MHRA GMP INSPECTION DEFICIENCIES FOR 2018

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SUMMARY

In this report, you will see:

- An overview of 2018 data, including trends since 2015.
- Evaluation of critical and major deficiencies with Chapters and Annexes identified.
- The ten most frequently cited paragraphs for the Chapters and Annexes with the most frequently cited deficiencies.

The MHRA has taken a different approach this year in the publication of the GMP deficiencies for drug product issued during inspections in 2018 and published in October 2019. In 2015 and 2016, MHRA provided approximately 100 slide decks with tables, figures, and text from deficiencies against the requirements in the Chapters and Annexes. No data were published for 2017. The MHRA published a 6,200-plus line excel spreadsheet of their 2018 GMP inspection data so that individuals can parse and present the data according to their needs.

This article is data dense and includes many figures in three sections.

Section I begins with a high-level overview of the 2018 data including additional trends from the two most recent MHRA reports, 2015 and 2016.

In Section II we identify and evaluate the critical and major deficiencies from 2018. This section identifies the Chapters and Annexes associated with critical and major deficiencies. For critical deficiencies citing Chapter 1 and Annex 1, we identify the specific paragraphs and requirements with which they are associated.

In Section III we present the ten most frequently cited paragraphs for the ten Chapters and Annexes with the most frequently cited deficiencies identified in Section I, **Figure 5**.

Section IV provides conclusions.

Background

I found the "Notes and Guidance" segment of the MHRA spreadsheet a bit confusing. In light of this, here's how I've parsed the data. 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 data are mine, not the MHRAs.

I. Overall Data

The MHRA conducted 285 GMP inspections, both domestic and outside of the UK, in 2018. Inspections outside the UK were conducted in Bangladesh, China, India, Japan, Singapore, South Korea, and the United States. Country

Figure 1 MHRA Inspections by Country

Country	Number of Inspections 2015 / % total	Number of Inspections 2016 / % total	Number of Inspections 2018 / % total
Total	303	324	285
UK	224 / 74%	242 / 75%	228 / 80%
Overseas Inspections	79 / 26%	82 / 25%	57 / 20%
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%

Figure 2 Overall Deficiency Trend Comparison, Top Ten

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

specific data, other than that provided for the UK and "overseas", was not provided in the 2015 and 2016 MHRA reports. The 285 inspections from 2018 reflect a decrease from the number of inspections conducted in both 2015 and 2016.

Figure 1 identifies the number of drug product inspections, by country, performed by the MHRA in 2018. As in past years, almost all MHRa inspections were conducted in the UK. The percentage of inspections conducted in the UK in 2018 increased slightly from 2015 and 2016 and the percentage of overseas inspection decreased slightly in 2018 to 20 percent of the total.

In 2018, largest number of inspections conducted outside the UK were performed in India with a total of 43. The remaining 14 inspections outside the UK were conducted in six countries with China and the US each having been the subject of five inspections, and the other countries had one each.

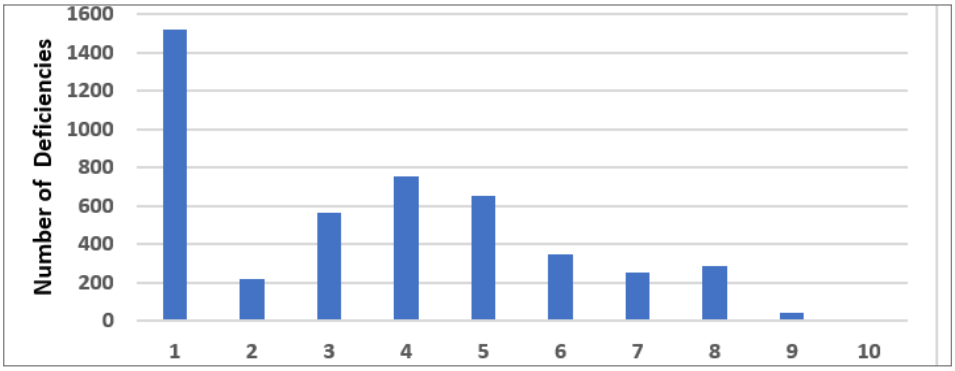

Figure 3 Inspection Citation by GMP Chapter

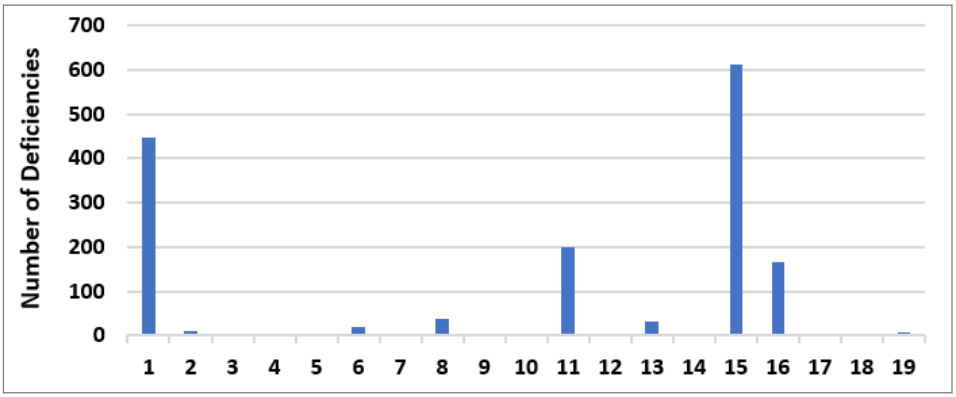

Figure 4 Inspection Citations by GMP Annex

Figure 2 shows the trend including all classification of deficiencies from 2015, 2016 and 2018 identified in the top ten Chapters and Annexes. Data from 2015 and 2016 are taken directly from the 2016 report published by the MHRA. *Quality Systems* leads the list in all three years. Notable changes in 2018 from the two previous years include:

- Outsourced Activities (Chapter 7) appears within the

top ten in 2018 though it did not appear in either of the two other years.

