REDICA Systems

GMP REGULATORY INTELLIGENCE

MONTHLY SUMMARY | April 2021

Weekly Summaries by Barb and Jane

WEEK OF APRIL 2

We provide a small group of guidance in the area of GMP, and GCP/GVP this week. An interesting one from FDA addresses questions from ANDA sponsors that they received during the pandemic. Would that have been published a few months earlier, but better late than never. We also provide a collection of non-guidance this week from global authorities.

We have no drug, or device, or outsourcing facility GMP warning letters this week, just one untitled letter from CBER. We provide one form 483 from an outsourcing facility that is particularly troubling from a sterility assurance perspective. The third party janitorial service identified extensive mold contamination on facility surfaces. We also provide the April 2020 form 483 issued to Emergent BioSolutions in Baltimore Maryland. They have been front and center for the news items in Editors Choice. We also provide drug shortages, import alerts and drug and device recalls. We did not have any reports of GDMP non-compliance from EDQM in Europe.

We provide an ever-growing collection of documents in the animal health area as well as COVID-focused guidance and actions. We continue the comprehensive coverage of global health authorities regulations, guidance, and other publications, animal health guidance and information, specific company news, product approvals, news from trade organizations along with coverage of COVID-19 actions and animal health laws and guidance.

WEEK OF APRIL 11

Four documents from the FDA this week including two device announcements and a long-awaited guidance from FDA on “remote interactive evaluations” of facilities, records and documents. CBER also published the list of guidance they plan to issue this year. Nothing in the GMP area from EMA or MHRA this week.

As for enforcement this week we have a drug GMP warning letter, the fourth now, that is based exclusively on the review of requested records rather than on site inspections. This most recent site is located in Cali, Colombia. EDQM posted a report of non-compliance for a wholesale distribution site in Romania. We have a full list of drug and device recalls and drug product shortages, particularly in the US.

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WEEK OF APRIL 18

We take this opportunity to introduce another of the Redica Systems experts, Jerry Chapman who will be managing the animal health area. Senior GMP Quality Expert Jerry Chapman has over 40 years in the pharma industry. He designed and implemented GMP external monitoring systems at both Lilly and Elanco. At Redica Systems, Jerry is a key player in building Expert Systems and authors the Conference Spotlight. He has consulted in numerous areas of GMP compliance for the 503B compounding and animal health industries and teaches undergraduate classes on manufacturing deviation investigation and documentation.

This was a sparse week for publication of regulations and guidance across the GXP spectrum.

Warning letters were non-existent again this week having none posted for drugs, API sites, device manufacturers, or compounding pharmacies. We do, however, have two items that should be read by staff at gene and cell therapy firms. EDQM posted an interesting report of GMP non-compliance to the manufacturer of an ATMP immunotherapy product. Definitely worth reading if you are in the cell and gene therapy field. We also provide the form-483 issued to Emergent BioSolutions on April 20, 2021. I would encourage any firm that manufactures product(s) using multiple viral vectors to read this and consider their own operations and means by which they prevent cross contamination.

We provide an ever-growing collection of documents in the animal health area with Jerry's attention in this area along with COVID-focused guidance and actions. We continue the comprehensive coverage of global health authorities regulations, guidance, and other publications, animal health guidance and information, specific company news, product approvals, news from trade organizations along with coverage of COVID-19 actions and animal health laws and guidance.

WEEK OF APRIL 25

In the guidance area, one of the most interesting in the GMP field is the Q&As on starting materials for ATMP products. This should be required reading for all in the gene and cell therapy area. EMA also updated their webpage on nitrosamine assessments, which are now past due. Firms are encouraged to submit these ASAP. We include a couple of items in the area of GCP/GLP/GPV, and RA/Filing.

The EMA provides an update on submission of risk assessments for potential nitrosamine contamination of drug products and APIs. The original deadline has passed and EMA encourages those who have not yet submitted their assessments to do so as soon as possible. In the non-guidance section we post a memorandum that resulted from a meeting of FDA with Boehringer Ingelheim.

Enforcement this week included four warning letters to compounding pharmacies, a couple of these were issued more than 2 years after the inspection. Personally, that makes no sense, but perhaps they were buried on someone's desk. We also have the first letter of non-compliance issued to a firm that failed to update the clinical trials online database. Finally. We include the usual collection of drug and device recalls, and import alerts in the expanded collection of areas we now follow.

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guidance and information, specific company news, product approvals, news from trade organizations along with coverage of COVID-19 actions and animal health laws and guidance.

Regulations and Guidance Documents

All COVID-19 guidance from FDA, EMA, and MHRA are now included in the PUBLIC HEALTH/ COVID-19 Guidance section. These are temporary and will be withdrawn or rescinded when the pandemic is over. This way we won't end up with the longer-lasting regulations/guidance lost in that other large collection.

FDA

- **RA, Generics:** The FDA posted a final guidance, without consultation, on "Development of Abbreviated New Drug Applications During the COVID-19 Pandemic --- Questions and Answers." This includes fifteen questions that FDA received from generic manufacturers during the pandemic. Not to put too fine a point on it but we are more than one year into the pandemic, one might have hoped this would have been published sooner.
- **CBER** published their guidance agenda for 2021, identifying guidance documents they plan to publish during the calendar year. The guidance proposed include the areas of Blood and Blood Components, Tissue and Advanced Therapies (this include gene and cell therapies); vaccines and changes to approved applications for certain biological products.
- **GCP, GMP:** FDA released a final guidance "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency." This guidance describes ways that FDA "conducts an evaluation" at a facility. This applies to drug manufacturing facilities including biological products, outsourcing facilities and facilities subject to BIMO inspections.
    - **Redica Comment:** This falls into the better late than never category of guidance but still avoids stating that FDA is going to conduct remote inspections. Rather, these are "remote interactive evaluations of documents and records," and the guidance specifically states the FDA will not issue a Form 482, notice of inspection. I can only assume that there is something in the legality of this that troubles the General Counsel. The close out meeting will include presentations of a list of observations but this will not represent issuance of a form 483. Firms are encouraged to respond to that list of observations within 15 business days. The guidance does address remotely viewing operations at the facility. So, we will have both facility evaluations and documents and record reviews. A significant improvement over existing practices is that FDA is going to permit interactive portions for this "evaluation" and that should significantly improve the situation for industry. FDA issued a notification from the Office of Global Policy and Strategy with additional information. How this will actually work out remains to be seen. 'Watch this space' as an MSNBC host frequently says.
- **Devices:** The FR is withdrawing proposed exemptions for certain medical devices that were put in place at the beginning of the COVID-19 pandemic. These include 83 class II devices and 1 unclassified device that would have been exempted from premarket notification.
    - **Redica Comment:** This publication in the Federal Register documents the evaluation by the FDA in discussion with HHS concerning a Notice published on January 15,

2021 exempting 84 devices from premarket notification. Upon review, the FDA found that the approach and decision to exempt the devices listed in the Notice appropriately addressed patient risk. The determination by HHS at the time was based upon adverse events reporting data in the MAUDE database only and in certain circumstances, only a subset of those events resulting in deaths into their consideration. The information in the MAUDE has challenges due to underreporting and potential reporting inaccuracies which makes it difficult to paint a full picture of the risk profile for a device. The FDA has a premarket notification process that manufacturers are required to follow in bringing Class II devices to market. In the Federal Register, the FDA indicates that these devices need to go through this premarket notification process to ensure a level of safety and effectiveness. Therefore, resulting in the removal of the listed devices as being exempt in the Notice published on January 15, 2021.

