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PHARMACEUTICAL REGULATORY INSPECTION/ENFORCEMENT TRENDS

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Since the COVID-19 pandemic began, we've seen disruptions to regulatory inspection and enforcement. What has this looked like, and what has been the impact to the pharmaceutical industry? In this e-book, we dive in specifically to the regulatory agencies of the FDA in the U.S. and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK.

The first article examines observations and trends from the FDA's FY2020 drug inspections. The second article discusses two unique warning letters that all pharmaceutical and API firms, regardless of their product category, should consider and evaluate. The following article from Madeleine Giaquinto of Greenleaf Health explores the FDA's COVID-19 Pandemic Recovery and Preparedness Plan (PREPP) Initiative Summary Report and its key takeaways for manufacturers. Next, Kalah Auchincloss of Greenleaf Health muses about the changes that we might expect to see in the FDA's inspections as the agency begins to shift back to more normal operations. The e-book then examines the FDA's new guidance on remote interactive evaluations of drug manufacturing and bioresearch monitoring facilities during COVID-19, and shares how to plan, conduct, and conclude a remote interactive evaluation. The last FDA-oriented article details the FDA's "Resiliency Roadmap" and the FDA's next steps for inspections.

The e-book then shares two articles of insights regarding the MHRA. The first provides an analysis of MHRA's latest annual good manufacturing practice (GMP) inspection deficiencies report. The second delves into the top 10 most-cited MHRA GMP inspection deficiencies by annex/chapter in 2019.

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FDA FY2020 DRUG INSPECTION OBSERVATIONS & TRENDS

Barbara Unger

President, Unger Consulting, Inc.

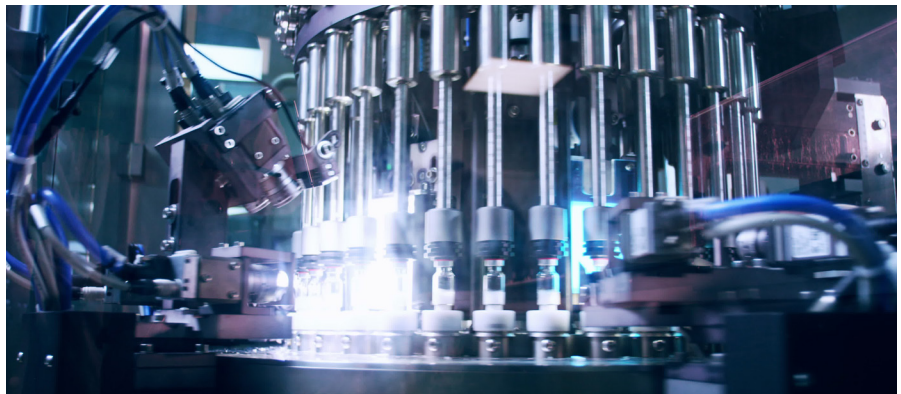
A comprehensive GMP intelligence program includes monitoring health authority enforcement actions. The actions include FDA Form 483s, Establishment Inspection Reports, warning letters, recalls, import alerts, consent decree agreements, MHRA annual summaries of inspection deficiencies, and EU reports of GMDP noncompliance. This article presents the most recent publication of GMP drug inspection data, which address drug inspections conducted in FY2020. We examine data from FY2020 and evaluate five years' worth of trends in drug GMP inspection enforcement. For additional data on years before 2016, please refer to the article published last year.

The presentation of some data herein differs from data presented on the FDA website, even though it uses the same raw data. For example, I combine all observation listings that cite 21 CFR 211.42(c) into a single value, rather than identifying them in separate line items with the exact same citation text. Likewise, I've consolidated §211.192 into a single item, rather than the five line items in the FDA's data presentation.

The data do not represent the FDA's complete collection of inspection observations for the year. In past years, these data represented approximately one-third of all Form 483s issued, so conclusions must be tempered by the incomplete nature of the data. The FDA data include only Form 483s issued through its electronic system; it does not include Form 483s issued to API manufacturers because §211 is not applied to those manufacturers or Form 483s that are issued outside of the electronic system.

FDA FORM 483 INSPECTION OBSERVATIONS

The striking feature for FY2020 is the number of Form 483s, which decreased to less than half of those issued in FY2019. This is shown below in Figure 1. FDA inspections came to a grinding halt early in the year with the travel and safety limitations based on the COVID-19 pandemic. This limitation will likely ensure that the number of inspections conducted and Form 483s issued continue to remain under the FY2019 values well into FY2021.



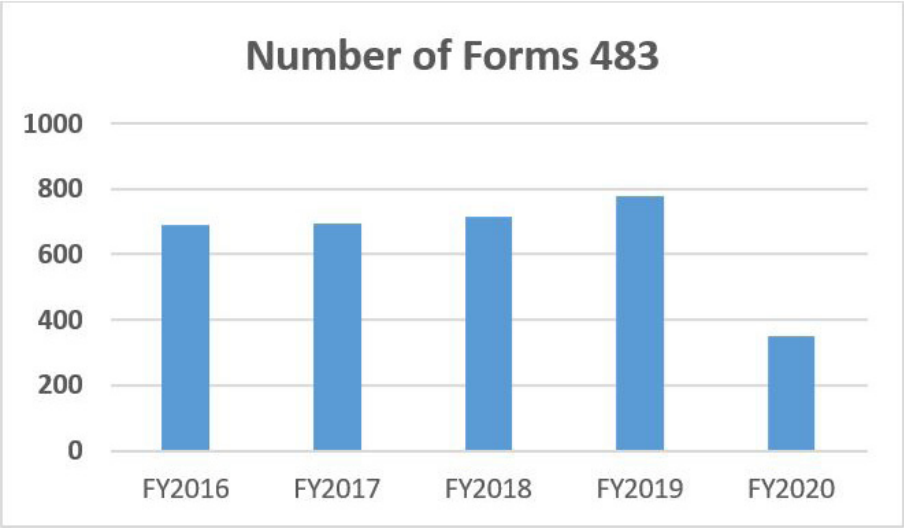


Figure 1: Total number of Form 438s in the system

Table 1 shows only the 15 most frequent inspection observation citations between FY2016 and FY 2020, while the tabulation on the FDA website shows all citations used in the fiscal year. The FDA uses the term "*frequency*" to represent the number of times the agency identified a specific citation in its tabulation. Table 1 presents those observations from the highest to lowest number for FY2020. Table 1 shows consistency in the years between FY2016 and FY2020 with respect to the identity of the most frequently cited regulations. The four most frequently cited regulations for FY2020 include:

- §211.192 *Investigations of discrepancies* moved from third place in FY2018 to second place in FY2019 and is in first place in FY2020. It has historically been among the most frequently cited regulations.
- §211.22(d) *Procedures applicable to the quality control unit shall be in writing and shall be followed* moved from first place in FY2019 to second place this year. Again, this is another regulation that has been among the top group for many years.
- §211.160(b) *Lab controls should include scientifically sound specifications* was fourth place last year and third place this year.
- §211.100(a) *Production and process controls shall be supported by written procedures* is a common observation issued to OTC manufacturers who frequently have not conducted process validation for some or all products.

New in the top group for FY2020 are §211.68(b) and §211.160(a). §211.68(b) likely represents the FDA's continued focus on data management and data integrity, particularly for electronic data both in manufacturing (e.g., electronic batch records) and laboratory instrumentation. §211.160(a) also fits into the group of data integrity regulations, requiring data to be saved at the time of performance, data must not be obscured or lost, and adequate procedures must be in place to control laboratory documentation.

Based on the limitations of having far fewer Form 483s in this year's collection, it's virtually impossible to identify year over year trends. Instead, I've taken a cumulative approach over the past five years, shown in Figure 2. The four most frequently cited regulations for these five years include:

- §211.192 *Investigations of discrepancies* moved from third place in FY2018 to second place in FY2019 and is in first place in FY2020. It has historically been among the most frequently cited regulations.
- §211.22(d) *Procedures applicable to the quality unit shall be in writing and shall be followed* moved from first place in FY2019 to second place this year. Again, this is another regulation that has been among the top group for many years.
- §211.160(b) *Lab controls should include scientifically sound specifications* was fourth place last year and third place this year.
- §211.42(c) *Facilities shall include defined areas of sufficient size.*

The top three in the group above are the same as the top three for FY202. Fourth place for this five-year aggregate period is 211.42(c) rather than 211.100(a), which was fourth place in FY2020.

The FDA's focus on OTC manufacturers may explain some of the reasons that having and following procedures for the quality unit, §211.22(d), continues at or near the top of the list. Often, these firms often either do not have a quality unit or have one that fails to perform its responsibilities. The FDA continues to hold the quality unit responsible for implementing an effective quality system at all pharmaceutical firms. Also, OTC firms are often deficient in the validation of the manufacturing process, as captured in §211.100(a).

Table 1: Drug GMP Inspections, §211 Citation Frequency by Fiscal Year

CITATION	SHORT DESCRIPTION	2016	2017	2018	2019	2020
Total Form 483s issued using the FDA tool for Drug Inspections		691	694	716	779	349
§211.192	Investigations of discrepancies	227	278	183	167	128
§211.22(d)	Procedures applicable to the quality unit shall be in writing and shall be followed	153	185	208	215	111
§211.160(b)	Lab controls should include scientifically sound specifications	133	207	209	145	84
§211.100(a)	Production and process controls shall be supported by written procedures	110	116	102	129	59
§211.68(b)	Appropriate controls shall be exercised over computer systems					57
§211.42(c)	Facilities shall include defined areas of sufficient size	227	148	134	156	56
§211.188	Master production and control records	100	208	93	123	54
§211.166(a)	Stability testing	124	72	111	135	42
§211.67(b)	Equipment cleaning and maintenance	102	91	112	124	45
§211.113(b)	Control of microbiological contamination	118	92	71	121	43
§211.67(a)	Equipment shall be cleaned/sanitized or sterilized	94	54	81	99	42
§211.25(a)	Personnel qualifications	99	113	47	113	39
§211.160(a)	Following / documenting laboratory controls					38
§211.68(a)	Automatic, mechanical, and electronic equipment	80	67	60	67	33
§211.110(a)	Sampling and testing of in-process materials and final product	65	68	86	94	33

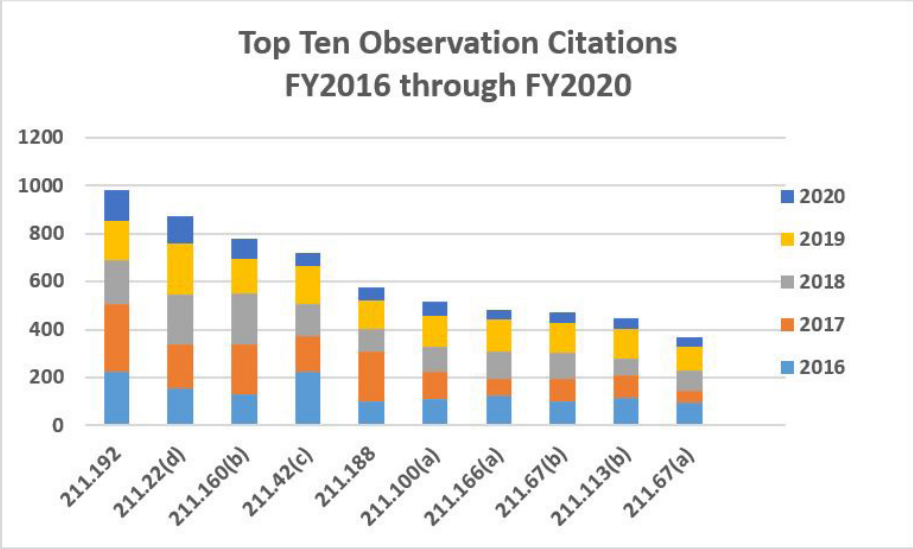


Figure 2: Top 10 Citations From 2016 Through 2020

CONCLUSIONS

For those who use inspection observations to monitor and improve their quality systems, the FDA's annual data provide ample resources against which firms can measure their potential vulnerabilities and gauge the probable focus areas during upcoming GMP inspections. The shuffling of positions among the most frequent observations likely reflects the FDA's recent focus on OTC manufacturers, where fundamental GMP understanding and compliance seems to be missing. Most of the observations at these sites reflect either a basic lack of understanding of FDA requirements or a conscious decision that compliance with these requirements would represent an unnecessary cost. Identifying and monitoring trends this year within the collection of 483 observations is difficult because of the substantial decrease in the number of inspections and Form 483s.

§211.192 moved up to first place this year after being in second place last year. It has consistently ranked among the most frequent citations; the industry still struggles with ensuring that investigations, including those for out of specification events, meet expectations. The lack of adequate written

procedures and responsibilities for the quality unit, §211.22(d), remains a very consistent citation over the five years addressed herein. Form 483 observations that include text such as “The quality unit is inadequate…” often result in additional enforcement action, including warning letters.

I expect that even with effective vaccines available in the first half of CY2021, the number of on-site FDA inspections may remain limited through much of FY2021, continuing to provide challenges in identifying inspection trends. While the FDA is performing remote data reviews, it does not appear to count these as inspections and is not issuing forms 482 or 483, though this is all subject to change as we move forward. It would be reasonable to expect that the FDA will develop processes for the conduct of remote inspections or incorporate elements of remote inspections even when it returns to more frequent on-site inspections. The world has changed, and while it may take a while for the FDA to develop processes and procedures for this, we should expect that it will happen.

ABOUT THE AUTHOR

Barbara Unger formed Unger Consulting, Inc. to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry, including general GMP auditing and auditing and remediation in the area of data management and data integrity. Her corporate auditing experience includes leadership of the Amgen corporate GMP audit group for APIs and quality systems. She also developed, implemented, and maintained the GMP regulatory intelligence program for eight years at Amgen. This included surveillance, analysis, and communication of GMP related legislation, regulations, guidance, and industry compliance enforcement trends. Unger was the first chairperson of the Rx-360 Monitoring and Reporting work group that summarized and published relevant GMP and supply chain related laws, regulations, and guidance. In addition, she was previously co-lead of the Rx-360 Data Integrity Working Group.

