Case No. UNCT/14/2

Under the Arbitration Rules of the United Nations Commission on International Trade Law and the North American Free Trade Agreement

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ELI LILLY AND COMPANY

Claimant

v.

GOVERNMENT OF CANADA

Respondent

SECOND WITNESS STATEMENT OF ROBERT A. ARMITAGE

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1. My name is Robert Armitage. As set out in my prior witness statement of September 27, 2014, I spent almost three decades as a senior legal counsel to The Upjohn Company and, later, Eli Lilly and Company ("Lilly"), retiring in 2012 as Lilly's Senior Vice President and General Counsel. I have also led several significant intellectual property law and policy organizations, including the American Intellectual Property Law Association, where I served as President, and the Intellectual Property Law Section of the American Bar Association, which I chaired.

2. I am submitting this second witness statement to address certain assertions that Canada has made about Lilly's patenting strategy and to explain the fundamental role that patents like the '113 Patent on Zyprexa and the '735 Patent on Strattera play in Lilly's business. As I set out in my first witness statement, Canada is the only country to invalidate patents on Zyprexa or Strattera for lack of utility.

I. Not every patented invention can become a marketed product

3. I have reviewed paragraphs 150-164 of Canada's Counter-Memorial, which take issue with Lilly's patenting practices. Specifically, Canada suggests that Lilly files too many patents; seeks multiple patents on individual compounds; and abandons too many of its patents and patent applications. These criticisms are unfounded and I will address them in turn. It is helpful to begin, however, with additional context on how the decision to file a patent application is made.

4. In my experience, patent efforts in the research-based biopharmaceutical industry are initiated as a consequence of a scientist coming forward with a new scientific discovery. The nature of the discovery may range from an unexpected new insight into the operation of a biological system to data generated by months or years of painstaking trial-and-error effort aimed at translating an experimental idea into a useful discovery. Patent attorneys then assess whether these discoveries meet the requirements of patent law. The requirements of patentability filter out many potential patent filings and prevent an applicant from obtaining a patent unless the discovery is novel, useful and sufficiently inventive over existing technology, including technology reflected in earlier-sought patents.

5. In addition, patents are filed based on at least some expectation that a commercially viable product may result from the research or development activities on which the patent is based. This is no less true at Lilly than at other companies that I have worked with. At the same time, as I will explain below, this expectation cannot always be brought to fruition.

6. In the context in which Lilly undertakes patent filings, therefore, any suggestion that the number of patents sought by Lilly was the result of some form of speculation flies in the face of my experience to the contrary. Patenting at Lilly proceeds or not because of a

combination of underlying scientific discovery, the anticipated viability of the patent filing under the requirements imposed under patent laws, and expectations for commercial possibilities. In my view, Canada's rhetorical characterization of Lilly's patenting efforts as "speculative" can be properly evaluated only in the context of the actual practices within Lilly under which patenting proceeds, or not, which is based upon a balancing of the various factors set forth above.

A. Lilly files for significantly fewer patents than most large companies with significant research and development programs

7. At paragraph 152 of its Counter-Memorial, Canada asserts that Lilly filed 96 patent applications relating to the compounds olanzapine, atomoxetine and raloxifene. Canada argues that the number of patent applications Lilly filed on these compounds suggest that it is engaged in "speculative patent filing."[1] This criticism is based largely on patents obtained on a compound that is not at issue in this arbitration: only 28 of the 96 patents cited by Canada (29%) relate to olanzapine (Zyprexa) and atomoxetine (Strattera), the two drugs at issue. The remainder relate to raloxifene.

8. In any event, Lilly's patenting practices – including with respect to olanzapine, atomoxetine and raloxifene – are in fact consistent with (or more conservative than) those of its competitors. The following statistics illustrate this point:

- In 2002, the year the '735 Patent was granted, Lilly spent almost $19 million in research and development (R&D) per U.S. patent granted, obtaining 116 U.S. patents and spending $2.2 billion on R&D.[2]

[1] Resp. CM at ¶ 150.

[2] The U.S. patent statistics in my statement have been sourced from the U.S. Patent and Trademark Office's Patenting by Organization Reports for 2002 (C-396) and 2014 (C-397). Lilly's R&D expenditures are disclosed in its Annual Reports on U.S. Securities and Exchange Commission Form 10-K for the Years Ended December 31, 2002 (C-398) and 2014 (C-399).

