



Medicines & Healthcare products  
Regulatory Agency

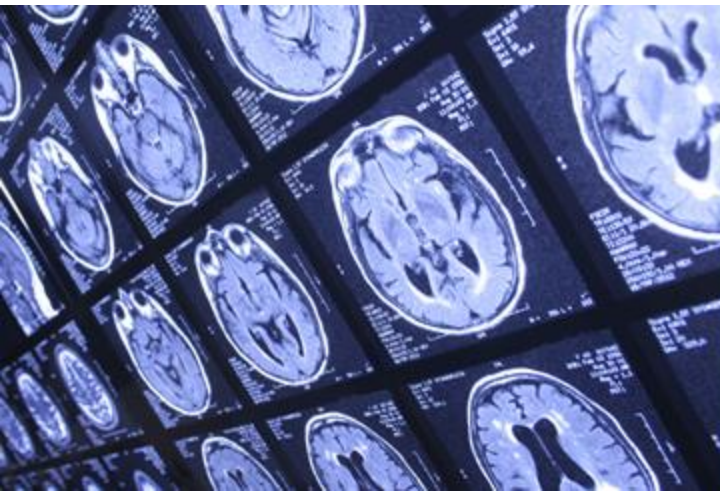


**MHRA**  
Regulating Medicines and Medical Devices

# MHRA GDP Inspection Deficiency Data 2016

Peter Brown, Terry Madigan and Madeleine Ault

November 2017



# Introduction

The GDP Inspectorate has reviewed the GDP inspection deficiency data for 2016 to allow identification of:

- severity and frequency of deficiencies associated with EU GDP references
- high impact and high frequency issues.

The purpose of publishing the inspection deficiency data is to allow industry to perform its own assessment against the deficiency findings as part of self-inspection and continuous improvement activity.

Only inspections conducted by the GDP Inspectorate against the Human Medicines Regulations 2012 as amended (HMR) and European Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01) (EU GDP) are included; those performed as part of GMDP inspections are not included.

The data is presented graphically followed by illustrative examples of deficiencies against the Human Medicines Regulations 2012 and deficiencies against GDP (critical, major and other).

# Comparison of most-cited GDP deficiency groups between 2016 and earlier data

A comparison of inspection year 2016 against 2015 has not been conducted due to changes made to the regulatory requirements for GDP in 2013 e.g. export becoming a licensable activity. Until a full inspection cycle has been achieved, any identified trends may appear misleading.

It is intended that trends will be considered in future years.

# Sampling method

Due to the large number of inspections carried out by GDP inspectors (1428 in 2016) it was necessary to create a sample for review that represents approximately 10% of inspections (148 selected). The following criteria were used to create the sample:

- Data from inspections for the whole of year 2016 were considered.
- Sample extracted to represent approximately 10% of inspections.
- Some inspections in the initial sample were replaced as it was considered that their inspection types were not representative of the general wholesaler population. e.g. Brokers, new applications.

Only Major findings against GDP are included in the detailed review of deficiencies. These represent common, significant threats to patient health and product quality. Critical deficiencies were excluded as they generally cover broader sections of the GDP guidelines and are assessed individually due to the seriousness of issues. Others were not reviewed in detail due to the comparative high number and lower impact relative to Major deficiencies.

Deficiencies against The Human Medicines Regulations 2012 have not been included in the data but examples of these deficiencies are given.

# Sampling method, the final sample

- Inspections from all 18 GDP Inspectors are reflected in the sample.
- Inspections were carried out across the whole year.
- A wide range of business models are represented, e.g. full line, short line, third party logistics, Marketing Authorisation Holders, exporters, virtual, pharmacies in possession of a WDA(H), NHS.
- Inspections include those associated with variations to licences and for-cause inspections in addition to routine inspections.
- Chapter sub-sections have been included as deficiencies in their own right, as these are considered significant enough to be referenced as stand alone deficiencies during inspection.

Please note, the first section of a GDP chapter is not often cited as a deficiency. This is because this generally refers to the principle of that chapter. The deficiency is much more likely to relate to elsewhere in the chapter.

