Enter at Your Own Risk: FDA Draft Guidance Highlights the Uncertainty in the Abbreviated Biosimilar Approval Pathway

By 2015, sales of biosimilars in the United States are expected to reach as high as $2.6 billion.[1] Recognizing this market opportunity, biotech companies of all sizes are devoting significant resources to developing these biologic products, which are novel yet dependent on currently approved biologic drug products (at least in part). Following the passage of the *Biologics Price Competition and Innovation Act* (BPCIA) on March 23, 2010, an entity seeking to bring a biosimilar product to market now has two pathways to consider for securing Food and Drug Administration (FDA) approval. One pathway allows the biosimilar applicant (BA) to seek FDA approval of the product as a new biologic by filing a biologic license application (BLA) under § 351(a) of the Public Health Service Act (PHSA).[2] Alternatively, the BA can follow the newly enacted abbreviated pathway under PHSA § 351(k), which created a new approval pathway for biologics that the FDA determines are "biosimilar" to a BLA-approved reference product (RP). This second option has been available since the passage of the BPCIA on March 23, 2010, yet the FDA still awaits the filing of the first § 351(k) application (referred to as abbreviated biologic license application – "ABLA").

The statutory language of the BPCIA outlines the structure of the pathway, but contains minimal guidance on the standards used by the FDA to determine biosimilarity as required for ABLA approval. Faced with this uncertainty, it comes as no surprise that BAs have been hesitant to test the ABLA approval pathway. In a first step toward addressing this uncertainty, on February 9, 2012, the FDA released three draft guidance documents on the development of biosimilar products. These guidance documents were published in the *Federal Register* on February 15, 2012,[3] with a 60-day period for comment ending April 16, 2012. Commentary and reaction to these long-awaited guidances have been mostly negative,[4] with common criticisms being that these supposed "guidances" provide only broad conceptual ideas, lacking any sufficient detail to set BA expectations, and do not resolve any uncertainty over the FDA's decision for awarding ABLA approval. Despite the lack of explicit guidance in the documents, the FDA does provide some clarity regarding the most pressing of issues facing BAs in the early stages of biosimilar development. Whether intentional or not, the FDA message that manifests from this clarity is that there is little to gain, but much to lose, by following the ABLA pathway.

A Brief Introduction to the Guidance

The FDA draft guidances were intended to implement the follow-on biologic drug pathway mandated by the BPCIA, and are set forth in three separate guidance documents, forming a "suite" of guidances that references one another throughout each document. The first draft guidance, titled *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*,[5] is considered the "core" document by the FDA and is directed to the scientific issues in proving biosimilarity. As recited in the statute, to qualify for approval of a biologic using an ABLA, the BA must prove that its biologic product is "biosimilar," which requires the product to be highly similar to an approved biologic with no clinically meaningful differences in the safety, purity, and potency of the product.[6]

The first guidance, which is limited to therapeutic proteins,[7] suggests the FDA will determine biosimilarity by applying a "step-wise" approach.[8] The first step is analytical studies, which compare the physicochemical characteristics and functional properties of a candidate biosimilar drug with the reference drug product. Following this determination, if the differences in the two products are not "clinically meaningful," the FDA will require fewer or narrower studies in the subsequent approval step. As it hinted at last year,[9] the FDA intends to evaluate the data presented at each step based on its long-standing "totality-of-theevidence" standard,[10] while focusing on assessment of the effects of any differences in the products, rather than requiring an independent safety determination of the biosimilar product. In this way, the FDA seeks to eliminate human or animal clinical studies that are redundant or only incrementally aid the biosimilarity determination, a practice the agency considers highly unethical.[11] Based on the analytical results, the FDA will determine the scope of animal toxicity testing it considers necessary, as expressly required by the statute.[12] Finally, based on the results of the first two steps, other RP studies, and any other relevant data (*i.e.,* the "totality-ofthe-evidence"), the FDA will decide as the final step which human pharmacokinetic (PK) and pharmacodynamic studies (PD), immunogenicity studies, and clinical safety and effectiveness trials are required.[13] The list of public comments on the *Scientific Considerations* guidance is available at *Regulations.gov* under FDA Docket No. FDA-2011-D-0605.[14]