- In that year, Lilly obtained a comparable or somewhat smaller number of U.S. patents than other leading pharmaceutical firms. For example, in 2002, Merck & Co. obtained 174 patents (or 58 more than Lilly) and Pfizer obtained 187 patents (or 71 more than Lilly).

- In 2014, Lilly spent on average $107 million in R&D per U.S. patent granted, obtaining 44 patents and spending $4.7 billion on R&D. This increased expenditure reflects a wider trend in the research-based biopharmaceutical industry.

- Lilly's 2014 patenting activity was either comparable to, or lower than, other leading biopharmaceutical research firms. Merck & Co. obtained 175 patents (131 more than Lilly) and Pfizer obtained 49 patents (or five more than Lilly).

9. I have focused on the United States because it is Lilly's home jurisdiction and the place where Lilly seeks and receives the largest number of patents. But similar trends hold in Canada,[3] where Lilly again obtained a comparable number of patents to Merck & Co. and Pfizer in both 2002 and 2014.[4]

10. To put Lilly's patenting practices in perspective, it is helpful to look at other industries as well. I am familiar with the patenting practices of manufacturing, electronic and other non-pharmaceutical firms through my leadership of the American Intellectual Property Law Association (AIPLA) and the Intellectual Property Law Section of the American Bar Association (the ABA), as well as my work with several other significant, multi-industry intellectual property organizations. (Among other things, I have served as President of the Association of Corporate Patent Counsel and as a member of the Board of Directors of the Intellectual Property Owner's Association).

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[3] The Canadian patent statistics in my statement have been sourced from the online database of Canadian patents maintained by the Canadian Intellectual Property Office (CIPO), and relevant extracts from that database are provided as exhibits (*see* C-400).

[4] Specifically, Lilly obtained 18 Canadian patents in 2002 and 46 in 2014. For Pfizer, the corresponding figures were 84 and 18, and for Merck & Co. the figures were 35 and 38 (C-400).

11. Lilly and other innovative pharmaceutical firms patent significantly less frequently than companies in most other research-based industries, despite spending a great deal more on R&D. In both 2002 and 2014, Lilly obtained fewer U.S. patents than leading innovators outside the pharmaceutical industry, such as IBM (3,288 patents in 2002 and 7,481 in 2014), Sony Corp. (1,434 patents in 2002 and 3,214 in 2014) and Eastman Kodak (694 patents in 2002 and 391 in 2014). Lilly was also outdone by several patentees outside the high-technology sector, such as the cosmetics company L'Oreal S.A. (280 patents in 2002 and 170 in 2014) and the paper products company Kimberly-Clark Corp. (247 patents in 2002 and 172 in 2014). These companies generally obtained fewer patents in Canada than in the United States. But pharmaceutical companies still were not at the head of the pack.[5] The consumer goods company Procter & Gamble, for example, obtained 216 Canadian patents in 2002 and 184 Canadian patents in 2014.

12. Lilly's patenting practices have been and remain typical within the research-based biopharmaceutical industry, and have been and remain more conservative than practices in other industry sectors. The biopharma industry as a whole spends more in R&D for each patent it receives than any other industry. According to data compiled by the U.S. National Science Foundation,[6] in 2008 the research-based biopharmaceutical industry spent $74 billion in R&D, or $20 million per U.S. patent granted. The comparable figure for the chemicals

[5] According to CIPO's Annual Report for 2002-2003 (C-401) and its Annual Report for 2013-2014 (C-402), only one pharmaceutical company (Novartis AG) was among the top ten patentees in Canada in 2002 and no pharmaceutical companies were among the top ten patentees in Canada in 2014.

[6] National Center for Science and Engineering Statistics, February 2013 InfoBrief (NSF 13-307), http://www.nsf.gov/statistics/infbrief/nsf13307/nsf13307.pdf (C-403).

industry was $4.6 million per patent, while across all other industries the figure was $4.1 million per patent.