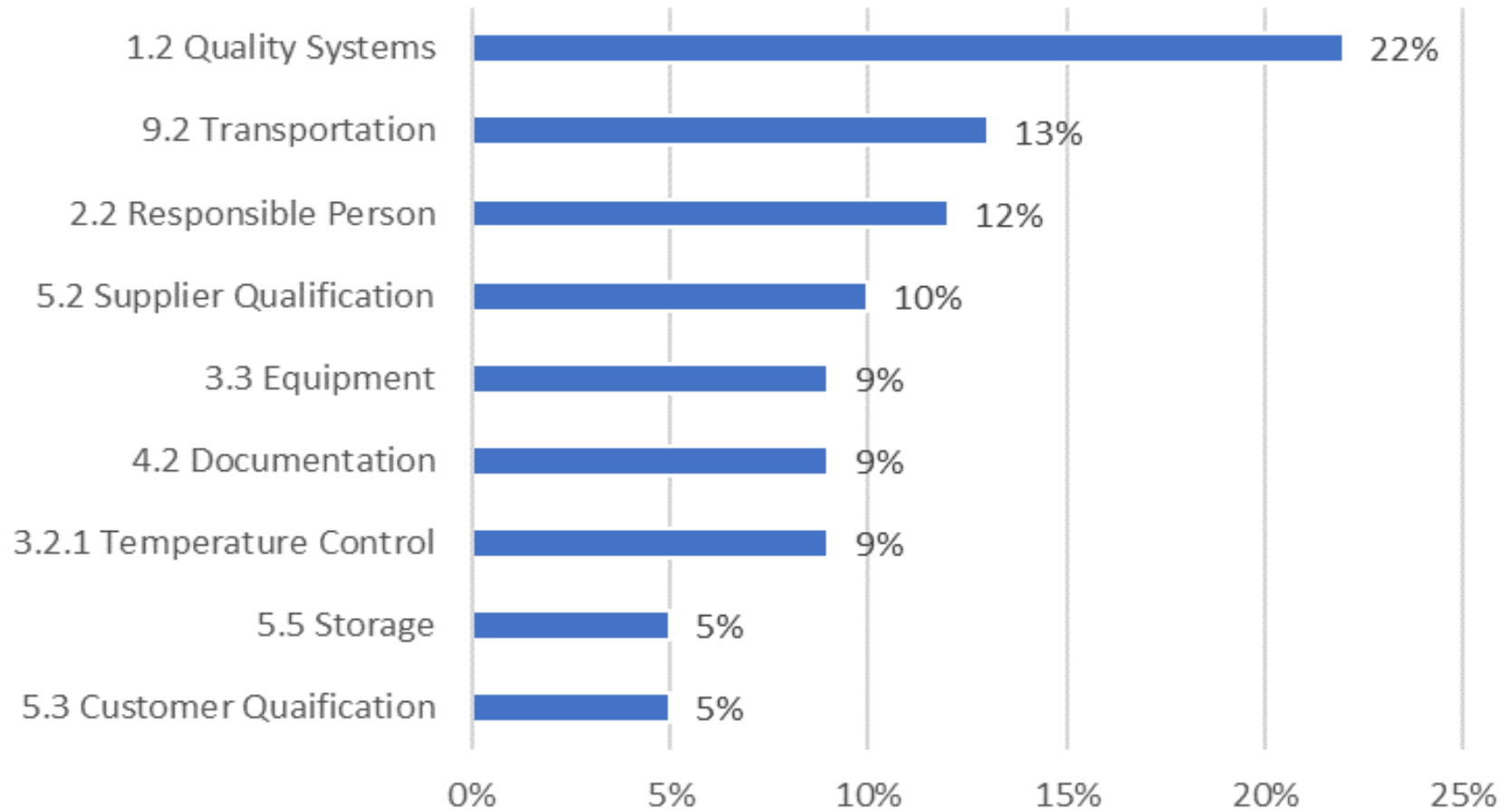
# Deficiency Data 2016:

Deficiencies against GDP and  
The Human Medicines Regulations 2012



# Top cited Major GDP deficiency groups

Values represent the percentage of inspections in the sample that had Major deficiencies raised against the associated GDP reference.



# GDP Chapter 1 Deficiencies

## Quality Management

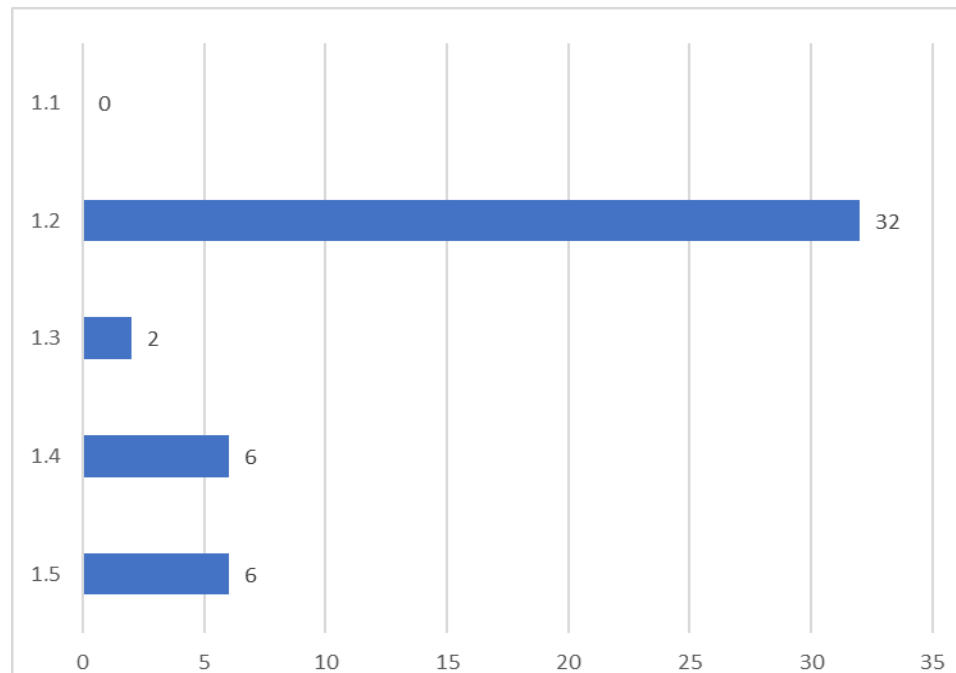
1.1 Principle

1.2 Quality system

1.3 Management of outsourced activities

1.4 Management review and monitoring

1.5 Quality risk management



Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.



