warning Letter.[26] When FDA completed that review, it found that Apotex's response adequately addressed its concerns.[27]

C. FDA Did Not Analyze or Verify Its Data on Adverse Event Reports

21. The "key issues" document observed that consumer complaints and adverse event reports "were not covered during the December 2008 inspection."[28] It nonetheless stated specific numbers for alleged complaints and adverse events allegedly reported against Apotex.[29]

22. When transmitting the "key issues" document and the draft Etobicoke warning letter to Ms. Woodcock on June 7, 2009, Ms. Autor noted that "there's a paragraph on adverse

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23 **Exhibit C-493**, FDA Internal Email Chain, dated June 6, 2009 at US12528 (Email from Joseph Famulare to Kristi Hampton-Thurston, Gerald Dal Pan and Rick Friedman).

24 **Exhibit C-41**, Etobicoke Warning Letter, dated June 25, 2009 at 2 (Item I.A).

25 *See* Memorial, para. 157 (citing **Exhibit C-44**, Apotex's Response to Etobicoke Warning Letter, dated July 17, 2009; Witness Statement of Jeremy Desai, para. 39); Reply, para. 57.

26 *See* Reply, paras. 57, 79 (citing **Exhibit C-373**, FDA Internal Email Chain, dated August 18, 2009 ("Response to WL received 8/4; currently under review.")).

27 *See infra* para. 52.

28 **Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009 (the "key issues" document) at US3016.

29 *Id.* (noting there were "approximately [redacted] consumer complaints and [redacted] total Adverse Event Reports" over a three-year period). These numbers were not high "given that Apotex manufactures [redacted] to [redacted] billion dosages annually, and that customer complaints do not necessarily relate to the quality of [Apotex] products." Second Witness Statement of Jeremy Desai, para. 13. *See also* Second Witness Statement of Edmund Carey, paras. 13-14 (noting that FDA found "no issues" with the customer complaints for Carbidopa-Levodopa); *id*., para. 26 (noting that consumer complaints regarding [redacted] and [redacted] were properly investigated by the firm).

event reports. I'm trying to find out where those counts came from."[30]

23. Gerald Dal Pan, who was then Director of CDER's Office of Drug Safety and a recipient of Ms. Autor's June 7, 2009 email and attachments, followed up on the source of the adverse event data:

> Deb – It would be great if your staff could let me know where the AE [Adverse Event] report data come from.[31]

24. Ms. Autor forwarded the question to her CDER colleague, Giuseppe Randazzo, who was puzzled since the draft Etobicoke warning letter did not mention adverse events:

> I know it is late and I need to go to sleep but I read the draft WL and did not see anything related to adverse event reports??[32]

25. Carmelo Rosa confirmed that the draft Etobicoke warning letter did not address adverse events and that this information came from a question raised by Joseph Famulare, deputy director of CDER's Office of Compliance:

> I also reviewed the WL … and couldn't find "AE" mentioned in the WL. The discussion of the Adverse Events comes from a set question raised by J. Famulare, which we answered through an explanatory memo attached to this email.[33]

26. Mr. Randazzo thus informed Deborah Autor that the discussion on adverse events came

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[30] **Exhibit C-495**, FDA Internal Email Chain, dated June 9, 2009 at US9077 (Email from Deborah Autor to Janet Woodcock and others, dated June 7, 2009). CDER had "complaints without underlyng [sic] information." *See* **Exhibit C-493**, FDA Internal Email Chain, dated June 6, 2009 at US12528 (Email from Joseph Famulare to Kristi Hampton-Thurston, Gerald Dal Pan and Rick Friedman).

[31] **Exhibit C-495**, FDA Internal Email Chain, dated June 9, 2009 at US9076 (Email from Gerald Dal Pan to Deborah Autor, dated June 8, 2009).