DO THESE RECENT DRUG GMP WARNING LETTERS SIGNAL A SHIFT IN FDA ENFORCEMENT FOCUS?

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The FDA's posting of drug GMP warning letters citing product adulteration has substantially decreased in the past several months. Warning letters are generally issued approximately seven months after inspections. The decrease we are now seeing is due to the slowdown of on-site inspections with COVID travel limitations and concerns regarding investigator safety.

However, the FDA recently posted two unique warning letters that all pharmaceutical and API firms, regardless of their product category, should consider and evaluate. These first-of-a-kind warning letters often signal a new enforcement focus or process for the FDA. (For example, when the FDA issued a warning letter to McKesson Corp. in Feb. 2019, it was the first — and so far, the only — time the agency cited failure to comply with the requirements in the November 2013 Drug Supply Chain Security Act (DSCSA) amendments to the Food, Drug, and Cosmetic [FD&C] Act.) The two warning letters posted the week of Jan. 27, 2021 and addressed here, have broad applicability to pharma companies and represent the FDA's renewed emphasis on both alternatives to on-site inspections and the importance of purchasing controls and supplier management.

YUYAO YIJIA DAILY CHEMICAL CO., LTD

The FDA posted a warning letter issued Jan. 22, 2021 to Yuyao YiJia Daily Chemical Co., Ltd., located in Ningbo, China. Products made at this location were placed on import alert on Sept. 23, 2020. The firm manufactures over-the-counter (OTC) drug products, including hand sanitizers. Unlike other warning letters issued for violations of GMPs, the letter does not identify an inspection date, nor is the firm currently listed in the FDA's inspection database. The warning letter, however, does list an FDA Establishment Identifier (FEI) number. The second sentence of the opening paragraph states, *"FDA has reviewed the records you submitted in response to our March 31, 2020 request for records and other information pursuant to section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for your facility…"*. Note in the discussion below a follow-up set of requests made on May 8, 2020. It would be interesting to know what precipitated the request for documents and whether a Form-482 was issued.

The warning letter identifies four deficiencies: one associated with final product testing, one associated with material controls, one addressing deficiencies in the stability program, and one that identifies lack of a functioning quality unit. Each deficiency ends with a comprehensive list of requested actions and information to be provided as part of the response to the warning letter. Let us go through each deficiency briefly and identify the specifics that the FDA found problematic. I will not address the substantial FDA follow-up requests; readers can peruse those separately.

1. Deficiency No. 1 addresses the firm's failure to adequately test finished product shipped to the United States. Records submitted to the FDA by the company indicated identity and strength of the active ingredient were not tested prior to distribution. Further, the company did not provide test methods and only listed equipment. The FDA requested the missing information on May 8, 2020. In response, the firm *"restated [their] original response"* to indicate a third-party laboratory was used but again did not provide specifications or methods for testing of identity and strength. The FDA notes that after the request for documents, the firm shipped several lots of hand sanitizer for U.S. distribution.

2. Deficiency No. 2 addresses failure to test incoming raw materials, minimally to determine identity. When the FDA requested whether the firm tested purchased raw materials, the firm replied *"…that the testing was done by their supplier."* The FDA then asked which identity test was performed by their supplier, and the firm provided the supplier CoA, which did not include a specification or results. Further, the company could not provide evidence that it qualified the supplier or verified the results on the CoA.

3. Deficiency No. 3 identified that the stability data did not include evaluation of the active ingredient nor did it include any microbiological data.

4. Deficiency No. 4 cited an inadequate quality unit because the firm failed to develop and implement adequate written procedures for the quality unit.

The FDA concludes the warning letter by suggesting the firm hire a qualified consultant and stating that *"Based on FDA's review of records and information provided in response to our request, your firm's quality systems are inadequate."* It will be interesting to see if additional warning letters are issued based on this practice. This warning letter should serve as a wake-up call to all firms that have submitted documentation to FDA at its request that enforcement actions may be taken on the basis of those documents.

PROFESSIONAL COMPOUNDING CENTERS OF AMERICA

The second warning letter was issued to Professional Compounding Centers of America dba PCCA in Houston, Texas, on Jan. 27, 2021. The warning letter was based on the outcome of an inspection ending Oct. 29, 2019. The FDA notes that it replaces a warning letter dated Jan. 7, 2021. Considering the nature of the deficiencies, it is surprising it took almost 15 months to issue the warning letter. PCCA is not a total stranger to enforcement actions. The FDA inspection database identifies a 2009 inspection classified as OAI (official action indicated), though I've been unable to find a warning letter resulting from the inspection. Two inspections before this warning letter were classified NAI (no action indicated) and VAI (voluntary action indicated), respectively. In this warning letter, the FDA identifies four areas where the firm is in violation of the FD&C Act:

- The firm purchased APIs that were deemed adulterated; its supplier was placed on import alert and was issued a warning letter.
- At least 23 API suppliers in the PCCA supply chain have a history of GMP non-compliance.
- The firm's glycerin USP product is adulterated and misbranded and four pain drugs manufactured by PCCA were deemed misbranded.
- Labeling of repackaged APIs did not accurately identify all manufacturers.

In this article, we focus primarily on supplier qualification and oversight activities at PCCA. Supplier qualification and ongoing oversight should include an evaluation of enforcement actions that may be in place against the supplier. This warning letter provides a unique perspective of the importance the FDA places on this assessment. Although previous warning letters have cited use of materials from a supplier on import alert, this enforcement action takes failures in this area to a new level based on the number of examples provided. The FDA states, *"Your receipt in interstate commerce of adulterated drugs (i.e., those listed on an import alert) and the delivery or proffered delivery thereof, is a violation of section 301(c) of the FD&C Act, 21 U.S.C. 331(c)."*

The FDA begins the warning letter by citing purchase of materials that were the subject of an import alert put in place on July 30, 2018. The firm in question refused an FDA inspection and destroyed batch records. It also received a warning letter, though the date of the letter was redacted. The FDA proceeds to identify that at least 23 other API suppliers to PCCA were under import alert and/or received warning letters. Some of the import alerts have been removed and some warning letters were closed out, though others remain in effect. *"To understand whether PCCA has received or introduced additional adulterated drugs in interstate commerce, we are therefore requesting information regarding timing of receipt and distribution of drugs from the 23 facilities listed below."* Further, *"FDA has evidence that the drugs listed in the import alert appear to be adulterated. You [PCCA] are responsible for ensuring that the drugs you distribute are manufactured in compliance with all relevant CGMP requirements for drugs."* Nine of the firms remain on import alert 99-32 for *"…delaying, denying, limiting, or refusing an FDA Drug Inspection."* Six firms have been the subject of a warning letter.

Because the FDA identified a *"pattern"* of problematic manufacturers that supply PCCA, the firm is asked to *"…provide the lot numbers and dates of distribution for all drugs received from each facility listed above"* in response to this warning letter so the FDA can determine the extent of the adulterated drug products that PCCA introduced into interstate commerce. For those materials that were used during the period when the supplier was either under import alert or the subject of a warning letter, the FDA asks whether PCCA customers were notified that they were supplied adulterated drug products. For those who were not notified, the FDA asks that PCCA do so and provide the agency with a copy of the notification. The FDA enforcement report does not identify any product recalls from either PCCA or Professional Compounding Centers of America, though not all recalls may be included.

PCCA must provide the FDA an *"evaluation of their supplier program including a plan to audit [their] suppliers."* It also was asked to perform a full reconciliation of drugs from the manufacturers identified in the warning letter. For firms and drugs that may be on import alert, PCCA must identify whether any adulterated drugs remain in its possession. The FDA also asked the firm to schedule a meeting to *"discuss the adequacy of the corrective actions"* that the firm proposed to prevent *"continued introduction of adulterated and misbranded goods into interstate commerce."*

Switching to the topic of the firm's adulterated glycerin, USP product, PCCA stated that each lot was tested by the supplier prior to receipt. Supplier qualification included testing for ethylene glycol (EG) and diethylene glycol (DEG), and PCCA is *"confident"* that the glycerin is free from EG or DEG impurities. PCCA does not believe it needs to test incoming glycerin for EG and DEG impurities because it is *"superfluous, and simply not required."* As you might expect, the FDA deemed this response inadequate, stating, *"You cannot ensure the quality and security of the supply chain with regard to DEG and EG adulteration given your current practice because you do not independently verify that the API manufacturer's reports are reliable…"*

And finally, four PCCA relabeled and repackaged APIs were deemed to be misbranded because other firms were involved in the production of four APIs, but the label identifies only PCCA and does not identify activities performed by the firm. Thus, the label is *"false and misleading."*

CONCLUSIONS

Both warning letters are directly relevant to all prescription drug pharmaceutical manufacturers even though these enforcement actions were issued to an OTC drug manufacturer and a compounding pharmacy. All would be well served to evaluate the deficiencies and determine if their firms share any that are similar. Take-home lessons from these warning letters include but are not limited to:

- The FDA has taken GMP **enforcement action against a company based on remote document review, without an on-site inspection**. Firms

should take requests for documents by the FDA seriously and ensure that correct and complete information is provided. Responses that are "revised" after additional requests are made for information may likely be problematic.

- Firms should closely **monitor the enforcement status of their current and potential suppliers, including CMOs**. The FDA posts and updates import alert actions and warning letters and status on its website.

- Firms, such as PCCA, that **receive or introduce adulterated drugs, including APIs**, into interstate commerce have and **will face enforcement action**. This includes extensive actions they must take at the FDA's direction, such as those described in this warning letter.

- **Supplier management and purchasing controls** remain a focal point of the FDA's inspection and enforcement activities.

ABOUT THE AUTHOR

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FDA'S COVID-19 PREPP INITIATIVE SUMMARY REPORT — KEY TAKEAWAYS FOR MANUFACTURERS

Madeleine Giaquinto

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In January 2021, as one of his last official acts as the Commissioner of the FDA, Stephen Hahn, M.D., published the *FDA COVID-19 Pandemic Recovery and Preparedness Plan (PREPP) Initiative Summary Report*.[1] The PREPP report is the culmination of work performed by the FDA's PREPP Initiative, which launched in April 2020 to examine lessons learned from the agency's response — spanning FDA policies, processes, operations, communications, and intra-agency coordination — to the global COVID-19 pandemic.[2] The FDA asked an independent non-government organization to conduct an objective review of its ongoing COVID-19 response and to summarize findings in the PREPP report. To that end, the third-party organization solicited insights from key FDA staff and external stakeholders, collated lessons learned, and suggested 12 potential "action areas," bucketed across three overarching themes, where change could be implemented to improve resiliency against the current pandemic and to strengthen preparedness for future public health emergencies.

In publishing the PREPP report, the FDA caveated that it is not required to implement the third-party's suggested action areas but that it will carefully review such recommendations in light of current statutory authorities and available resources.[3] Additionally, the agency will continue to evaluate its regulatory activities moving forward as it continues its COVID-19 response and, thus, may consider additional or alternative lessons learned in the future. This article provides a brief overview of the PREPP report's overarching themes and highlights key regulatory insights for manufacturers in light of two action areas in particular.

OVERARCHING THEMES AND ACTION AREAS

The PREPP report is largely dedicated to detailing findings in response to two questions: (1) what the FDA did in response to public health threats posed by COVID-19; and (2) what the FDA could do to enhance its response to COVID-19 and to future threats (i.e., the 12 potential action areas). Both sets of findings are presented under three overarching themes: (1) accelerating FDA's immediate COVID-19 response; (2) selectively sustaining and scaling regulatory innovation; and (3) enhancing future pandemic preparedness.

1. Accelerating Immediate COVID-19 Response

First, the PREPP report describes FDA's work to enhance the efficiency and transparency of its ongoing regulatory activities during the pandemic. To advance the development of COVID-19 vaccines, therapeutics, and diagnostics, the agency issued a slew of guidances supporting industry with respect to this endeavor. In addition, the FDA implemented processes and tools aimed at maintaining the flow of product review and managing a groundswell of emergency use authorization (EUA) requests and new drug application submissions for COVID-19-related products. For example, the Center for Devices and Radiological Health (CDRH) posted EUA submission templates to aid sponsors requesting EUAs. The agency also boosted transparency around its scientific decision-making, in order to educate the public and ease vaccine hesitancy, by broadcasting Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings for the Pfizer/BioNTech and Moderna vaccines.

Under this overarching theme, the potential action areas identified include: continuing to plan and prepare for review of COVID-19 medical products (Section 3.1); strengthening EUA processes and supporting tools (Section 3.2); strengthening COVID-19-related communications with industry, external stakeholders, and the general public (Section 3.3); and deepening U.S. government partnerships (Section 3.4).

2. Selectively Sustaining and Scaling Innovations

Next, the PREPP report highlights FDA's engagement with innovative regulatory activities during the pandemic. These activities included release of segmented and targeted guidance, such that industry was made more frequently aware of the most relevant and up-to-date information.[4] The use and sharing of COVID-19-related real-world data (RWD) among public health stakeholders, including FDA, became a huge accelerator in understanding the coronavirus disease and quickly initiating the development of capable medical countermeasures. Additionally, the agency utilized alternative approaches to conducting inspectional work when on-site inspection capability became limited at the outset of the pandemic due to social distancing and travel restrictions. Such alternative approaches included use of remote records review and information made available under the Mutual Recognition Agreement (MRA) for products evaluated by the EU, the U.K., and other qualified health authorities. Alternative approaches to inspectional work are discussed further below.

Under this overarching theme, the potential action areas identified include: consideration of how to carry forward interactive engagement with innovators and industry (Section 3.5); creation of an environment conducive to sustained innovation in clinical trial conduct (Section 3.6); collectively strengthening policy guidance development and transition processes (Section 3.7); enhancing real-world monitoring of COVID-19 products (Section 3.8); and continuing to evolve and optimize inspectional operations, building on the COVID-19 experience as a catalyst (Section 3.9).

