Visante Webinar **Q&A**

FDA Draft Guidance for Hospital & Health Systems Compounding Under Section 503A of the FD&C Act

October 14, 2021 – The intent of this webinar was to bring to light some of the changes to this FDA draft guidance for Hospitals and Health Systems and highlight areas where there may be confusion requiring more clarity. **NOTE: The comment period for this guidance ends 12/6/21. Comments can be made on the Federal Register website at: https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act**. Visante highly recommends and encourages stakeholders to make their comments known as there are major discrepancies in this guidance as noted by the questions asked during the webinar presented below. **Disclaimer**: This Q&A document is intended to answer questions presented during the webinar as accurately as possible. However, the views expressed in this document are the author's and not intended to provide guidance for how any health care provider, hospital or health system should conduct themselves and/or their business. The opinion's expressed by this document do not necessarily reflect the opinions of Visante LLC.

Questions & Comments	Visante Answers
1. Do you have a link to the FDA announcement?	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hospital-and-health-system-compounding-under-section-503a-federal-food-drug-and-cosmetic-act
2. What do you think the FDA's timeline is for this proposal?	The comment period ends 12/6/21 (please see NOTE above for link to make comments). Since this is a draft guidance document, it could be withdrawn entirely, changed in consideration of comments or made final in its current form. However, the timeline for when this may or may not be made final is unknown.
3. Has the FDA completed an Economic Impact Analysis for this draft guidance document, as required by the law? (https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations)	Answered by Michael Storey: "it was in the federal register. Mostly addresses the cost of documenting reason for compounding."

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4. Do you feel that the FDA is completely shutting out and ignoring USP guidelines?	The release of this FDA Guidance in relation to the release of the latest revision to USP Chapters <795> & <797> seems timely with only a month between each release.
5. I see a direct conflict with USP and a disadvantage for centralized compounding at health systems	The "24-hour rule" certainly conflicts with current and proposed USP standards regarding beyond-use dates. Visante recommends submitting a formal comment by 12/6/21 at: https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act
6. Having inspected the majority of the outsourcers shipping into CA, there is vast quality differences across sites.	True. Not all 503Bs are created equal. Visante recommends a thorough vendor qualification be performed for 503Bs under consideration for use by hospitals and health systems. Visante is experienced in performing a vendor qualification and evaluation of 503Bs.
7. How many 503Bs do not have 483s?	Most 503Bs have been issued 483 observations forms. The range of observations by risk vary greatly among 503Bs which is why Visante recommends personally performing an evaluation or vendor qualification on any 503B being considered.
8. Do you think an automated dispensing cabinet could be considered control by the pharmacy and meet the 24hr requirement by the FDA?	Automated Dispensing Cabinets (ADCs) were not addressed by this guidance and clarity is needed to fully determine what the intentions and thoughts are by the FDA. Since ADCs are typically located outside of the pharmacy, this could be interpreted as being "transferred out" of the pharmacy which would put a burden on the pharmacy to change stock of compounded, non-patient specific medications every 24 hours. Visante recommends submitting this question for clarification by 12/6/21 at:

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9. I was wondering that as well. Depends on what "transfer out" of pharmacy means?	This was something the panelists debated offline and had mixed answers. Answers ranged from the end of compounding, exiting the pharmacy and exiting the hospital. This verbiage needs more clarification by the FDA. Visante recommends commenting on this specific point at: https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act
10. Do you feel the new guidance actually improves the ultimate patient safety?	Visante sees elements of the FDA trying to protect public safety through the guidance document. However, there is need for further clarification and input by hospitals and health systems for FDA consideration.
11. 24 hours seems arbitrary. What sterility information did the FDA use to dictate this time period?	The FDA's rationale for what the 24-hour rule was not made public. From a microbiological standpoint, it stands to reason the less time allowed for a potentially contaminated compounded medication to remain available for use, the less chance for an infection to occur, depending on the microorganism, rate of replication, route of transmission or administration and a microorganism's infection potential. Visante recommends this question be submitted to the FDA by 12/6/21 at: https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act