[32] **Exhibit C-494**, FDA Internal Email Chain, dated June 9, 2009 at US10522 (Email from Giuseppe Randazzo to Rick Friedman, Carmelo Rosa and Edwin Rivera Martinez, dated June 8, 2009). *See also id.*, at US10521 (Email from Giuseppe Randazzo to Carmelo Rosa, dated June 9, 2009 at 8:53 AM) ("We may need to bring this to Deb's attention letting her know we had conversation with Joe to discuss the situation but ADE language did not go into the WL."); *id.*, at US10520 (Email from Giuseppe Randazzo to Carmelo Rosa, dated June 9, 2009 at 8:58 AM) ("We may need to delicately ask Deb what she was referring to [with respect to Adverse Events]?").

[33] *Id.*, at US10521 (Email from Carmelo Rosa to Giuseppe Randazzo, dated June 9, 2009 at 7:25 AM). The "explanatory memo" referred to by Dr. Rosa in this email is the June 4, 2009 "key issues" document discussed above (**Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009).

from "a set question raised by J. Famulare."[34] He added that he and his CDER colleagues "believe[d] this ADE data was in an exhibit gathered and submitted by the inspector."[35]

27. However, Ms. Autor's recollection was different:

> The ADE data first showed up (to me) in the NTK report – before the memo."[36]

28. In the meantime, Dr. Rosa inquired as to the source of the information included in the "key issues" memorandum – which had been issued under his name:

> They [management] need to know where the numbers of AEs included under question 5 came from. Are you saying Hidee [Molina] provided these numbers to you [Edwin Rivera Martinez]?[37]

29. Mr. Rivera Martinez answered that Ms. Molina, CDER's case officer in charge of Apotex, "mentioned" adverse events "in an email … when she first started reviewing the case."[38]

30. It was later confirmed that Ms. Molina had "requested DCRMS [Division of Compliance Risk Management and Surveillance] to look up data" on Apotex adverse events.[39] As such, contrary to what had been previously announced, the data on adverse events did not appear in an "exhibit gathered and submitted by the inspector."[40] Quite the opposite, Ms. Autor stressed that "these numbers only appear on some [FDA]

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34 **Exhibit C-496**, FDA Internal Email Chain, dated June 9, 2009 at US9083 (Email from Giuseppe Randazzo to Deborah Author, dated June 9, 2009 at 10:00 AM).

35 *Id*., at US9084 (Email from Giuseppe Randazzo to Deborah Autor, dated June 9, 2009 at 10:00 AM).

36 *Id*., at US9083 (Email from Deborah Autor to Giuseppe Randazzo, dated June 9, 2009 at 12:16 PM).

37 **Exhibit C-497**, FDA Internal Email Chain, dated June 9, 2009 at US10516 (Email from Carmelo Rosa to Edwin Rivera Martinez, dated June 9, 2009 at 10:45 AM).

38 *Id.* (Email from Edwin Rivera Martinez to Carmelo Rosa, dated June 9, 2009 at 4:24 PM).

39 **Exhibit C-500**, FDA Internal Email Chain, dated June 15, 2009 at US13081 (Email from Giuseppe Randazzo to Deborah Autor). *See also* **Exhibit C-498**, FDA Internal Email Chain, dated June 9, 2009 at US6185 (Email from Hidee Molina to Carmelo Rosa).

40 **Exhibit C-496**, FDA Internal Email Chain, dated June 9, 2009 at US9084 (Email from Giuseppe Randazzo to Deborah Autor, dated June 9, 2009 at 10:00 AM).

internal documents."[41]

31. There is no indication in the contemporaneous documents disclosed by the US that anyone at FDA analyzed or checked the accuracy of the adverse events data.[42]

32. This issue of adverse event reports was never communicated to, let alone discussed with, Apotex although it was addressed in the "key issues" memorandum that Ms. Woodcock received on June 7, 2009.

33. In other words, Ms. Woodcock's June 8, 2009 conclusion that Apotex should not be "shipping drug[s] to the US[]"[43] was based on a "key issues" document containing mistaken and unverified assumptions based on Apotex's allegedly withdrawn ANDA applications, rejected batches and adverse event reports, among others.

