GMP REGULATORY INTELLIGENCE NEWSLETTER

Week of October 20th, 2019

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CONTENTS:
New laws, Regulations, Guidance, Concept papers published or posted this week. You'll also get updates on: FDA warning letters, FDA drug recalls, FDA import alerts for drugs and selected devices, Eudra GMDP reports of non-compliance, Regulatory actions that were published this week, including links to the source documents.

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GMP REGULATORY INTELLIGENCE

WEEKLY SURVEILLANCE ON NEW REGULATIONS, GUIDANCE, & ENFORCEMENT ACTIONS

SUMMARY SCAN, Week of October 20, 2019

Two of the three guidance from FDA this week address homeopathic products. Perhaps the FDA is finally beginning their 'modernization' of the regulation of these products. None too soon! Other guidance is provided by Hong Kong, Malaysia and TGA. We also provide the usual collection of non-guidance publications.

Enforcement this week includes only two drug warning letters, one of which was issued to a PET drug manufacturer. Firms that are bedeviled by mold findings in both surface and personnel EM would be well served to read this warning letter and the one issued to a sister site last year. We have a few recalls and a limited number of import alerts this week.

Happy Reading,
Barb

REGULATIONS and GUIDANCE DOCUMENTS

FDA:

- **QUALITY:** The FDA published a final, level 2 guidance, 'Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers.' The purpose of this guidance is to ensure firms know how to submit information in a way that it isn't lost or misplace or confused…and to prevent Refusal actions by the FDA.
- **HOMEOPATHIC DRUGS:** The FR announced the withdrawal of Compliance Policy Guide 400.400 'Conditions Under Which Homeopathic Drugs May be Marketed' that was published in 1988. This represent the beginning of FDA's stated intent to modernize the regulation of these products. See also the FDA press release on this topic.
- **HOMEOPATHIC DRUGS:** The FR announced availability of a revised draft guidance on "Drug Products Labeled as Homeopathic". Similar to the initial publication of this draft guidance, the FDA describes how they intend to prioritize and enforce actions against these manufacturers. Lachman Consultants reports on this too.

EMA: none this week

OTHER:

- **Hong Kong,** Pharmacy and Poisons (Amendment) Bill 2019. The Bill amends the regulations to address advanced therapy products. Also published was a press release.

- **Malaysia** published a guidance on atypical active pharmaceutical ingredients. The original publication became effective April 2018. The current update now addresses excipients, food additives and cosmetic ingredients that are used as APIs in medicines.
- **TGA** published 'Microbiological Quality of prescription and over-the-counter medicines.

NON-GUIDANCE PUBLICATIONS FROM HEALTH AUTHORITIES AND RELATED GOVERNMENT ORGANIZATIONS

- **MHRA** published the following updates:
  - Comparator products in Bioequivalence/Therapeutic Equivalence studies after Brexit.
  - Renewing Marketing Authorisations for medicines after Brexit
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  - Webinars: preparing to make submissions to the MHRA after Brexit
  - MHRA Inspectorate blog: Inaugural GCP Laboratories Stakeholder Engagement Meeting

- **EMA:**
  - How to Prepare and Review a Summary of Product Characteristics
  - Enhancing consistency in wording of therapeutic indications to support healthcare decision-making'
  - The EC's Medical Device Coordination Group published an update to Questions and answers: Requirements relating to notified bodies.
  - Recommendations on eligibility to PRIMIE scheme – Adopted at the CHMP meeting of 14-17 October 2019
  - The GDP Association of the ECA published a Q&A on Good Distribution Practices.
  - PRESS RELEASE: Dialogue with Chinese authorities on medicine regulation

- **FDA,** OIG, GAO etc. published the following/updates:
  - **CDRH** published a new module in CDRH learn on "How to Study and Market your Device" on October 21, and "Specialty Technical Topics" on October 2, 2019.
  - Eight **tobacco products** have been granted the 'first-ever" modified risk designation.
  - FDA released a second LC Mass Spectrophotometric test method for NDMA detection in ranitidine.
  - Updates and Press Announcements on NDMA in Zantac
  - Progress toward Track and Trace compliance, '2019 Update: Barcode Readability for DSCSA 2023 Interoperability"

- **OTHER:**
  - **HPRA:** published a revision to the Guide to Clinical Trial Applications.
  - **HPRA:** 2018 Annual Report
  - **TGA:** Annual performance statistics report
  - **PMDA** Alert for Proper Use of Drugs: No 12

ENFORCEMENT

WARNING LETTERS:
FDA's focus on **e-cigarette supplies** continues to be the subject of a flurry of warning letters. In areas we cover, there was one warning letter to an API site in China and one PET drug manufacturer posted this week.