- **Devices:** The FR announced a request for comment, and a 30-day comment period, on a **proposal** to remove the exemption from submission of a premarket notification for Class I surgeon and exam gloves.
    - **Redica Comment:** This Federal Register publication provides an explanation by the FDA to rescind the notification of an exempt status for seven (7) types of gloves intended for use either in patient examination or by a surgeon. Due process of premarket notification was not followed for these devices. The FDA is seeking to reverse the decision by HHS in a Notice published on January 15, 2021 to make these Class I devices exempt.
- **Devices:** The FR published a **final rule** on 'Medical Device Classification Regulations to Conform to Medical Software Provisions in the 21st Century Cures Act.' *FDA is amending the "identification" description in eight classification regulations, so that they no longer include software functions that are excluded from the device definition by section 520(o)(1) of the FD&C Act and thus are not subject to FDA's device statutory authority. Among the software functions excluded from the definition of device in the FD&C Act, most relevant to this rule are the software functions excluded by section 520(o)(1)(D) of the FD&C Act.*
    - **Redica Comment:** This rule updates eight classification regulations by amending these regulations to exclude software functions that no longer fall within the device definition under 201(h) of the FD&C Act.
- **Compounding Pharmacies:** Memorandum of understanding - Addressing Certain Distributions of Compounded Human Drug Products Between the [insert STATE BOARD OF PHARMACY OR OTHER APPROPRIATE STATE AGENCY] and the U.S. Food and Drug Administration. Compounding pharmacies will now be limited to distributing 5% of their compounded drugs out of state. Many distribute far more than this and thus economic impact may be significant for them. This rule becomes effective October 27, 2021. However, "*The 5% limit to intrastate shipping will not apply to pharmacies located in states that sign an MOU with the FDA guaranteeing greater information sharing and complaint investigations.*"
- **Devices, Standards:** FR Notice Modifications to the List of Recognized Standards, Recognition List.

EC / EMA / EDQM

- **ATMP, GMP:** Advanced Therapeutic Medicinal Products: Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs.
    - **Redica Comment:** This set of seven questions and answers addresses GMP controls that apply to starting materials used in the production of ATMPs. Starting materials for this class of products is defined as "*...all the materials from which the active substance is manufactured or extracted. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells."* Question 3 has a clear tabulation of which requirements apply to which materials.
    - Further, for starting materials, not all the requirements in Part IV of the GMP Guide (The Guide on ATMP GMPs) are required to be met. *ATMP manufacturers [however] have the responsibility to verify that appropriate GMP requirements are implemented for the manufacturing/testing of the starting materials according to the methodology described in the questions 4 and 5 of the documen*t. This is similar to the requirements for excipients where the sponsor must decide which elements of GMP are appropriate to require for a given excipient. ATMP manufacturers are required to take a risk based approach in identifying and understanding the risks that the starting materials pose to the final ATMP. Thus, this may well be different for different products, and one cannot apply a one-size-fits-all approach in this area.
- **Impurities, Nitrosamines, Risk Assessments, EMA:** updated their information on nitrosamines. *"Update: The deadline has passed for submitting step 1 risk evaluations for medicines containing chemically synthesised active substances. Any marketing authorisation holder for such products that has not yet submitted a step 1 risk evaluation should do so as a matter of priority, in line with the CHMP's Article 5(3) opinion. Marketing authorisation holders for medicines containing biological active substances should respect the step 1 submission deadline of July 1, 2021."*

MHRA

- None this month.

OTHER

- **WHO:** Draft working document for comments. WHO guidelines on the transfer of technology in pharmaceutical manufacturing (QAS/20.869/Rev.1). Comments close June 1, 2021.
- **WHO:** Policy – Evaluating and publicly designating regulatory authorities as WHO listed authorities (QAS/19.828/Rev. 1)
- **ICH:** The ICH Q3C(R8) Guideline reaches Step 4 of the ICH Process. The ICH Q3C(R8) Guideline reached Step 4 of the ICH process in April 2021.

GLP, GCP, GVP Regulations and Guidance

FDA

- **GVP:** The FR announced availability of version 2.2 of the 'Specifications for Preparing and Submitting Postmarket Individual Case Safety Reports for Vaccines." While the FR announcement is dated April 5, 2021, the document is from November 2020.
- **RA-Preclinical, Draft Guidance:** The FR announced availability of a draft guidance, 'Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases." Comments close on June 28, 2021

EC, EMA, EDQM

- The **EMA** posted an overview of comments on the 'ICH Reflection Paper on Proposed ICH Guideline Work to Advance Patient Focused Drug Development.' This reflection paper was open for comments that closed on March 7, 2021.

MHRA

- None this month.

OTHER

- **ICH:** Expert Working Group has published, The Draft Principles of ICH E6 Good Clinical Practice (GCP). R3 is intended to address "the application of GCP principles to the increasingly diverse trial types and data sources being employed to support regulatory and healthcare related decision-making on drugs, and provide flexibility whenever appropriate to facilitate the use of technological innovations in clinical trials." The EWG will be hosting a global web conference to present the current draft on May 18-19, 2021.
- **China, RA-Clinical, GCP, GVP:** Announcement of the Center for Drug Evaluation of the State Food and Drug Administration on the issuance of the "Guiding Principles of Real World Data Used to Generate Real World Evidence (Trial)" (No. 27 of 2021)
    - Attachment: "Guiding Principles of Real World Data Used to Generate Real World Evidence (Trial)"

Filings and Labeling

FDA

- None this month.

EC / EMA / EDQM

- **Human Drugs, Biologics, RA Labeling, RA Filing, RA CMC**: Public guidance - Parallel application for EU-M4all (Article 58) opinion and Centralised Marketing Authorisation procedure
    - Overview of comments received on 'Public guidance - Parallel application for EU-M4all (Article 58) opinion and Centralised Marketing Authorisation procedure' (EMA/104275/2021)
- **EMA, Forms / Templates, RA-Labeling, GMP, Human Drugs, Biologics, RA-Filing:** EMA updates "Mutual-recognition, decentralised and referral product-information template version 4.2". Version 4.1 was last updated on February 17, 2020. View track change version. The changes for version 4.2 relates to the text for the EEA and the United Kingdom (Northern Ireland).

OTHER

- None this month.

Non-guidance Publications from Health Authorities and Related Government Organizations

FDA

- **Meeting minutes:** GDUFA III Reauthorization Negotiation Sessions (updated). This link provides meeting minutes for all the GDUFA III negotiation sessions. The most recent is from the March 18, 2021 session.
- **Proposed legislation:** Congress: H.R.2435 — 117th Congress (2021-2022). To amend the Federal Food, Drug, and Cosmetic Act to require the label of a drug that is intended for human use and contains an ingredient that is derived directly or indirectly from a gluten-containing grain to identify each such ingredient, and for other purposes. Sponsor: Rep. Ryan, Tim [D-OH-13] (Introduced 04/08/2021) (All Actions). Text of the legislation has not yet been posted.
- **MAPP 5310.3 Rev.2** Office of Pharmaceutical Quality Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes *"This MAPP specifies both the criteria that OPQ uses to make an expedited review designation and the roles and responsibilities of the OPQ quality assessment team members for making this designation."*

