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Enforcement Throughout the Supply Chain

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- Opinions are Mine and not those of Duane Morris
- The Material in this Presentation is not Intended as Legal Advice
- You Should Consult with Your own Counsel for Specific Questions

What to Expect When FDA's Inspecting

- No *new* rules at play—continue to inspect against the FDCA and cGMP regulations, and all parties continue to be subject to the same requirements.
- FDA routinely requests and reviews evidence of Quality Agreements (or the lack of Quality Agreements).
  - Implication: Compliant contract drug manufacturing without a written Quality Agreement is difficult.

WL to Contract Facility: I Know a Guy Who Knows a Guy… (October 2016)

- Charge: 211.165(a)--"You released finished drug products…to your customer without conducting or reviewing release testing to determine if your products conformed to their specifications…FDA laboratory analysis indicated that the drug was sub-potent for both labelled active ingredients…"
- "Your written quality agreement with [Customer] indicates that [Customer] is responsible for final product release to the market. The same agreement also states that [you (Contract Facility) are] responsible for release of products to the customer, but *you did not conduct any laboratory analysis to determine whether your products conformed with specifications prior to releasing them to [your customer]*."
- *Based on FDA's analysis, Customer recalled all lots in expiry.*

WL to Contracted Facility: Everything But the Kitchen Sink (December 2016)

- FDF: 211.100(a) (no PV); 211.165(e) (no method validation); 211.160(b) (no data for anti microbial effectiveness of preservatives; 211.166(a) (inadequacy of stability program)
- API Deviations: lack of PV; cleaning validation; failure to establish impurity profiles; failure to verify USP methods
- Repeat **Deficiencies**
- ***"You are responsible for the quality of drugs you produce, regardless of agreements in place with product owners.*** You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FDCA for safety, identity, strength, quality, and purity."

WL to Contracted Facility: CHANGES! (January 2017)

- Failure to conduct adequate change controls prior to using new materials/process. Failure to ensure sufficient change control oversight to assure the new materials/process were acceptable for use in the commercial operation.
- "You manufacture [drug] under contract on behalf of [Owner], which holds the [application] for [finished drug]. The process changes discussed above were not approved by FDA before you manufactured, or your customer, [Owner], distributed, [finished drug]. Specifically, [new materials/process] were used in commercial production prior to approval. These [new materials/process] were not reviewed and approved by the Agency for their suitability for [drug] manufacture, even though the changes in the [material/process] have a substantial potential to adversely affect the identity, strength, quality, purity or potency of [finished drug].
- *Plus: CC to Customer*

WL to Contracted Facility: Separation Anxiety (June 2017)

(also, we need to talk about your lab)

- Three Charges
  1. ***Your firm failed to maintain adequate separate defined areas necessary to prevent mix-up. (21 CFR § 211.42(c)).***
  2. Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a))
  3. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products***, including drug products manufactured, processed, packed or held under contract by another company (211.22(a)).***
- Special Paras: Repeat Observations + Contract Mfg
- CC Customer

Other Things We have Seen in WLs

- Not Allowing an Inspection
- Delaying an Inspection
- Shredding Documents During an Inspection
- Refusing to Allow Video or Photographs
- Data Integrity Issues

WL to Owner: YOU get a Warning Letter, Too! (July 2017)

Drugs Made for You by [Contractor]

You have engaged [Contractor]to manufacture [drug]. These products, which you test using the [micro] method discussed above, are adulterated as enumerated in the preceding violations. ***They are also adulterated for the reasons set forth in Warning Letter XXXXX, issued by FDA to [Contractor] on June XX, 2017. Among other things, [Contractor] manufactured your oral solution drugs using the same equipment in which [Contractor] manufactured toxic industrial-grade car washes and waxes.*** You are responsible for ensuring that all of your products are manufactured in accordance with CGMP, including oversight of the manufacturing operations conducted by your contractor, [Contractor], on your behalf. Contractors are extensions of the manufacturer, and you are required to ensure that your drugs are made in accordance with section 501(a)(2)(B) of the FDCA