- Personnel (Chapter 2) is no longer among the top ten this year.
- Computerized Systems (Annex 11) remains within the top ten in 2018 though it has fallen from fifth place in 2015 to seventh in 2016 to tenth place in 2018.
- Complaints and Recalls (Chapter 8) also diminishes in rank over the time period from second in 2015, to fourth in 2016 and eighth in 2018.

Figure 3 and **Figure 4** present the number of total number of deficiencies according to the GMP Chapter or GMP Annex cited, respectively. These figures include all deficiency classifications, critical, major and other. Annex 15, *Qualification and Validation*, and Annex 1, *Sterility Assurance*, take first and second place among the most frequently cited annexes with approximately 600 and 450 deficiencies, 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 a double-digit or fewer number of deficiencies.

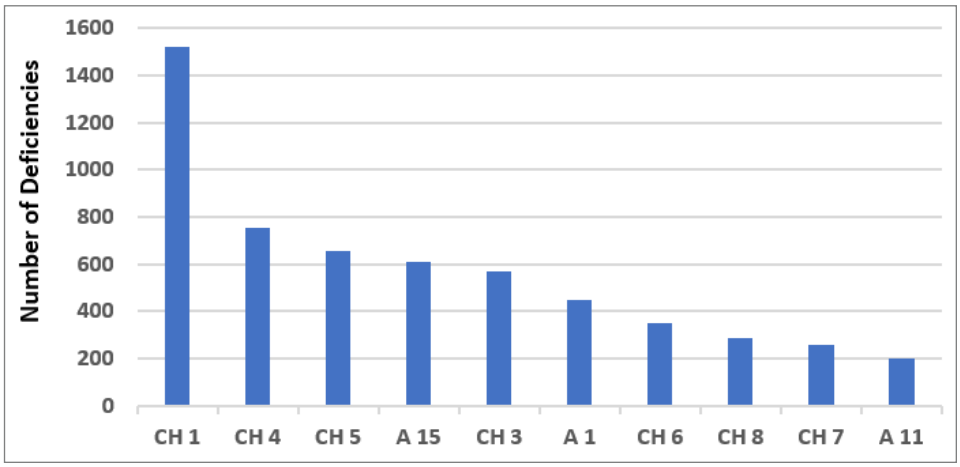

Figure 5 Top Ten Chapters and Annexes Cited in Deficiencies

Figure 6 Number of Deficiencies by Classification in 2018

Classification	Number	Percentage of Total
Critical	142	2
Major	2391	39
Other	3676	59

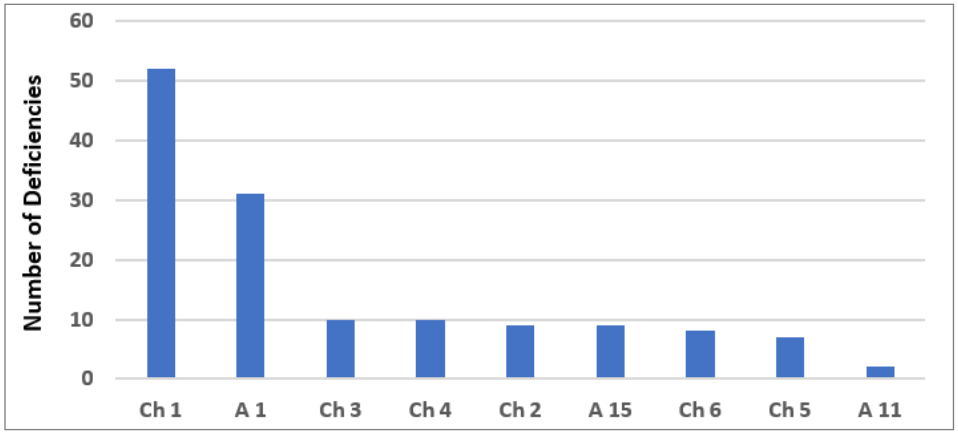

Figure 7 Critical Deficiencies

Chapter 1, *Quality Management*, with approximately 1500 citations has more than twice the number of deficiency citations as the nearest chapter. Chapter 4, *Documentation*, with almost 760 deficiencies is closely followed by Chapter 5, *Production*, with just over 650, and Chapter 3, *Premises and Equipment*, at just under 570 citations. Chapters 2, 6, 7 and 8 each had between 200 and 400 deficiencies and the remaining two chapters had fewer than 50 and 1 citation respectively.

Figure 5 shows the top ten categories when values from Annexes and Chapters are combined, the same information provided in **Figure 2** with the number of associated deficiencies. Again,

this includes all categories of deficiencies. We will identify the top ten citations in each of these later in this report.