D. The Signet Inspection Was Hastily Prepared

34. Upon receipt of Ms. Woodcock's conclusion that Apotex "should not be shipping drug[s] to the US[,]"[44] Ms. Autor immediately asked her team if they could "do an import alert sooner than later[.]"[45] On the following day, Ms. Autor informed Ms. Woodcock that FDA was, among other things, "gearing up to do a fuller inspection" of Apotex.[46]

35. On July 10, 2009 FDA notified Apotex that the inspection would begin just two weeks

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41 **Exhibit C-500**, FDA Internal Email Chain, dated June 15, 2009 at US13081 (Email from Deborah Autor to Gerald Dal Pan).

42 *See* **Exhibit C-504**, FDA Internal Email, dated June 22, 2009 (Dr. Rosa noted that CDER's Office of Compliance had "over 1000 pages of AES" – not that anyone at FDA was analyzing the accuracy of such data.); **Exhibit C-511**, FDA Internal Email, dated August 2, 2009 (Elizabeth Johnson transmitted adverse event data to the inspection team in the middle of the Signet Inspection, "hop[ing] it's better late than never."); **Exhibit R-42**, 2009 Signet EIR (no investigation of adverse event reports).

43 **Exhibit C-359**, FDA Internal Email Chain, dated June 8, 2009 at US7270 (Email from Janet Woodcock to Deborah Autor, dated June 8, 2009 at 5:08 PM).

44 *Id.*

45 *Id.* (Email from Deborah Autor to Joseph Famulare, Rick Friedman, Edwin Rivera Martinez and Hidee Molina, dated June 8, 2009 at 5:16 PM).

46 **Exhibit C-499**, FDA Internal Email Chain, dated June 15, 2009 at US7163 (Email from Deborah Autor to Janet Woodcock, dated June 8, 2009). *See id.* (Email from Deborah Autor to Rick Friedman, Edwin Rivera Martinez, Hidee Molina, Giuseppe Randazzo and Carmelo Rosa, dated June 15, 2009) (in mid-June, Ms. Autor followed up with her team about "the status of any import alert, the reg meeting plan, and the full inspection plan[.]").

later – from July 27 to August 14, 2009.[47] The team was to be led by investigator Lloyd Payne, from FDA's Office of Regulatory Affairs (ORA), who was to be accompanied by two safety compliance officers from CDER, Ms. Kristy Zielny and Mr. Brian Belz, as well as a chemist, Mr. Walden Lee (also from ORA).[48]

36. As the inspectors were preparing for the inspection, on July 22, 2009, Mr. Payne asked Ms. Zielny the following question:

> Have you ever been involved in a foreign inspection trip where nobody seemed to know what to do like this one?[49]

37. Ms. Zielny replied:

> Not quite this bad. We'll figure it out.[50]

38. Other CDER officers also complained of missteps and miscommunication in the preparation of the inspection:

> I think I officially give up caring about this stupid inspection.[51]
>
> …
>
> I almost feel bad for the firm because we're so scrambled and unorganized.[52]

39. The miscommunication and lack of coordination within FDA continued during and after the inspection as well, notably as between CDER and ORA, which was in charge of coordinating the Signet Inspection.[53]

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47 **Exhibit C-368**, Letter from FDA to Apotex, dated June 10, 2009.

48 Witness Statement of Lloyd Payne, para. 8. *See also* **Exhibit C-510**, FDA Internal Email Chain, dated July 24, 2009 (Email from Susan Laska to Heriberto Negron-Rivera) ("As we have discussed ORA has to be the lead. I corrected the one FACTs assignment that had CDER Zelny [sic] as the lead.").

49 **Exhibit C-508**, FDA Internal Email Chain, dated July 22, 2009.

50 *Id.*

51 **Exhibit C-509**, FDA Internal Email Chain, dated July 23, 2009 (Email from Elizabeth Johnson to Marisa Stock).

52 *Id.* (Email from Marisa Stock to Elizabeth Johnson).

53 *See* US Counter-Memorial, para. 39 ("Inspection staffing is coordinated by FDA's Office of Regulatory Affairs (ORA), and may include personnel from district offices, the Division of Foreign Field Investigations, and the Center for Drug Evaluation and Research, or CDER.").