# GDP Chapter 2 Deficiencies

## Personnel

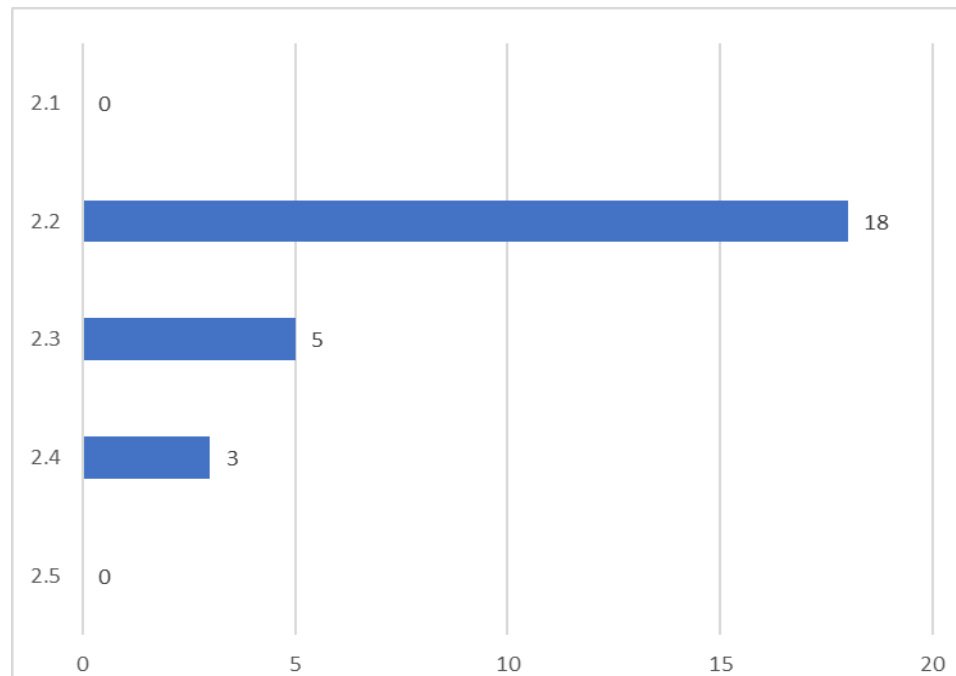
2.1 Principle

2.2 Responsible person

2.3 Other personnel

2.4 Training

2.5 Hygiene



Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

# GDP Chapter 3 Deficiencies

## Premises and Equipment

3.1 Principle

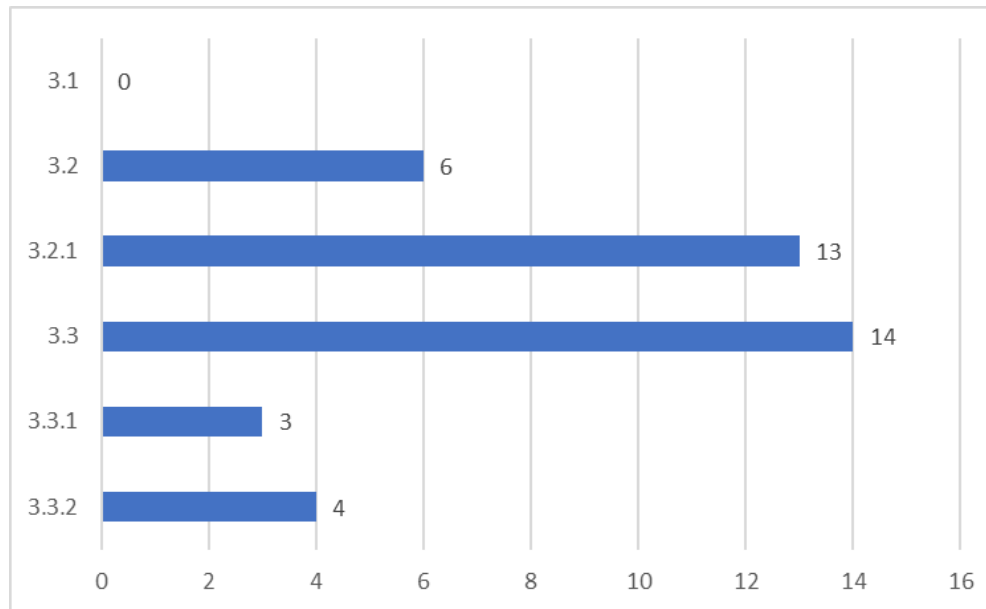
3.2 Premises

3.2.1 Temperature and environment control

3.3 Equipment

3.3.1 Computerised systems

3.3.2 Qualification and validation



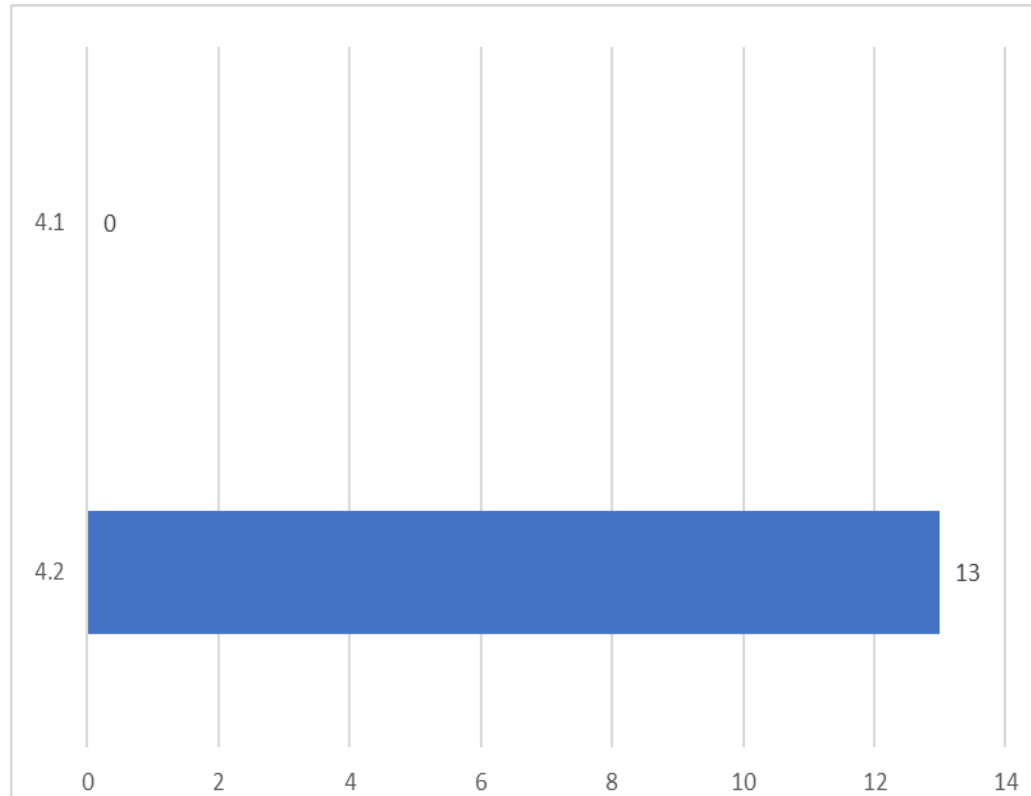
Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

# GDP Chapter 4 Deficiencies

## Documentation

4.1 Principle

4.2 General