The second draft guidance, titled *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*,[15] is specifically concerned with chemistry, manufacturing, and controls (CMC) of biosimilar products. The draft guidance also advocates a "risk-based" approach, which will permit variances in biologic drug properties and characteristics if justified by the biosimilar applicant. Assessments will be made under a "totality of the analytical data" standard, intended to take into account interactions between various measured parameters. Specific aspects of biologic drug production falling within the scope of this guidance include the expression system, manufacturing processes, assessments of physicochemical properties, functional assays, receptor binding (when appropriate) and immunochemical properties, impurities (both product- and process-related), reference product and reference standards, the finished drug product, and stability studies. Public comment on the *Quality Considerations* guidance is available at FDA Docket No. FDA-2011-D-0602.[16]

The third guidance document, titled *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,*[17] is presented as a response to questions raised during public hearings on the FDA rulemaking. Generally, the agency said it will take a permissive approach to changes in formulation, delivery device, or container, and to changes involving fewer than all the routes of administration, presentations, or conditions of use of the reference biologic drug, provided that the BA can establish biosimilarity. The FDA also indicates in this draft guidance that animal and/or clinical data from non-U.S. licensed biosimilar products will be considered in support of an ABLA, but only under specific circumstances set forth in the guidance. The list of public comments on the *Q&A Guidance* is available at FDA Docket No. FDA-2011-D-0611.[18]

Industry Comments and Reactions

Several industry commentators have criticized the draft guidances as severely disappointing to anyone looking for clear FDA expectations for biosimilar applications.[19] In contrast to European Medicines Agency (EMA) guidelines, which recite more specific standards for biosimilarity for different classes of biologics,[20] the FDA guidances advocate a product-specific inquiry in every case. Many comments suggest that the FDA should strive to harmonize with the EMA and publish class-specific guidance for complex proteins,[21] and the FDA has not ruled this out in the future.[22] The guidances spend a great deal of time reciting well-known concepts, continually reminding the reader (in each of the three documents) that therapeutic proteins have inherently more variability and chemical complexity than small molecule drugs.

Without clear guidelines on the requirements for biosimilarity, BAs possess no ability to project the costs of taking a biosimilar drug product successfully through the approval process. Since the financial commitment required for development of a biosimilar product is enormous, failure to secure approval on the first try can spell doom for many small-to-medium-sized biotech firms. The estimated cost for development of a biosimilar product is $50 million to $60 million, with an additional $250 million to $1 billion for the manufacturing facility, whereas generic small molecule drugs typically require an investment of about $5 million.[23] When the fate of a company depends on a finding of biosimilarity by the FDA, until more details on this determination become available, BAs are unlikely to follow the ABLA pathway. There always will be some uncertainty on these costs, as they depend on positive data resulting from each study. But without a better idea regarding the expectations on testing, the traditional BLA approach is a safer, albeit more expensive, option for FDA approval.

Clinical trials (arguably) represent the largest expense in the biologic drug approval process regardless of pathway choice. In the months leading up to publication of the guidances, many industry representatives expressed concern that the FDA would require several clinical studies to establish biosimilarity. As clinical trial requirements for biosimilarity increase, the cost savings of the ABLA pathway compared to a traditional BLA begin to evaporate. This pre-guidance concern remains, for the FDA falls short in defining which clinical studies the agency considers most persuasive. As expected, innovator companies have advocated that extensive clinical studies must be required for all biosimilar products, while BAs argue that many products may not call for such studies. Patient groups generally call for the FDA to promote greater safety by requiring more extensive clinical testing and robust pharmacovigilance.[24] With these competing interests in mind, rather than take a definitive position, the FDA guidance instead lists generalities and non-standards, such as requiring the trials be “state-of-the-art” and “rigorous,” which are not defined in any way.