- **MAPP 7700.5** Rev.1 Office of Translational Sciences Critical Path Innovation Meetings Policy and Procedures. "*The purpose of this MAPP is to delineate the roles and responsibilities of CDER staff and outline the procedures to be followed for a Critical Path Innovation Meeting (CPIM)…A CPIM is a forum for the general discussion of challenges in drug development—as well as innovative strategies to address them—and is not specific to any particular medical product. The CPIM is not intended to replace discussions with review divisions on drug specific development efforts.*"
- **Device, MDSAP:** MDSAP AU P0002.006 Audit Approach
- **MAPP 4100.1 Rev.2** Office of Management CDER Co-Sponsorship Agreements for Events Staff Resources and Services
- FDA Published the following, Memorandum of Meeting Boehringer Ingelheim March 17, 2021, 12:00 to 1:00pm Via Teleconference SUBJECT: Meeting with Boehringer Ingelheim and their counsel to listen to their comments and views on FDA's interpretation of the statutory term "strength" in the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).
- **GCP:** FDA has taken its first action for a failure to submit required clinical trial results to clinicaltrials.gov. After notifying Acceleron Pharma in JUL 2020 that they appeared to be in noncompliance with the requirement, on April 27, 2021, FDA sent Acceleron a Notice of Noncompliance. Acceleron now has 30 calendar days to submit the required information or face monetary penalties of up to $10,000 a day for each day of violation.
- **US NIST:** NISTIR 8276 Key Practices in Cyber Supply Chain Risk Management: Observations from Industry. Download: NISTIR 8276 (DOI); Local Download; Cyber SCRM Key Practices and Case Studies
- **US NIST:** 800-161 Rev. 1 Cyber Supply Chain Risk Management Practices for Systems and Organizations. Download: SP 800-161 Rev. 1 (Draft) (DOI); Local Download; Comment template; Workshop; NIST's Cyber Supply Chain Risk Management Program Draft for comment
- **GAO:** Prescription Drugs: U.S. Prices for Selected Brand Drugs Were Higher on Average than Prices in Australia, Canada, and France GAO-21-282, March 29, 2021
- Changes to the eCFR for Title 21 Food and Drugs: Medical Devices, Controlled Substances.

EC, EMA, EDQM

- **GVP:** European Union individual case safety report (ICSR) implementation guide Adopted. First published on April 30, 2014, Last updated April 7, 2021
    - EU Individual Case Safety Report (ICSR) implementation guide business rules spreadsheets
    - European Union individual case safety report (ICSR) implementation guide
- **GVP:** Change management for the EudraVigilance system
    - EU reference instances (EDQM revision)
    - EU E2B (R3) testing files (EDQM revision)
- **GVP:** EudraVigilance eXtended Medicinal Product Dictionary (XEVMPD) organisations. First published on March 5, 2012, Last updated on April 7, 2021
- **GVP:** EudraVigilance eXtended Medicinal Product Dictionary (XEVMPD) pharmaceutical dose forms. First published on March 5, 2012, Last updated on April 7, 2021
- **EC, Devices, EU MDR, EU IVDR:** Updated Implementation Rolling Plan - Regulation (EU) 2017/745 and Regulation (EU) 2017/746. This tabulation addresses the implementation of the MDR and IVDR requirements. It identifies the implementing acts, the expected timeline and the next step(s) if any.

- **EC, Devices, EU MDR/IVDR:** EU MDR MDCG Update. *"The European Commission provides a range of guidance documents to assist stakeholders in implementing the medical devices regulations, including documents endorsed by the Medical Device Coordination Group (MDCG) and other informative texts."*
- **EC, MDCG, NonGuidance, EU MDR/IVDR:** Guidance on Standardisation for Medical Devices. This 18-page document does not officially reflect the opinion of the European Commission. It has been endorsed by the Medical Device Coordination Group. *"This document aims to provide guidance on different aspects related to standards in the medical devices sector in support of the requirements laid down in the applicable EU legislation, taking into account its specificities."*
    - **Redica Comment:** This is the latest in MDCG published guidance documents to help further define and interpret EU MDR/IVDR. MDCG -5 is broken into four (4) topics. Further, the MDCG-5 guidance helps to define terms such as "State of the Art" in the context of EU MDR and relevant standards to demonstrate compliance to the regulations.
- **EC, Devices, MDR, IVDR, ELECTRICAL:** M/575 Commission Implementing Decision of April 14, 2021 on a standardisation request to the European Committee for Standardization and the European Committee for Electrotechnical Standardization as regards medical devices in support of Regulation (EU) 2017/745 of the European Parliament and of the Council and in vitro diagnostic medical devices in support of Regulation (EU) 2017/746 of the European Parliament and of the Council
- **EC, Devices, MDR, Clinical:** MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation. This document is intended for sponsors of clinical investigations of medical devices conducted within the scope of the Regulation (EU) 2017/745 (MDR).
    - **Redica Comment:** The MDCG guidance for clinical investigations provides clarity in support of the applicable sections of EU MDR. The guidance in support of EU MDR provides further harmonization leading to greater certainty, which will support an environment that provides greater predictability and is more favorable for conducting clinical investigations as compared to MDD, with the highest standards of patient safety, for all EU Member States. "*It will not only harmonize decisions, but also foster work sharing and collaboration between Member States and enhance the transparency regarding these studies.*" The guidance provides answers to a number of relevant questions regarding clinical investigations conducted in the EU member states.
- **Devices, EU MDR:** MDCG 2018-1 Revision 4 - Guidance on basic UDI-DI and changes to UDI-DI
    - **Redica Comment:** The only noteworthy change to the previous revision of MDCG 2018-1 is the added language concerning the communication of the maximum number of reuses for applicable devices. It is interesting to note that reprocessed devices, systems or procedure packs, software, Annex XVI, nor for cases of parallel trade or own brand labelling would not be applicable to this requirement in the guidance.

MHRA

- Clinical Trials for Medications: authorisation assessment performance. This includes data on the duration of time taken to assess clinical trial applications and substantial amendments.

OTHER

- **Canada, Inspections:** Canada's approach to onsite inspections during COVID-19: Notice "*During the COVID-19 pandemic, we continue to take a risk-based approach to inspections.... When onsite activities are conducted, Health Canada is implementing appropriate COVID-19 mitigation measures in adherence with public health guidance.*"
- **WHO:** Regulatory System Strengthening in the Americas. Lessons Learned from the National Regulatory Authorities of Regional Reference. "The aim of this document is to better understand the regulatory landscape of the Americas, with an emphasis on Latin American National Regulatory Authorities of Reference. This report presents data and analysis....to understand current practices, identify critical issues, and present a series of recommendations for action."

Procedural

FDA

- Manual of Policies and Procedures (MAPP) 7700.5 Rev. 1 Critical Path Innovation Meetings Policy and Procedures

EC, EMA, EDQM

- **EMA:** eSubmissions: "*Updated eCTD EU M1 specification now available. The eCTD EU Module 1 specification has been updated. The updated EU M1 spec v3.0.4 and the related release notes are available here. There are no changes to the CTD and hence this version enters into force as of date of publication and can be used immediately. It is recommended to use the new version as soon as possible. Please note that the release notes provide practical information on the changes and it is strongly recommended to review the release notes to fully understand the changes made in the specification.*"
- **EMA:** An updated document, "European Medicines Agency post-authorisation procedural advice for users of the centralised procedure." You can track changes here.
- **EMA, RA-Labeling:** The EMA site, "Changing the labelling and package leaflet (Article 61(3) notifications)" has updated Questions 1 and 4.
- **EMA:** Pre-authorisation procedural advice for users of the centralised procedure: document with tracked changes First published on February 7, 2017, Last updated on April 16, 2021
    - 4. Submission, validation and fees Question 4.4 updated.

Warning Letters

By Barbara W. Unger

Drug Warning and Untitled Letters

Curex Inc

CBER posted an untitled letter to **Curex, Inc.,** (NY, NY) issued on March 23, 2021 based on a review of the firm's website. The firm advertises their allergenic extracts to treat a variety of allergies. These drugs are not supported by a BLA or IND and thus are unapproved new drugs.