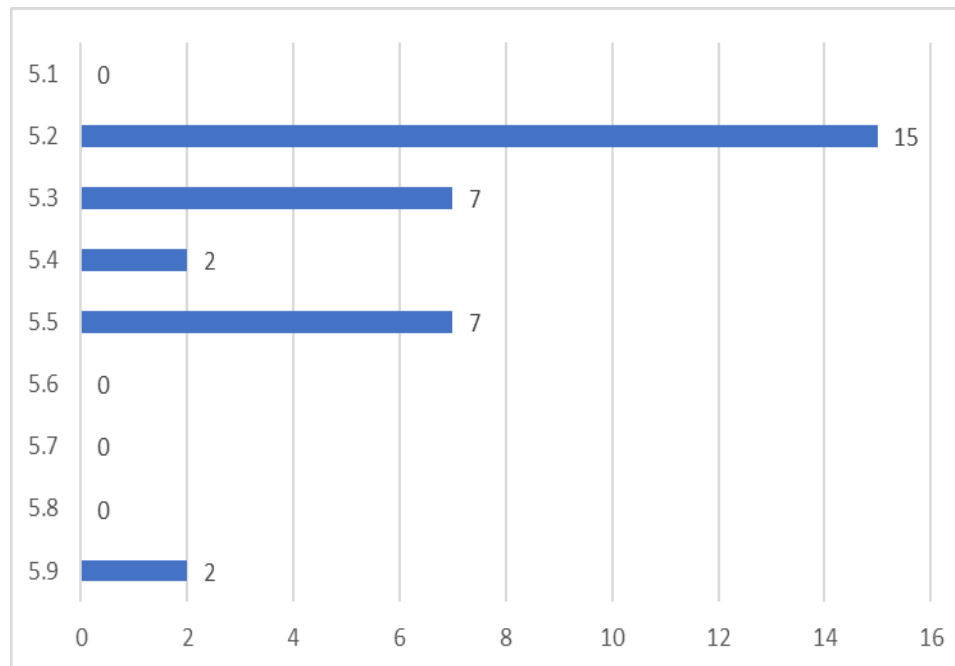


Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

# GDP Chapter 5 Deficiencies

## Operations

|                                   |                                |                                   |
|-----------------------------------|--------------------------------|-----------------------------------|
| 5.1 Principle                     | 5.2 Qualification of suppliers | 5.3 Qualification of customers    |
| 5.4 Receipt of medicinal products | 5.5 Storage                    | 5.6 Destruction of obsolete goods |
| 5.7 Picking                       | 5.8 Supply                     | 5.9 Export to third countries     |



Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

# GDP Chapter 6 Deficiencies

## Complaints, Returns, Suspected Falsified Medicinal Products and Medicinal Product Recalls

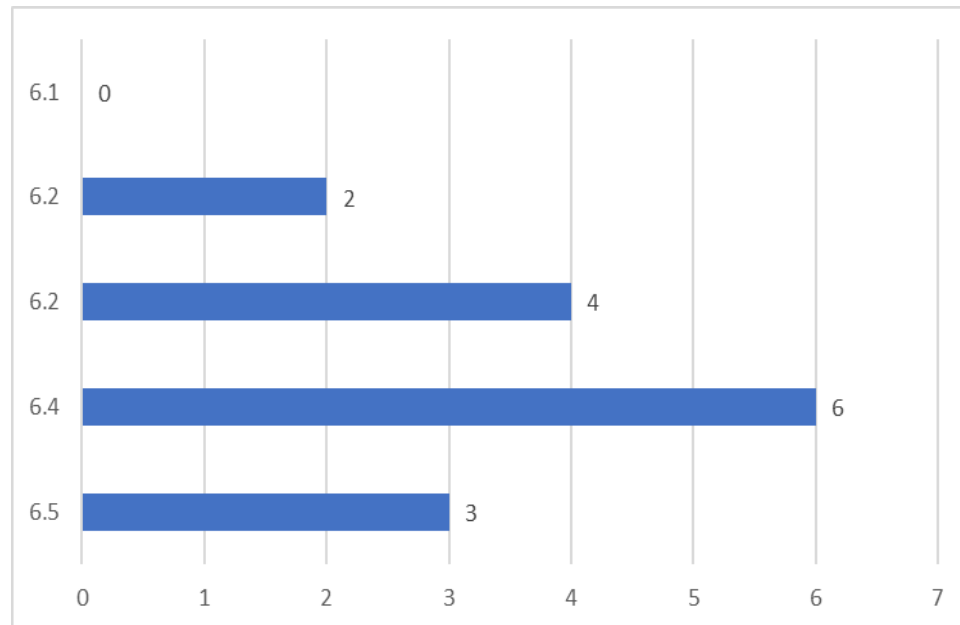
6.1 Principle

6.2 Complaints

6.3 Returned medicinal products

6.4 Falsified medicinal products

6.5 Medicinal product recalls



Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

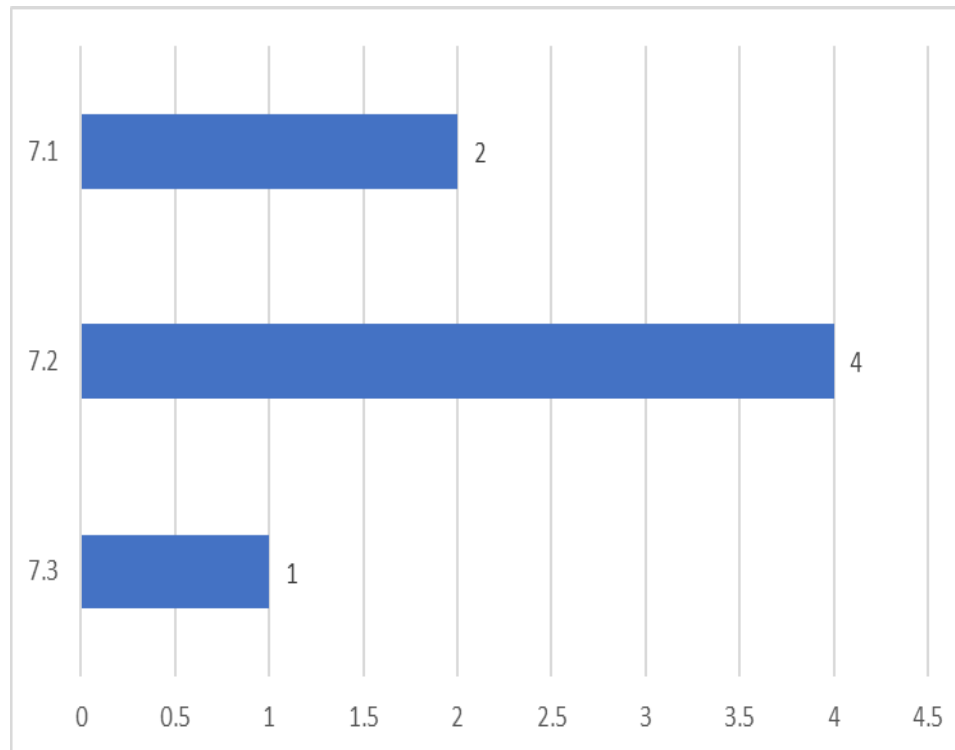
# GDP Chapter 7 Deficiencies

## Outsourced Activities

7.1 Principle

7.2 Contract Giver

7.3 Contract Acceptor