Also, the **Federal Trade Commission** and the FDA issued a joint warning letter to **Rooted Apothecary LLC** in Naples FL. The warning letter is based on a review of the firm's website and other social media sites from which FDA concludes the **CBD products** are unapproved new drugs.

- **DRUGS: Jiangsu NHWA Pharmaceutical Co., Ltd** (China) received a warning letter on September 10, 2019 based on the outcome of an inspection ending April 5, 2019. The firm manufactures a variety of USP **APIs**, including those that were imported into the US by compounding pharmacies. The firm decided they would not ship any products to the US until the remediations have been completed and verified by the FDA to be effective. The warning letter does not mention imposition of an import alert. Deficiencies include but are not limited to:
  - The firm's stability protocol and methods are based on the Chinese Pharmacopoeia but did not demonstrate that they are equivalent to those in the USP. Required tests in the USP are not identified in the Chinese Pharmacopoeia. Thus, the products distributed into the US are adulterated. Further, degradation studies were not validated. The firm is asked to provide the following in response to the warning letter:
    - *Your commitment to using current USP compendial methods until any alternative methods have been demonstrated to be equivalent or better than the USP methods.*
    - *A comprehensive study that determines whether your test methods for your API are equivalent to, or better than, the USP method, if you are not using current USP compendial methods. Include all findings and deviations encountered in assessing whether your alternative method is equivalent or superior to the USP compendial method. For FDA's current thinking regarding analytical test method validation, see Analytical Procedures and Methods Validation for Drugs and Biologics at https://www.fda.gov/media/87801/download.*
    - *Updated test results using a validated test method (e.g., USP method) of all reserve samples for all drugs released to the U.S. market within expiry to ensure that your drug products conform to appropriate standards of identity, strength, quality, and purity.*
    - *Your action plan to address any product quality or patient safety risks for your drug products in U.S. distribution, including potential customer notifications, recalls, or market withdrawals.*
    - *Your procedure for documenting and investigating any deviations from laboratory control procedures.*
  - The firm did not adequately investigate when foreign particles are identified during color/clarity testing. The root cause and source of the particles was not identified. In response the firm is asked to provide:
    - *A retrospective, independent review of all invalidated OOS (in-process and finished testing) results for products currently on the U.S. market within expiry. Assess*

whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that establish laboratory root cause, ensure that other laboratory methods vulnerable to the same root cause are identified for remediation.

- *A thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, batch failure history) for any OOS results with inconclusive or no root cause identified.*
- *A corrective actions and preventive actions (CAPA) plan that identifies manufacturing root causes and specifies meaningful improvements.*
- *A review and remediation of your system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigations procedure includes:*
  - *Enhanced quality unit oversight of laboratory investigations*
  - *Identification of adverse laboratory control trends*
  - *Resolution of causes of laboratory variation*
  - *Investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified*

- **DRUGS: Sofie Co., dba Sofie** (Sanford FL) received a warning letter on October 10, 2019 based on the outcome of an inspection ending April 12, 2019. Note the warning letter was not sent to the site, but was sent to the President and CEO in Dulles, VA. The warning letter **identifies deficiencies that have been identified at other sites** in the company's network including a warning letter issued on September 24, 2018 after an inspection at a site in Haverhill, MA. The firm manufactures drugs used in **positron emission tomography** (PET) imaging studies.

  FDA states "*These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs is inadequate. Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems, processes, and the products manufactured conform to FDA requirements.*"

  The single deficiency states that the facilities are not adequate to prevent product contamination that might have an adverse impact on product quality. PET drugs are sterile, intended for parenteral administration. The EM program repeatedly covered micro-organisms including multiple fungal isolates in ISO 5 areas. The firm did not put any additional controls or measures in place. Several causes of the **mold** were identified including a water leak in the raw material acceptance room but remediation actions were not adequate. Fungal isolates were also isolated from personnel monitoring. In response to the warning letter the firm is asked to provide:
  - *In response to this letter, provide:*
    - *Comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide an independent assessment that includes, but is not limited to:*
      - *oAll human interactions within the ISO 5 area*
      - *o Equipment placement and ergonomics*
      - *o Air quality in the ISO 5 area and surrounding room*
      - *o Facility layout*

o Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)
o Adequacy of procedures to ensure ongoing maintenance and control of your facility

- *A detailed remediation plan with timelines to address the findings of the contamination hazards risk assessment. Describe specific tangible improvements to be made to aseptic processing operation design and control.*
- *Your action levels for ISO 5 surfaces, air, and operator gloves, and revised procedures that describe appropriate response to contamination (i.e., 2:1 CFU) in critical environments.*
- *A list of all results outside action limits for ISO 5 and ISO 7 areas since April 1, 2019. Also include all organism identifications and the location(s) where microbe(s) were recovered. Also include investigations associated with any action level excursions in your classified environments.*