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12. If we have a consolidated service center that sends anticipatory compounded items directly to another licensed pharmacy within our health system, when does the 24-hour clock start? When it leaves the compounding location? When it leaves the pharmacy? When it's accessible?	This is a good question and needs further clarification by FDA as the guidance document was not clear to this regard. The presentation panelists also had this same comment. Visante encourages hospitals and health systems to comment directly to the FDA at: https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act
13. I read the 24-hour rule as applying only to items without a prescription; USP BUD requirements take over for patient-specific items.	That is correct, the FDA does not intend to take action against hospitals or health systems that are meeting the prescription requirement in section 503A of the FD&C Act for compounded medications. The challenge with the 24-hour rule would arise from dispensation of non-patient specific items to areas with anticipated need, for example dispensing stock doses of CSPs into an automated dispensing cabinet without a patient specific label. See response to question #8.
14. I would rather the FDA give guidance with USP 1079 for best way to transport (temperature control) compounded medications between hospitals within the same system.	This might make sense, USP Chapter <1079.2> does apply to compounding pharmacies and temporary temperature excursions from a product or preparations prescribed storage temperature. However, the FDA's primary concern is with sterility and temperature excursions for contaminated compounded medications would exponentially affect the proliferation of microorganisms.
15. Is a 503B product considered commercial?	Answered by Linda Panofsky: "503B = outsourcer. Commercially available usually means from an FDA approved manufacturer, usually via wholesaler distribution."

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16. So would you say that every time a dose of oral liquid omeprazole requires documenting a reason on the order/prescription?	According to the FDA draft guidance, yes, if the omeprazole oral liquid is made and distributed prior to the receipt of a valid prescription or chart order. The guidance says, “a statement is on file for each prescriber that covers each drug product that is compounded.” However, if limited quantities are made according to the FDA’s guidance for industry Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, the FDA does not intend to take any action. (Reference: https://www.fda.gov/media/97347/download)
17. Perhaps influence being applied from manufacturers pressuring FDA to take such a hard stance on essential copies?	This could be a possibility but is only speculation.
18. Agree with cost challenges. Can the FDA focus on working with manufacturers to prepare drugs the way we actually use/administer them?	Visante recommends that this question should be submitted to the Federal Register website by 12/6/21 at: **https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act**
19. What about "pop together" Mini-bag Plus. Does the 24 hours rule still apply? Mini-bag Plus isn't compounding is it?	Answered by Ken Fukushima: “Correct; minibag plus is not considered compounding.” However, there are caveats to this answer according to USP Chapter <797>. To further clarify this answer, USP <797> (2021 revision) has a section on “Proprietary bag and vial systems.” It says, “Docking and activation of proprietary bag and vial systems in accordance with the manufacturer’s labeling for *immediate* administration to an individual patient is not considered compounding and may be performed outside of an International Organization for Standardization (ISO) Class 5 environment.

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	Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed in accordance with this chapter, with the exception of 14. *Establishing Beyond-Use Dates*. Beyond-use dates (BUDs) for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling." (Italics were in original text)
20. The FDA definition of compounding is not the same definition as USP's. Most compounding as we know it (transfer from a vial to a bag) does not fall under the FDA Draft Guidance.	The USP defines sterile compounding, "as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication." (USP Chapter <797> 2021 revision) However, USP further clarifies that, "Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling. Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of this chapter only if: 1. The product is prepared as a single dose for an individual patient; and 2. The approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time." According to the FDA, "Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding includes the combining of two or more drugs. Compounded drugs are not FDA-approved."

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	(https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers) In the current version of USP Chapter <797> it states, "[NOTE-The FDA states that 'Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling' [21 USC 321 (k) and (m)]."
21. I was confused by the acknowledgement that hospitals have P&T committees that may approve essential copy compounding for specific patient populations, which supports an institutional review process could be acceptable. But in the list of requirements, they require a "statement on file for each prescriber." That is particularly difficult in academic medical centers.	Your understanding of the guidance is correct. As an example, the guidance states, "a P&T committee may determine that all patients in a neonatal unit administered certain oral medications should receive a compounded liquid dosage form because the approved drug product, available only in a tablet formulation, is medically inappropriate for them." Further, the FDA outlines circumstances that must be met with regard to "essentially copies," in which the agency does not intend to take action: • "The compounded drug product is administered only to patients within the hospital or health system. • The pharmacy obtains from the prescriber a statement that: specifies a change between the compounded drug product and the commercially available drug product; indicates that the compounded drug product will be administered only to patients for whom the change produces a significant difference from the commercially available drug product; and describes the intended patient population for the compounded drug product. • A statement is on file for each prescriber that covers each drug product that is compounded. • The statement is maintained in the hospital or health system pharmacy to address routine orders for patients for whom the change produces a significant difference."