II. Critical And Major Deficiencies

Figure 6 provides a tabulation of all 2018 deficiencies by their classification. Critical deficiencies

Figure 8 Critical Deficiencies Cited in Chapter 1

Paragraph	#	Short Text
1.4(xiv)	9	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...
1.4(viii)	6	A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.
1.8(vii)	6	Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;
1.8(vi)	4	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.
1 Principle	4	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...
1.5	3	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...
1.4(i)	2	Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes.
1.4(xii)	2	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.
1.8(iii)	2	All necessary facilities for GMP are provided including...
1.8(xi)	2	Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.
1.3	1	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...
1.1	1	Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product...
1.12	1	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.
1.4(xi)	1	Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.
1.4(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.
1.6	1	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.
C1.8(i)	1	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(v)	1	Procedures are carried out correctly and operators are trained to do so;
C1.8(x)	1	A system is available to recall any batch of product, from sale or supply;
C1.9(iii)	1	Test methods are validated;
C1.9(iv)	1	Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out...
C1.9(i-viii)	1	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 supply, until their quality has been judged to be satisfactory...

clearly constitute the smallest category and we will provide additional detail on them later. Major deficiencies constitute almost 40 percent of the total and other deficiencies constitute the majority of the deficiencies at almost 60 percent of the total.

The majority of critical and major deficiencies among the 6,200-plus deficiencies, cluster in a few Chapters and Annexes. **Figure 7** shows the number of critical deficiencies and the Chapters or Annexes which are referenced. Among the

Figure 9 Critical Deficiencies Cited in Annex 1

Paragraph	#	Short Text
A1.18	3	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.
A1.19	2	Recommended limits for microbiological monitoring of clean areas during operation:...
A1.46	2	In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.
A1.51	2	Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing...
A1.52	2	Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
A1.73	2	Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity...
A1.1	1	The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials...
A1.21	1	The utilisation of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment...
A1.3	1	Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment...
A1.33	1	Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.
A1.37	1	All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products...
A1.40	1	Wristwatches, make-up and jewelry should not be worn in clean areas.
A1.41	1	Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
A1.44	1	Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms.
A1.45	1	Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed...
A1.49	1	Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
A1.53	1	A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively...
A1.55	1	A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important...
A1.62	1	Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised...
A1.64	1	Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.
A1.85	1	For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.

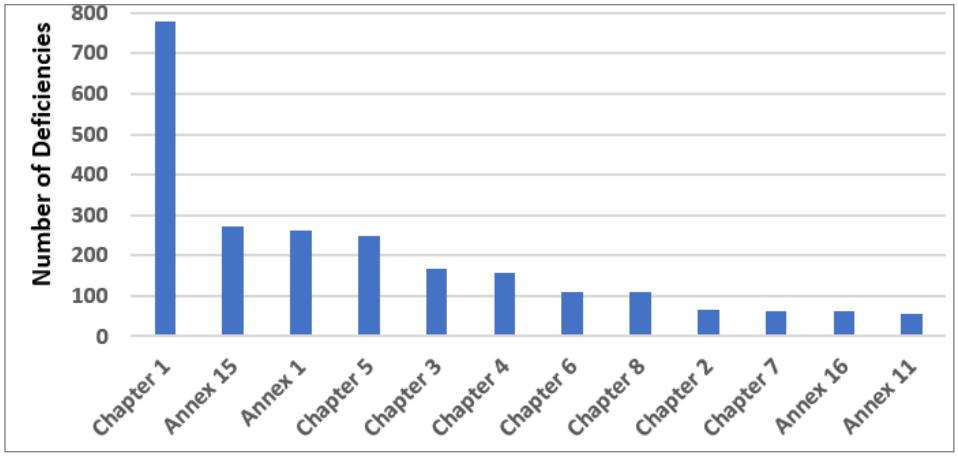

Figure 10 Major Deficiencies

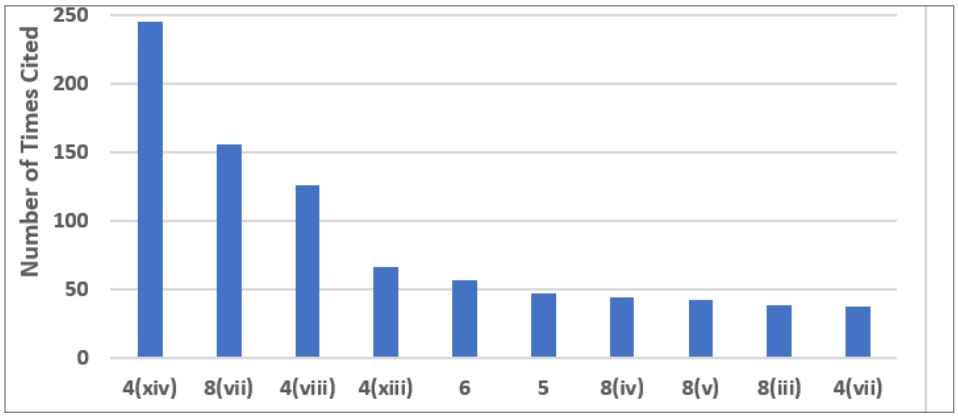

Figure 11 Top Deficiencies Citing Chapter 1

critical deficiencies, 37 percent are associated with Chapter 1, *Quality Systems*, and 22 percent are associated with Annex 1, *Sterility Assurance*. Annexes 1 and 11 are the only other Annexes that include citations for critical deficiencies, the remainder cite GMP Chapters.