Proquimes Productis Quimicos Especializados

Proquimes S.A. Productos Quimicos Especializados S.A. (Cali, Colombia) received a warning letter on April 5, 2021 based on a review of records that were first requested on April 16, 2020. The firm manufactures APIs. FDA placed all products made at the firm on import alert 66-40 on December 3, 2020. The FDA recommends that the firm hire a consultant to assist them in coming into compliance. The deficiencies include but are not limited to:

- The firm **did not validate the API manufacturing process** and indicated so in response to questions from the investigator. FDA requested the firm provide information in response to the warning letter including but not limited to:
    - A remediation plan that assures the firm will be manufactured under control during its lifecycle which includes evaluation of raw materials, sources of variability in API manufacture, and ensure adequate controls are in place.
    - Develop an ongoing process monitoring program
    - A timeline that identifies when all APIs will be validated
- Critical manufacturing **equipment has not been qualified.** The firm indicated they did not perform equipment qualification and had no documentation on the topic, and that the equipment was “unqualified.” FDA requested the firm provide information in response to the warning letter including but not limited to:
    - Providing a CAPA plant to ensure that only suitable and qualified equipment is used in manufacture of APIs.
- **Cleaning of shared equipment is not validated.** When the firm was asked for cleaning validation documentation they could not provide any and stated that they did not perform cleaning validation. FDA requested the firm provide information in response to the warning letter including but not limited to:
    - Improvements to the cleaning validation program with emphasis on addressing worst case conditions in manufacturing operations.
    - Steps that must be taken under change management process prior to introduction of new equipment or a new API product into the facility.
    - A summary of updated SOPs to ensure an appropriate program is implemented to support cleaning verification and cleaning validation.
- Incoming **raw materials are not tested for identity.** The firm stated that they do not perform an identity test due to lack of resources. FDA requested the firm provide information in response to the warning letter including but not limited to:
    - A comprehensive review of the materials program to ensure all materials are qualified
    - Chemical and microbiological QC specifications used to test and release each lot of raw materials

- If the firm intends to accept materials on a CoA from the vendor, along with an identity test, they must describe how they will "robustly" establish the reliability of their supplier's results and how this will be confirmed periodically.

Device Warning and Untitled Letters

- None this month.

BIMO, GCP and GLP Warning and Untitled Letters

- None this month.

Compounding Pharmacies / Outsourcing Facilities

- **American Specialty Pharmacy, Inc.** dba ASP Cares (Farmers Branch, TX) received a warning letter on April 5, 2021 based on the outcome of an inspection ending August 23, 2018 (no, not a typo) and a request for additional information on February 4, 2019. In addition to the adulteration deficiencies, the firm also manufactures unapproved new drugs, which are misbranded. With the delay of 2.5 years between inspection and the warning letter it does make you wonder where this was "lost" in the interim.
- **Exela Pharma Sciences LLC** (Lenoir, NC) received a warning letter on April 8, 2021 based on an inspection ending July 18, 2018 (no type there either). The firm fails to meet the conditions of section 503(B) because they fail to submit adverse event reports to FDA. Further they compound unapproved news drugs that are misbranded.
- **Pharmacygeoff.md** received a warning letter on April 15, 2021 based on their unlawful sale of unapproved and misbranded drugs to consumers over the internet. FDA states they reviewed the website on March 22, 2021. FDA notes that the company website offers drug product intended, "*...to mitigate, prevent, treat, diagnose, por cure COVID-19 in people."* Among the drugs offered for sale is hydroxychloroquine. The firm is to respond within 48 hours of receipt of the warning letter to the FDAInternetTaskForce-CDER. I would look for more warning letters to be sent to these type of entities.
- **Joe Wise Pharmacy, Inc.,** dba Wise Pharmacy (Littleton CO) received a warning letter on April 15, 2021based on the outcome of an inspection ending June 21 2019. The firm recalled all drug products that were intended to be sterile that were within expiry. Another one that's essentially 2 years post inspection.

Recently Published 483s and similar

FDA

- **Emergent BioSolutions** in Baltimore, Maryland received a 6-page form 483 at the close of inspection on April 20, 2020. As a reminder, this firm makes drug substance vaccine for the J&J COVID-19 vaccine, and in the past made drug substance for the AstraZeneca COVID-19 vaccine. Please see Editors Choice for articles about Emergent and the current situation regarding manufacture of the COVID vaccines. The April 2020 inspection was conducted by a single investigator. Observations include but are not limited to:
    - Adequate **controls are not exercised over computer systems.** Electronic data generated during testing of drug substance, drug product and stability evaluations were not protected from manipulation or deletion. Analytical balances are not controlled to prevent users from changing the date/time of the activity. Audit trails are not reviewed. No deviation or investigation has been conducted of these data integrity type failures and their impact on product. The Windows OS **does not prevent modification of the date/time** settings by laboratory staff.
    - Sample identification numbers are inconsistent and were corrected days after the data acquisition. No deviation was opened or investigation performed.
    - Responsibilities of the **quality unit** were not in writing nor were they fully followed.
    - Employees are **not adequately trained** for the operations they perform, nor were they adequately trained in CGMPs.
    - **Rejected components are not adequately controlled** to prevent contamination or mix-up.
- **Wells Pharmacy Inc,** an outsourcing facility in Dyersburg, TN, received a 13-page form 483 at the close of inspection on January 28, 2021. Content is pretty much standard fare for these sites: lack of sterility assurance, repeat observations from previous inspections:
    - Facilities are not adequate for their intended use
    - Lack of Quality Unit authority.
    - Note the comments in observation #1 that the third party janitorial party concluded *"the HVAC system including the [redacted] , the air returns, walls, ceilings, and floors of the suite were all contaminated with mold."* Whoops! I would look for a warning letter to follow this inspection.
- The FR announced a final and **permanent debarment order** for Mr. Mark Reinhard, that prevents him from providing services to any firm with a pending or approved drug product application. Mr. Reinhard was a pharmacist in West Virginia and "*...aided and abetted others, through Meds 2 Go Express, by engaging in unlicensed wholesale distribution of Tramadol from West Virginia to Alabama through Kentucky. Specifically, Mr. Reinhard aided and abetted individuals who combined, conspired, confederated, and agreed to engage in a scheme to sell, distribute, and dispense prescription drugs over the internet and to deliver those prescription drugs to customers, without the issuance of valid prescriptions*."
- For the backstory, or at least part of it, see Editor's Choice this week. **Emergent BioSolutions** received a 12-page form 483 at the close of inspection on April 20, 2021. Three investigators conducted the inspection that resulted in nine multi-part observations. Any firm that operates a multi-product facility with **multiple viral vectors** would be well served to consider the observations. Note that many of the observations are supported by security

camera footage in the facility. FDA has also weighed in with a press release on the topic. Observations include but are not limited to:

- **Cross contamination was not adequately investigated** and did not include consideration of:
  - Operator movement, particularly for the person who prepared media
  - Other personnel movements, the recipe "abort" and how that was managed and documented;
- **Buildings were not maintained properly** with evidence of peeling paint on floors, waste transport for disposal may serve to contaminate other areas including:
  - The warehouse, damage to the wallboard may limit the ability to clean and disinfect the areas.
- **Buildings were not of suitable size, design and location** to provide for adequate operations, cleaning and maintenance. FDA notes that an assessment of the *"building's capacity to decontaminate waste was not performed as part of the incoming process gap assessment*" prior to the introduction of a viral vaccine into the facility. Further areas were congested and did not have space for use of a pallet jack but rather large containers were simply pushed along the floor.
- **Activities are not documented contemporaneous** with their performance. Further staff were observed entering what seems to be areas where two different products were manufactured without documenting de-gowning, showering and gowning activities as described in their own SOP. They also failed to comply with designated gowning zones. FDA provides six examples and three examples respectively.
- **Components were not handled in a manner to prevent contamination.** The firm was notified by their client that the vaccine drug substance was contaminated with another client's material. There are a laundry list of examples here.
- **Procedures for cleaning and decontamination**, and periodic monitoring of the same, are not adequate or are not followed.
- **Employees are not trained** in the particular operation they perform.
- **Equipment are not cleaned and maintained** at appropriate intervals.