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	Perhaps this could be met with a standard operating procedure for drugs determined by the P&T Committee that require an essential copy of a medication must be compounded for a particular patient population and a statement of understanding of the policy is signed by all applicable physicians. It is unknown at this time what the FDA will enforce as this is a draft guidance thus Visante recommends organizations consult legal counsel when determining their practice approach.
22. Thoughts on batch compounding that has the IDN's stability studies supporting longer dating than 24 hours....do you think FDA would still enforce the 24-hour rule?	There does not seem to be any exceptions about stability studies in this guidance. According to the current language in the guidance, the 24-hour rule would be enforced regardless of any stability studies performed by the IDN. However, if that same hypothetical situation were to come from an FDA registered outsourcing facility (503B), the 24-hour rule would not be enforced provided that a stability study has been performed justifying the extended beyond-use dating. Again, this is guidance for hospitals and health systems, not registered outsourcing facilities.
23. What is the usual timeline for when this guidance would become finalized?	Previously answered above, please refer to question 2.
24. Most preparations made in a hospital are made in accordance with official product labelling. USP and FDA have different definitions of compounding which adds to confusion.	The FDA and USP seem to have adopted similar language for commercially available products that are prepared according to the manufacturer's instructions. Both organizations regard this NOT to be considered compounding. See questions 20 above for further explanation.
25. How many 503B have closed due to the cost to support or are they expanding in number now?	Visante does not have an exact number but knows there has been contraction and consolidation in the market space.

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26. You can still prepare vancomycin from a commercial bulk, even if an RTU product is available. The commercial bulk is approved by the FDA.	That is correct, however the final dose, diluent, container closure, route of administration etc will determine if the preparation violates the FDA guidance on essential copies.
27. There is a vast difference between a 503B and a hospital pharmacy.	This was discussed during the webinar. A 503B is held to cGMP standards and hospitals are supposed to be compliant with USP Standards. There is a vast difference between these two types of standards. The decision for a hospital pharmacy to acquire or build a 503B needs to be taken very seriously as there are great costs involved in becoming compliant with the FDAs cGMP requirements.
28. Purchasing from 503B can also be unreliable, due to shortages, etc. Then falls back to pharmacy for compounding.	There are certainly issues around the idea of 503Bs meeting the needs of all situations. For example, several ophthalmologists spoke before the FDA stating that some of the medications that they use for surgeries are not prepared by 503Bs due to the lower demand for certain compounded injections. The ophthalmologists stated that if they weren't allowed to get some of these medications from 503A compounding pharmacies and keep on hand for when a need arises, patients would go without critical treatments like antibiotics for eye surgeries. (Reference: https://www.fda.gov/media/126864/download) Another article to read about the role of outsourcing facilities in the drug supply chain can be found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7453203/pdf/main.pdf Between this guidance and the FDAs MOU, pharmacies are being forced to make tough decisions with patient care and safety in the balance.

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29. “Leaving a compounding facility” needs to be defined.	Reference: Circumstances When FDA Generally Does Not Intend To take Action (2) The compounded drug products are used or discarded within 24 hours of transfer out of the pharmacy. Agreed, this idea of transferring out of the pharmacy needs to be clarified as to what the exact meaning and intention of the FDA is supposed to be by this rule. Visante recommends submitting this as a comment by 12/6/21 at: https://www.federalregister.gov/documents/2021/10/07/2021-21970/hospital-and-health-system-compounding-under-section-503a-of-the-federal-food-drug-and-cosmetic-act