3. Enhancing Future Pandemic Preparedness

Lastly, the PREPP report discusses the agency's undertakings with respect to its longer-term pandemic preparedness capabilities. For example, the FDA engaged in forums that were established to cultivate and coordinate development of COVID-19 therapeutics and vaccines through use of master protocols, such as the Accelerating COVID-19 Therapeutic Innovations and Vaccines (ACTIV) consortia. Additionally, the FDA invested in supply chain risk surveillance technologies and expanded data analytics modeling across the drug, medical device, and food supply chains. Supply chain surveillance and resiliency is discussed further below.

Under this overarching theme, the potential action areas identified include: strengthening supply chain surveillance for regulated products (Section 3.10); developing emergency management capabilities and approaches (Section 3.11); and developing a regulatory framework to encourage broader use of adaptive trial designs and master protocols (Section 3.12).

KEY ACTION AREAS FOR MANUFACTURERS

While action areas identified in the PREPP report span FDA's regulatory processes and product life cycles, several may be particularly important to manufacturers of FDA-regulated products, including the evolution and operationalizing of FDA's inspectional operations (Section 3.9) and the strengthening of its supply chain

surveillance work (Section 3.10). These potential action areas are important for manufacturers because they indicate that the FDA's activity, guidance, and/or communication regarding modernized regulatory requirements with respect to inspections and supply chain surveillance may be under development, and opportunities for engagement with the agency on the development and implementation of such new approaches may be forthcoming.

EVOLVE AND OPTIMIZE INSPECTIONAL OPERATIONS

In March 2020, then-Commissioner Hahn suspended most foreign and domestic inspections of facilities that manufacture FDA-regulated products in order to reduce the spread of COVID-19, although "mission-critical" activities continued.[5, 6] It wasn't until July 2020 that on-site, prioritized domestic inspections resumed, and only on a limited basis (i.e., depending on the local risk of COVID-19 infection).[7] Thus, safe on-site inspection capability remained (and continues to remain) limited.

To address the growing backlog of inspectional work created by the pandemic, and to maintain the review of medical product applications, the agency employed a suite of alternative tools under several of its authorities. First, the FDA leveraged its authority under Section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act to make over 400 records requests "in advance of or in lieu of" inspections of certain drug manufacturing facilities,[8] allowing some of its review work to occur remotely. This meant that prioritized inspectional work, requiring on-site personnel, could be done in an abbreviated, safer manner. Second, FDA leveraged flexibilities under the MRA, allowing it to rely on information from regulatory reviews conducted by the EU and other health authorities, shoring up limited FDA resources for higher risk sites.

The PREPP report discusses the potential for further adoption of these approaches, including reviewing its current authority to conduct Section 704(a)(4) records requests and exploring expanded use of such records requests across other types of FDA inspections not explicitly mentioned in Section 704(a)(4), as well as expanded use of other remote assessment functions. To further this optimization, the agency is undertaking a comprehensive risk-based assessment of its inspectional operations to develop a better understanding of risks and benefits associated with preannounced inspections, remote records review, and other remote assessment activities. To coordinate the implementation and governance of such innovative approaches, the FDA is establishing a dedicated body called the Intra-Agency Inspectional Affairs Council (IIAC).

Looking ahead, the PREPP report highlights key areas where the FDA could further increase the effectiveness and resiliency of its inspection programs. In the short term, the FDA could enhance communications with industry about expectations and how it plans to conduct inspectional activities. Notably, on Jan. 29, 2021, the agency demonstrated its commitment to setting expectations in this regard through issuance of revised Q&A guidance (initially issued in August 2020) implementing an interim process for communicating issues identified in Section 704(a)(4) records requests that are made "in advance of or in lieu of a pre-approval or pre-license Inspection."[9] This means that following review of requested records, the agency plans to convey identified issues to respective facilities and will weigh formal written responses regarding those issues before making determinations on applications in question.

Moreover, in the longer term, the PREPP report notes that there is still space for FDA to move toward strategic, comprehensive modernization of alternate inspectional capabilities, including the scaled use of virtual technologies with adequate streaming infrastructure, secure databases holding sponsor information for streamlined review, and aligned approaches with other health authorities around the globe. To that end, the agency could also develop a framework to quantify and measure the effectiveness of such a strategy (through pilot programs, etc.) in order to codify this modernization.

STRENGTHEN SUPPLY CHAIN RESILIENCE

In addition to strains placed on the agency's entrenched regulatory processes for conducting on-site inspections during COVID-19, the PREPP report discusses enormous strains placed on supply chains for crucial medical products. These strains were created in part by surging demands for certain products and also by disruptions in global manufacturing operations due to worker safety concerns. Disruptions in supply chains have led to shortages, and risks of shortages, of essential products like ventilators, hand sanitizer, personal protective equipment (PPE), testing supplies, vials, and syringes, as well as certain critical care drugs (e.g., Propofol, azithromycin, etc.).

To address these shortages, the FDA wielded EUAs and guidances to increase the availability of certain high-demand products, specifically for COVID-19 diagnostics and protective medical devices. The PREPP report acknowledges implementation efforts underway at the agency that aim to strengthen supply chain surveillance and risk-mitigation capabilities moving forward, including four distinct bodies of work. First, CDER set up a Supply Chain Surveillance Task Force that analyzed supply chain and shortage data to detect and mitigate risks. To accompany these efforts, the task force is implementing an integrative data analytics platform to further support supply chain surveillance. In another example, the CDRH began collecting information from certain device manufacturers, as directed under the Coronavirus Aid, Relief, and Economic Security (CARES) Act, indicating a discontinuance or interruption in manufacturing "that is likely to lead to a meaningful disruption" in supplies during a public health emergency.[10]

Additionally, the FDA, via CDRH, engaged in a memorandum of understanding with the National Institutes of Health and the Department of Veterans Affairs to inform and support 3D printing of PPE and other important supplies. Lastly, the PREPP report notes development of FDA's Essential Medicine's List, directed under Executive Order 13944[11] and composed of 227 essential drugs, biologics, and medical devices, as a way to shore up supplies of the most crucial medical countermeasures.[12]

Looking ahead, the PREPP report highlights key areas where the FDA could further strengthen supply chain resiliency. For one, the agency could develop finer data analytics and risk surveillance and mitigation mechanisms that can be scaled and applied across FDA-regulated products. The FDA could also more sharply focus on proliferating new manufacturing technologies, like advanced/continuous manufacturing and artificial intelligence/machine learning (AI/ML) for operation and quality control management. Specifically, the PREPP report notes the agency's potential opportunity to build out its current regulatory frameworks at CDER, CDRH, and the Center for Biologics Evaluation and Research (CBER), incorporating these new technologies. This would involve providing guidance on the development, validation, and processes of AI/ML in the good manufacturing practice (GMP) context and on using analytical models designed to reduce process-driven lapses in quality. Notably, on Jan. 12, 2021, the FDA took steps toward answering this regulatory call through release of its *AI/ML-Based Software as a Medical Device (SaMD) Action Plan*, describing five forthcoming efforts aimed at furthering oversight of these technologies.[13]

CONCLUSION

In sum, the PREPP report lays out a comprehensive map of FDA's efforts during the pandemic thus far and provides a robust framework for how the agency could enhance its regulatory capabilities both as it continues to combat COVID-19 and as it prepares for future public health emergencies. Although not obligated to implement any of the suggested action areas, considering the third-party recommendations only to be a snapshot in time and not contemplative of resource or statutory limitations, recent communications indicate the FDA is hyper-focused on addressing challenges discussed in the PREPP report, particularly in areas impacting those in the manufacturing space.

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FDA INSPECTIONS: ARE CHANGES ON THE HORIZON?

Kalah Auchincloss

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Almost exactly one year ago, in March 2020, the U.S. FDA announced that it was suspending all foreign and domestic inspections except those it deemed "mission critical."[1] This unusual move was a response to the then-emerging COVID-19 pandemic—an attempt to reduce transmission of the virus and protect both FDA personnel and industry employees.

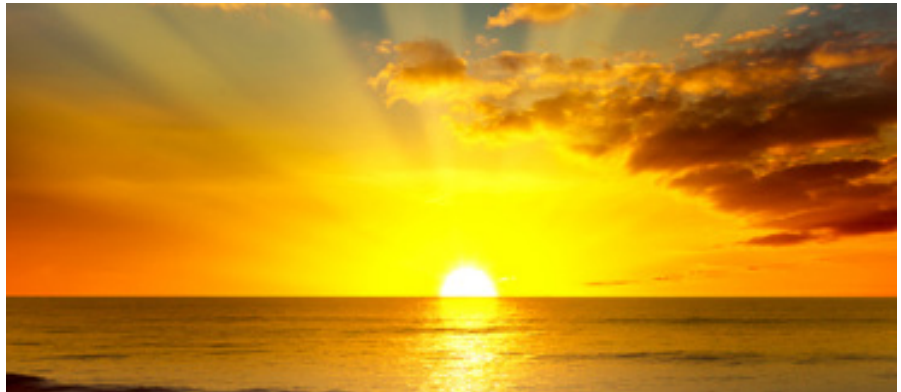
Even as it suspended inspections, the agency assured the public that it had "full confidence in the safety and quality of the products we all use every day and that the FDA will continue to leverage all available authorities to continue to ensure the integrity of the products we regulate."[2] A year into the pandemic, the FDA is still conducting only limited inspections in the U.S. and evidence has emerged of a significant inspection backlog that could compromise the safety and quality of the U.S. drug supply.

This article provides a brief timeline of inspection-related events over the last year (see Figure 1). It then discusses the impact of a year of limited inspections and the changes that we might expect as the FDA begins to shift back to more normal operations.

WHERE ARE WE TODAY?

The press releases in March 2020 referred to "alternative tools" the FDA would use in lieu of inspections to continue to approve new medical products and keep existing products safe. The FDA has described these authorities in numerous speeches and presentations, as well as in guidance, including: requesting and reviewing records "in advance of or in lieu of" an inspection under section 704(a)(4) of the Federal Food Drug and Cosmetic Act (FD&C Act)[3]; examining the previous inspection and compliance history of a facility; leveraging inspection reports from recognized foreign authorities under the Mutual Recognition Agreement (MRA) or from capable authorities that are members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S); and employing import controls at the border to prevent unsafe products from entering the U.S.[4]

In particular, the FDA has frequently used its authority to request records under section 704(a)(4) of the FD&C Act and its ability to rely on foreign inspection reports under the MRA. For example, in a speech from September 2020, an FDA



representative indicated that it had requested records under section 704(a)(4) more than 500 times since the start of the pandemic, and that more than 100 of those requests were part of the review of medical product applications, supporting decisions on whether or not to approve a product.[5] Further, the Office of Pharmaceutical Quality (OPQ) 2020 Annual Report stated that reliance on alternative tools avoided the need to conduct 153 on-site facility inspections prior to application approval.[6] The Pandemic Recovery and Preparedness Plan (PREPP) Initiative Report confirms the FDA's increasingly frequent use of these alternative authorities, noting that the use of the MRA with the European Union increased by close to 35% between March and October 2020 compared to the same time frame in 2019.[7] (For a closer look at the PREPP report, see "FDA's COVID-19 PREPP Initiative Summary Report — Key Takeaways For Manufacturers.")

As a result of its switch to alternative tools, the agency has done a remarkable job of continuing to meet user fee goal dates. An FDA website indicates that for drug and biological products (except biosimilars), the FDA met application user fee goal dates at least 90% of the time in 2020; this is in keeping with the FDA's commitments to industry in the user fee letters.[8] The website also states that by relying on alternative tools to complete facility assessments, CDER reduced the need to conduct preapproval inspections about 50% of the time over the last year.[9]

By my own independent research, I can find only 11 instances since March 2020 in which the FDA has issued a complete response letter or missed a decision date solely as a result of an inability to conduct an on-site inspection.[10] This is in comparison to more than 50 novel drug approvals and more than 900 generic drug application approvals in 2020.[11] All in all, the data indicate that the FDA has successfully continued to meet user fee dates to bring critical drugs to patients.

Unfortunately, routine surveillance inspections have not fared so well. A GAO report on the COVID-19 response painted a disturbing picture of a significant inspection backlog, finding that the FDA conducted only about 500 of the approximately 1,500 anticipated surveillance inspections in FY2020.[12] From March to October 2020—the first six months of the pandemic—the FDA conducted only 52 domestic and three foreign inspections, compared to about 400 domestic and 600 foreign inspections in the same time frame in each of the previous two years.[13] The inability to conduct inspections is not surprising—until recently the COVID-19 case rate was too high in most U.S. counties to safely send FDA investigators on-site. It is, however, disappointing that the FDA has not managed to utilize its "alternative tools" as effectively for surveillance inspections as it has in the preapproval arena.

It is also notable that remote or virtual inspections have been absent from the FDA's toolbox. The agency has been clear that section 704(a)(4) records requests and reliance on foreign inspection reports and other "alternative tools" are not the same as an inspection. These tools may provide data that can inform the need for an inspection, but they do not start with a Form-482, the traditional opening of an on-site inspection, nor do they result in a Form-483 list of observations. In short, these tools are "assessments" that may supplement inspections, but they are not equivalent.[14] The FDA has also refused to consider the use of video technology to conduct a virtual inspection, and until recently it has been reluctant even to use technology to add virtual components to its remote assessments.

THE FUTURE

While the FDA has largely managed to meet user fee goal dates, it clearly has not been as successful in mitigating the impact of suspending other types of inspections. Although an understandable immediate response to a public health emergency, continuing along this path will have significant consequences for the future. For example, companies classified as Official Action Indicated (OAI) will continue to linger in that status (preventing approval of new drugs made at those facilities), drug shortages may worsen, and the current risk-based inspection model will prove inadequate to properly prioritize the highest-risk facilities.

GAO recognized the need for the FDA to shift its thinking from short-term emergency response to longer-term strategic planning. The report noted that the inspection backlog could jeopardize the agency's goal of risk-based inspections and recommended that the FDA ensure inspection plans for future fiscal years "identify, analyze, and respond" to those issues.[15] Both GAO and the PREPP Initiative Report also recognized the need for a better set of

tools for the FDA, including virtual components. For example, GAO's second recommendation in its report is that the FDA:

> *"fully assess the agency's alternative inspection tools and consider whether these tools or others could provide the information needed to supplement regular inspection activities or help meet the agency's drug oversight objectives when inspections are not possible in the future."[16]*

The PREPP Initiative Report proposed similar action items, including that the FDA: improve its communications regarding its approach to inspections; develop a comprehensive "inspection optimization roadmap" that could include the scale up and use of virtual tools; and create a framework to define and measure the effectiveness of inspectional approaches.[17] Industry trade associations and other stakeholders have also submitted proposals suggesting similar next steps.