40. On August 21, 2009, the lead inspector, Mr. Lloyd Payne, wrote the following to Ms. Laska, Deputy Director of ORA's DFI (Division of Field Investigations):

> If there are any more telecons with CDER I will insist in ORA being involved. There were just too many going on during the inspection, that apparently ORA wasn't privy too [sic]. There is more to that story but, I'll need more time to overcome the sizzle that remains in me since the inspection.[54]

41. Mr. Payne also explained that his role in the adoption of the Import Alert was minor.[55]

42. CDER, on the other hand, criticized "the poor work done by the ORA representatives identifying violations (or lack thereof)[]" during the Signet Inspection.[56]

E. FDA Adopted the Import Alert Without Evidence of Risk to Public Health and Ignoring Information Addressing Its Concerns

43. On August 13, 2009 – before the close out meeting between the inspectors and the firm held on the following day – CDER began to update a draft of the Import Alert recommendation.[57] Dr. Rosa stated that FDA was "against the clock" in this respect.[58]

44. FDA's rush to judgment was such that it adopted the Import Alert without completing its review of Apotex's response to the Etobicoke Warning Letter or waiting for the firm's response to the Signet Form 483.[59] Instead, FDA adopted the Import Alert "just 10 business days after the close-out of the [Signet] inspection … ."[60]

45. Furthermore, FDA did not take into account the explanations provided by Apotex in telephone conferences with CDER on July 9 and August 17, 2009. As shown in FDA's

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54 **Exhibit C-516**, FDA Internal Email Chain, dated August 21, 2009 at US4077 (Email from Lloyd Payne to Susan Laska).

55 **Exhibit C-515**, FDA Internal Email, dated August 19, 2009 (Mr. Payne noted that he did not "deserve much of the credit in this happening [impending Import Alert and recall].").

56 **Exhibit C-524**, FDA Internal Email Chain, dated September 17, 2009 (Email from Carmelo Rosa to Kristy Zielny, dated September 16, 2009).

57 **Exhibit C-512**, FDA Internal Email Chain, dated August 17, 2009 at US8182 (Email from Carmelo Rosa to Hidee Molina, dated August 13, 2009, instructing her to "start updating the Import Alert Recommendation.").

58 *Id.*

59 *See* Reply, para. 79; Memorial, paras. 195-96.

60 **Exhibit C-384**, FDA Internal Email Chain, dated August 28, 2009 at US7254 (Email from Edwin Rivera Martinez to Rick Friedman, Joseph Famulare and Deborah Autor).

June 4, 2009 "key issues" document, CDER was concerned – based on its unadvised review of records as opposed to on-site observations – that two rejected batches of [redacted] might have been shipped to the United States.[61] On July 9, 2009, Apotex assured CDER that these specific batches were not shipped to the United States and committed to provide evidence on this issue with its response to the Etobicoke Warning Letter.[62] Apotex did so.[63] However, CDER proceeded with the Import Alert before completing its review of the firm's response.[64] Similarly, CDER began drafting the Import Alert recommendation even before the call with Apotex on August 17, 2009 when the firm proposed to voluntarily recall over 600 batches of products.[65]

46. And it was only after the Import Alert was adopted that FDA performed a comprehensive drug shortage analysis covering products manufactured at Etobicoke.[66] FDA's practice, by contrast, was to perform a shortage analysis before consideration of a ban such as an import alert.[67]

47. The documents, in short, show that FDA prepared the Signet Inspection in haste and rushed to place both Etobicoke and Signet on Import Alert.

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61 **Exhibit C-358**, FDA Internal Memorandum, dated June 4, 2009 (the "key issues" document) at US3016.

62 *See, e.g*., **Exhibit C-373**, FDA Internal Email, dated August 18, 2009 ("Firm assured CDER Compliance in 7/9 telecon that they did not ship product which failed release specifications to U.S. Firm agreed to supply supporting documentation as part of their response to the WL.").

63 **Exhibit C-44**, Apotex's Response to Etobicoke Warning Letter, dated July 17, 2009 at 1-3.