- FDA sent a Notice of Noncompliance to **Acceleron Pharma Inc,** (Cambridge, MA) for their failure to comply with submitting clinical trial results to ClinicalTrials.gov data bank. Acceleron is not alone in failing to comply with this requirement, but FDA has apparently made them the test case. FDA indicates they may seek civil monetary penalties and other regulatory actions such as "*injunctions or criminal prosecution*." Time will tell, but I would not expect a letter alone to be successful in achieving compliance. Let's make it a financially meaningful cost to get everyone else's attention. Threats alone won't work in my opinion, follow the money.

OTHER, including EDQM reports of GMDP Non-Compliance

- **WHO** issued a Medical Product Alert for Falsified COVID-19 Vaccine BNT162b2. The falsified vaccine was identified in Mexico in February 2021 and has been confirmed as such. It may continue to be in distribution and offered to patients. It is distributed outside of "*authorized vaccination programs.*" Laboratory analysis of the falsified product is pending.
- **ANVISA** published their decisions regarding issuance of GMP Certificates for manufacturers of COVID-19 vaccine. Note the decision regarding Bharat Biotech International of India where ANVISA declined to issue a GMP certificate and rejected the application for reasons associated with:

    - Eterminations of vaccine potency
    - Inactivation of virus (this is an inactivated virus vaccine)
    - Sterilization and apparently sterility assurance
    - Purity
    - A common thread also appears to be that the firm did not demonstrate comparability of the scaled up process product with the one that was used in clinical studies.
- **Acadia Pharmaceuticals** received a Complete Response Letter for their NDA supplement that proposed to expand the indication for use of their single product, NUPLAZID. The basis of the refusal was clinical, **Yahoo Finance** states, "*Despite prior agreements with the Division of Psychiatry regarding the pivotal Phase 3 HARMONY study design targeting a broad DRP patient population analyzed as a single group, the Division, in the CRL, cited a lack of statistical significance in some of the subgroups of dementia, and insufficient numbers of patients with certain less common dementia subtypes as lack of substantial evidence of effectiveness to support approval.*" This would appear to be an issue where FDA changed their mind, didn't communicate effectively with the sponsor even upon questioning, but rather chose to surprise them, and the investment community.
- **NatureMedicine** responds to a Federal Register notice from January of this year that removed FDA oversight from over 91 medical devices. The correspondence is titled, "Do not Sell Regulatory Science Short." The authors are not in agreement with removing FDA oversight.
- The FR announced that five ANDA approvals from multiple sponsors have been withdrawn by FDA because the ANDA holders have repeatedly failed to file annual reports and failed to have an approved REMS.
- **BL TECH EUROPE MED S.R.L**. in Satu Mare, Romania received a statement of non compliance with GDP requirements based on an inspection conducted by the Romanian authorities on March 4, 2021. The nature of the non-compliance included failure of the company to include the services of a responsible person. As a result, the wholesale Distribution license was suspended. The firm only supplies products to customers in Romania.
- **Health Canada** updated their inspection tracker for the following firms:
    - Tris Pharma Inc. Monmouth Junction, NJ
    - Zhejiang Huahai Pharmaceutical
- The EDQM posted a report of GMP non-compliance for **ERC The Netherlands, B.V.** based on an inspection of February 25, 2021 by the competent authority of the Netherlands. The products impacted are aseptically produced sterile drug products and biological medicinal products. Thirteen deficiencies were identified, one of which was critical and one was major. *"The Netherlands B.V. showed a lack of ability to adhere to the principles of Good Manufacturing Practice for ATMPs. The five main parts of the critical deficiency are summarized here: ERC has not sufficiently ensured the safety and effectiveness of their product according to the following observations:*
    - *"Quality and safety of starting materials is not guaranteed. Inspection of chemicals and consumables is insufficient.*
    - *The quality and safety of the final product is not guaranteed. The product is not sufficiently defined and characterized.*
    - *The effectiveness of a gama irradiation step, and therefore the safety of the product, is not guaranteed. The change for the transition from Contractor 1 to Contractor 2 for gamma irradiation of cells has not been carried out as referred to in the GMP for ATMPs.*

- *Prevention of (cross) contamination is not sufficiently guaranteed.*
- *The environmental monitoring program and personnel monitoring are inadequate. As a result of this, the quality and safety of the product ERC1671 Gliovac manufactured at the site is not ensured."*

This ATMP is composed of both autologous and allogeneic components. with multiple treatments per patient. The authorities will not recall the product because all distributed product has been administered to patients. No additional product may be distributed. Licensed activities have been suspended until appropriate GMP compliance is confirmed by the NCA.
From the ERC website regarding the product in question: *"The ERC1671 (Gliovac™) vaccine is an advanced immunotherapy based on freshly extracted tumour cells and lysates that stimulates the patient's immune system to recognise and reject cancer cells.*

The vaccine contains a combination of autologous tumour cells, and allogeneic tumour cells, generated from the glioma tumour tissues of three different donor cancer patients, and the lysates of all of these cells. Upon injection, this mixture stimulates the patient's immune system to mount an immune response against the tumour cells, which may lead to their destruction."

Import Alerts

IMPORT ALERT 66-40, Detention Without Physical Examination of Drugs from Firms Which Have Not Met Drug GMP

- No new alerts under 66-40.

IMPORT ALERT 66-41, Detention Without Physical Examination of Unapproved New Drugs Promoted in the U.S.

- April 5, 2021 | Bond Chemical | Adesakin Laout Awe, Lagoxlagox, **NIGERIA**
- April 20, 2021 |COSRX INC | 8, Gumi-Ro, Bundang, Seongnamsi, Gyeonggi, **KOREA (THE REPUBLIC OF)**
- April 21, 2021 | DREAM COSMETICS | Zone Industrielle Yopougon 23, Abigian, **IVORY COAST**
- April 21, 2021 | Erhald Transit Import-Export | 05 Bp 2939, Abidjan, **IVORY COAST**

IMPORT ALERT 99-32, detention without physical examination of products from firms refusing FDA foreign establishment inspection

- April 12, 2021 | Eyesome Co., Ltd | 309 Gieopdanji-Ro, Wongok-Myeon, Anseong, Gyeonggi **KOREA (THE REPUBLIC OF)**

IMPORT ALERT 55-05, Detention Without Physical Examination Of Finished Dosage Drug Products, Active Pharmaceutical Ingredients And Inactive Ingredients For Potentially Hazardous Microbiological Contamination

- No new alerts under 55-05.

IMPORT ALERT 62-05 Sterile Dosage Form

- No new alerts under 62-05.

IMPORT ALERT 66-57 Detention without Physical Examination of Foreign Manufactured Unapproved Prescription Drugs Promoted to Individuals in the U.S.

- April 19, 2021 |PRICEMDS.COM INC | 720 Brooker Creek Blvd Ste 221 , Oldsmar, FL 34677-2937 **UNITED STATES**

IMPORT ALERT 66-72 Detention without physical examination of Misbranded Drugs and Marketed New Drugs Without Approved Applications

- No new alerts under 66-72.

IMPORT ALERT 66-78 Detention without physical examination of Drugs, based upon analytic test results

IMPORT ALERT 99-34 Detention without Physical Examination of Drugs or Medical Devices from Frms Without a Valid Drug or Medical Device Registration

- No new alerts under 99-34.

IMPORT ALERT 66-66 APIs that Appear to be Misbranded Under 502(f)(1) Because They Do Not Meet the Requirements for the Labeling Exemptions in 21 CFR 201.122

- No new alerts under 66-66.