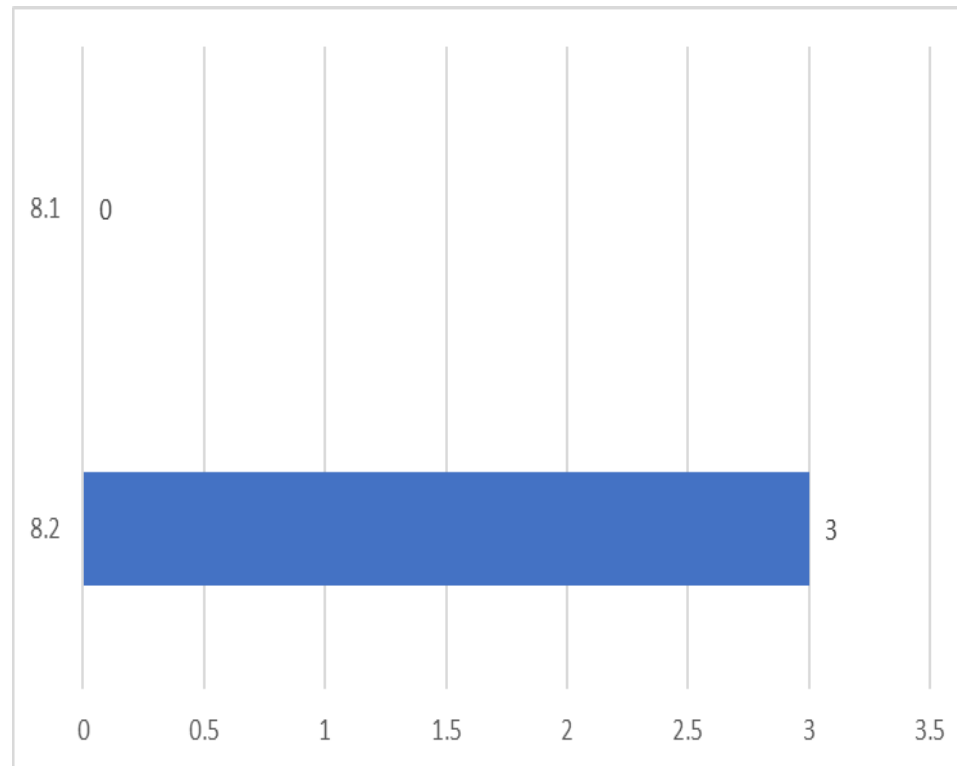
Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

# GDP Chapter 8 Deficiencies

## Self-inspections

8.1 Principle

8.2 Self-inspections



Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.

# GDP Chapter 9 Deficiencies

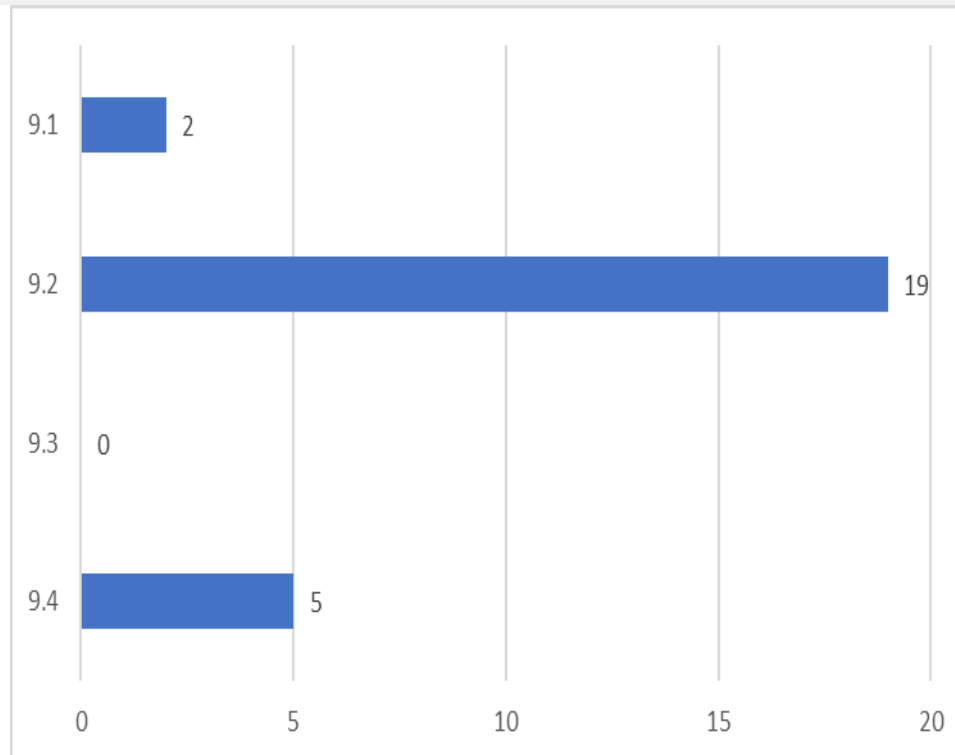
## Transportation

9.1 Principle

9.2 Transportation

9.3 Containers, Packaging and Labelling

9.4 Products Requiring Special Conditions



Values represent the number of inspections in the sample that had Major deficiencies raised against the associated GDP reference.