Fortunately, these recommendations have not fallen on deaf ears. In the weeks since the two reports were released, the FDA has indicated its willingness to conduct "remote interactive evaluations" of facilities, potentially incorporating some level of virtual technology—e.g., video conferences or virtual site walk-throughs as part of a 704(a)(4) records request.[18] The FDA is still unwilling to move to true virtual inspections or to label its alternative tools an inspectional equivalent, but this is a big step in the right direction. The FDA has also begun to conduct more on-site inspections as vaccination rates increase and COVID-19 case rates decrease.

Nonetheless, the pandemic has wreaked havoc with the agency's traditional inspectional model. The FDA will need to consider serious changes in the future, including consistent use of technology to enhance the use of alternative tools, and perhaps even a move toward virtual inspections, in addition to an altered risk-based model to more effectively prioritize facilities for physical inspection in light of the current backlog. An on-site physical inspection can no longer be the gold standard for all facilities; continued reliance on the current set of "alternative tools," with additional tools and technology added, must be part of the solution, in addition to on-site inspections.

FIGURE 1. TIMELINE OF KEY INSPECTION-RELATED EVENTS MARCH 2020 – MARCH 2021

March 2020

- FDA announces suspension of most foreign and domestic inspections with the exception of "mission critical" inspections.

May

- Statement from FDA continuing to postpone inspections except those that are "mission critical."

July

- FDA announces it will resume domestic inspections on July 20 based on the COVID-19 Advisory Level (a safety assessment by county).

August

- FDA issues *Guidance for Industry, Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* (Manufacturing Q&A Guidance).
- The guidance discusses the use of "alternative tools" in lieu of an inspection and when FDA will issue a complete response letter (CRL), among other items.

September

- FDA issues *Guidance for Industry, Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency.*

December

- FDA issues *Guidance for Industry, Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency.*
- Notably, the timelines apply to CRLs issued after an inspection or if alternative tools to assess the facility are "resource intensive."

January 2021

- FDA releases the PREPP Initiative Report, which includes a section on inspections.
- GAO publishes a report, *COVID-19 Critical Vaccine Distribution, Supply Chain, Program Integrity, and Other Challenges Require Focused Federal Attention*, which recommends actions related to FDA inspections.
- GDUDFA & PDUFA negotiations include discussions of "a set of proposals around inspections" and potential guidance on alternative tools.
- FDA publishes a webpage on CDER's Work to Meet User Fee Goals During the Pandemic.
- FDA issues a Warning Letter to YuYao YiJia Daily Chemical Co, Lt. based on a records request (no inspection) for its hand sanitizer product.
- FDA updates the August Manufacturing Q&A Guidance to reflect a new communications process for records requests under section 704(a)(4) of the FD&C Act.

February

- OPQ's 2020 Annual Report mentions inspections, particularly focused on preapproval inspections (PAI) and the use of alternative tools.

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FDA ISSUES PANDEMIC REMOTE INSPECTION GUIDANCE FOR DRUG MANUFACTURING FACILITIES

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On April 14, 2021, the FDA released a new guidance, *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*, to address the coronavirus disease 2019 (COVID-19) public health emergency. This guidance was implemented without prior public comment because the FDA determined that prior public participation was not feasible or appropriate. However, public comments may be submitted at any time for agency consideration.*

During the COVID-19 public health emergency, the FDA is limiting unnecessary contact by only conducting prioritized domestic facility inspections and those that are deemed mission-critical. For unprioritized inspections, non-mission-critical domestic inspections, and inspections impacted by travel restrictions resulting from the public health emergency, the agency is using voluntary remote interactive tools to support regulatory decisions and oversight of facilities.

PLANNING A REMOTE INTERACTIVE EVALUATION

The FDA may request to conduct a remote interactive evaluation for pre-approval inspections (PAIs), pre-license inspections (PLIs), post-approval inspections (PoAIs), surveillance inspections, follow-up inspections, compliance inspections, and bioresearch monitoring (BIMO) inspections using a risk-based approach. The FDA may request records or request that a facility participate in a remote interactive evaluation prior to an on-site inspection. Facilities or applicants are unable to request the FDA to perform a remote interactive evaluation.

Facilities eligible for a remote interactive evaluation will be notified by electronic correspondence or phone call. The correspondence will confirm the facility's willingness and ability to participate in a remote interactive evaluation, including the use of teleconference, livestream video, and screen sharing of data and documents. Once a remote interactive evaluation is confirmed, the FDA will schedule a brief virtual meeting to discuss the logistics, responsibilities, and expectations. The FDA will not issue a Form FDA 482, Notice of Inspection, to announce or open a remote interactive evaluation.

CONDUCTING A REMOTE INTERACTIVE EVALUATION

The FDA has an expectation that the connectivity and image quality will be adequate to remotely review, observe, examine, and evaluate the information requested, with minimal issues. The FDA will initiate remote interactive evaluations using FDA Microsoft Teams, FDA Zoom for Government, or FDA Adobe Connect to ensure security of the platform. The agency will provide a secure means to send requested information (documents and videos) during a remote interactive evaluation. All documents submitted to the FDA must be in English with paper documents scanned and provided as searchable bookmarked Portable Document Format (PDF) files when possible, to facilitate review.

CONCLUDING A REMOTE INTERACTIVE EVALUATION

The FDA will have a closeout meeting with the facility's management upon completion of a remote interactive evaluation. If necessary, the FDA will present a written list of observations describing and discussing any observations. This will replace the traditional issuance of Inspectional Observations Form FDA 483. These written observations are not a final agency action or decision. The FDA will encourage the facility to submit a formal response to the observations in writing within 15 business days.

The FDA will provide a copy of the final remote interactive evaluation report to the facility. The report and any written list of observations may be subject to a disclosure request under the Freedom of Information Act. The results of a remote interactive evaluation may be used by the FDA to determine if an on-site inspection is required. The information obtained from the remote interactive evaluation can be used by the FDA to prepare for and conduct the on-site inspection.

IMPACTS OF REMOTE INTERACTIVE EVALUATIONS ON ESTABLISHED COMMITMENTS AND TIMEFRAMES

The FDA intends to operate within normal timeframes using remote interactive evaluations, which should allow for prioritization of other activities. The agency intends to use information from remote interactive evaluations to meet user fee commitments (ensure timely reviews of applications for drugs and biological products) and intends to adhere to existing response timeframes applicable to pre-approval and pre-license inspections. The FDA will consider responses or corrective actions to observations if provided within 15 business days. Responses or corrective actions to observations received after 15 business days may be deferred for consideration and will be considered in the next application cycle.

For other inspections, the FDA generally intends to use existing timelines established for reporting on and evaluating the outcome of an inspection for remote interactive evaluations. The FDA will consider responses or corrective actions to observations if provided within 15 business days with respect to further regulatory action.

CONCLUSION

Recent changes in the organization, structure, and philosophy at the FDA are a positive sign for the pharmaceutical industry. By rapidly adapting to situations such as the COVID-19 public health emergency, the FDA continues to promote safety, efficacy, and security of drugs through fostering pharmaceutical development and manufacturing innovation and streamlining the compilation and assessment of marketing applications. It is important for organizations to treat remote interactive evaluations with the same degree of seriousness as any on-site inspection. Additionally, organizations **must** ensure that appropriate responses are submitted in 15 business days.

As an industry, I hope we can prove that using remote interactive evaluations is an effective means to interact with the FDA, enabling the FDA to build confidence in the process and consider using remote interactive evaluations when the COVID-19 public health emergency passes.

* Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 or electronic comments to https://www.regulations.gov. Please reference docket number FDA-2020-D-1136 and the complete title of the guidance with all comments.

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THE "RESILIENCY ROADMAP" — NEXT STEPS FOR FDA INSPECTIONS

Kalah Auchincloss
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More than a year into the COVID-19 pandemic and FDA's abrupt suspension of on-site inspections in March 2020, the agency released the *Resiliency Roadmap for FDA Inspectional Oversight* in May 2021.[1] The first part of the roadmap provides data on the conduct of inspections during the pandemic and FDA's use of remote, alternative tools; the second section of the document discusses future plans to address the backlog of routine surveillance inspections. This article summarizes the roadmap and offers several predictions about the future of FDA inspections.

STATE OF FDA INSPECTIONS

In general, FDA was able to conduct only mission-critical and high-priority inspections from March 2020 to March 2021 (see Table 1). FDA determines whether a given inspection is mission critical on a case-by-case basis, weighing "its resources and capabilities for the inspection during the public health emergency against the public health risk or benefit posed by the potential inspection site."[2] Factors such as breakthrough or regenerative medicine advanced therapy designation; whether the product is for a serious disease or medical condition with no substitute; presence of serious adverse event(s) or recall(s); and whether the product is related to FDA's COVID-19 response are all part of FDA's mission critical calculus.

Prioritized domestic inspections include surveillance and for-cause inspections that are not mission critical, but that are high priority based on factors such as whether the inspections is intended to follow up on a previous violative inspection; needed to support a product approval decision; considered high risk under statutory inspection frequency mandates (generally related to food facilities); or "otherwise maximizes the use of limited inspectional resources to achieve the greatest public health impact during the COVID-19 pandemic."[3] FDA only conducts prioritized inspections if the COVID-19 Advisory Rating Level indicates travel to the region is safe.

Table 1. Data on FDA Inspections During the Pandemic

Type of Inspection	Number of Inspections
	Timeframe: March 2020 - March 2021
Mission Critical	821[4] (29 foreign, remainder domestic)
Prioritized	777[5] (all domestic)
PAI/PLI/pre-market	~600 of >13,500 application required inspectional oversight 68 application delays[6]
	Timeframe: Fiscal Year 2021
For-cause	90% of planned domestic OAI follow-up activities completed in FY20 164 planned domestic OAI follow-up activities in FY21 • 49 complete • 115 remaining[7]

Surveillance	26,250 planned inspections (includes most, but not all postponed from FY20)[8]
	
	• 2,953 complete
	• 23,297 remaining[9]
	  ◦ Majority are domestic facilities (21,521)
	  ◦ Majority are food facilities (19,245)

Despite its limited ability to conduct on-site inspections, during the pandemic the agency managed to meet most user fee dates for pending applications and to complete follow-up on domestic facilities classified as "official action indicated" (OAI) during a previous inspection (see Table 1). This was partly due to mission-critical and high-priority on-site inspections, but also a result of FDA's use of "alternative tools" such as records requests under section 704(a)(4) of the Federal Food, Drug and Cosmetic Act (FD&C Act) to review information about a facility and reliance on foreign inspection reports from trusted foreign partners.

However, the agency was generally not able to conduct lower-priority routine surveillance inspections: a backlog of more than 23,000 routine surveillance inspections remains in FY21 (see Table 1), even after FDA used remote tools to reprioritize relative risk and eliminate the need for some of those inspections. Notably, many of the outstanding inspections are statutorily mandated inspections of lower-risk food facilities. A second sizeable portion is related to annual inspections of mammography facilities, which are also required by statute.

LOOKING AHEAD

After providing data on the current status of FDA inspectional activities, the roadmap turns to the future, outlining a "detailed plan for a more consistent state of operations and [FDA's] priorities going forward."[10]

The FDA emphasizes that it will continue its prioritized inspectional approach for all commodities through the end of the pandemic and even when travel restrictions and other impediments are lifted. More specifically, FDA will first conduct mission-critical inspections (Tier 1) and will then prioritize pre-approval and for-cause inspections (Tier 2). Lower-priority inspections that do not meet these criteria (Tier 3) may be postponed, which could include some routine surveillance inspections. As such, FDA cautions that there may be a longer interval between inspections of lower-risk facilities as FDA adjusts to the impact of the pandemic. [11]

Based on the tiered priority system, FDA then estimates how many routine surveillance inspections it could accomplish in the remainder of FY21 based on certain workload assumptions and possible trajectories of COVID-19. In none of the scenarios will FDA be able to complete all pending routine surveillance inspections. In the base case scenario, FDA expects to be able to complete approximately 26% of remaining domestic surveillance inspections of medical products in FY21. That number drops to zero (no non-mission-critical work) in the worst-case scenario and increases to 50% of remaining domestic medical product inspections in the best-case scenario (see Table 2).

Table 2. Conduct of Routine Surveillance Inspections[12]

Program Area	Remaining Surveillance Inspections
Human/animal food	12,285*
Human/animal medical products and tobacco**	3,229*

Base Case
• Gradual transition to standard operations by July 2021
• 2,123 (14%) remaining inspections conducted
  ◦ Food: 1,272 (10%)
  ◦ Medical products: 851 (26%)	

Best Case
• Standard operations by May 2021
• 4,192 (27%) remaining inspections conducted
  ◦ Food: 2,579 (21%)
  ◦ Medical products: 1,613 (50%)	

Worst Case • Continued restrictions through end of FY21 • Focus on mission critical work; no non-mission critical surveillance work conducted, thus increased reliance on alternative oversight tools.	

** Total inspections remaining does not add up to the total in Table 1, because FDA assumes state and local partners will conduct 35% of remaining food facility inspections, and foreign partners will conduct 25% of remaining medical product facility inspections. FDA also focuses on domestic rather than foreign inspections.*

*** Note that Table 7 in the Roadmap refers to "Human and Animal Medical Products and Tobacco." Tables 8 and 9 refer only to "Human and Animal Medical Products." All three tables, however, cite 3,229 as the number of remaining inspections in that category, thus we believe there is an error: either Table 7 should not include tobacco, or Tables 8 and 9 should include tobacco. Our best guess is that tobacco was accidentally deleted from Tables 8 and 9, as these are routine domestic surveillance inspections, thus there is no reason not to include tobacco (particularly as other tables in the Roadmap also refer to tobacco).*

4 PREDICTIONS ON THE FUTURE OF INSPECTIONS

Even in FDA's best-case scenario, the agency will need to address a growing backlog of surveillance inspections in future years. Delayed surveillance inspections may worsen drug shortages, bleed over into missed user fee goal dates or postponed for-cause follow-up, and put patients at risk of adverse events from sub-quality products. FDA clearly recognizes the need to adjust to this new reality; thus, we can expect certain pandemic practices to become permanent and new changes to be implemented. Below, I make four predictions on the future of FDA inspections:

1. ***The agency will conduct lower-risk surveillance inspections only as workloads and the pandemic permit***. Surveillance work is likely to increase over time as the agency returns to more normal operations, but not in the immediate future; thus, the backlog may grow unless FDA is able to contain it through means other than on-site inspections.