Corporate Integrity Agreements

- None this month.

Consent Decree Agreements

- None this month.

Public Health / COVID-19 Guidance & News

FDA

- FDA Makes Two Revisions to Moderna COVID-19 Vaccine Emergency Use Authorization to Help Increase the Number of Vaccine Doses Available. The first revision permits 11 doses may be removed from a single vial with a range of 10-11 doses. The second revision authorizes a multi-use vial from which a maximum of 15 doses may be delivered, with a range of 13-15. These changes support getting doses into more arms as quickly as possible.
- FDA Provides Update on COVID-19 Pandemic Recovery and Preparedness Plan Initiative
- Virtual Town Hall:
    - Presentation and Transcript added - March 31, 2021
    - April 14, 2021
- **HHS:** CNN Op-Ed by Christi A. Grimm & Michael E. Horowitz: Four crucial lessons for improving COVID-19 testing
- Presentation and Transcript added to Virtual Town Hall Series - Coronavirus (COVID-19) Test Development and Validation - April 7, 2021
- Vaccine Ready: Addressing COVID-19 Health Disparities among Racial and Ethnic Minority Communities
- Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine
- FDA Takes Action to Address Coronavirus Disease 2019 (COVID-19) FDA is working with U.S. Government partners, including CDC, and international partners to address the pandemic.
- FDA Announces New Streamlined Approach to Add Pooled Serial Screening Claims to Certain Authorized Tests for Use in Serial Testing Programs
- **Administrative:** The FR announced the listing of guidance the FDA has published during the COVID-19 pandemic. The tabulations identify the CFR's that are referenced in the document, the title, the OMB control number and other guidance referenced within the specific documents.
- PAHO report: COVID-19 highlights need for strengthening national regulatory authorities in Latin America and the Caribbean - PAHO/WHO | Pan American Health Organization Press Release, PAHO, April 202.1
- **HHS:** Report to Congress: October 2020 through March 2021
- We wrote this report to update Congress on our efforts to promote public transparency and ensure coordinated oversight of more than $5 trillion in pandemic response spending. Check out the highlights or read the full report.

EMA / EC / EDQM

- EMA and ECDC join forces for enhanced post-marketing monitoring of COVID-19 vaccines in Europe

MHRA

- None this month.

OTHER

- **Australia:** COVID-19 vaccine weekly safety report - April 7, 2021. The Therapeutic Goods Administration (TGA) has been closely monitoring suspected side effects (also known as adverse events) from the use ...
- **Italy:** Webinar "Causality and chance in recent pharmacovigilance signals of Covid-19 vaccines: what evidence for public health decisions?"
- **Spain:** 4th Pharmacovigilance Report on COVID-19 Vaccines
- **Australia:** COVID-19 vaccine weekly safety report - April 14, 2021. The Therapeutic Goods Administration (TGA) has been closely monitoring suspected side effects (also known as adverse events) from the use ...
- **Canada:** COVID-19 clinical trials IO and clinical trials records retention: Consultation report
- **Australia:** COVID-19 vaccine weekly safety report - April 21, 2021
- **Australia:** COVID-19 vaccine weekly safety report - April 28, 2021
- **Order, GMP, Vaccines, Biologics, Devices,Ukraine:** Ministry of Health issued an Order "On Amendments to the Procedure for Recognition of Inspection Results for Conformity of Conditions of Production of Vaccines and Other Medical Immunobiological Preparations for Specific Prevention of Coronavirus Disease (COVID-19) to the Requirements of Good Manufacturing Practice." Please request a machine translation.

Daily Updates from the FDA

- Coronavirus (COVID-19) Update: April 2, 2021
- Coronavirus (COVID-19) Update: April 6, 2021
- Coronavirus (COVID-19) Update: April 9, 2021
- Coronavirus (COVID-19) Update: April 13, 2021
- Coronavirus (COVID-19) Update: April 16, 2021
- Coronavirus (COVID-19) Update: April 20, 2021
- Coronavirus (COVID-19) Update: April 23, 2021
- Coronavirus (COVID-19) Update: April 27, 2021

Animal Health

- **FDA, News:** FDA Announces Improved Performance Measure Dashboards for Animal Drug and Food Key Initiatives. CVM announced April 6, 2021 that it is posting new and enhanced performance measure dashboards on its FDA-TRACK website highlighting its accomplishments toward the center's mission of protecting human and animal health. FDA-TRACK is the FDA-wide performance management system that monitors, analyzes and reports key performance data and projects for the agency.
- **FDA:** FDA is reopening the comment period on the Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs until April 18, 2021. The comment period is being reopened due to difficulties with the comment submission portal. This concept paper outlines part of the agency's overall strategy for addressing antimicrobial resistance risks associated with the use of antimicrobial drugs in animals.
- **FDA:** Animal Drug User Fee Act (ADUFA) Reauthorization Meetings. The statutory authority for ADUFA expires September 30, 2023. Public meetings on reauthorization will be held periodically beginning October 21. Submit notification of intention to participate by May 20, 2021.
- **FDA:** Animal Drug User Fee Act public comment meeting registration. The public meeting will be hosted via a live virtual webcast on Thursday, May 20, 2021, from 2 p.m. to 4 p.m. EDT.
- **FDA:** Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs: Reopening of the Comment Period. Due to technical difficulties submitting comments for the November 16, 2020 meeting on this topic, the comment period is reopened. Submit either electronic or written comments by April 22, 2021.
- **FDA: CVM**: CVM GFI #188, "Data Elements for Submission of Veterinary Adverse Event Reports to CVM." This guidance is meant to assist applicants and non-applicants with filling out Form FDA 1932, "Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report." CVM revised the form to harmonize with VICH standards.
- **USDA, CVB:** CVB notice of new process for Issuance of Inspection Certificates for U.S. Veterinary Biologics Establishment Licensed sites. USDA APHIS VS Memorandum 800.91 was updated in December 2020 to include the issuance of Inspection Certificates, which are issued after in-depth inspections to indicate the manufacturing site or sites have been inspected by CVB and determined compliant. This notice describes the process. While in-depth inspections have been postponed at present, issuance of an Inspection Certificate based on the last in-depth inspection conducted at the establishment site can be requested.
- **USDA:** Environmental Impact Statement; Movement of Certain Genetically Engineered Organisms; Record of Decision by the Animal and Plant Health Inspection Service on April 5, 2021. This notice advises the public of the Animal and Plant Health Inspection Service's record of decision for the final environmental impact statement titled, "Revisions to USDA-APHIS 7 CFR part 340 Regulations Governing the Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms."
- **EMA:** Mandate, objectives and rules of procedure for the CVMP Safety Working Party (SWP-V). The approved procedural document includes six sections:
    - General considerations
    - Mandate and objectives