# GDP Chapter 10 Deficiencies

## Specific Provisions for Brokers

10.1 Principle

10.2 Quality System

10.3 Personnel

10.4 Documentation

There were no Major deficiencies raised against this GDP chapter

The following are examples of citations against:

The Human Medicines Regulations 2012

# Failure to comply with HMR 2012

- Medicinal product had been wholesaled from this site although the site was not named on the WDA(H). (HMR 18(3) and Schedule 4 (29)).
- The licence holder had failed to notify the MHRA prior to structural alterations of the premises to which the licence relates. (HMR 43(4)).
- Medicinal products had been obtained from outside of the licenced supply chain by way of donation from members of the public. Wholesale distributors must obtain their supplies of medicinal products only from persons who are themselves in possession of an appropriate WDA(H) or manufacturing authorisation. (HMR (44) (2)).
- Medicinal product had been supplied without an enclosed document that carried the name and address of the licence holder making the supply. The document enclosed with the product carried the name of another legal entity so customers were not able to see the true source of the medicinal products. (HMR 44 (6)(d)).
- The licence holder had failed to nominate a Responsible Person with sufficient knowledge of the activities to be carried out. The RP was unaware of how additional requirements imposed on certain products by national law would be adhered to, for example, the MHRA published guidance on export that related to 'controls on strategic goods and drugs used in execution by lethal injection'. (HMR 45 (1)(a)).

The following are examples of citations against:

European Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01)

# EU GDP Chapter 1 – Quality Management

## Deficiency Examples

- The quality system did not describe the processes for procurement, holding and supply of medicinal product without a marketing authorisation in the EEA.
- The scope of Management Reviews did not include deviation analysis and there was no visibility of deviation detail at Management Review level.
- There was little or no evidence of the effective implementation of change control, risk management, deviation capture, CAPA reporting or management review.
- The application of change control was inadequately detailed. For example, not all GDP impacts of the move to new premises and proposed activities had been considered.
- There was evidence of deviations being closed prior to CAPA being implemented, e.g. the deviation relating to the breaking down of packs at a third party logistics (3PL) provider had actions outstanding but had been signed off as complete.

# EU GDP Chapter 1 – Quality Management

## Deficiency Examples continued

- There was no formal process for review of the outsourced activities including review of the written contracts. Some of the written contracts with 3<sup>rd</sup> party service providers for storage and distribution were out of date.
- There was no written procedure which described the arrangements for qualifying suppliers or third party contractors to ensure they are suitably authorised to supply medicines or conduct third part activity.
- The quality risk management (QRM) functions were found to be inadequately applied as some risk-based activities were incompletely recorded or not recorded.

# EU GDP Chapter 2 – Personnel Deficiency Examples

- The RP was not able to demonstrate sufficient knowledge of the GDP activities to be carried out and the procedures to be performed to ensure the licence conditions are being complied with.
- There was no formal training record in place for the Responsible Person, demonstrating his ongoing awareness of and competence in GDP.
- The Responsible Person had not fulfilled all his responsibilities ensuring that the conditions under which the licence was granted had been complied with: ensuring the accuracy and quality of records of all transactions; ensuring that suppliers licences were approved; ensuring self-inspections were performed; had not appointed, trained and kept appropriate records of any delegated duties.
- There was no process defined for the initial and continual training programme of all personnel involved in wholesale distribution activities.

# EU GDP Chapter 3 – Premises and Equipment Deficiency Examples

- The large walk-in refrigerator had a build-up of dirt on the ceiling, and around the fans and no documented schedule or cleaning record in relation to the area.
- There were no quarantine areas in place for cold chain or ambient areas.
- At the unannounced inspection, not all wholesale products were stored on the shelves assigned for them, and some were stored adjacent to a door which was used occasionally to access the public area.
- Temperature mapping exercises had not been adequately conducted, to establish the suitability of the storage areas or to determine the placement of the thermometers in the areas that experience the extremes of temperature fluctuations. No conclusion had been drawn as to the suitability of the storage areas.
- Cold chain temperature deviations had been recorded but not subjected to CAPA reporting.



# EU GDP Chapter 3 – Premises and Equipment Deficiency Examples - continued

- The description of the computer system to be used was incomplete.
- The refrigerator could not be demonstrated as suitable for the storage of medicinal product in that there was a build-up of ice, a low temperature of 0.6°C was observed at the time of the inspection and changes to the refrigerator control dial were not recorded.
- The warehouse thermometer had not been calibrated across the operating range and had not been recorded as being assessed as fit for purpose.
- The thermometer in the ambient storage area had been incorrectly installed – readings were not being taken from the calibrated probe.

# EU GDP Chapter 4 – Documentation Deficiency Examples

- There were considerable gaps in contemporaneous temperature records. The Responsible Person confirmed he had added fabricated readings to fill gaps.
- There was no formal process for document control and retention of documents.
- Historic records of trading were not available for inspection.
- Evidence had been obtained prior to the inspection that a purchase of products had been made from an unlicensed local pharmacy, X. This could not be confirmed at the inspection, as no transaction records were available for review and there were no qualification records available for any suppliers or customers.
- Documentation was not compliant with GDP in that some records had been made in pencil, some temperature records were unsigned and there were a number of unapproved corrections.
- Completion of deviation records did not comply with GDP expectations of data integrity; a report of missing stock to the police was not completed contemporaneously.