Figures 8 and **9** provide the specifics on the citations for Chapter 1 and Annex 1 respectively. The able includes the identifying paragraph, the number of times the deficiency was cited and a short version of the text in the GMP guide.

Figure 10 shows twelve Annexes and Chapters associated with major deficiencies and the number of times they were cit-

Figure 12 Top Ten Deficiencies Citing Chapter 1

Paragraph	#	Short Text
1.4(xiv)	245	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...
1.8(vii)	156	Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;
1.4(viii)	126	A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.
1.4(xiii)	66	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;
1.6	56	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.
1.5	47	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.
1.8(iv)	44	Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
1.8(v)	42	Procedures are carried out correctly and operators are trained to do so;
1.8(iii)	38	All necessary facilities for GMP are provided including: • Appropriately qualified and trained personnel; • Adequate premises and space; • Suitable equipment and services; • Correct materials, containers and labels; • Approved procedures and instructions, in accordance with the Pharmaceutical Quality System; • Suitable storage and transport;
1.4(vii)	37	Processes are in place to assure the management of outsourced activities.

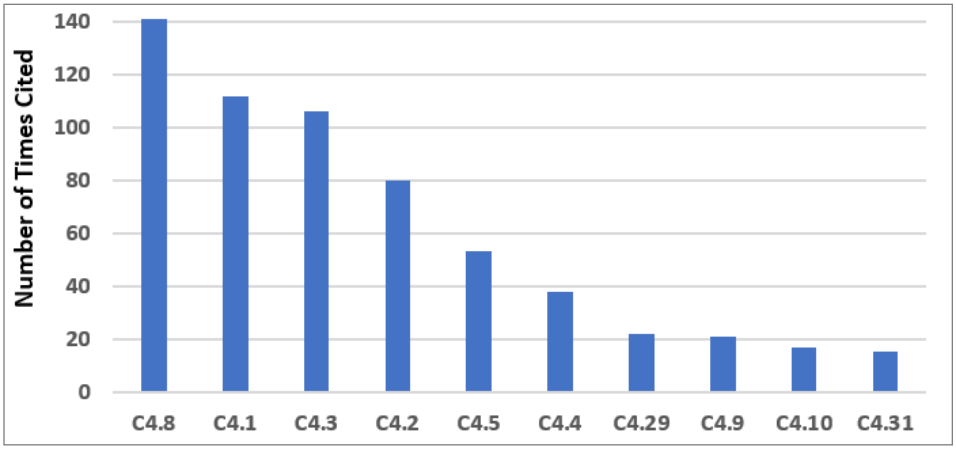

Figure 13 Top Deficiencies Citing Chapter 4

Figure 14 Top Ten Deficiencies Citing Chapter 4

Paragraph	#	Short Text
4.8	141	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	112	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...
4.3	106	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.
4.2	80	Documents should be designed, prepared, reviewed, and distributed with care...
4.5	53	Documents within the Quality Management System should be regularly reviewed and kept up to date.
4.4	38	Documents containing instructions should be laid out in an orderly fashion and be easy to check...
4.29	22	There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:...
4.9	21	Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
4.10	17	It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.
4.31	15	Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed...

ed. In addition to these twelve Chapters and Annexes, major deficiencies were identified in Chapter 9 (11), Annex 2 (4), Annex 8 (8), Annex 3 (3), Annex 13 (3) and one each in Annex 6 and Annex 19. More GMP Chapters and Annexes were cited in major deficiencies than were cited in critical deficiencies. Among the major deficiencies, 33 percent are associated with Chapter 1, 11 percent are associated with Annex 15, 11 percent are associated with Annex 1, and 10 percent are associated with Chapter 5. Shortcomings in Quality Systems clearly leads the list of both critical and major deficiencies demonstrating the agencies' focus on the importance of a sound Quality System to GMP compliance.

III. Specific Deficiencies In The Top Ten Annexes/Chapters

In the following sections, we take a granular look at individual Chapters and Annexes identified in Section I, **Figure 5** and how the deficiencies are divided among the various paragraphs. We address Chapters 1, 3, 4 and 5, 6, 7, 8 and Annexes 1, 11, and 15. These are provided in decreasing order of deficiencies as in **Figure 5**. We provide the top ten citations for each, or more in the two instances where there are ties for this

honor. Each figure is followed by the short version of text of the top citations. The previous reports from MHRA in 2015 and 2016 include text from actual inspections as examples, but that is not provided this year.

Chapter 1, Pharmaceutical Quality System

Figure 11 shows the top ten citations from Chapter 1 and **Figure 12** provides the short text of the requirements, along with the number of times each was cited. The top two citations address problems with investigations and root cause analysis which is not a surprise. This topic is among the most frequently cited FDA inspection observations. These two citations constitute 48 percent among the top ten citing Chapter 1 and 29 percent of the total number of deficiencies citing Chapter 1. Also, notable, are the two citations associated with management oversight, paragraphs 5 and 6, which together constitute 12 percent of the total number of the top ten and 7 percent of all deficiencies citing Chapter 1.