B. Use patents motivate scientific research and are driven by the underlying science

13. At paragraph 164 of its Counter-Memorial, Canada takes issue with the fact that Lilly applies for patents on multiple uses of individual compounds. It argues that such filings are intended to create "thickets" (or clusters) of patents that deter innovation. In reality, such filings have just the opposite effect.

14. The three compounds highlighted by Canada – olanzapine, atomoxetine, and raloxifene – each started life in a Lilly research laboratory as a new molecule. Each was protected by a molecule patent in a wide range of jurisdictions around the world. It was the strength of these molecule patents that initially allowed Lilly to make substantial investments in the development of these molecules as medical treatments.

15. In general, the original molecule patents on olanzapine, atomoxetine and raloxifine existed for 20 years from the date of the patent filings in the respective countries where these patents were sought. These patents provided the economic rationale for Lilly's initial research, and they permitted Lilly to persist with research even where clinical trials were initially unsuccessful in establishing the safety and effectiveness of the drugs (as with atomoxetine and raloxifene).

16. As new uses for these drugs were discovered and patented, use patents served as an incentive to devote additional time and money to clinical research on additional conditions to be treated by the same underlying molecule. In this way, patenting of uses serves as an economic force for fostering, rather than deterring, innovation.

17. Obtaining multiple use patents is common in our industry. Each use claimed for a particular compound only qualifies for a patent if the invention satisfies all three patentability criteria – novelty, utility and, of greatest practical significance, non-obviousness. Thus the ability to patent multiple uses is inherently limited by the need to show that each new use was not obvious in light of each of the other already known uses of the compound.

18. Not only did Lilly's use patents on olanzapine, atomoxetine and raloxifene meet this standard, they are also well justified by the underlying science. I have spent my career working closely with pharmaceutical scientists and have always made it a priority to understand the medical innovations that were being developed by the companies I worked for. Understanding the basic science behind these innovations is a key factor in assessing the patentability of new inventions.

19. I have reviewed Mr. Brisebois's list of patents related to olanzapine, atomoxetine and raloxifine. The number of patents filed in relation to these compounds reflects to a significant degree both the nature of these molecules and the science behind their use as drugs. Creating new molecules and then investing extensively in research over many years to fully understand their potential as human medicines inherently leads to new discoveries. These downstream research opportunities are distinct from those available in other industries.

20. The intensity and complexity of the R&D efforts that are associated with the development of new uses of a medicine can be contrasted with the minimal such efforts that are typically undertaken to identify potential new uses for inventions in other industries. A new chemical molecule – especially a new molecule that affects the functioning of the human mind – opens the opportunity for wide-ranging exploration of possible effects that might be translated into previously unknown uses. The resulting discoveries can be of great scientific significance –

for example, they may shed light on principles of brain chemistry – and they can also be of great practical significance to patients.

21. To understand the importance of research into the full range of uses of drugs like olanzapine and atomoxetine, it is important to recall that many medical conditions that are classified separately for clinical purposes stem from overlapping biology and provide common "targets" for drug action at a cellular and systems level. This is particularly true of conditions of the central nervous system. For example, anorexia, depression and addictive substance abuse (all claimed uses for olanzapine) are each separate medical conditions but tend to result from biochemical abnormalities that may be affected by the same chemical compound. The same is true of oppositional defiant disorder, conduct disorder and ADHD (all claimed uses of atomoxetine) because the norepinephrine transporter that is impacted by atomoxetine affects brain regions and receptors associated with all of these conditions.

22. Raloxifene also provides a good example of the research opportunities that can be generated by a single molecule. Today, this medicine is approved for use in postmenopausal women both to treat and prevent osteoporosis and to reduce the risk of developing invasive breast cancer. In preventing and treating osteoporosis, raloxifene acts like estrogen. In preventing invasive breast cancer, raloxifene acts like an anti-estrogen. In other words, the one molecule – based upon Lilly's extensive research into its effects on the body – was found to play both the role of both Dr. Jekyll and Mr. Hyde depending upon whether the drug was working on bone tissue (estrogen-like behavior) or on breast tissue (anti-estrogen-like behavior). As the

biology of this unique agent was explored, Lilly scientists were able to develop multiple additional insights into its potential as a human medicine.[7]

23. In short, separate patent applications are filed because of the natural progression of research in the life sciences. Scientists seeking to better elucidate a compound's activity may initially focus on one clinical endpoint, and then shift their efforts to a second, a third, and so on to more fully explore the therapeutic benefits of a compound. This natural evolution of patent protection for a product tends to occur particularly in the context of biopharmaceuticals that treat the central nervous system, where, as noted, a single pharmaceutical product can have therapeutic effects that are relevant to multiple medical conditions.