# EU GDP Chapter 5 – Operations Deficiency Examples

- Supplier qualification was incomplete as there had been no verification of the supplier's compliance with GDP e.g. by checking the GDP certificate.
- The written procedure did not describe customer qualification for all customers including pharmacies, retail shops and non-UK or export customers.
- Unusual and irregular sales patterns of narcotics and/or psychotropic substances were not being appropriately monitored.
- There were no instructions for staff to prioritize the handling of cold-chain medicinal products.
- The quality management system did not reflect the licenced category, export, in that the following processes were not described:
  - Customer qualification in accordance with the applicable legal and administrative provisions of the country concerned.
  - Transport of medicines to customers in third countries.
  - Identification, completion and storage of all export documentation

# EU GDP Chapter 6 – Complaints, Returns, Falsified Medicines and Recall Deficiency Examples

- The complaints procedure did not differentiate between product quality and distribution issues, including instructing staff to notify the Marketing Authorisation Holder / Manufacturer and relevant Competent Authority in the event of a product quality issue arising.
- The process for handling customer returns was deficient in that there was a lack of evidence supporting the return of damaged stock to the supply chain.
- The written procedure and self –inspection template repeatedly referred to counterfeit medicines rather than the full scope of the term ‘falsified medicines’. The SOP did not indicate that all suspected falsified meds must be notified to MHRA.
- The process for regularly assessing the effectiveness of recall activities lacked sufficient detail so as to permit staff to follow the process consistently and for the Responsible Person to make an objective assessment as to the effectiveness of recall arrangements.

# EU GDP Chapter 7 – Outsourced Activities

## Deficiency Examples

- There was no contract in place with X defining their responsibilities for the proposed transportation of medicines.
- Written agreements were not signed or duly authorised by appropriate parties and did not reflect outsourcing of procurement.
- There had been no audit conducted of the contract acceptor by the contract giver and the contract giver had not had sight of or reviewed the written procedures being used by the contract acceptor.
- The organisation had insufficient control over outsourced 3PL activities in that some providers were contractually authorised to sub-contract without company review.
- The third party contracts provided by X to their suppliers failed to include the invoicing activity they conducted on the supplier's behalf.
- The proposed activity whereby (the licence holder) is to act as a third party supplier for X had not been suitability defined in respect of the responsibilities and communication processes between the two parties.

# EU GDP Chapter 8 – Self-inspection Deficiency Examples

- Self-inspection had not been performed to the frequency defined in the company procedure. The RPs had failed to conduct a self-inspection since appointment.
- The GDP activities at the X branch were not included as part of the company wide self-inspection schedule.
- The self-inspection / audit SOP did not incorporate a review of deficiencies, root cause, CAPA reports, change control or follow up.

# EU GDP Chapter 9 – Transportation

## Deficiency Examples

- Transportation was deficient in that the division of GDP responsibilities under the “customer collects” arrangements had not been formalized; including incorporating any specific packaging requirements into the quality system.
- There was inadequate reassurance that a robust process was in place assessing the need for temperature controls for ambient storage medicinal products across the full range of the company’s transport arrangements, including third-party distribution services.
- The site utilised uncontrolled ambient transportation for customer delivery with no risk assessment or definition of responsibilities with customers.
- Uncalibrated equipment was being utilised to monitor temperature during transport.
- The risk assessment identifying the need for temperature controls for the company’s own transport arrangements lacked detail and contained erroneous assumptions concerning UK climatic conditions.
- It could not be demonstrated that ambient medicinal products had been shipped in a manner to ensure temperature conditions are maintained within acceptable limits during the entire journey.

# EU GDP Chapter 10 – Specific Provisions for Brokers Deficiency Examples

- The licence holder had utilised the services of independent negotiating personnel in Spain. There had been no check of the status of these people as registered brokers.



# Concluding remark

This data is presented in order to assist wholesalers, and those that intend to obtain a WDA(H), to understand areas where significant GDP failures have been observed. Exclusion of a deficiency does not mean that it does not exist as a problem, only that it is not represented within the sample. Organisations are therefore recommended to not use these deficiencies as a point of focus at the expense of risks that may be higher for their particular organisation.

This data was presented in a different format during the 2017 GDP Symposium – referencing whole chapters instead.

We welcome feedback on the presentation of this data.

# © Crown copyright 2017

## **About copyright**

All material created by the MHRA, including materials featured within these MHRA presentation notes and delegate pack, is subject to Crown copyright protection. We control the copyright to our work (which includes all information, database rights, logos and visual images), under a delegation of authority from the Controller of Her Majesty's Stationery Office (HMSO).

The MHRA authorises you to make one free copy, by downloading to printer or to electronic, magnetic or optical storage media, of these presentations for the purposes of private research, study and reference. Any other copy or use of Crown copyright materials featured on this site, in any form or medium is subject to the prior approval of the MHRA.

Further information, including an application form for requests to reproduce our material can be found at [www.mhra.gov.uk/crowncopyright](http://www.mhra.gov.uk/crowncopyright)

## **Material from other organisations**

The permission to reproduce Crown copyright protected material does not extend to any material in this pack which is subject to a separate licence or is the copyright of a third party. Authorisation to reproduce such material must be obtained from the copyright holders concerned.