2. ***The COVID-19 focus on domestic facilities may signal a reverse in the recent trend toward greater numbers of foreign inspections***, particularly if FDA continues to rely on inspection reports from trusted foreign authorities. It almost certainly will accelerate FDA's shift in focus to conducting inspections in China and India, which are not party to information sharing agreements with FDA, rather than Europe.

3. ***Given the limited ability to conduct on-site inspections, FDA will continue to rely heavily on alternative tools,*** including new Remote Interactive Inspections (RIE)13 and Remote Regulatory Assessments (RRA). FDA is likely to continue to rely on these tools even as pandemic restrictions subside, to eliminate the need for on-site inspections in certain cases and lower the relative risk of facilities in other instances.

4. ***Over time, FDA will both refine and expand its arsenal of oversight tools***. For example, it may extend mutual reliance or other information sharing agreements to additional trusted regulatory partners and new commodities and/or refine the process for RIEs and RRAs. The agency may also expand its remote capabilities with new technology as part of the Data Modernization Action Plan (*Editor's Note: covered here*) and use data analytics to better estimate risk and adapt its risk-based inspection model. As relative risk is adjusted, FDA may be able to reduce the inspection backlog.

Perhaps one silver lining in the black cloud of COVID-19 is that the pandemic has forced FDA to rethink its inspectional oversight and modernize its approach. The FDA announced the creation of an agency-wide Inspectional Affairs Council at the same time as the release of the roadmap, which may help guide the new inspectional approach.

REFERENCES & NOTES

1. *Resiliency Roadmap for FDA Inspectional Oversight, May 2021*, https://www.fda.gov/media/148197/download.
2. Roadmap, p. 2.
3. Roadmap, p. 4.
4. Table 1 in the roadmap breaks down these inspections by commodity. More than half (475) were medical product inspections, excluding tobacco products, which FDA does not consider "mission critical" work. Interestingly, 408 of those 475 medical product inspections were bioresearch monitoring (BIMO) site inspections. Roadmap Table 1, p. 3.
5. Table 2 in the roadmap breaks down these inspections by commodity. FDA conducted 266 prioritized medical product inspections, again excluding tobacco products. Roadmap Table 2, p. 4.
6. Table 3 in the roadmap breaks down these inspections by commodity. 48 human drug applications were delayed solely as a result of FDA's inability to conduct an on-site inspection. Six of those applications were mission critical; FDA has scheduled those inspection to take place in FY21. Roadmap Table 3, p. 8.
7. Table 4 in the roadmap breaks down these inspections by commodity. 108 of the remaining 115 inspections are medical product inspections. Roadmap Table 3, p. 8.
8. Most, but not all inspections postponed in FY20 are included in FDA's FY21 planned surveillance inspections. However, FDA was able to use remote tools to provide oversight that lowered the relative risk for some facilities, bumping them out of the risk-based site selection model in favor of higher risk facilities. Roadmap, p. 11.
9. Table 5 in the roadmap breaks down these inspections by commodity. FDA estimates that there are 857 human drug, 110 biologic, and 279 BIMO surveillance inspections remaining. Roadmap Table 5, p. 12.
10. Forward to the Roadmap by Dr. Janet Woodcock, acting FDA commissioner.
11. Roadmap Table 6, p. 14; roadmap, p. 15.
12. Roadmap Tables 8 and 9 and p. 20
13. Guidance for Industry, Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency, April 2021, https://www.fda.gov/media/147582/download.

ABOUT THE AUTHOR

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AN ANALYSIS OF MHRA'S LATEST ANNUAL GMP INSPECTION DEFICIENCIES REPORT

Barbara Unger

President, Unger Consulting, Inc.

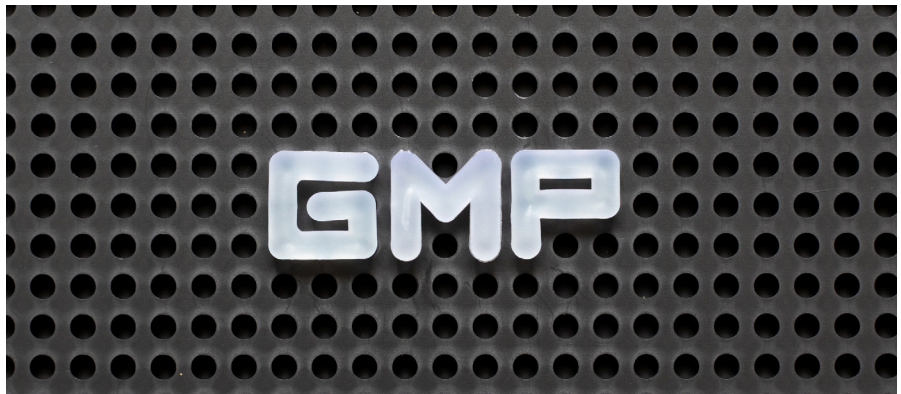
The U.K.'s Medicines and Healthcare products Regulatory Agency (**MHRA**) has taken a different approach in the publication of the **GMP deficiencies for drug product** issued during inspections in 2018 and 2019. In 2015 and 2016, the MHRA provided approximately a 100-slide deck each year with tables, figures, and text from deficiencies against the requirements in the chapters and annexes. No data were formally published for 2017. The MHRA published a 6,200-plus line Excel spreadsheet of its 2018 GMP inspection data so that individuals could parse and present the data according to their needs. Last year we published analysis of the data in a two-part set of articles: "An Analysis Of MHRA's Annual GMP Inspection Deficiencies Report" and "The 10 Most-Cited MHRA GMP Inspection Deficiencies By Annex/Chapter."

The 2019 data were provided in October 2020 in a just under 5,300-line Excel spreadsheet, and this year we again present the data in two articles. The first article begins with a high-level overview of the 2019 data, including trends from the four most recent MHRA reports, from 2015, 2016, 2018, and 2019. It proceeds to identify and evaluate the critical and major deficiencies from 2019, identifying the chapters and annexes associated with 137 critical deficiencies and the chapters and annexes most frequently associated with the 1,999 major deficiencies. Similar to the results in 2018, the most frequently cited chapter and annexes in 2019 are Chapter 1, *Quality System*, and Annex 1, *Manufacture of Sterile Medicinal Products*. For critical deficiencies citing Chapter 1 and Annex 1, the specific paragraphs and requirements with which they are associated are identified.

Part 2 will look in more detail at the most frequent citations in each of the top 10 chapters and annexes.

BACKGROUND

Here is how I parsed the data from the MHRA spreadsheet. Each row in the spreadsheet is treated as a unique deficiency, regardless of whether it is a "deficiency" or a "sub-point" as identified in the *Notes and Guidance* section of the MHRA publication. I cannot discern which is which in the spreadsheet, so I treat them all equally. The summary data from 2015 and 2016 are taken directly from the MHRA 2016 report. Data were not posted for 2017. Any mistakes in this analysis and reporting of the 2018 and 2019 data are mine, not the MHRA's.



OVERALL DATA

The MHRA conducted a total of 258 inspections in 2019, a decrease from the 285 inspections conducted in 2018. The number of inspections has decreased since 2016. Insufficient data are available to determine if the inspections outside the U.K. decreased because of the Mutual Recognition Agreement with the FDA. For example, only five inspections were conducted in the U.S. in 2018, and the 2019 inspections outside the U.K. were not identified as to the country.

Table 1 identifies the number of drug GMP inspections, by country, performed by the MHRA in 2015, 2016, 2018, and 2019. As in past years, almost all MHRa inspections were conducted in the U.K. The percentage of inspections conducted in the U.K. in 2019 increased from previous years, and the percentage of overseas inspections decreased over the four years. In 2019, only 12 percent of inspections were conducted outside the U.K. Next year, when we receive the data for 2020, both inspections outside and within the U.K. will likely be far lower based on the travel limitations posed by the COVID-19 pandemic. In 2018, approximately 75 percent of inspections conducted outside the U.K. were performed in India. In 2019, MHRA did not provide a breakdown by country for the 12 percent of inspections that were conducted outside the U.K.

Table 1: MHRA Inspections by Geography

Country	Number of Inspections 2015 / % total	Number of Inspections 2016 / % total	Number of Inspections 2018 / % total	Number of Inspections 2019 / % total
Total	303	324	285	258
U.K.	224 / 74%	242 / 75%	228 / 80%	228 / 88%
Overseas Inspections	79 / 26%	82 / 25%	57 / 20%	30 / 12%
India			43 / 15%	
China			5 / 2%	
United States			5 / 2%	
Bangladesh			1 / 0.3%	
South Korea			1 / 0.3%	
Singapore			1 / 0.3%	
Japan			1 / 0.3%	

Table 2 shows the top 10 areas of *all* deficiencies from 2015, 2016, 2018, and 2019. Data from 2015 and 2016 are taken directly from the 2016 report published by the MHRA. Quality Systems leads the list in all four years. Notable features in 2019 include:

- The top six categories remain the same, and in the same order, as they were in 2018.
- All of the chapters and annexes in the top 10 for 2019 were among that same group in 2018.
- Quality System (Chapter 1) deficiencies exceed the number of deficiencies in the combination of the next two areas, Documentation (Chapter 4) and Production (Chapter 5). See the data in Figure 1.
- Computerized Systems (Annex 11) moved up one notch from 10th in 2018 to ninth in 2019 and Outsourced Activities dropped to 10th in 2019.

Rank	2015	2016	2018	2019
1	Quality Systems	Quality System	Quality System	Quality Systems
2	Complaints and Recalls	Sterility Assurance	Documentation	Documentation
3	Documentation	Production	Production	Production
4	Quality Control	Complaints and Recall	Validation / Qualification	Validation / Qualification
5	Computerized Systems	Qualification / Validation	Premises and Equipment	Premises and Equipment
6	Production	Premises and Equipment	Sterility Assurance	Sterility Assurance
7	Premises and Equipment	Computerized Systems	Quality Control	Complaints and Product Recall
8	Validation	Personnel	Complaints and Recall	Quality Control
9	Personnel	Documentation	Outsourced Activities	Computerized Systems
10	Materials Management	Quality Control	Computerized Systems	Outsourced Activities

Table 2: Overall Deficiency Trend Comparison, Top 10

Figure 1 presents the total number of deficiencies identified in 2018 and 2019 for the top 10 combined chapters and annexes. These figures include *all* deficiency classifications – critical, major, and other. Figures 2 and 3 present the top groups for those, citing chapters and annexes, respectively.

Figure 2 shows that among the chapters, Chapter 1, *Quality System*, with just over 1,300 citations in 2019, has more than twice the number of deficiency citations as the next nearest chapter. Chapter 4, *Documentation*, with 700

deficiencies, is closely followed by Chapter 5, *Production*, with just under 600, and Chapter 3, *Premises and Equipment*, received almost 425 citations. Chapters 2, 6, 7, and 8 each had between 200 and 250 cited deficiencies. The remaining chapter, Chapter 9, *Self-Inspection*, had 30 citations.

The top six annexes cited in deficiencies in 2018 and 2019 are shown in Figure 3. Annex 15, *Qualification and Validation*, and Annex 1, *Sterility Assurance*, take first and second place among the most frequently cited annexes, respectively. This is followed by Annex 11, *Computerized Systems*, and Annex 16, *Certification by a Qualified Person and Batch Release*. All other annexes are associated with double-digit or fewer deficiencies.

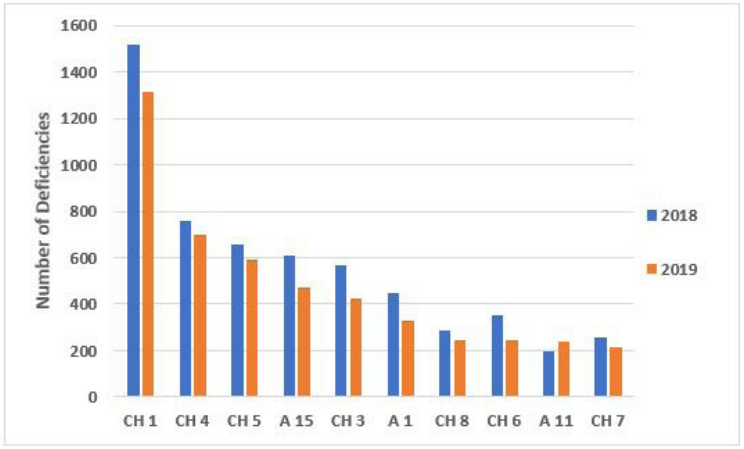


Figure 1: *Top 10 chapters and annexes cited in deficiencies*

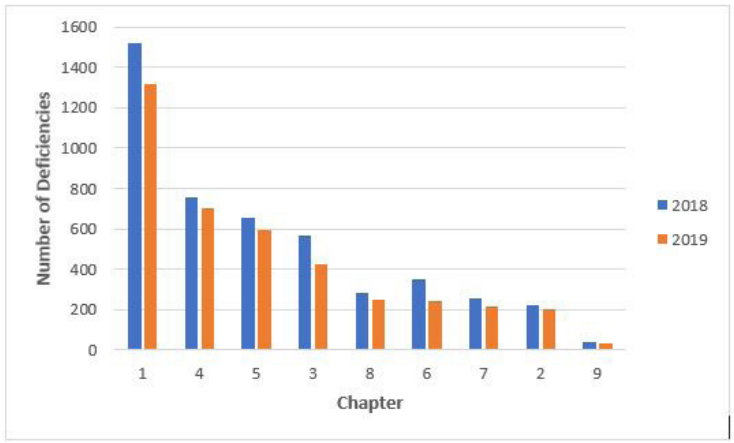


Figure 2: *Inspection citation by GMP chapter*

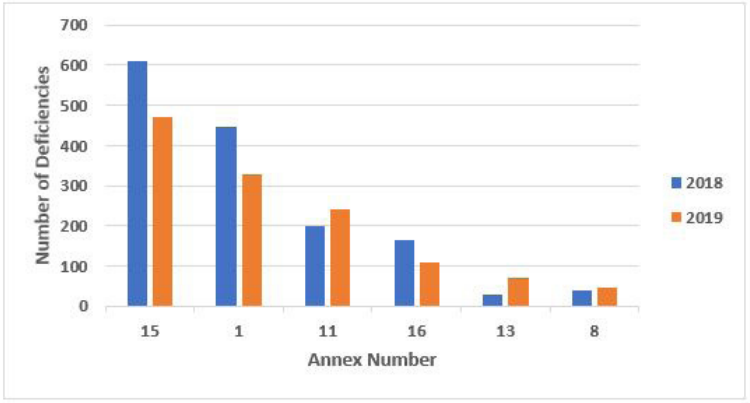


Figure 3: *Inspection citations by GMP annex*

CRITICAL AND MAJOR DEFICIENCIES

Table 3 provides a tabulation of all 2018 and 2019 deficiencies by their classification. Critical deficiencies constitute the smallest category; additional specific detail on these is provided later. Major deficiencies consistently constitute almost 40 percent of the total, and "other" deficiencies consistently constitute the majority at almost 60 percent of the total.