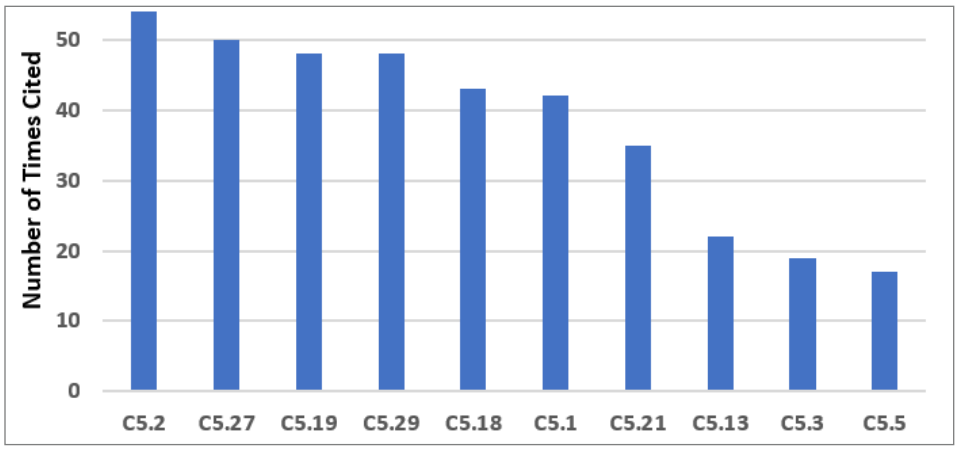

Figure 15 Top Deficiencies Citing Chapter 5

Chapter 4, Documentation

Figure 13 and **Figure 14** address the ten most frequently cited requirements in Chapter 4. The most frequent citation addresses contemporaneous documentation of data and information, and the requirement that these actions are traceable. Document management is also among the most frequent citations.

Figure 16 Top Ten Deficiencies Citing Chapter 5

Paragraph	#	Short Text
5.2	54	All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
5.27	50	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...
5.19	48	Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3...
5.29	48	For the approval and maintenance of suppliers of active substances and excipients, the following is required: ...
5.18	43	Contamination of a starting material or of a product by another material or product should be prevented...
5.1	42	Production should be performed and supervised by competent people.
5.21	35	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:...
5.13	22	Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format...
5.3	19	All incoming materials should be checked to ensure that the consignment corresponds to the order...
5.5	17	Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

Chapter 5, Production

Figure 15 and **Figure 16** identify the ten most frequent deficiencies that cite Chapter 5. Many of the requirements are cited with a similar frequency, thus no single requirement stands out as with some other areas.

Annex 15, Qualification and Validation

Figure 17 and **Figure 18** show the ten most frequent requirements cited in Annex 15. The most frequently cited requirement includes the need to identify and investigate deviations

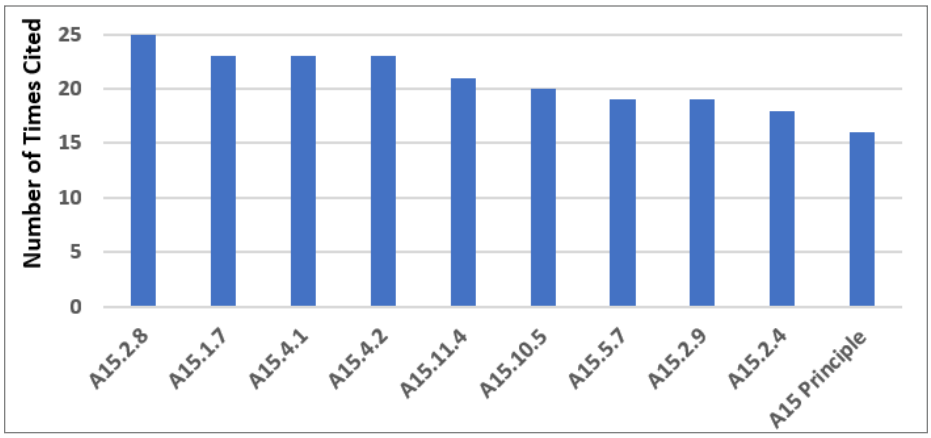

Figure 17 Top Deficiencies Citing Annex 15

Figure 18 Top Deficiencies Citing in Annex 15

Paragraph	#	Short Text
15.2.8	25	Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report.
15.1.7	23	A quality risk management approach should be used for qualification and validation activities...
15.4.1	23	A quality risk management approach should be used for qualification and validation activities.
15.4.2	23	Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined...
15.11.4	21	Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.
15.10.5	20	For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc...
15.5.7	19	Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process.
15.2.9	19	The review and conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria...
15.2.4	18	Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.
Principle	16	This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II...