FORMS 483 from FDA and other publicly available sources: none this week

COMPOUNDING PHARMACIES / OUTSOURCING FACILITIES: none this week

OTHER:

- **Proposal to withdraw drug approval:** FDA intends to withdraw an ANDA approval for generic trandolapril tablets and offers the firm, **InvaGen**, an opportunity for a hearing. To support its initial approval, the firm submitted **bioequivalence data** generated by **Cetero Research** in Houston, Texas generated between 2005 and 2006. FDA's BIMO inspections at Cetero Research raised significant concerns about the authenticity of the data they generated. FDA identified data manipulation and falsification at the site (forms 483 HERE and HERE). In July 2011, FDA notified all firms that relied on bioequivalence data from Cetero Research between 2005 and 2010 needed to be repeated or confirmed. InvaGen repeatedly failed to comply with this requirement, and now FDA is moving to rescind the ANDA approval. My question is why did this take 8 years, and how many other firms have failed to repeat the bioequivalence studies?
- **Assertio Therapeutics** received a complete response letter (CRL) for an NDA for injectable long-acting cosyntropin (ACTH). The press release announced that "*the primary focus of the CRL relates to the FDA determination that certain pharmacodynamic parameters were not adequately achieved.*"
- **TGA** Laboratories testing of ranitidine medicines.
- **WHO** published a public inspection report based on the inspection of **Lupin Limited**, Unit-1, in Pithampur, India. The inspection was conducted between March 18 and 22, 2019 and covered Norethisterone / Norethindrone.

Drug Recalls Posted October 23, 2019

Recalling Firm	Class	Product(s)	Reason
Jubilant Cadista	II	Pantoprazole Sodium Delayed Release Tablets, USP, 40 mg,	CGMP Deviation: Presence of dark brown discoloration on edges of tablets
Atlas Pharmaceuticals	II	Ascorbic Acid Sterile Injection Solution,	Labeling: Not Elsewhere Classified; product is labeled as

			"Non-Corn Source" however the product is from a corn source.
Spectrum Laboratory Products	II	Fentanyl Citrate USP, Active Pharmaceutical Ingredient	CGMP Deviations: Received notice from supplier that there is potential glass contamination.
Aurobindo Pharma USA Inc	II	Dextroamphetamine Sacharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets, Mixed Salts of a single Entity Amphetamine Product)	Superpotent Drug: Amphetamine Mixed Salts 20mg have been found to be out of specification for weight and thickness.
Macleods Pharma USA	II	Pioglitazone Hydrochloride Tablets USP	Superpotent
Ingenus Pharmaceuticals LLC	II	Leucovorin Calcium Injection,	Crystallization: Presence of particulate matter identified as API crystallization
KVK-Tech Inc	III	Methylphenidate Hydrochloride Oral Solution	Presence of Foreign Substance; Fiber particles.

Unclassified Recalls or Alerts or Seizures

Firm	Product(s)	Reason
Dr. Reddy's Laboratories	All ranitidine products	confirmed contamination with N-Nitrosodimethylamine (NDMA) above levels established by the FDA
Perrigo Company	All ranitidine products	confirmed contamination with N-Nitrosodimethylamine (NDMA) above levels established by the FDA

FDA Import Alerts posted this week

IMPORT ALERT 66-40, Detention Without Physical Examination of Drugs from Firms Which Have Not Met Drug GMPs		
	NONE	
IMPORT ALERT 66-41, Detention Without Physical Examination of Unapproved New Drugs Promoted in the U.S.		

Oct 23, 2015	**Hongsamdan Co., Ltd** 17-2 Jayang-Dong , Dong-Gu, KR-30 KOREA, REPUBLIC OF (SOUTH)	SOUTH KOREA
IMPORT ALERT 99-32, detention without physical examination of products from firms refusing FDA foreign establishment inspection		
Oct 22, 2019	**Sichuan Qingmu Pharmaceutical Co., Ltd** Dongpo District , No. 55 South Shunjiang Avenue; East Economic Development Zone , Meishan, Sichuan CHINA	CHINA

Corporate Integrity Agreements: none

Consent Decree Agreement: none

Editor's Choice - Stories of the Week:

- **The NYT** reports on 'Making Drug Companies Pay for the Opioid Epidemic'
- **Reuters** reports that **'**Johnson & Johnson CEO testified Baby Powder was safe 13 days before FDA bombshell**.'**
- Duodenoscopes yet again. **FierceBiotech** reports that FDA has cleared the use of disposable, sterile covers for these devices in an attempt to reduce bacterial contamination that can be spread from patient to patient.