Table 3: Number of Deficiencies by Classification

Classification	2018 Number / % Total	2019 Number / % Total
Critical	142 / 2%	137 / 3%
Major	2,391 / 39%	1,999 / 38%
Other	3,676 / 59%	3,156 / 60%

Most critical and major deficiencies cluster in a few chapters and annexes. Figure 4 shows the number of critical deficiencies identified in 2019 and the chapters or annexes that are referenced. Among the critical deficiencies in 2019, 34 percent are associated with Chapter 1, *Quality System*, and 23 percent are associated with Annex 1, *Sterility Assurance*. Annexes 1 and 11 are the only annexes that include citations for critical deficiencies; the remainder cite GMP chapters.

Figure 4 provides the specifics on the 11 most frequently cited chapters and annexes in critical deficiencies in both 2018 and 2019. Chapter 7, *Outsourced Activities*, and Chapter 8, *Complaints and Product Recall*, were cited among critical deficiencies in 2019 but were not cited in critical deficiencies in 2018.

Figure 5 shows critical deficiency data for 2019 and presents these by location, a U.K. site or in a site outside the U.K. Interesting this year is that the number of critical deficiencies for Chapter 5, *Production*, more than doubled from last year, and the vast majority of these deficiencies are cited for locations outside the U.K., when only approximately 12 percent of inspections were conducted outside the U.K. In total, Chapter 1 and Annex 1 top the list for both 2018 and 2019, with Chapter 5 coming in third. Annex 1 critical deficiencies in 2019 are identified exclusively in the U.K. It is worth noting that critical deficiencies citing Chapter 5, Annex 11, and Annex 15 were cited exclusively at sites outside the U.K. in 2019.

Figure 6 shows the critical deficiencies identifying Chapter 1 presented by the paragraph most frequently cited. Sections 1.4 and 1.8, taken together, comprise 77 percent of the critical deficiencies cited Chapter 1. Table 4 provides specific citations and more granularity on these two sections. Section 1.4 identifies the purpose and activities to be ensured by the quality system, and section 1.8 describes the basic requirements of GMP.

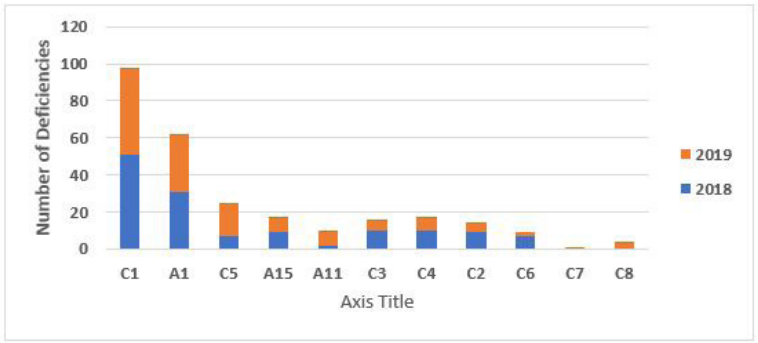


Figure 4: *Critical deficiencies by year*

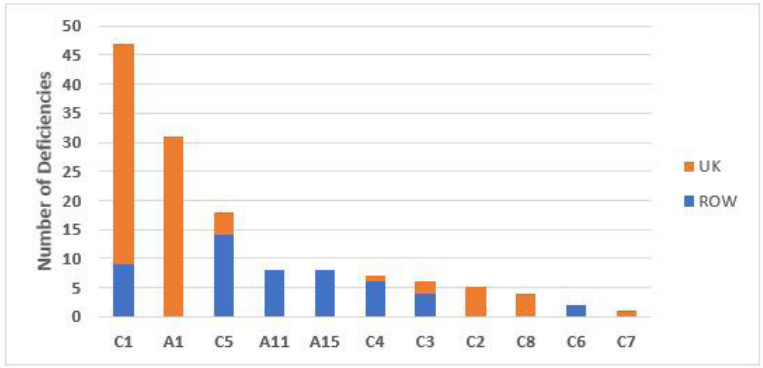


Figure 5: *2019 critical deficiencies by country*

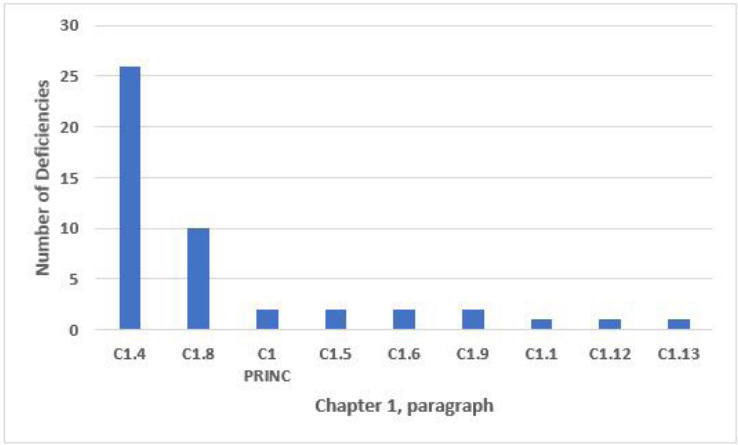


Figure 6: *2019 critical deficiencies citing Chapter 1*

Table 4: 2019 Critical Deficiencies Cited in Chapter 1

Critical Deficiencies Chapter 1, *Pharmaceutical Quality System*		
Paragraph	**#**	**Short Version of Text**
C1.4(i-xvii)	2	Please refer to the link above
C1.4(vi)	3	Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;
C1.4(vii)	3	Processes are in place to assure the management of outsourced activities.
C1.4(viii)	4	A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.
C1.4(ix)	2	The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.
C1.4(x)	1	All necessary controls on intermediate products, and any other in-process controls and validations are carried out;
C1.4(xi)	1	Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.
C1.4(xii)	3	Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;
C1.4(xiii)	1	After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;
C1.4(xiv)	6	An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles… Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles.
C1.8(i)	2	All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications.
C1.8(iii)	1	All necessary facilities for GMP are provided, including…
C1.8(iv)	1	Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
C1.8(vi)	1	Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected.
C1.8(vii)	4	Any significant deviations are fully recorded, investigated with the objective of determining the root cause, and appropriate corrective and preventive action implemented;

Figure 7 presents the critical deficiencies citing Annex 1. These do not cluster as closely as the deficiencies in Chapter 1 but are rather spread over the entire annex. Most of the requirements are cited in only a single critical deficiency. Only six paragraphs are cited more than once, and the abbreviated text for these are provided in Table 5.

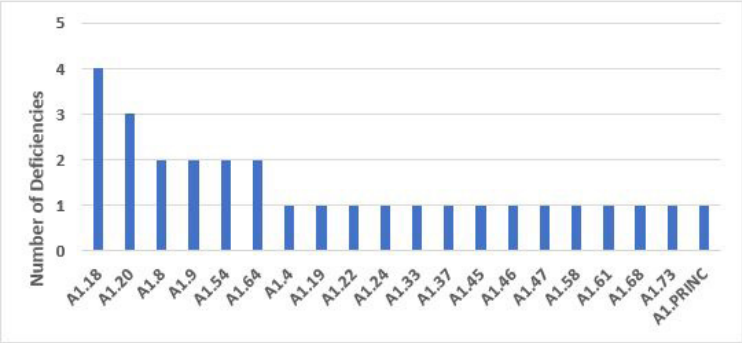


Figure 7: *2019 critical deficiencies citing Annex 1*

Table 5: 2019 Critical Deficiencies Cited in Annex 1

Critical Deficiencies *Annex 1, Manufacture of Sterile Medicinal Products*		
Paragraph	**#**	**Short Version of Text**
A1.18	4	Where aseptic operations are performed, monitoring should be frequent, using methods such as settle plates, volumetric air, and surface sampling (e.g., swabs and contact plates) …
A1.20	3	Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.
A1.8	2	Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.
A1.9	2	For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, … Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample …
A1.54	2	It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk.
A1.64	2	Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.

Figure 8 shows 11 annexes and chapters associated with a subset of the major deficiencies and the number of times they were cited during inspections both in the U.K. and outside the U.K. (ROW). In addition to these 11 chapters and annexes shown in Figure 8, major deficiencies were also identified in Chapter 2, Chapter 7, Chapter 9, Annex 2, Annex 3, Annex 6, Annex 8, Annex 9, Annex 12, Annex 17, and Annex 19. More GMP chapters and annexes were cited in major deficiencies than were cited in critical deficiencies. Among the major deficiencies, 31 percent are associated with Chapter 1, 29 percent are associated with Annex 1, 10 percent are associated with Annex 15, and 9 percent are associated with Chapter 4. Shortcomings in quality systems clearly lead the list of both critical and major deficiencies, demonstrating the agency's focus on the importance of a sound quality system to GMP compliance. Annex 1 ranks a very close second, emphasizing the prioritization of the manufacture of sterile products during inspections.

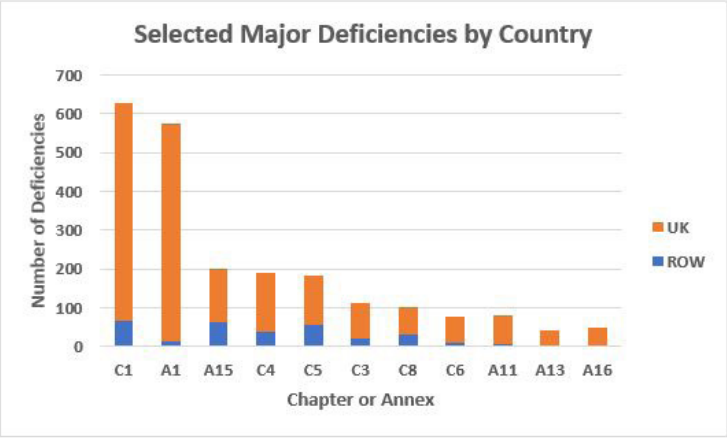


***Figure 8:** 2019 major deficiencies*

CONCLUSIONS

We conclude Part 1 after presenting an overall view of MHRA GMP inspection deficiencies from 2019, including trends from previous years. We have looked at differences year over year, and in 2019 we show the differences between inspections conducted in the U.K. and those conducted outside the U.K. Overall conclusions include:

- In 2019, the MHRA continued to conduct fewer inspections year over year. The percentage of inspections conducted in the U.K. increased slightly, and those outside the U.K. decreased by almost half since 2015. It will be useful to monitor whether the MRA with the FDA results in a decrease in the number of inspections of sites that they may both inspect. Because the MHRA only conducted five inspections in the U.S., it will be difficult to determine if the MRA with the FDA results in a decrease in inspections in the U.S.
- It is no surprise that Quality Systems, Chapter 1, continues to be first among the areas cited in inspection deficiencies, regardless of classification. It has remained in the number one position for all four years covered in this article.
- Critical deficiencies constitute just under 3 percent of the total deficiencies identified in 2019, and these are associated primarily with Chapter 1 and Annex 1. Approximately 37 percent of critical deficiencies cite requirements in Chapter 1, and approximately 22 percent cite requirements in Annex 1. It is noteworthy that among the inspections conducted outside the U.K., critical deficiencies make up 5 percent of the deficiencies identified.
- Among the major deficiencies that constitute approximately 40 percent of the total deficiencies, Chapter 1 again leads the group with just over 600 deficiencies. The next two include Annex 1 with almost 600 deficiencies and Annex 15 with approximately 200. Clearly, Quality Systems is the clear leader as it is for critical deficiencies.
- Computerised Systems, Annex 11, remains in the top 10 for both critical and major deficiencies, reinforcing the importance of this area to data integrity and the regulator's focus on the control and management of electronic data. This year the critical deficiencies citing Annex 11 were identified at sites outside of the U.K.

Hopefully, the MHRA will continue to publish data in the Excel format in the future and expand to include its GCP and GDP inspection findings. It would also be useful for the MHRA to publish the actual text of critical deficiencies from the various areas in future years as it did in the past. But in the absence of that, the publication of these data is valuable and appreciated by the industry.

ABOUT THE AUTHOR

Barbara Unger formed Unger Consulting, Inc. to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry, including general GMP auditing and auditing and remediation in the area of data management and data integrity. Her corporate auditing experience includes leadership of the Amgen corporate GMP audit group for APIs and quality systems. She also developed, implemented, and maintained the GMP regulatory intelligence program for eight years at Amgen. This included surveillance, analysis, and communication of GMP related legislation, regulations, guidance, and industry compliance enforcement trends. Unger was the first chairperson of the Rx-360 Monitoring and Reporting work group that summarized and published relevant GMP and supply chain related laws, regulations, and guidance. In addition, she was previously co-lead of the Rx-360 Data Integrity Working Group.