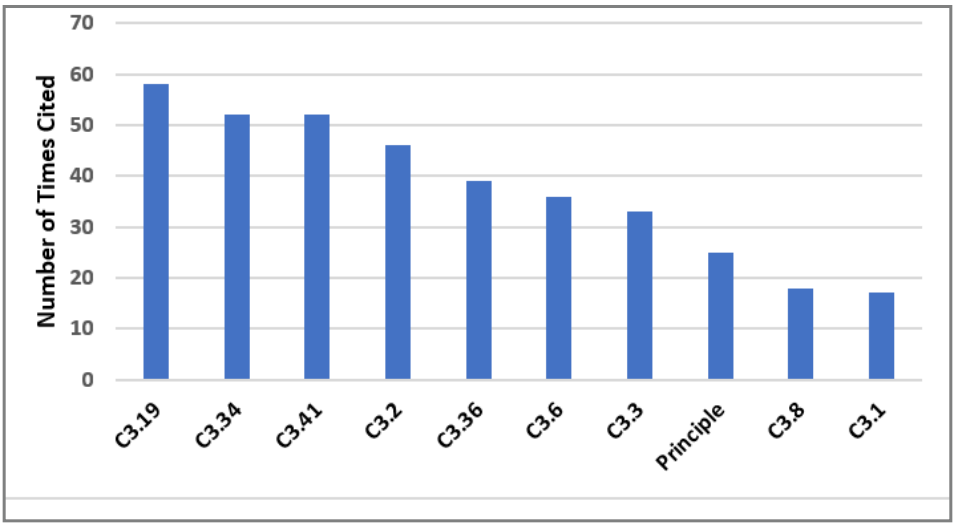

Figure 19 Top Deficiencies Citing Chapter 3

including failures to meet acceptance criteria, once again emphasizing the importance of this area which is also identified as the most frequent citation of Chapter 1 requirements.

Chapter 3, Premises and Equipment

Figure 19 and **Figure 20** identify the ten most frequent deficiencies in Chapter 3. The three most frequently cited requirements include the need to have

Figure 20 Top Deficiencies Citing Chapter 3

Paragraph	#	Short Text
3.19	58	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...
3.34	52	Highly active materials or products should be stored in safe and secure areas.
3.41	52	Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods...
3.2	46	Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products...
3.36	39	Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned...
3.6	36	Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities...
3.3	33	Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.
Principle	25	Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out...
3.8	18	The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
3.1	17	Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

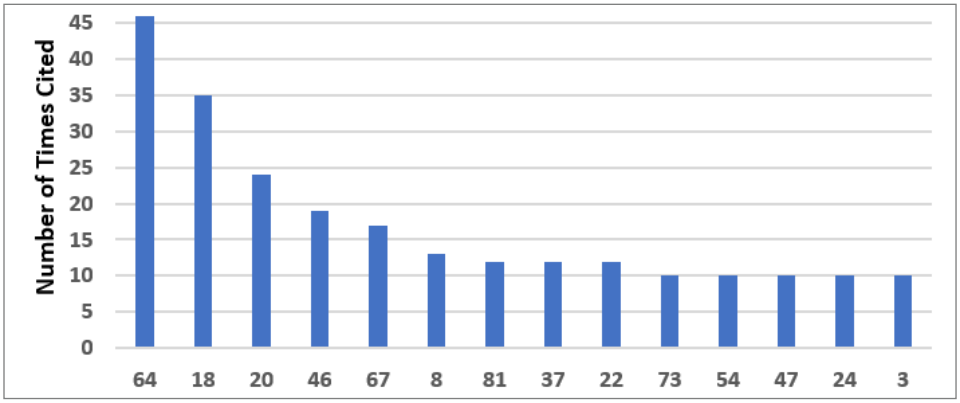

Figure 21 Top Deficiencies Citing Annex 1

adequate storage areas with appropriate environmental controls, secure storage of highly active materials and the need to calibrate and maintain weighing and measuring equipment.

Annex 1, Manufacture of Sterile Medicinal Products

Figure 21 and **Figure 22** iden-

Figure 22 Top Deficiencies Citing Annex 1

Paragraph	#	Short Text
64	46	Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.
18	35	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...
20	24	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.
46	19	In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.
67	17	The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps...
8	13	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.
81	12	Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination...
37	12	All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products...
22	12	The transfer of materials into and out of the unit is one of the greatest potential sources of contamination...
73	10	Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity...
54	10	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 per son, operation or machine to a zone of higher product risk.
47	10	To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment...
24	10	Isolators should be introduced only after appropriate validation...
3	10	Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment...

tify the fourteen most frequent requirements cited in Annex 1. The most frequent citation addresses precautions to avoid contamination and the second addresses environmental monitoring in the areas where aseptic operations are performed. The third most frequent requirement cited is associated with setting appropriate alert and action limits for the results of environmental monitoring. Five requirements are tied for tenth place, so we include them all.

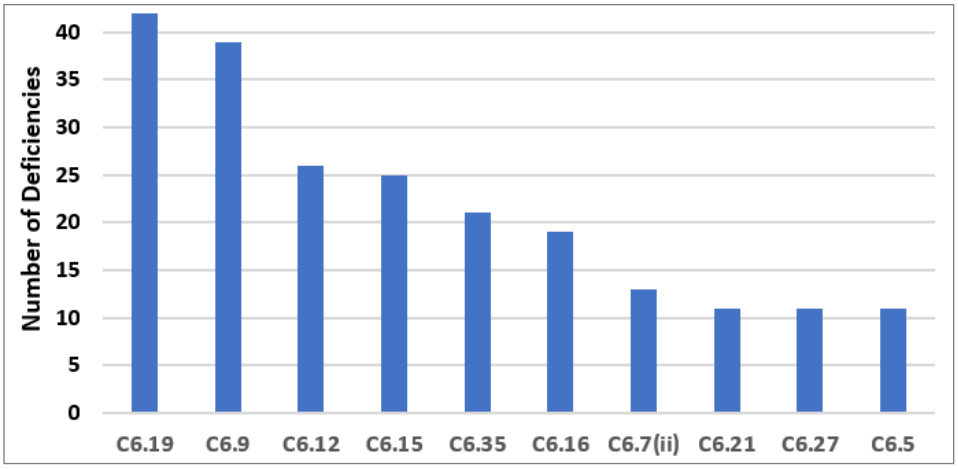

Figure 23 Top Deficiencies Citing Chapter 6

Chapter 6, Quality Control

Figure 23 and **Figure 24** identify the most frequently cited requirements in Chapter 6. The two most frequently cited requirements are the need to adequately control laboratory components and reagents and the need to trend data and investigate OOT and OOS events. Again, we find the importance of investigating such events similar to those identified in deficiencies cited in Chapter 5 and Chapter 1.

