Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Bristol Laboratories Ltd

MHRA Inspection Number: Insp GPvP 17907/29140-0021

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Bristol Laboratories Ltd [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	09 – 10 & 14 – 15 September 2020 (remote)
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	30 March – 01 April 2016 03 – 05 June 2014 03 – 05 May 2011 03 – 05 June & 06 August 2008 21 – 23 May 2007
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	ARISg (v7.4.5.3.1) commercially available.
Key service provider(s):	APCER had been contracted as a pharmacovigilance service provider, including the QPPV.
Inspection finding summary:	1 Major finding
Date of first issue of report to MAH:	21 Oct 2020
Deadline for submission of responses by MAH:	25 Nov 2020
Date(s) of receipt of responses from MAH:	24 Nov 2020
Date of final version of report:	03 Dec 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Bristol Laboratories Ltd (hereafter "Bristol Labs") was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at Appendix I.

Bristol Labs are a global pharmaceutical company, headquartered in Berkhamsted, Hertfordshire, UK. Bristol Labs specialise in the manufacture and supply of generic medicines. The product portfolio contains over 800 licences in the EU, across MAHs Bristol Laboratories, Brillpharma Ltd, Brill Pharma S.L, Brillpharma (Ireland) Ltd and Axcount Generika GmbH. All of the MAHs listed sit under [redacted]

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Pharmacovigilance activities were being performed by contractor, [redacted] This included provision of the EU-QPPV, case processing activities, literature searching, authoring of aggregate reports and signal management. A full list of activities and responsibilities was available in the [redacted]

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance systems and was performed remotely to the COVID-19 pandemic. Personnel from Bristol Labs and [redacted] were available through videoconference facilities.

The inspection was performed using interviews and document review. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix III).

Areas not included within the inspection plan were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

B.3 Documents submitted prior to the inspection

The company submitted a [redacted] updated 17 August 2020) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. Amendments to the initially agreed plan appear in red text in Appendix III.

A closing meeting was held remotely to review the inspection findings on Tuesday 15th September 2020.

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

C.1 Summary of significant changes and action taken since the last inspection

Since the previous inspection in 2016 the company had made the following changes to the pharmacovigilance system:

- Bristol Labs had acquired Brill Pharma SL En. At the time of the inspection the pharmacovigilance system was being integrated into Bristol Labs' pharmacovigilance system.

C.2 Definitions of inspection finding gradings

Critical (CR): a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major (MA): a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor (MI): a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Comment: the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

Findings from any inspection which are graded as critical or major will be shared with the EMA, other EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered directly into the table(s) in section C.4. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

Root Cause Analysis Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
Further Assessment Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
Corrective Action(s) Detail the action(s) taken / proposed to correct the identified deficiency.
Preventative Action(s) Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
Deliverable(s) Detail the specific outputs from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due Date(s) Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Further information relating to inspection responses can be found under 'Inspection outcomes' at: https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp

C.4 Inspection findings

C.4.1 Critical findings

No critical findings were identified from the review of pharmacovigilance processes, procedures and documents performed during this inspection.

C.4.2 Major findings

MA.1 Reference Safety Information

Requirements:

Directive 2001/83/EC (as amended) Paragraph 40

'The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.'

Article 23(3) "*The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.*"

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 5 Pharmacovigilance, Regulation 76(1)

'The holder of a UK marketing authorisation or parallel import licence for a medicinal product must ensure that the product information relating to the product is kept up to date with current scientific knowledge'

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Finding MA.1 a)

There were examples identified of superseded PILs being released into the market over six months since the approval of a new PIL.

Variations for licences [redacted] were approved by the MHRA on the 11 March 2019, these variations were to align Bristol's product information with the innovator. Changes impacted sections 4.2, 4.4, 4.6, 4.7, 4.8, 4.9, 5.1 and 5.3 of the SmPC. There were consequential changes to the PIL limited to removal of repeated information, rewording of safety concerns already present in the PIL and some additional wording regarding the prescribing of the product.

The six-month deadline for the introduction of changes to the PIL described above was September 2019.

Batches [redacted] were QP-certified for release on the 20 January 2020 with a previous version of the PIL, four months after the six-month deadline.

Bristol Labs had identified these batches and several others for [redacted]

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and [redacted] in preparation for the inspection. Deviation record [redacted] had been raised on the 31 August 2020 covering the concerned batches. The accompanying investigation indicated no substantial safety information had been missing from superseded PILs which had been released.

Bristol Labs were instructed to contact DMRC at the end of the inspection with details of the batches which had been released with out of date PILs. This action was completed on the 16 September 2020.

Root Cause Analysis

[redacted]