TOP 10 MOST-CITED MHRA GMP INSPECTION DEFICIENCIES BY ANNEX/CHAPTER IN 2019

Barbara Unger

President, Unger Consulting, Inc.

We evaluated the U.K. Medicines and Healthcare products Regulatory Agency's (MHRA) GMP inspection data for 2019, including trends associated with prior years, in Part 1 of this two-part article. We also addressed the critical and major deficiencies and the annexes and chapters with which they are associated. In this part, we take the 10 chapters and annexes with the highest numbers of deficiencies and do a deeper dive into the specifics of each.

In the figures that follow, we identify the paragraphs that were cited most frequently for each of the 10 chapters and annexes identified in Figure 1 of part 1 of this series. For two of these, Chapter 1 and Annex 15, we provide two figures for each because a handful of the paragraphs dominate the deficiencies in those areas. The following figures include *all* deficiencies, regardless of their classification as critical, major, or other.

In all cases, the table that accompanies each figure lists the paragraph content in the same order as it is found in the figure; they do not follow in numerical sequence.

CHAPTER 1, QUALITY SYSTEM

Let us start with Chapter 1, *Quality System*, as failure to comply with this chapter is the source of the largest number of total deficiencies, critical deficiencies, and major deficiencies. See also part 1's Table 2 and Figures 4, 5, and 8. Approximately 25 percent of all deficiencies in 2019 cite Chapter 1.

The data from all deficiencies in Chapter 1 are presented in two figures below because of the disproportionate representation of C1.4 and C1.8 in the total. C1.4 addresses the purpose of the pharmaceutical quality system, and C1.8 addresses, at a very high level, the basic requirements of GMP. Taken together, C1.4 and C1.8 make up 70 percent of the total number of deficiencies that cite Chapter 1 (see the two bars on the left side of Figure 1). Taking a more granular look, the five specific paragraphs representing the bars on the right side in Figure 1 make up 42 percent of all deficiencies that cite Chapter 1. The third through 10th most frequent deficiencies that identify Chapter 1 are presented in Figure 2. The eight paragraphs identified in Figure 2 constitute 27 percent of all deficiencies that cite Chapter 1. Table 1 identifies the text of requirements for the 10 most frequent deficiencies citing Chapter 1.

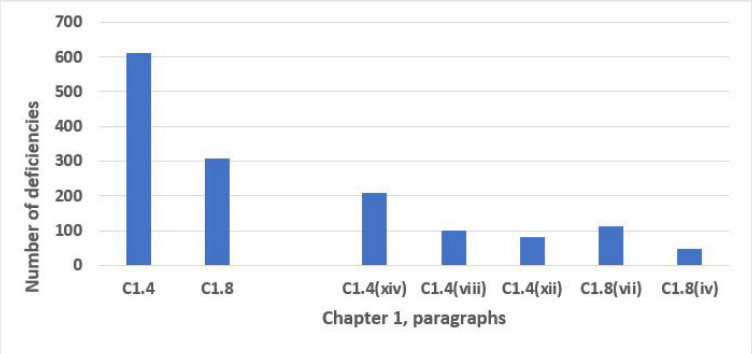


Figure 1: Chapter 1, paragraphs 1.4 and 1.8

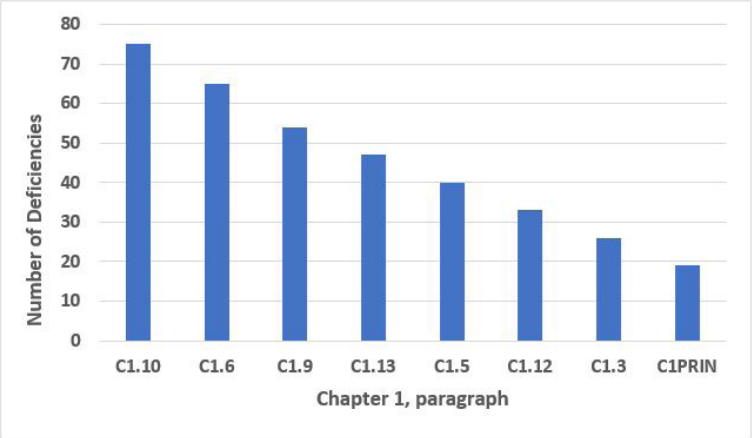


Figure 2: Chapter 1, numbers 3 through 10 in frequency

Table 1: Chapter 1

Paragraph	Short Version of Text *Chapter 1, Quality System*
1.4	A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that…(i) through (xvii)
1.8	Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that…(i) through (xii)
1.10	Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying…Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least…(i) through (xii)
1.6	There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.
1.9	Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or 6 supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that…(i) through (viii)

Paragraph	Short Version of Text *Chapter 1, Quality System*
1.13	The principles of quality risk management are that…(i) and (ii)… Examples of the processes and applications of quality risk management can be found inter alia in ICH Q9 which is reproduced in Part III of the Guide.
1.5	Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential…
1.12	Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.
1.3	The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. The design of the system should incorporate appropriate risk management principles…the effectiveness of the system is normally demonstrated at the site level.
Principle	The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy…They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

CHAPTER 4, DOCUMENTATION

Running a very distant second place to Chapter 1 is Chapter 4, *Documentation*, which is cited in approximately 13 percent of all deficiencies in 2019. Figure 3 shows the 10 most frequent citations of Chapter 4. Six of the paragraphs make up almost 75 percent of the citations of Chapter 4, and these can be found in Table 2. Note that 4.8 addresses contemporaneous documentation of GMP records, often recognized in data integrity deficiencies.

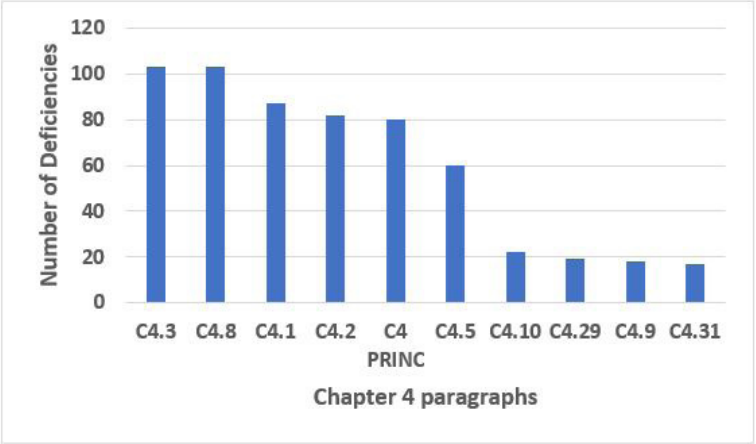


Figure 3: Chapter 4

Table 2: Chapter 4

Paragraph	Short Version of Text *Chapter 4, Documentation*
4.3	Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.
4.8	Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.
4.1	All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.
4.2	Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.

Paragraph	Short Version of Text *Chapter 4, Documentation*
C4 Principle	Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements…There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document… Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents…

CHAPTER 5, PRODUCTION

The top 10 citations of Chapter 5, *Production*, which make up just under 60 percent of the deficiencies that cite this chapter, are shown in Figure 4. The six most frequent citations in this group constitute 40 percent of the deficiencies for this chapter and are addressed in Table 3. Unlike some of the groups of deficiencies, Chapter 1 and Annex 15, for example, none seem disproportionate in their frequency of citation. Interestingly, the two most frequently cited paragraphs address the use of Quality Risk Management to evaluate and minimize the risks of cross-contamination. In the future, look for this to be a key requirement in the Annex 1 contamination control strategy currently under revision that each firm will need to prepare for.

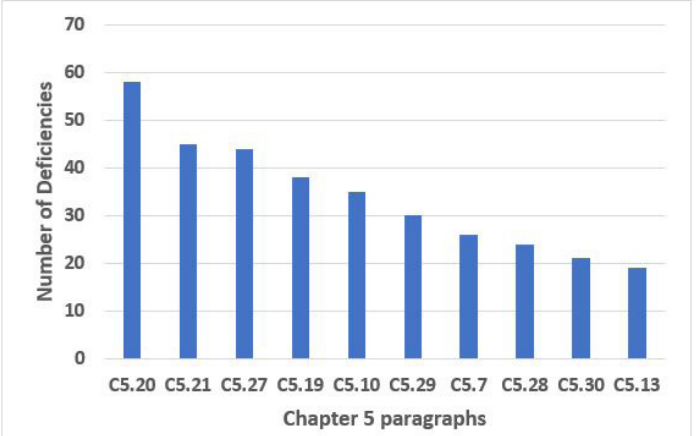


Figure 4: Chapter 5

Table 3: Chapter 5

Paragraph	Short Version of Text *Chapter 5, Production*
5.20	A Quality Risk Management process…should be used to assess and control the cross-contamination risks presented by the products manufactured…The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family…
5.21	The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following…Technical Measures (i) through (xiii)… Organizational Measures (i) through (x).
5.27	The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks…Where possible, starting materials should be purchased directly from the manufacturer of the starting material.
5.19	Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.
5.10	At every stage of processing, products and materials should be protected from microbial and other contamination.
5.29	For the approval and maintenance of suppliers of active substances and excipients, the following is required…

ANNEX 15, QUALIFICATION AND VALIDATION

Annex 15, *Qualification and Validation*, provides an interesting story this year. The four most frequently cited paragraphs constitute 68 percent of all citations from Annex 15. Citations of A15.10, Cleaning Validation, constitute 24 percent of the total. Thus, it seemed appropriate to present those data in more detail. Figure 5 shows the 10 most frequently cited paragraphs in Annex 15, and Table 4 provides the detail for the four most frequent. Figure 6 provides the 10 more frequent citations within A15.10, *Cleaning Validation*, and Table 5 provides detail for the five areas cited most frequently.

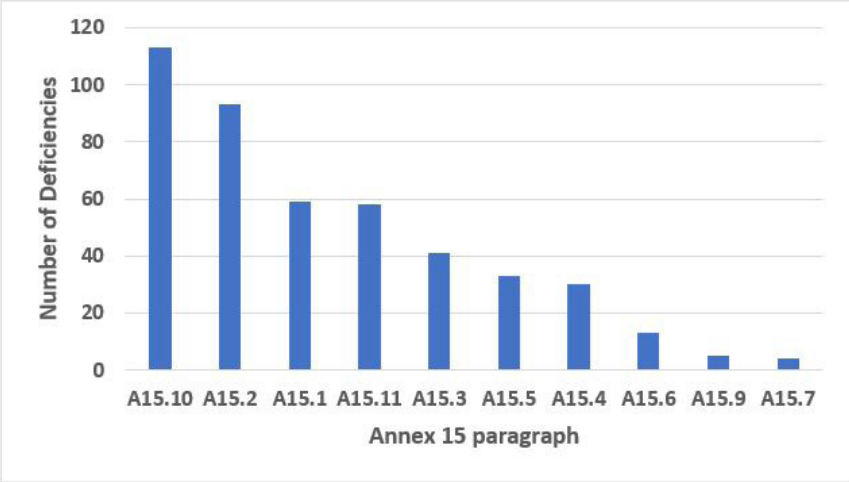


Figure 5: Annex 15

Table 4: Annex 15

Paragraph	Short Version of Text *Annex 15, Qualification and Validation*
15.10	Cleaning Validation (10.1 through 10.15)
15.2	Documentation, Including VMP (2.1 through 2.10)
15.1	Organising and Planning for Qualification and Validation (1.1 through 1.8)
15.11	Change Control (11.1 through 11.7)

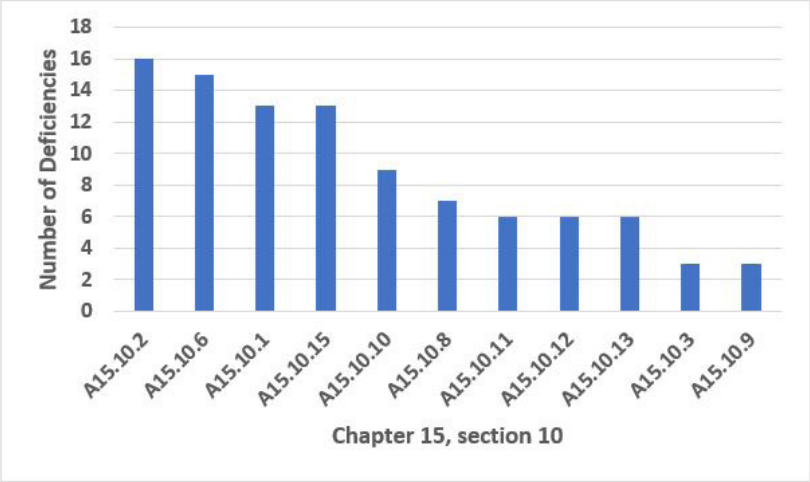


Figure 6: Annex 15.10, Cleaning Validation

Table 5: Annex 15.10

Paragraph	Short Version of Text *Annex 15, Qualification and Validation*
15.10.2	A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.
15.10.6	Limits for the carryover of product residues should be based on a toxicological evaluation. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references…Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train…
15.10.1	Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.
15.10.15	Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.
15.10.10	Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency.

CHAPTER 3, PREMISES AND EQUIPMENT

Chapter 3, *Premises and Equipment*, was in fifth place in both 2018 and 2019. While it may seem a bit of a mundane topic, the industry still has plenty of shortcomings in this area. The four most frequent citations from Chapter 3 constitute just under 40 percent of all Chapter 3 deficiencies. The four areas cover equipment (3.34 and 3.41), storage areas (C.19), and general (C.2). Details and text are provided in Table 6.