24. Even when a patentable new use has been identified, there is no rule, at least at Lilly, that a patent must actually be filed on the use. There are situations where the use is never patented; Lilly scientists simply publish on the use, thereby dedicating the use to the public. However, if there is no patent on the molecule (or little or no remaining patent life on the molecule) and the potential clinical use has been dedicated to the public, the potential for developing the medicine for such a use may be lost. Again, that is because patent protection is frequently necessary to justify the expense of obtaining regulatory approval and bringing a medicine to market. No matter how valuable the medicine might have been, a company is not likely to develop that medicine unless it can protect its investment with a patent.

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[7] For example, in addition to the approved uses for the drug, Lilly conducted extensive research directed to treatment of heart disease, schizophrenia and Alzheimer's disease with raloxifene. A large-scale clinical trial in Alzheimer's disease demonstrated a reduced risk of cognitive impairment at a dose of 120 mg/day. *See* K. Yaffe et al., Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial, Abstract, online: http://www.ncbi.nlm.nih.gov/pubmed/15800139 (April 2005) (C-404).

25. Therefore, as each new use is developed, Lilly must make a binary decision: publish, and forego the opportunity for clinical development of the molecule, or patent, and preserve the opportunity to develop a new medical treatment. The fact that Lilly sought patents was not to speculate and not to deter competition, but to preserve opportunities that otherwise were certain to go unrealized – opportunities both for itself and for patients that would otherwise be lost.

C. Abandoned patents reflect the fact that drug development is a process of attrition

26. Because of the nature of their business, research-based biopharmaceutical companies go to great lengths to ensure that their products will work as expected. The law requires it, as only a drug that is safe and effective will receive marketing approval from health regulators. A typical drug goes through more than a decade of preclinical and clinical testing prior to obtaining regulatory approval. Many drugs take far longer to run the regulatory gauntlet.

27. Along the way, many drugs that performed well in the laboratory or in animal testing prove to be unsatisfactory in treating diseases in humans for one reason or another. For example, a drug may be very effective but may exhibit significant side effects that cause further drug development to cease. The balance between a medicine's side effects and its effectiveness determines whether it will secure regulatory approval, and a drug's side effect profile, *i.e.*, its toxicity, is ultimately established through human testing.

28. In short, the development of a new medicine is fraught with risks of failure and putting new drugs through a pharmaceutical pipeline to regulatory approval is mostly a process of attrition. Many molecules are selected for clinical development; few become approved medicines.

29. The attrition statistics are truly staggering. Annual industry R&D expenditures of over $40 billion a year translate into the U.S. Food and Drug Administration approving on average only 25 "new molecular entity" drugs each year (*i.e.*, drugs, like Strattera and Zyprexa, that contain active compounds never before marketed in the U.S.).[8] Approximately 9 out of 10 drugs fail in clinical trials despite positive preclinical testing. This failure rate stems partly from the fact that laboratory and animal models cannot reproduce all the complexities of the human body. But it is also because the standards for clinical success are – with good reason – extremely high.

30. Moreover, the decision to commercialize a drug is not simply a scientific one. It is also an ethical decision, requiring a complex balancing of the drug's benefits and its side effects, both on a standalone basis and in the context of other available treatment alternatives. And, like product development choices in any industry, it is a business decision, requiring at every stage an analysis of whether, for example, a new and better competitor has entered the market. In other words, the viability of a drug as a commercialized treatment is completely distinct from whether a drug is patentable.

31. Lilly, like companies in all industries, abandons patents and patent applications in the course of selecting products to bring to market. Abandonment refers to the relinquishment of all rights in the patent or the patent application at issue. An abandonment thus allows the public to use the claimed invention as if the patent had simply expired in the normal course.

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[8] FDA Center for Drug Evaluation and Research, Novel New Drugs Summary 2014 (January 2015) at 3 (C-405).