Figure 24 Top Ten Deficiencies Citing Chapter 6

Paragraph	#	Short Text
6.19	42	Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media...
6.9	39	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.
6.12	26	Samples should be representative of the batch of materials or products from which they are taken...
6.15	25	Testing methods should be validated...
6.35	21	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...
6.16	19	The results obtained should be recorded. Results of parameters identified as quality attribute or as critical should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
6.7(ii)	13	Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;
6.21	11	Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them...
6.27	11	The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.
6.5	11	Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3...

Chapter 8, Complaints and Product Recall

Figure 25 and **Figure 26** identify the top ten deficiencies that cite Chapter 8. By far the most frequent citation addresses the need to periodically challenge and determine the effectiveness of the recall process. Generally, this exercise is expected to be conducted annually. The

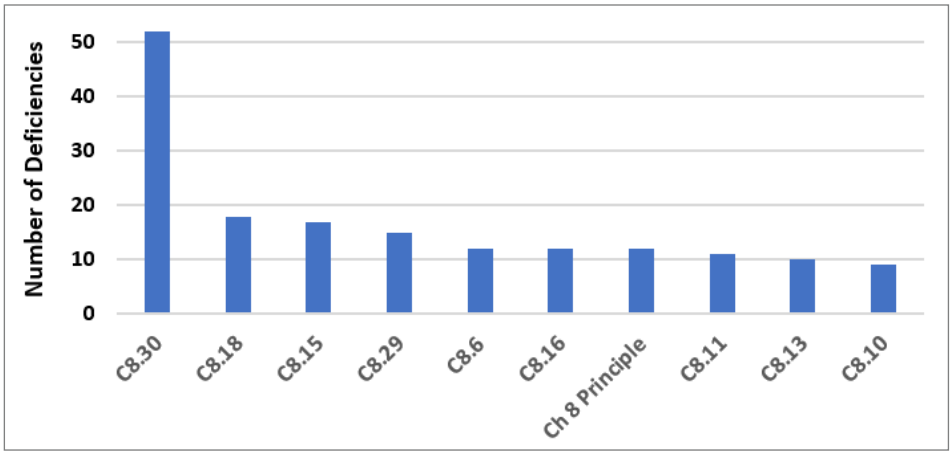

Figure 25 Top Deficiencies Citing Chapter 8

Figure 26 Top Ten Deficiencies Citing Chapter 8

Paragraph	#	Short Text
8.30	52	The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use...
8.18	18	Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.
8.15	17	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.
8.29	15	The progress of the recall process should be recorded until closure and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.
8.6	12	Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.
8.16	12	An appropriate level of root cause analysis work should be applied during the investigation of quality defects...
Principle	12	In order to protect public and animal health, a system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network...
8.11	11	If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches, and in some cases other products, in order to determine whether they are also affected...
8.13	10	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...
8.10	9	When a quality defect investigation is initiated, procedures should be in place to address at least the following:...

next two most frequent deficiencies address the need to implement appropriate corrective and preventive actions in response to quality defects, and to report qualify defects to the health authorities when this may result in a product recall.

Chapter 7, Outsourced Activities

Figure 27 and **Figure 28** shows the deficiencies that cite Chapter 7. Among the two most fre-

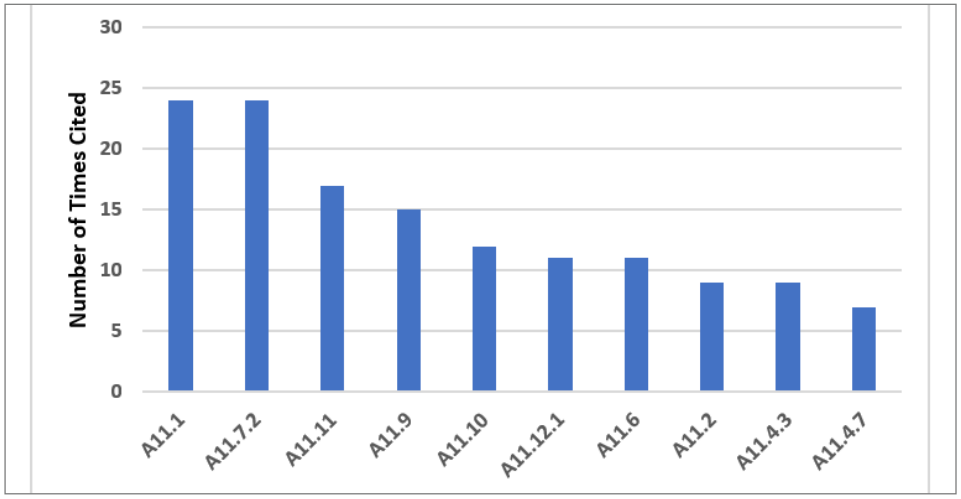

Figure 27 Top Deficiencies Citing Chapter 7

Figure 28 Top Deficiencies Citing Chapter 7

Paragraph	#	Short Text
7.1	47	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.
7.15	43	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).
7.14	35	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.
7.5	25	Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities...
7.4	23	The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities...
7.7	20	The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.
Principle	18	Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality...
7.8	8	The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities...
7.17	7	The Contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors
7.2	6	All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.

quent citations is the need for a Quality Agreement and the content of that agreement with regard to the outsourced activity.