The FDA reserves the right to waive any of the clinical trial requirements at the discretion of the agency, with the exception of the statutorily-mandated clinical trials such as those directed to pharmacokinetics/pharmacodynamics and immunogenicity.[25] The FDA’s reservation of waiver of these studies has been criticized by several innovator companies, such as Genentech and Novo Nordisk.[26] These innovator companies, as well as industry organizations such as the Biotechnology

Industry Organization (BIO), take issue with the agency's word choice regarding these analytical and comparative studies, particularly the use of "should" and "where available and appropriate," as these imply that these studies do not need to be done.[27,28] BIO prefers definitive terms such as "is expected to" or "will need to." BIO further asserts that language in the guidance is inconsistent with the statute, for it implies that clinical trials are only a "residual requirement" that is triggered if there are gaps in the analytical, PK/PD, and safety results. Instead, BIO advocates for a more extensive clinical trial requirement for biosimilarity, requesting the FDA necessarily require several additional studies beyond the statutory minimum, including animal toxicity studies and human clinical trials evaluating safety and efficacy.[29] The vague language choice in the guidance supports the FDA's "totality of the evidence" approach, where the FDA is able to maximize agency flexibility while minimizing the need to take a position on the evidence required to prove biosimilarity.

The most detailed guidance provided in the FDA documents is by reference in the *Quality Considerations* guidance. This guidance references several FDA and *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) guidances relating to biologic drug regulations, particularly the production of recombinant protein products. The ICH guidances provide detailed information on key assays, controls, and statistical analyses (among others) that BAs should consult when initiating study design and development.[30] By integrating the study design principles disclosed in the ICH guidances with the newest assay technology, a BA can develop a more complete package of early-stage study plan materials to present at its next meeting with the FDA.

Amino Acid Sequence Identity and Biosimilarity

The FDA's strict position on requiring amino acid sequence identity for biosimilarity is a significant message from the guidance. The guidance documents authorize only small changes at the N- and C- terminal truncations in amino acid chains with scientific justification.[31] As has been seen with small molecule drugs, a BA will specifically design its product such that it achieves RP biosimilarity, yet still falls outside the scope of the patent claims protecting the RP. Many of the currently approved biologic drugs are protected by patent claims directed to the specific amino acid sequence of the therapeutic protein. Since the FDA guidance requires identical amino acid sequences (outside of the terminal regions) for a finding of biosimilarity, the BA's product must share the amino acid sequence with the RP to qualify for the ABLA pathway. Therefore, for the FDA to make a finding of biosimilarity, a BA necessarily would infringe the patents covering most current RPs.

The BA thus has two alternatives: Enter the ABLA pathway with the hopes of invalidating the patent, or make changes in the amino acid sequence of its new product, abandon the ABLA pathway, avoid potential infringement, and file a BLA. There is minimal incentive for a BA to force an infringing product through the ABLA pathway, unless the patent covering the RP is particularly weak and the BA's invalidation argument is bulletproof. Both options will be expensive, but the BLA pathway choice also enjoys the PHSA's exclusivity provisions for new approvals, which has indeterminate, yet significant, value. Considering all of the unresolved issues surrounding the ABLA pathway in the

United States, a third potential strategy for a BA that is ready to file may be to seek approval in Europe first, then seek approval in the United States. The FDA, in an effort for harmonization with the EMA, is currently exploring a proposal for expedited U.S. approval if the biosimilar is already approved in Europe.[32] Depending on how the FDA adopts the EMA biosimilarity determination, this "end-around" strategy could prove to be a more predictable approval option, at least in the short-term.