32. Because of the potential importance of patents to Lilly's ability to continue development of a medicine, Lilly does not abandon patents lightly. At the same time, applying for, issuing and maintaining patents entails significant expenditure (particularly because costs are separately incurred across numerous jurisdictions in the world). Thus, when I oversaw Lilly's legal team, our policy was that the company should abandon patents and patent applications once the point was reached where the protection afforded under the patent no longer supported a plausible scenario under which the patent could have commercial value.

33. Given the attrition rates for the industry discussed above—which reflected Lilly's own attrition within its pipeline—patent abandonments were commonplace events. When 90% of new medicines fail to emerge from clinical development, and many more promising ideas fail in preclinical evaluation, the "plausible scenario" standard means that more than 90% of patent filings are likely to be abandoned before reaching the end of their statutory term of protection.

II. It is a legal and business imperative that patent applications be filed before significant clinical testing takes place

34. Canada suggests that Lilly – and the rest of the research-based biopharmaceutical industry – should only obtain patents late in the research process. Such a practice would be highly undesirable from a patent policy perspective even if it were feasible under the patent laws, which it was not. Patents are intended to stimulate disclosure to the public of new, non-obvious and useful technology so that such technology can be relied on by skilled researchers as a platform from which to make further improvements to what has been patented and further advance the state of the art, and there is no good reason to delay this process of advancement.

35. But in any event, pushing the filing date of a patent application any later in the process is untenable. Given the vast costs involved in large scale clinical testing – not just

money, but also the cost of scarce employee time and other research foregone – biopharmaceutical companies like Lilly must be confident that they have a secure legal right to the fruits of their investment.

36. Without a filed application, and thus a legally fixed "priority date" for the invention, Lilly's ability to obtain a patent could be defeated at any time by a disclosure of Lilly's research. As I noted above, an invention must be novel, non-obvious and useful to receive a patent. A pre-filing disclosure of the research behind an invention, which patent lawyers call an "anticipatory disclosure," frequently defeats the requirements of novelty and non-obviousness.

37. Large scale clinical testing significantly increases the risk of such an anticipatory disclosure. In fact, the '735 Patent was challenged in Canada (albeit unsuccessfully) on the basis of an alleged anticipatory disclosure made in the course of a conversation about a potential clinical trial. Other companies have faced similar issues. In 2011, for example, Bayer lost a European patent on the birth control drug Yasmin – once its second-best selling drug – as a result of clinical trials conducted prior to patenting.[9]

38. Lilly goes to great lengths to maintain the confidentiality of research conducted prior to patent filing. In some countries, Lilly also benefits from rules that may protect disclosures made to patients and their doctors from being treated as anticipatory. But such protections are limited and uneven, and once research is disclosed to the scores of patients often involved in a clinical trial, as well as their family members and doctors, leaks are possible. In many jurisdictions, public disclosure of clinical trials is effectively required under health regulatory and securities laws (in the United States, such disclosures are collected at

[9] *See* European Patent Office, Technical Board of Appeal, Decision T 0007/07 (2011) (C-514).

www.clinicaltrials.gov). Without patent applications already in place, Lilly simply could not risk conducting the large scale clinical trials necessary to demonstrate that its medicines can safely be prescribed and used by patients.

39. It bears emphasis that filing prior to significant clinical trials carries a substantial cost for firms such as Lilly. In Canada, as elsewhere, the 20-year term of protection afforded by the patent runs from the date of filing. Because filing often occurs prior to significant clinical trials, patent protection often expires within less than ten years of a drug reaching market. If it were a feasible option (which it is not, under existing law), pushing filing to later in the research process – when the drug is closer to marketing approval – would substantially expand the period of protection for the drug toward the full 20 year term of the patent.

III. Patents are among Lilly's most important assets

40. As explained more fully in my first witness statement, patents are the lifeblood of Lilly and of the research-based biopharmaceutical industry as a whole. Lilly's patents are the core assets that allow the company to recoup the billions of dollars it spends each year in developing, testing and improving new medicines.

41. A patent on a drug like Zyprexa can represent billions of dollars in market capitalization for Lilly. Patents are also at the center of how Lilly values other pharmaceutical firms. For example, when Lilly purchased the Icos Corporation for $2.3 billion in 2006, Lilly did so based on its valuation of Icos's 50 percent interest in the patents protecting the drug Cialis.