Annex 11, Computerised Systems

The ten most frequent inspection deficiencies that identify requirements in Annex 11 are shown in **Figure 29** and **Figure 30**. The first most frequent deficiency addresses the application of risk management throughout the lifecycle of computerized systems. The second most frequent deficiency addressed the failure to ensure integrity of that data and that it is routinely backed up.

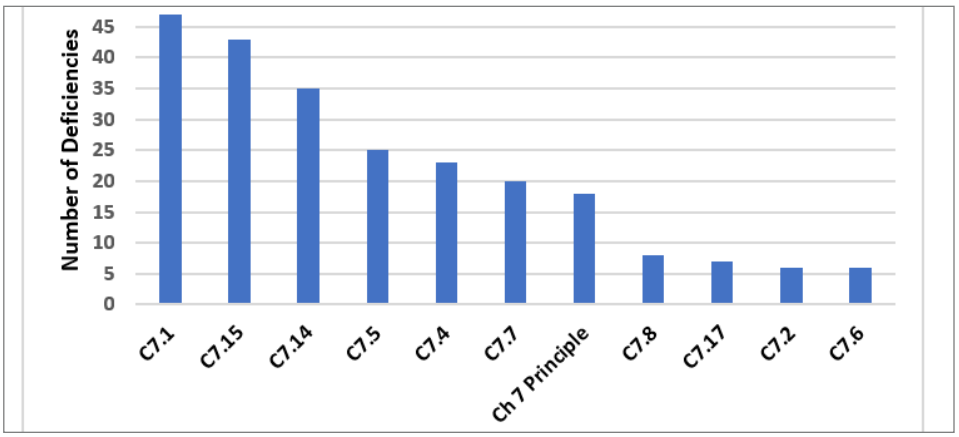

Figure 29 Top Deficiencies Citing Annex 11

Figure 30 Top Deficiencies Citing Annex 11

Paragraph	#	Short Text
11.1	24	Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality...
11.7.2	24	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.
11.11	17	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...
11.9	15	Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail")...
A1.10	12	Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.
11.12.1	11	Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons...
11.6	11	For critical data entered manually, there should be an additional check on the accuracy of the data...
11.2	9	There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT...
11.4.3	9	An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.
11.4.7	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...

IV. Conclusions

In 2018 THE MHRA conducted fewer inspections than in 2015 and 2016. The percentage of inspections conducted in the UK increased slightly and those outside the UK decreased slightly over that period. It will be useful to monitor whether the MRA with the FDA results in a decrease in inspections of sites that they may both inspect. It is interesting that the MHRA only conducted five inspections in the US so it would be difficult to determine if the MRA with FDA results in a decrease of inspection in the US.

Chapter 7, *Outsource Activities*, was new among the top ten in 2018 but was not in the top ten in either 2015 or 2016 and Chapter 2, *Personnel*, was no longer in the top ten this year.

In no surprise, Chapter 1, *Quality Systems*, continues to be first among the areas cited in inspection deficiencies, regardless of classification, with more than double the number deficiencies of the next area, Chapter 4. Chapter 1 is first among all deficiencies regardless of classification, first in number among the critical deficiencies, and first in number among the major deficiencies.

Critical deficiencies constitute only 2 percent of the total identified in 2018 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.

Among the major deficiencies which constitute approximately 40 percent of the total of all deficiencies, Chapter 1 again leads the group with almost 800 deficiencies. The next three include Annex 15 with approximately 270, Annex 1 with approximately 260 and Chapter 5 with approximately 250. Clearly, *Quality Systems* is again the substantial leader as it is for critical deficiencies. Chapter 7, Chapter 8 and Annex 16 were among the top ten in major deficiencies yet not among the top ten for critical deficiencies.

Computerised Systems, Annex 11, remains in the top ten, reinforcing the importance of this area to data integrity and the regulator's focus regarding the control and management of electronic data.

Hopefully MHRA will publish similar data in 2019 to which we can compare these data. It would be useful for MHRA to publish actual text of deficiencies from the various areas in future years as they did in the past. But in the absence of that, publication of these data are valuable and appreciated by the industry.

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Barbara Unger formed Unger Consulting, Inc. in December 2014 to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry, including general GMP auditing, gene and cell therapy, and auditing for data management and data integrity. Her 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. Barbara was the first chairperson of the Rx-360 Monitoring and Reporting work group (2009 to 2014) that summarized and published relevant GMP and supply chain related laws, regulations, and guidance. She also served as the chairperson of the Midwest Discussion Group GMP-Intelligence sub-group from 2010 to 2014. Barbara was the co-lead of the Rx-360 Data Integrity Working Group from 2017 through 2019.

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