This imbalance favoring BLA over ABLA filings is unlikely to remain for long. The FDA is likely to relax these strict amino acid identity requirements for biosimilarity in the future, or at minimum provide for a clear mechanism to scientifically justify amino acid changes, based on the knowledge that human proteins in nature are variable and there are many "neutral" amino acid sequence variants. Biosimilar producers will certainly push for FDA tolerance of amino acid changes. For example, Biocon has suggested that the FDA should allow for intermediate processing steps, provided that the final protein comprises the same primary amino acid sequence as the reference product.[33] However, innovator representatives in turn will resist allowing any differences in amino acids, as seen in comments to the guidances by Amgen, Novo Nordisk, and BIO.[34,35] Innovators cite safety concerns as justification for requiring strict identity of amino acid sequences, while others request that the FDA reject all ABLAs that include intentional differences with the RP in host cell type, primary structure, formulation, or immediate packaging.[36] Indeed, the FDA must begin conservatively because all is not known regarding the equivalence of these neutral variants. What is neutral in an evolutionary sense may not be neutral pharmacologically, and the importance of 3-D structures and post-translational modifications in protein function must be addressed. Most likely, more expansive analytical and clinical studies will be required to scientifically justify any difference in amino acid sequence between the RP and the BA product. Hypothetically, a BA product comprising a well-characterized silent mutation (outside of the N- or C- termini) could readily be proven as biosimilar to the RP with carefully designed studies. Both BA and BLA holders should take an active role in FDA approval meetings to educate as well as advocate their respective positions.

Interchangeability Still Remote

The BPCIA biosimilars framework is unique in that it permits a finding of "interchangeability" with the RP,[37] which is considered the most enticing aspect of the ABLA pathway. A finding of interchangeability allows substitution of the biosimilar for the RP without requiring specific intervention from the health care provider.[38] Thus, just as a generic pharmaceutical drug can be substituted for the brand name drug at the pharmacy counter, a biosimilar product could be substituted for the RP.[39] In this scenario, the biosimilar is a true "biogeneric," and therefore the BA can benefit from the marketing, promotion, and educational resources devoted to the RP. However, to prove interchangeability, the BA product must meet a stricter compatibility standard with the RP by establishing that a provider can switch back and forth between the biosimilar product and the RP without any additional risks.[40]

The *Q&A Guidance* explicitly discusses the issue of interchangeability, but unsurprisingly, the only guidance is a proposed "stepwise" approach. Under this approach, the FDA must first find biosimilarity with the RP, followed by FDA meetings to determine which additional studies are needed to prove interchangeability. The FDA has noted that it expects to require at least one additional human study, but expects that multiple studies are more likely.[41] The *Q&A Guidance* further notes that while requests for interchangeability can be filed, the FDA is not close to deciding how to evaluate interchangeability, and believes that the technology has not progressed enough to make such a determination.[42]

This is welcome news for BLA holders, and a disappointment for BAs, as it is clear that the first biosimilar with interchangeability is years away from being approved (if ever).

Innovator drug developers have advocated that interchangeability should not be available if the biosimilar requires additional training on its use, particularly for new devices or systems; a common route of administration for many currently available reference products.[43] Industry leaders estimate the year 2020 will bring the FDA's first determination of interchangeability.[44] Until that time, BLA holders can rest assured the RP will maintain its dominant position in the market. Against only competing biosimilar products, the RP is expected to maintain 70 percent to 90 percent of the market share, as switching a patient from the RP to a biosimilar product is expected to encounter significant barriers from patients, providers, and insurance companies.[45] Industry comments charged the FDA with evaluating how a determination of interchangeability will interact with state laws governing pharmacy substitution of prescribed drugs.[46] Patient groups such as the Global Healthy Living Foundation (GHLF) have expressed worry over pharmacist or insurer automatic substitution of interchangeable products while insufficient data is available.[47] With other more pressing concerns, providing guidance on interchangeability is currently a low priority at FDA, and the agency likely will defer any guidance on interchangeability until at least one ABLA has been approved as biosimilar. This first ABLA holder is expected to move quickly in requesting interchangeability, which could spur the FDA to publish more guidance on that concept. By then, the FDA should possess the requisite experience to provide more detailed standards than the instant guidance on biosimilarity.