64 **Exhibit C-373**, FDA Internal Email, dated August 18, 2009 ("Response to WL received 8/4; currently under review."); *id.* ("CDER Compliance is proceeding with an Import Alert covering all products from these two sites.").

65 *See* Reply, paras. 76-77 (quoting **Exhibit C-371**, FDA Internal Email Chain, dated August, 17, 2009 at 11:31 AM (Inspector Zielny transmitted the Signet Form 483 and requested CDER to "disseminate to whoever will be writing recommendations regarding the Import Alert[.]"); citing **Exhibit R-43**, FDA, Minutes of Teleconference with Apotex on August 17, 2009 at 2:00 PM)). *See also* **Exhibit C-512**, FDA Internal Email Chain, dated August 17, 2009 at US8182 (Email from Hidee Molina to Carmelo Rosa, dated August 13, 2009, attaching "updated draft of the Import Alert as requested.").

66 **Exhibit C-520**, FDA Internal Email Chain, dated September 8, 2009 at US10561 (Email from Karen Hirshfield to Edwin Rivera Martinez) ("I went back to the excel spreadsheets provided to us in June, and could not find anything for the Etobicoke site. We really do need the lists of drug products that are subject to import alert as soon as possible to avert spot shortages."); **Exhibit C-521**, FDA Internal Email, dated September 8, 2009 ("[P]lease let drug shortage know that there is a current import alert at two Apotex sites and that we are working on getting the specific list of products effected [sic].").

67 *See, e.g.,* **Exhibit C-359**, FDA Internal Email Chain, dated June 8, 2009 (Email from Joseph Famulare to Deborah Autor and others) (noting that a drug shortage determination had to be completed before adopting an import alert); **Exhibit C-499**, FDA Internal Email Chain, dated June 15, 2009 at US7163 (Email from Deborah Autor to Janet Woodcock, dated June 8, 2009) ("Once we have a full evaluation of the shortage issues, we will know whether we can impose an import alert/the scope of one.").

F. FDA Confused Teva and Apotex

48. Lastly, FDA, at least early in evaluating Apotex, misunderstood what Apotex was. This mistake arose when ORA DFI International Operations Branch associate director Mr. Heriberto Negron-Rivera informed CDER that Apotex was part of the Teva group:

> Apotex, Novopharm, Ivax, and Teva are all from the same Teva corporation and all has [sic] manufacturing operations in the same place known as Signet Campus in Toronto, Canada.[68]

49. This is wrong. Apotex has nothing to do with Novopharm, Ivax and Teva.

50. However, the associate director transmitted to CDER's case officer in charge of the Apotex matter a Form 483 issued to Novopharm, so that the observations made to Novopharm could be taken into account in CDER's review of the Apotex case in the spring of 2009.[69] This was significant given that at the time CDER aimed at issuing a "corporate wide warning letter" to Apotex.[70]

51. At the relevant time, Apotex was unaware of FDA's mistaken assumption concerning its corporate structure and had no opportunity to correct it.

III. HAD FDA ALLOWED APOTEX TO PROPOSE CORRECTIVE ACTION, THE IMPORT ALERT WOULD NOT HAVE BEEN ADOPTED

52. As noted above, CDER determined to "proceed[] with" the Import Alert even though it had not completed review of Apotex's response to the Etobicoke Warning Letter.[71]

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[68] **Exhibit C-485**, FDA Internal Email, dated March 4, 2009 (Email from Heriberto Negron-Rivera to Carmelo Rosa and others). *See also* **Exhibit C-487**, FDA Internal Email Chain, dated March 23, 2009 (Email from Heriberto Negron-Rivera to Carmelo Rosa and others, dated March 4, 2009) (transmitting to CDER the Form 483 issued to Novopharm while noting that "this firm is also Teva, Ivax, Apotex related[.]").

[69] **Exhibit C-487**, FDA Internal Email Chain, dated March 23, 2009 (Email from Heriberto Negron-Rivera to Hidee Molina) ("This is the 483 issued to Novopharm during the last inspection a month ago. Emphasis given to these observations to be considered in your Apotex presentation.").