    - Composition and rules of participation
    - Meeting frequency
    - Duration of activity
    - Rules / procedure.
- **EMA:** European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)
    - European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) web based data collection form (updated)
    - European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) web based data collection form
- **EMA:** Agenda - CVMP agenda of the March 13-15, 2021 meeting
- **EMA:** Monthly report on application procedures, guidelines and related documents for veterinary medicines: February 2021
- **EMA:** Webinar on reporting suspected side effects following administration of veterinary medicines, Virtual meeting was held on March30, 2021. Slide decks from two presentations are now available: *VMP REG (EU) 2019/6 Pharmacovigilance and the Veterinarian (J. Olaerts)*, and *PhV reporting - EV VET3 - Implementation (L. Descalzo)*
- **EMA:** Pharmacovigilance-related regulatory recommendations for centrally authorised veterinary medicinal products during 2021
- **EMA:** Veterinary Big Data stakeholder forum, Virtual event, June 1-2, 2021. Registration is open until 25 May 2021. The EMA-led forum aims to bring together regulators, the pharmaceutical industry, farm management system providers, academia, consumers and practitioners, to build awareness on the use of innovative digital technologies in the veterinary regulatory environment; share needs, ambitions and opportunities; and inspire future activities shaping the development of the European Veterinary Big Data Strategy.
- **EMA, CVMP, RA-Labeling:** Consultation: Concept paper for the revision of the guideline on the summary of product characteristics for anthelmintics (PDF/217.67 KB). The current guideline on the Summary of Product Characteristics (SPC) for anthelmintics recommends standard warnings aimed at delaying the development of anthelmintic resistance. The scope of the guideline is currently limited to products for sheep, goats, cattle and horses. It is proposed to extend the scope of the revision of the current guideline on the SPC for anthelmintics further, to also include other antiparasitic veterinary medicinal products, (i.e. ectoparasites). Comment period is April 22 - May 31, 2021.
- **EC**: Commission Implementing Regulation (EU) 2021/709 of April 29, 2021 concerning the authorisation of L-histidine monohydrochloride monohydrate produced by Escherichia coli KCCM 80212 as a feed additive for all animal species ([1])
- **EC:** Commission Implementing Regulation (EU) 2021/658 of April 21, 2021 concerning the authorisation of essential oil from Origanum vulgare L. subsp. hirtum (Link) letsw. Var. Vulkan (DOS 00001) as a feed additive for all animal species ([1]) Corrigenda Corrigendum to Commission Implementing Regulation (EU) 2016/896 of June 8, 2016 concerning the authorisation of iron sodium tartrates as a feed additive for all animal species (OJ L 152, 9.6.2016)
- **EC:** Commission Delegated Regulation (EU) 2021/578 of January 29, 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council with regard to requirements for the collection of data on the volume of sales and on the use of antimicrobial medicinal products in animals
- **EDQM:** Update on the Ph. Eur. policy on elemental impurities – Monographs on substances for veterinary use only. The European Pharmacopoeia (Ph. Eur.) has launched a public consultation on its proposal to delete the test for “heavy metals” (HMs, general chapter 2.4.8)

in monographs on substances “for veterinary use only”. The 16 monographs concerned have been published in Pharmeuropa 33.2.

- **HMA:** Packaging 'blue-box' requirements in NP/MRP/DCP/CP. Packaging ‘blue-box’ requirements and additional information on labelling/package leaflet for veterinary products authorized via national, mutual recognition, decentralized or centralized procedures. Additional information on labelling/package leaflet that may be required or permitted nationally in accordance with Articles 58 and 64 of Directive 2001/82/EC, as amended, is listed by country in this CMDv document.
- **HMA** updates the following veterinary medicines e-submission information
    - List of national official journals
    - National databases of authorised veterinary medicinal products
    - Overview of MSs' requirements during national phase
- **MHRA:** Top ten imported veterinary medicines - Quarterly report January 1, 2021 to March 31, 2021. Report of the ten products for which most Special Import and Special Treatment Certificates (SIC and STC) have been issued by VMD in the UK. Document type: Official Statistics Organisation: Veterinary Medicines Directorate. Updated onApril 21, 2021.
- **APVMA:** A revised Infringement Notice guideline was issued in late April by APVMA.
- Infringement Notices are issued by APVMA inspectors for violations of agvet regulations that do not rise to the level of a violation of the law perceived to require a court proceeding. If the Inspector finds multiple offences, an infringement notice may be given for each violation. Payment of an infringement notice is not an admission of guilt. If the recipient of the notice pays the specified penalty, their liability is discharged. If the penalty is not paid, the matter will go to court.
-
- **Canada:** Memorandum 2021-03: Renewal of veterinary biologics establishment licences, product licences, and import permits. This memorandum serves as a renewal reminder for holders of Canadian veterinary biologics establishment and product licenses and import permits. It notes that Veterinary biologics establishment and product license will expire on May 31, 2021 and annual import permits will expire on June 30, 2021. Forms and guidance for renewal of veterinary biologics import permits are provided.
- **Canada:** Food & Drug Act: Regulations Amending the Licensed Dealers for Controlled Drugs and Narcotics (Veterinary Use) Fees Regulations (Updated April 1, 2021). These amendments are administrative in nature, and thus have minimal impact on the regulated industry or the Canadian public.
- Regulations Amending the Pest Control Products Regulations (Data Protection During Post-Market Review - Re-evaluations and Special Reviews) (Updated April 1, 2021) [Associated with the targeted Regulatory Review Sectoral Roadmap] [Associated with the stock review plan]. These amendments aim to better align Canada’s data protection program for pest control products with the approach used in the United States. Publication of the final amendments is expected in Fall 2021.
- Regulations amending the Pest Control Products Regulations (Product exemptions and Pest Control Product Devices) (Updated April 1, 2021) [Associated with the targeted Regulatory Review Sectoral Roadmap] [Associated with the stock review plan]. These proposed regulatory amendments would exempt certain classes of pest control devices and products from the registration requirements
- Regulations amending the Pest Control Products Regulations (Labelling Modernization) (Updated April 1, 2021) [Associated with the targeted Regulatory Review Sectoral Roadmap] [Associated with the stock review plan]. The proposed regulatory amendment would

improve labels' readability, which would allow users to understand and find the information they need to use pest control products safely and effectively. In addition, it would allow the use of electronic labels, and international formats (i.e., the Globally Harmonized System of Classification and labelling of Chemicals), which would reduce costs for business.

- **Canada:** Updated Register of Certificates of Supplementary Protection and Applications. The issuance of a CSP grants the certificate's holder and their legal representatives the same legal rights, privileges and liberties that are granted by the patent set out in the certificate, but only with respect to the making, constructing, using and selling of any drug that contains the medicinal ingredient, or combination of medicinal ingredients. Three vet product ingredients are listed: lotilaner,sarolaner/moxidectin/pyrantel (as pyrantel pamoate), and sarolaner / selamectin
- **Canada:** CFIA Updates index of medicating ingredients by name and sponsor/manufacturer. Nine ingredients were added to the brochure, including: BI Ivomec Premix For Swine; Elanco Experior 10 Lubabegron Premix, Coban Premix, 2 Denagard premixes, 2 Tylan 40 and 100 premixes
- **Canada:** CFIA released an updated Ivermectin (IVR) – Medicating Ingredient Brochure
- **Health Canada**: The CFIA guidance document Inspection Documentation – Customer Formula Feeds – General Principles, was posted on April 27 as having been updated. What was updated is not clear. The purpose of the document is to provide clarification to stakeholders on the documentation required to support the manufacturing and labelling of customer formula feeds, including those imported into Canada and medicated feeds.
- **Ireland:** New Veterinary Regulation — March Update. All four projects under the EMA's veterinary regulation IT development scheme have now been initiated. The development is proceeding in an 'agile' manner. A further release of the Union Product Database (UPD) was issued March 16, and this will be tested by national competent authority users in the coming period.
- **Spain:** Information note on the meeting of the Veterinary Medicines Safety Committee, held on April 6, 2021. The Veterinary Medicines Safety Committee of the Spanish Agency for Medicines and Health Products (AEMPS) approved the 2020 Veterinary Pharmacovigilance Bulletin and reported on modifications of marketing authorizations for five medicines and compliance with the Quality Review of Documents (QRD) of 11 medicines.
- **Spain:** Quarterly bulletin of the AEMPS department of veterinary drugs, January - March 2021
- **Spain:** As of January 15, the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) application has been available here for the declaration of sales data of veterinary drugs that contain antibiotics in their composition. The deadline to make the declaration is May 15, 2021. More information is available here.
- **Australia:** APVMA: Veterinary Medicines Regulatory Newsletter, April 2021. The fourth edition of the Australian Pesticides and Veterinary Medicines Authority's (APVMA) quarterly *Veterinary Medicines Regulatory Newsletter* includes the following sections:, Directors' update: Dr Martin Ilott and Dr Donald Sibanda, Performance report, New product registrations, Veterinary Labelling Code review, Autogenous vaccine guideline update, Useful information for industry, 10A applications, Notifiable Variations, 13A applications, MQL news, and, Team news.
- **Netherlands:** Veterinary Medicines Regulation: update no.1. The new Veterinary Medicines Regulation (EU) 2019/6 and Regulation (EU) 2019/4 regarding medicated animal feed both apply from January 28, 2022. In particular, due to the new Veterinary Medicines Regulation (VMR), a lot will change from next year. Since its publication in January 2019, the elaboration

and further elaboration of the Veterinary Medicinal Products Regulation has been in full swing.