Conclusions

After considering the comments submitted to the docket, the FDA held a public hearing on the biosimilars guidance on May 11, 2012. While most of the hearing testimony praised the FDA for their initial efforts, a recurring theme throughout was that these FDA guidances fail to provide enough clarity to justify the substantial risk in ABLA filing. Without significant FDA revisions, the clinical trial requirements for establishing biosimilarity remain uncertain – setting up a BA for unpredictable and potentially enormous expenses should unexpected trials be required under the "totality of evidence." The amino acid identity standards for biosimilarity are set at such a high level that ABLA filers may have difficulty providing colorable arguments of non-infringement of RP patents. The FDA admits that interchangeability is years away, and frankly does not believe the current technology has progressed far enough to determine interchangeability.[48] Thus, the guidances provide BAs minimal optimism for interchangeability in the near future, or even hope for timely detailed information on the

issue. While the FDA has indicated its plan is to issue more guidance in the near future, without significant departure from the uncertain format of the instant FDA biosimilar draft guidances, the FDA will have quite a challenge to rehabilitate the disincentives presented by the ABLA approval pathway as it sits today. Without more guidance, it could be several years before any applicant decides to seek FDA approval via the ABLA pathway, thus delaying the development of a prosperous biosimilar market in the United States and the resulting improvement in health care, reduced patient costs, job growth, and advancement in the field of biologics.

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Endnotes

1 IMS Health, *Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape (December 2011),* available at http:// www.imshealth.com/ims/Global/ Content/Home%20Page%20Content/ IMS%20News/Biosimilars_Whitepaper. pdf (accessed April 17, 2012).

2 The *Public Health Service Act (PHSA)* provisions regulating BLA filings now represent the only pathway for FDA approval of a new therapeutic protein. In the past, certain biologic products have been approved under the *Federal Food, Drug and Cosmetic Act (FDCA)*, using the NDA approval process. However, the addition of the term "protein" to § 351 of the PHSA exemplifies the intent of the legislature to consolidate approval of all new proteins using the BLA process. "Protein" is defined in the guidance documents as a polypeptide that is greater than 40 amino acids. Anything smaller is considered merely a "peptide" and thus akin to a small molecule drug. For "peptides," filing of an NDA under the FDCA may still be appropriate.

3 77 Fed. Reg. 8885 (Feb. 15, 2012).

4 Alex Philippidis, *Comments Sent to FDA on Its Draft Biosimilars Guidance Mostly Conveyed Discontent,* Genetic Eng. & Biotech. News (April 16, 2012).

5 *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (Feb. 2012) (hereinafter "Scientific Considerations"), available at http:// www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatory Information/Guidances/UCM291128.pdf.

6 PHSA § 351(i)(2)(A) and (B).

7 The guidance states that the general scientific principles may be informative for the development of other proteins, such as in vivo protein diagnostic products. *Quality Considerations*, at 163-164.

8 *Scientific Considerations* at 7.

9 Steven Kozlowski, et al., *Developing the Nation's Biosimilars Program*, NEJM 365: 385-8 (2011); *also see* James V. DeGiulio, *FDA Looks to Multiple Sources, Including EMA Guidelines, in Developing Biosimilar Approval Standards*, Patent Docs Weblog (August 11, 2011), available at http://www.patentdocs.org/2011/08/ fda-looks-to-multiple-sources-includingema-guidelines-in-developing-biosimilarapproval-standards.html.

10 *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), available at http://www.fda. gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/ Guidances/ucm072008.pdf.

11 Rachel E. Sherman, Associate Director for Medical Policy at the Center for Drug Evaluation and Research, *FDA Biosimilar Biological Products Webinar*, Feb. 15, 2012, available at https://collaboration. fda.gov/p13473376/.

12 PHSA § 351(k)(2)(A)(i)(I)(cc).

13 *Id*.

14 Docket No. FDA-2011-D-0605, *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to Reference Product; Availability*, available at http://www. regulations.gov/#!docketDetail;rpp=25;po =0;D=FDA-2011-D-0605.

15 *Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* (Feb. 2012) (hereinafter "Quality Considerations"), available at http://www. fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/ Guidances/UCM291134.pdf.

16 Docket No. FDA-2011-D-0602, *Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; Availability*, available at http:// www.regulations.gov/#!docketDetail;rpp=25;po=0;D=FDA-2011-D-0602.