[70] **Exhibit C-349**, FDA Internal Email Chain, dated April 3, 2009 at US6447 (Email from Hidee Molina to Sally Eberhard, dated March 20, 2009); *id.*, at US6448 ("Additionally, I found out that on another recent FDA inspection, conducted on Novopharm (a sister company under TEVA corporation), the investigator reported as an observation inadequate analytical method validation. This may demonstrate a *corporate systemic deficiency*." (emphasis added)). *See also* **Exhibit C-490**, FDA Internal Email Chain, dated May 22, 2009 at US10467 (Email from Carmelo Rosa to Edwin Rivera Martinez) (the Apotex case "may result in a corporate action if the problems are confirmed.").

[71] *See supra* para. 44 (citing Reply, para. 79 (citing **Exhibit C-373**, FDA Internal Email Chain, dated August 18, 2009 (copying excerpts from "Sharfstein Report" of same date))).

After such review was completed, FDA concluded that the firm's response "appear[ed] to adequately address our concerns."[72] In other words, had the firm's response to the Etobicoke Warning Letter been taken into account by FDA *before* it issued the Import Alert, this measure would not have come into existence.

53. Similarly, the Import Alert was adopted before Apotex timely submitted its response to the Signet Form 483 on September 3, 2009.[73] Mr. Payne, the lead inspector for the Signet Inspection, reviewed the response to the observations for which he was responsible. He considered that the corrective measures stated in that response "appear[ed] to be sufficient[.]"[74] Unfortunately, at the time Mr. Payne expressed this view, the Import Alert had already been adopted.

54. In short, if Apotex had been given an opportunity to provide explanations and propose corrective actions *before* it was placed on Import Alert – as FDA permitted each of Apotex's comparators to do – the Import Alert almost certainly would not have been adopted.

IV. DIOP DID NOT INDEPENDENTLY REVIEW CDER'S IMPORT ALERT RECOMMENDATION

55. The August 18, 2009 Sharfstein Report (reproduced in **Exhibit C-373**) prompted John Verbeten, DIOP's director, to inquire as to when Apotex should be put on import alert.[75] The contemporaneous documents do not suggest an independent analysis by DIOP of CDER's recommendation to place Apotex on Import Alert. Instead, Rick Friedman queried why "OIP took 4 extra days to actually post the alert[]" – on August 28, 2009, four days from the issuance of CDER's Import Alert recommendation to DIOP dated

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72 **Exhibit C-532**, FDA Internal Email, dated June 9, 2010 at US7285 (Email from Maan Abduldayem to Carmelo Rosa).

73 *See supra* para. 44; **Exhibit C-81**, Apotex's Response to Signet Form 483, dated September 3, 2009.

74 **Exhibit C-525**, FDA Internal Email Chain, dated October 28, 2009 (Email from Lloyd Payne to Hidee Molina). *See also* **Exhibit C-526**, FDA Internal Email, dated November 24, 2009 (Apotex case officer confirmed that the protocols prepared by Apotex's consultants "appear[ed] to be adequate[.]"); **Exhibit C-532**, FDA Internal Email, dated June 9, 2010 at US7285 (Email from Maan Abduldayem to Carmelo Rosa) (Apotex's case officer noted that the firm's response to the Signet Warning Letter was deemed "to adequately address [CDER's] concerns sited [sic] in the WL.").

75 **Exhibit C-513**, FDA Internal Email, dated August 18, 2009. *See also* **Exhibit C-514**, FDA Internal Email Chain, dated August 18, 2009 (John Verbeten noted that he "reached out to CDER to see if they ha[d] something coming to [DIOP] for Apotex.").