Editors' Choice - Stories of the Week

By Barbara W. Unger

- And the story continues with **BIOPHARMADIVE** reporting on a 'Manufacturing mix-up could blunt supply boost from J&J vaccine'. This event will no doubt slow the approval of the Emergent BioSolutions site as an approved manufacturer of COVID-19 vaccine drug substance for J&J and AstraZeneca. The site was inspected by FDA in April 2020.
- And more on the above. **CNN** reports that "US government moves AstraZeneca out of vaccine plant that suffered contamination." I'm not sure that "contamination" is the correct term here; all publicly available information suggests it was a mix-up in materials between the J&J vaccine and the AstraZeneca vaccine. Perhaps inadequate room clearance between the two products, or they decided for some reason to manufacture both products simultaneously. The US government appears to have told AZ they must move out of the Emergent BioSolutions Baltimore facility and the firm is working with the Biomedical Advanced Research and Development Authority, (BARDA), to identify another manufacturing location. J&J now appears to be fully in charge of the Emergent BioSolutions plant in Baltimore. This is a painful result of poor GMP practices, a highly visible mistake and it resulted in the facility losing autonomy and control over their own operations. Many years ago, a similar action was taken at the Lansing Michigan plant where BioPort (since renamed Emergent BioSolutions) made the only US licenced anthrax vaccine and received a warning letter which resulted in significant oversight from consulting groups.
- And one more from the NYT. This article has a bit more color. Worth reading if you care about GMPs at CMO sites. And yet another from Politico. See the form 483 earlier in this collection.
- **FibroGen** issued a press release on April 7 regarding safety and efficacy data for their investigational product, Roxadustat. They "*clarified certain prior disclosures of U.S. Primary cardiovascular safety analyses*." **BIOPHARMADIVE** reports that Fibrogen reported data at, "*medical meetings and press releases since 2019 were misleading.*" "*FibroGen has used those inflated result to claim roxadustat was as good as a placebo or an injectable drug — and, in one particular patient subgroup, better — at reducing the risk of heart problems like strokes. But the numbers in a pre-specified statistical analysis plan agreed on by the FDA, released Tuesday, were less impressive in each patient group."* This event will not do anything to speed the approval of their oral dosage form to treat anemia.
- The importance of supply chains and seemingly small items that can disrupt the delivery of COVID-19 diagnostics and therapeutics is once again on the front page. **Fierce Pharma** reports that "Plastic bag shortage a hefty problem for Novovax's COVID-19 vaccine production push." For plastic bags here think about 2,000 liter sterile bags used in production of the Novavax vaccine.
- **Healthcare Packaging** reports "Two Key Areas of Cybersecurity Vulnerability in Manufacturing."
- Once again **Emergent BioSolutions** is in the news. **MarketWatch** reports that "Emergent BioSolutions says it has agreed with FDA not to manufacture new material at Baltimore

Facility." FDA was at the Baltimore facility last week to begin an inspection. We include the form 483 in the enforcement section of this publication.

- And more **Emergent BioSolutions** challenges. **Congressional leadership** (House Oversight Committee and the Select Subcommittee on the Coronavirus Crisis) wrote a 9-page, heavily footnoted letter to the CEO and the Executive chairman that raises questions about whether Emergent "*may have used it's political connections to acquire lucrative manufacturing contracts and significantly increase its profits, while failing to deliver on these contracts.*" The letter makes 16 requests for the production of documents, including four pages of instructions on how to provide the documents. I would expect a Congressional hearing at some point. See also the form-483 in the enforcement section this week.
- The due date for a "*fully electronic interoperable system*" to track drug products through the supply chain is November 2023 as required by the Drug Supply Chain Security Act amendments to the FD&C Act. **RAPS** reports on 'FDA overdue on guidance as DSCSA deadline looms.' This may be interesting to watch, because it's required by law, and FDA has been woefully behind in issuing guidance to industry to implement these requirements.
- The **WSJ Opinion** page reports "Drug Safety is FDA's Job, Not CDCs." This addresses the pause in administration of J&J's COVID-19 vaccine as CDC and FDA investigate rare blood clots. There is concern that CDC should not be making safety and efficacy decisions, that is the purview of the FDA.
- **RAPS** reports that "Time's up for questionable cell and tissue products, says Marks." It's been three and a half years of enforcement discretion in the area of cell therapy. FDA has been unable to get serious attention from most of the firms that are selling unapproved cell therapies without an IND or BLA in place.
    - **Redica Comment:** FDA states that CBER have sent more than 350 warning letters and notices since December 2019 to these firms. That's a stunning statement because there have been fewer than that total number of warning letters issued to drug manufacturers in that time period. So, virtually all of these actions must be in the category of "notices" which would seem to have no enforcement consequences. It will be interesting to watch FDA as they start actually enforcing requirements in June of this year. The playing field needs to be level to support those firms/clinics that are actually playing by the rules. If the FDA does not come down heavily on the "bad actors" they are not actually encouraging and supporting development of regenerative medicines, instead they would be propping up those firms that are gaming the system. In my opinion, there is simply too much money to be made for many firms and clinics and physicians for them to spend time and effort addressing compliance with FDA requirements. June 1, 2021 is the date to watch. We will keep tabs on this. FDA needs to send a resounding message to these firms, or else risk that others will not take their enforcement authority seriously.
- **Forbes** reports "China is at War with the FDA; Guess Who's Winning?" A clue, the winner is *not* the US consumer according to this article.
- And more on **Emergent BioSolutions** CEO stock purchases from the **Washington Post**. On the same topic, **Senator Elizabeth Warren** asks the SEC to conduct an investigation into "*reports that Mr. Robert G. Kramer…sold more than $10 million worth of this stock prior to public disclosures that the company had ruined 15 million doses"* of the J&J COVID-19 vaccine. She requests an investigation into four specific areas. And to round out this reporting the **NYT** reports on a "Shake-Up at Covid Vaccine Manufacturer That Tossed Millions of Doses." One executive responsible for manufacturing will depart from the firm and another is currently

on leave. The CEO, Robert Kramer, continues with a strong defense of the company and personnel.

- OK, the next shortage, pipette tips. **STAT** reports that this is due to a combination of circumstances including the statewide powerblackout in Texas.
- **Reuters** reports that 'Brazil Health Regulator Rejects Russia's Sputnik Vaccine.' "*A crucial issue for Anvisa was the presence in the vaccine of the adenovirus that could reproduce, a "serious" defect, according to Anvisa's medicines and biological products manager Gustavo Mendes*." This comes on the heels of the Anvisa refusal to approve a COVID-19 vaccine from India for safety concerns.
- From the **GMP Journal**, 'GMP Update 2020/2021.' This provides an excellent summary on a variety of topics, worth at least skimming.
- **McKinsey & Company** reports 'COVID-19: Implications for business.'