17 *Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (Feb. 2012) (hereinafter "Q&A Guidance"), available at http://www. fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/ Guidances/UCM273001.pdf.

18 Docket No. FDA-2011-D-0611, *Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; Availability*, available at http://www. regulations.gov/#!docketDetail;rpp=25;po =0;D=FDA-2011-D-0611.

19 *See, e.g.,* Philippidis, *supra*, at note 6.; Kevin E. Noonan, *More on FDA Draft Guidelines for "Follow-on" Biologic Drug Approval Pathway, Patent Docs Weblog (Feb. 14, 2012), available at http://www/patentdocs.org/2012/02/more-on-fda-draft-guidelines-for-follow-on-biologic-drug-approval-pathway.html*.

20 *See* European Medicines Agency, *Multidisciplinary: Biosimilar*, available at http://www.ema.europa.eu/ema/ index.jsp?curl=pages/regulation/ general/general_content_000408. jsp&mid=WC0b01ac058002958c.

21 James C. Shehan, Corporate VP of Legal, Gov't, and Quality Affairs, Novo Nordisk, Inc., FDA-2011-D-0611-0004, available at http://www.regulations. gov/#!documentDetail;D=FDA2011-D-0611-0004.

22 *See* Sherman, *supra*, at note 13.

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25 PHSA § 351(k)(2)(A)(i)(I)(cc); *Scientific Considerations*, at 16.

26 *See* Philippidis, *supra*, at note 6.

27 Kelly Lai, BIO Director of Science & Regulatory Affairs, FDA-2011-D-0605-0049, available at http://www.regulations. gov/#!documentDetail;D=FDA2011-D-0605-0049.

28 Earl Dye, Genentech, FDA Docket No. FDA2011-D-0611, available at http://www. regulations.gov/#!documentDetail;D=FDA2011-D-0611.

29 *See* BIO, at note 29.

30 ICH guidance documents can be found on the FDA website at http://www.fda. gov/regulatoryinformation/guidances/ ucm122049.htm.

31 *See Scientific Considerations*, at 17 ("the expression construct for a proposed product will encode the same primary amino acid sequence as the reference product.").

32 *See Q&A Guidance,* at 7; Sherman, at gov/#!documentDetail;D=FDA2011-D-0611-0009.

33 *Siriam Akundi Associate VP, Biocon, FDA-2011-0611-0009, available at http://www.regualtions. Gov/#!documentDetail;D=FDA-2011-D-0611-0009*

34 *See e.g.*, Paul R. Eisenberg, Sr. VP of Global Regulatory Affairs and Safety, Amgen Inc., FDA-2011-D-0611-0033,

available at http://www.regulations. gov/#!documentDetail;D=FDA2011-D-0611-0033.

35 *See* Novo Nordisk, at note 23.

36 *Id*.; BIO, *supra*, at note 29.

37 The EU pharmaceutical legislation does not address interchangeability, which remains with the authority of the member states. Therefore, individual EU member states control prescription switching, not the EMA. *See* Howard Levine *et al*., *EMA Still Not Supporting Biosimilar Interchangeability*, Bioprocess Weblog, Oct. 30, 2011, *available at* http://www. bioprocessblog.com/archives/351 (accessed April 15, 2012).

38 PHSA § 351(i)(3).

39 PHSA § 351(k)(4).

40 *Id.*

41 *See* Sherman, *supra*, at note 13.

42 *Q&A Guidance*, at 11-12 ("At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment.")

43 *See* Novo Nordisk, at note 23.

44 Deena Beasley, *Slow, costly process stymies generic biotech drugs*, Reuters, Mar. 5, 2012, available at http://www.reuters. com/article/2012/03/05/us-genericbiotech-drugs-idUSTRE8240ZI20120305 (accessed April 12, 2012).

45 *See* FTC Report, at note 25.

46 Jonathan Mitchell, Aphelion Consultants, FDA-2011-D-0611-0006, available at http://www.regulations. gov/#!documentDetail;D=FDA2011-D-0611-0006 .

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48 *Q&A Guidance*, at 11-12.