42. I understand that Canada has stated that, because the '113 and '735 Patents were ultimately held invalid, they never qualified as a property interest in the first place. Canada

argues that a property interest in a patent is merely a conditional right until after the patent is litigated in court and finally determined to be valid.

43. Canada's position is completely at odds with my experience of commercial practice and commercial expectations. Patents are often significant sources of revenue and are routinely valued and monetized in corporate and other commercial transactions. Patents are assets that are also routinely taken by lending institutions as collateral to secure loans. In other words, the marketplace treats a patent as a property right regardless whether it has been the subject of litigation.

44. Firms are certainly aware that validity litigation may be a risk, just as litigation over the validity of title is a risk when acquiring real property. However, because most major markets offer stable and predictable patent regimes, the risks associated with validity challenges can generally be accounted for in advance. Moreover, all property rights are frankly open to being lost through litigation. Thus, neither Lilly nor any other firm I am aware of would put off the acquisition of a patent owned by another company until after someone brings litigation to challenge the validity of the patent.

IV. Global Patents on Olanzapine and Atomoxetine

45. In my prior witness statement, I set out some of the reasons that Canada's revocations of the '113 and '735 Patents make it a global outlier. I explained that Lilly held '113 Patent equivalents on Zyprexa in 81 jurisdictions; the patents were challenged post-grant in 24 of those jurisdictions; and the patents were upheld everywhere except Canada, Saudi Arabia and Slovenia. The Saudi and Slovenian challenges were only partially successful – a Gulf Cooperation Council patent continued to be valid in Saudi Arabia and the Slovenian outcome impacted only one of the two claims in the relevant patent. More to the point, outside Canada,

none of the 24 challenges involved even an argument that Zyprexa lacked utility or industrial applicability.

46. Similarly, Lilly held '735 Patent equivalents on Strattera in 36 jurisdictions. The patent was challenged post-grant in three countries and was upheld everywhere but Canada. As with Zyprexa, Canada was the only country in which Strattera was subject to a challenge on grounds of utility or industrial applicability.

47. Since I submitted my statement, I understand that Lilly has undertaken an extensive document collection and review process in order to respond to Canada's document requests. As part of that process, Lilly found records relating to an additional (*i.e.*, a 25th) post-grant challenge to the Zyprexa patent through revocation proceedings in Bosnia. These proceedings are consistent with the trends described above. The Bosnian generic challenger argued, unsuccessfully, that the patent lacked novelty and inventiveness but it did not question the patent's utility.

48. Counting the Bosnian challenge, the Zyprexa and Strattera patents were challenged in 26 different jurisdictions. Yet, Canada remains the only country to invalidate either of these patents on grounds of utility. It also remains the only country in which either patent faced a challenge on grounds of utility or industrial applicability.

49. The fact that patents on Zyprexa and Strattera remain valid (or have now expired in the normal course) in almost every relevant jurisdiction is particularly instructive given that both drugs are attractive targets for generic drug companies. Zyprexa became the world's top-selling antipsychotic for the treatment of schizophrenia and Strattera was the first non-stimulant treatment developed for ADHD. These were innovations that improved the quality of life of millions of patients. At various times, annual sales of Zyprexa met or exceeded US$10

million in more than 30 different markets and annual sales of Strattera met or exceeded US$10 million in 8 different markets.

50. Generic companies thus had ample reason to challenge the validity of global patents on Zyprexa and Strattera – and they did, filing challenges in 26 different jurisdictions. The fact that patents on both drugs continued to be valid in every major market is a testament to the strength of the patents. And the fact that, other than in Canada, no generic drug company ever brought a utility challenge against patents covering these drugs demonstrates that such a challenge simply would have been a waste of time in jurisdictions around the world that have a traditional utility requirement.

V. Conclusion

51. Canada's characterization of Lilly's patenting strategy, and its position on the value of patents as property, are both fundamentally at odds with my three decades of experience in the innovative pharmaceutical industry.

Signed at Centerville, Massachusetts on September 11, 2015.

[signed]

Robert A. Armitage