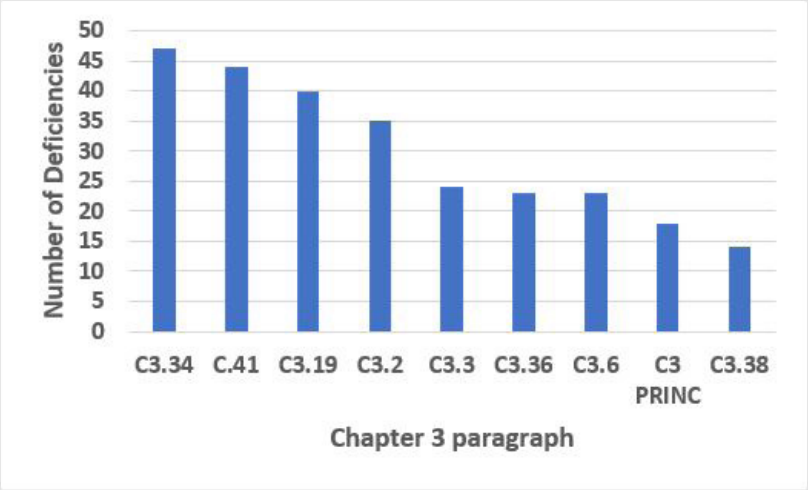


Figure 7: Chapter 3

Table 6: Chapter 3

Paragraph	Short Version of Text *Chapter 3, Premises and Equipment*
3.34	Manufacturing equipment should be designed, located and maintained to suit its intended purpose.
3.41	Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
3.19	Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
3.2	Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

ANNEX 1, MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Annex 1, *Manufacture of Sterile Medicinal Products*, was a close second to Annex 15 in the total number of deficiencies that cite the annexes (see part 1, Figure 3). It was, however, first among the annexes for the number of critical deficiencies in both 2018 and 2019. Annex 1 was a very close second place for the number of major deficiencies, just behind Chapter 1 (see Part 1, Figure 8). The 10 most frequently cited paragraphs from Annex 1 are shown in Figure 8. The four most frequently cited paragraphs constitute approximately 28 percent of all deficiencies citing Annex 1, and the top 10 include 47 percent of all deficiency citations. The text of those four requirements is provided in Table 7.

Looking forward to the revised Annex 1, it will be interesting to see how the deficiencies divide, though I imagine that shortcomings in the company developed contamination control strategy will be near the top of the list.

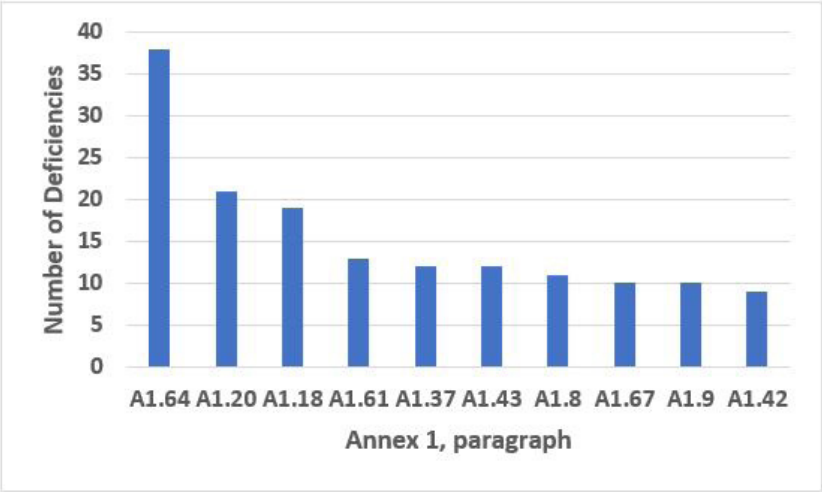


Figure 8: Annex 1

Table 7: Annex 1

Paragraph	Short Version of Text *Annex 1, Manufacture of Sterile Medicinal Products*
A1.64	Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.
A1.20	Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.
A1.18	Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release…
A1.61	The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

CHAPTER 8, COMPLAINTS AND PRODUCT RECALL

Among the top 10 chapters and annexes, Chapter 8, *Complaints and Product Recall*, was in seventh place this year. The deficiencies in the top 10 paragraphs shown in Figure 9 constitute 47 percent of all deficiencies citing Chapter 8. Clearly, C8.30 is cited most frequently, approximately the same number of times as the next three in the list, 8.10, 8.13, and 8.15. C8.30 is cited in approximately 18 percent of all deficiencies that cite Chapter 8. Table 8 provides the text of the four most frequent deficiencies that cite Chapter 8.

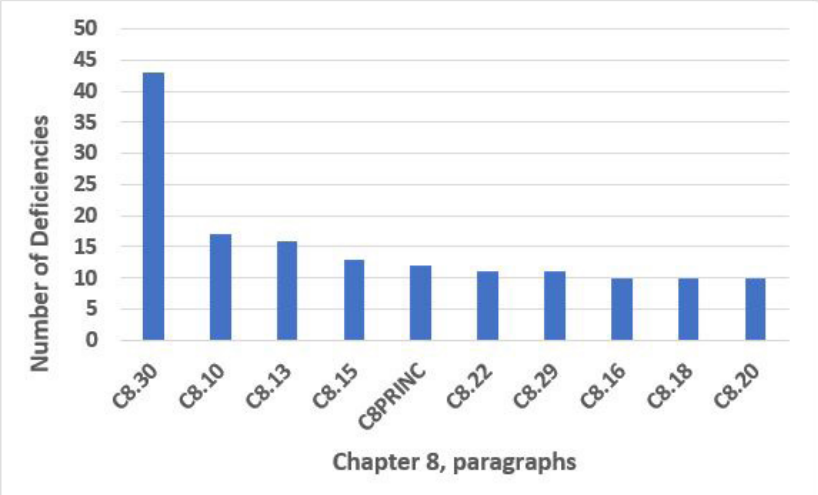


Figure 9: Chapter 8

Table 8: Chapter 8

Paragraph	Short Version *Chapter 8, Complaints and Product Recall*
8.30	The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.
8.10	The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.
8.13	The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/product specification file or GMP. Such decisions should be timely to ensure that patient and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.
8.15	Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.

CHAPTER 6, QUALITY CONTROL

Chapter 6, *Quality Control*, is eighth in the top 10 chapters/annexes cited in 2019. The 11 paragraphs identified in Figure 10 (two tied for 10th place) constitute just over 75 percent of all deficiencies that cite this chapter. Paragraphs C6.9 (data trending) and C6.19 (laboratory reagent controls) are the most frequent citations and include 25 percent of all deficiencies that cite Chapter 6.

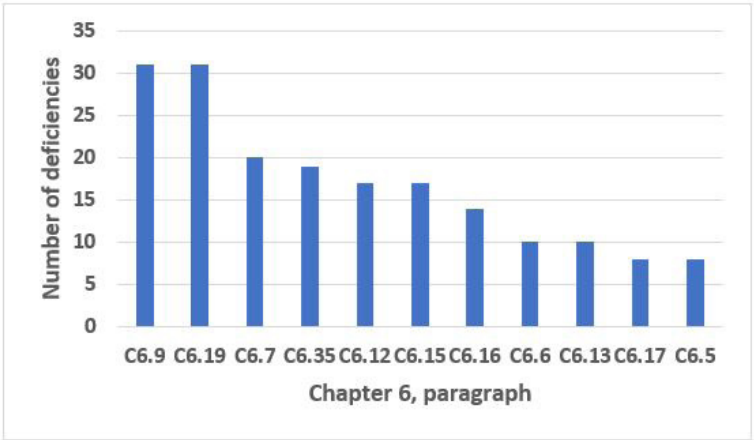


Figure 10: Chapter 6

Table 9: Chapter 6

Paragraph	Short Version *Chapter 6, Quality Control*
6.9	Some kinds of data (e.g., tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any out of trend or out of specification data should be addressed and subject to investigation.
6.19	Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures. The level of controls should be commensurate to their use and to the available stability data.
6.7	Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily 4 available to the Quality Control Department…
6.35	Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.

ANNEX 11, COMPUTER SYSTEMS

Annex 11, *Computer Systems*, is frequently cited when the firm does not have adequate controls over electronic systems and data. This annex is frequently associated with the broader data governance and data integrity area. Figure 11 shows the 10 most frequently cited sections from this annex. The section cited most frequently, A11.12, addresses the security of electronic systems and makes up just under 25 percent of the Annex 11 citations. The four most frequent paragraphs, shown in Figure 11, make up slightly over 60 percent of the total and, after security, include validation, data storage, and periodic evaluation of validated systems to ensure they remain in a state of control. The text of these four sections may be found in Table 10.

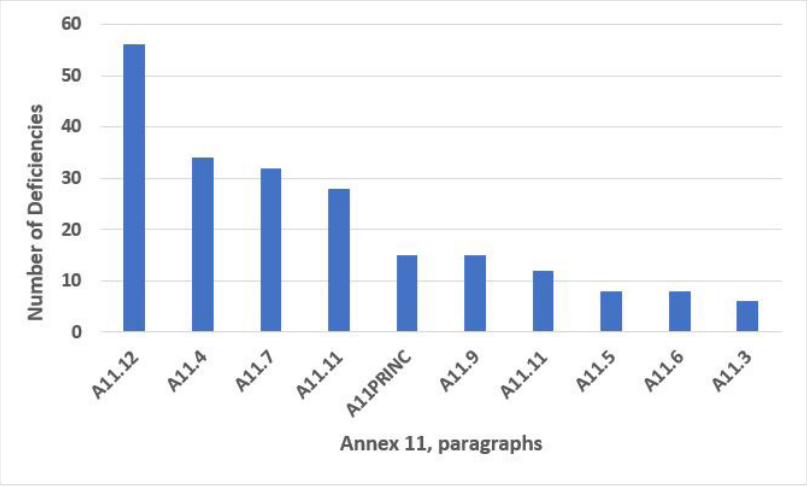


Figure 11: Annex 11

Table 10: Annex 11

Paragraph	Short Version *Annex 11, Computer Systems*
11.12	Security: 12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas. 12.2 The extent of security controls depends on the criticality of the computerised system. 12.3 Creation, change, and cancellation of access authorisations should be recorded. 12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.
11.4	Validation: 4.1 The validation documentation and reports should cover the relevant steps of the life cycle. ... 4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process. 4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available. For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.
11.4 Continued	4.4 User Requirements Specifications should describe the required functions of the computerised system ... User requirements should be traceable throughout the life-cycle. 4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately. 4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system. 4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy. 4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.
11.7	Data Storage: 7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period. 7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.

Paragraph	Short Version *Annex 11, Computer Systems*
11.11	Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.

CHAPTER 7, OUTSOURCED ACTIVITIES

Last but not least among the top 10 is Chapter 7, *Outsourced Activities*. With the increasing use of CDMOs and contract laboratories, this remains an important chapter and one where many companies have deficiencies. The three most frequent areas cited constitute just under 50 percent of the total deficiencies in this area, and the text for these is provided in Table 11. Figure 12 shows the frequency of the top 10 Chapter 7 citations, and these make up 90 percent of the citations of Chapter 7.

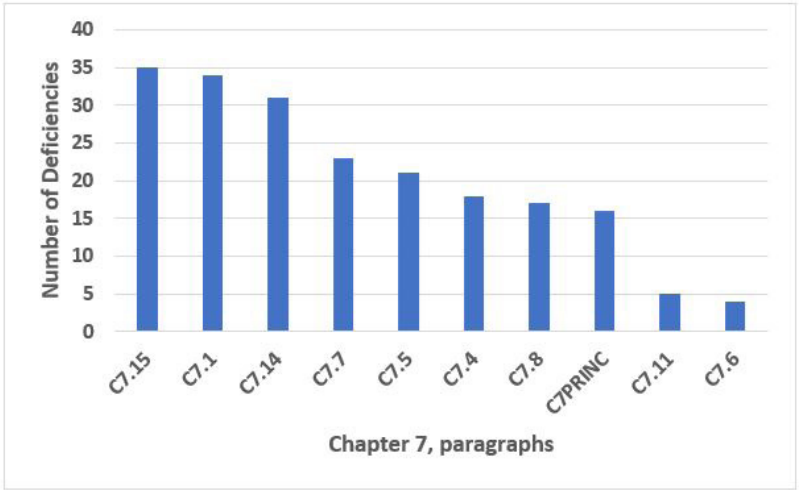


Figure 12: Chapter 7

Table 11: Chapter 7

Paragraph	Short Version *Chapter 7, Outsourced Activities*
7.15	The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).
7.1	There should be a written Contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.
7.14	A Contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.

CONCLUSION

This article builds on the conclusions of part 1 that address overall deficiencies, by type and by country over time, considering all chapters and annexes. In part 2, we focus on the 10 most frequently cited chapters/annexes and look at the primary citations within each. In Chapter 1, *Quality Systems*, deficiencies cluster in two sections, C1.4 and C1.8, addressing fundamental GMP requirements for pharmaceutical firms. We provide additional detail on each of those areas. For Annex 15, *Validation and Qualification*, much of the focus was on deficiencies in cleaning validation. We take a deep dive into this area in addition to covering

the other paragraphs that are cited in Annex 15. Annex 1 is another area where many of the deficiencies cluster in one area regarding failure to take precautions to minimize contamination. And finally, in Annex 11, Computerized Systems, failure to provide adequate system security is the most frequent deficiency.

As we stated at the end of part 1, we hope the MHRA will continue to publish data in the Excel format in the future and expand to include its GCP and GDP inspection findings. It would also be useful for the MHRA to publish the actual text of critical deficiencies from the various areas in future years as it did in the past. But in the absence of that, the publication of these data is valuable and appreciated by the industry.

ABOUT THE AUTHOR

Barbara Unger formed Unger Consulting, Inc. to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry, including general GMP auditing and auditing and remediation in the area of data management and data integrity. Her corporate auditing experience includes leadership of the Amgen corporate GMP audit group for APIs and quality systems. She also developed, implemented, and maintained the GMP regulatory intelligence program for eight years at Amgen. This included surveillance, analysis, and communication of GMP related legislation, regulations, guidance, and industry compliance enforcement trends. Unger was the first chairperson of the Rx-360 Monitoring and Reporting work group that summarized and published relevant GMP and supply chain related laws, regulations, and guidance. In addition, she was previously co-lead of the Rx-360 Data Integrity Working Group.

ABOUT US

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