August 24, 2009.[76]

56. The documents produced by the US thus confirm that DIOP's role in the issuance of the Import Alert merely consisted of implementing CDER's recommendation.[77]

V. FDA USED APOTEX AS AN EXAMPLE OF FDA'S TOUGH ENFORCEMENT POLICY

57. As noted before, one of the first initiatives of the FDA Commissioner appointed in 2009 was to place new emphasis on "'effective enforcement'" at FDA. To implement this initiative, FDA wanted to "'send a strong message'" by setting a precedent of major sanctions against at least one alleged offender.[78]

58. Additional documents disclosed by the US confirm that FDA used Apotex as the vehicle for this message, repeatedly holding up the Apotex case as an example of FDA's new approach of swift and aggressive action.[79]

59. In 2008, the US Government Accountability Office (GAO) had recommended, among other things, that FDA "[c]onduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics."[80] In 2010, FDA updated its response to this recommendation. It stated that FDA was no longer issuing multiple warning letters to non-compliant firms before taking enforcement action. Apotex was used to illustrate FDA's swiftness:

> For example, on August 28, 2009, FDA issued an import alert regarding products made at two facilities of

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76 **Exhibit C-518**, FDA Internal Email Chain, dated August 28, 2009. The Office of International Programs (OIP) is not involved in the adoption of import alerts. It is likely that Mr. Friedman meant DIOP, and not OIP.

77 *See* Reply, paras. 81-82, 440.

78 Memorial, paras. 150-51 (quoting **Exhibit C-51**, FDA, Remarks by Margaret A. Hamburg, Commissioner of Food and Drugs on *Effective Enforcement and Benefits to Public Health* at Food and Drug Law Institute, dated August. 6, 2009 at 1-2).

79 *See, e.g.*, **Exhibit C-529**, FDA Internal Email Chain, dated February 2, 2010 at US10717 (Edwin Rivera Martinez suggesting to "draft a detailed summary of the Apotex case, how we put the company on IA 10 days after completion of the inspection … .").

80 **Exhibit C-527**, GAO, Office of Policy and Planning, GAO Recommendations Review, *Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program*, GAO Recommendation 4 at US13803 (2010).

> Apotex[-Canada], the largest Canadian-owned pharmaceutical firm. The agency took this action just fourteen days after it completed the August 14, 2009, inspection of the company's Signet Drive, Toronto, Ontario facility.[81]

60. The Apotex example was specifically added by Mr. Edwin Rivera Martinez of CDER's Office of Compliance.[82] FDA repeatedly used Apotex as an example to stress its tough stance on cGMP compliance.[83]

CONCLUSION

61. The additional documents disclosed by the US do not support its suggestion that Apotex products posed "significant potential public health risks and required prompt action."[84] There is no evidence showing that Apotex products were unsafe or ineffective. To the contrary, the record shows that FDA's main concerns over Apotex's state of cGMP compliance were based on mistaken and unverified assumptions. FDA rushed to judgment and placed Apotex on Import Alert without giving it an opportunity to propose corrective actions. Had Apotex been able to address FDA's assumptions and propose corrective actions before FDA adopted the Import Alert – as FDA permitted each of Apotex's comparators to do – the Import Alert almost certainly would not have been adopted.

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81 *Id*., at US13806-07 (2010).

82 **Exhibit C-531**, FDA Internal Email Chain, dated April 30, 2010 at US10412 (Email from Edwin Rivera Martinez to Meredith Francis) ("I also reviewed the responses to GAO Questions … and included an example of FDA taking enforcement action prior to issuance of a Warning Letter (Apotex, Inc., Canada).").

83 *See, e.g.,* **Exhibit C-536**, FDA Internal Email Chain, dated August 11, 2010 at US12802 (Email from Maan Abduldayem to Edwin Rivera Martinez) (providing description of Apotex case to be used as illustration of important GMP case at the "GMP by the Sea" conference).

84 Witness Statement of Carmelo Rosa, para. 59.

62. The documents produced after April 19, 2013 thus further reinforce the showing of a breach by the US of NAFTA Articles 1102, 1103 and Article 1105 documented in the Memorial and in the Reply.

Date: July 22, 2013

Respectfully submitted,

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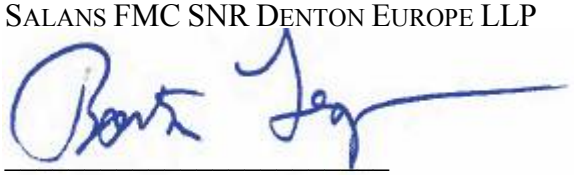

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