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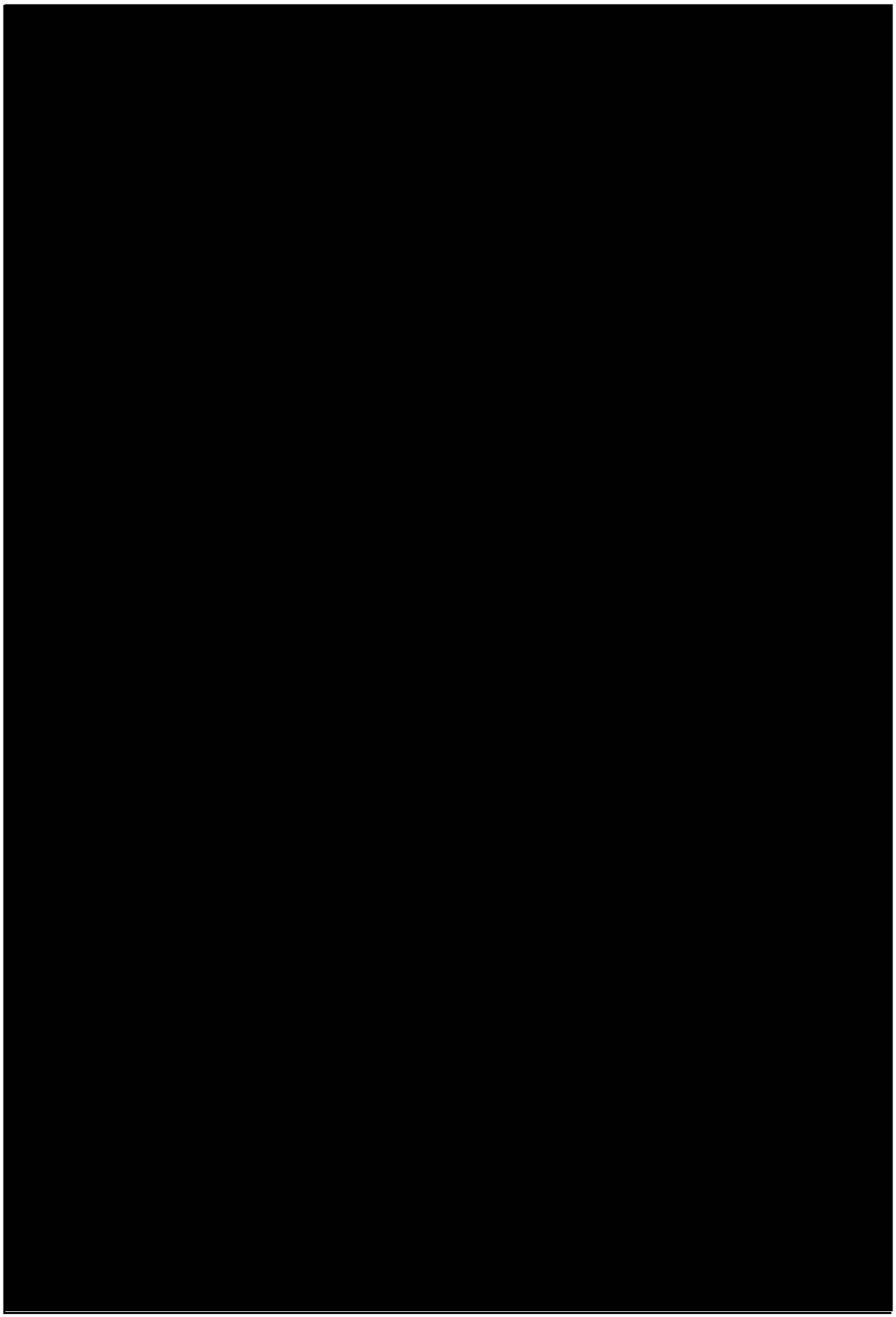

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)	
[redacted]	
[redacted]	

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[redacted]

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

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Finding MA.1 b)

There were deficiencies identified with product information uploaded to company sponsored websites.

i. The PILs which were hosted on the consumer care website (www.bristol-labsconsumercare.co.uk) were not the most current versions:

- The [redacted] PIL hosted on the site was dated August 2016, whereas the most current version was dated August 2020. There were minor changes to the leaflet such as re-wording, updates to headings and deletion of text approved during this time.
- The [redacted] PIL hosted on the site was dated September 2016, whereas the most current version was dated December 2018. There were minor changes such as a re-ordering of common side-effects, to the leaflet approved during this time.
- The [redacted] PIL hosted on the site was dated October 2017, whereas the most recent version was dated January 2019. There were no safety changes introduced since the October 2017 version.

ii. The company website www.bristol-labs.co.uk hosted the current SmPCs for Bristol Labs products, accessible through selecting a product from the portfolio displayed on the site. However, when searching for a product using the search function, archived SmPCs were available to download and view. Two example searches were performed during the inspection for "amlodipine" and "lisoretic".

The current version of the [redacted] was dated 24 Aug 2018 (PL [redacted] The current version of the [redacted] was dated 30 Jun 2020 (PL [redacted]

The [redacted] results showed [redacted] of the [redacted] for the [redacted] products from August 2014. Versions from 2015, 2016, 2017 and 2018 were also available to view.

The [redacted] results showed [redacted] of the [redacted] for the [redacted] and the [redacted] from December 2014. Versions from 2016, 2017, 2018 and 2020 were also available to view.

A general search was also performed in Google for [redacted] and a 2014 version was shown on the results page. Screenshots of all search results are included within Annex II.

[redacted] "Procedure for Creation and Maintenance of Product Information on Company Website" [redacted] effective 29-Oct-2018) stated that updated product information should be uploaded to company sponsored websites within 10 calendar days from the receipt of variation approval, in line with MHRA expectations.

Bristol Labs were asked during the inspection to remove all previous versions of [redacted] and PILs from company sponsored websites. This was actioned by the time of the closing meeting on the 15 September 2020.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.1 c)

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Examples were identified where the product information uploaded to the eMC either was not current or had been uploaded past the 10-calendar day's timeframe.

i. The [redacted] were dated 28 December 2018. However, the most recent version at the time of the inspection was dated 30 June 2020. Changes included in the June 2020 version included new contraindications, new warnings and precautions and new information regarding interactions with other medicines.

ii. The [redacted] was dated 07 November 2017; however, the most recent version at the time of the inspection was dated 01 April 2019. There were no safety updates in the new version of the PIL.

iii. The [redacted] were dated 26 September 2019, but were not uploaded to the eMC until 17 December 2019 constituting a delay of approx. 2.5 months. The update included a warning of sexual dysfunction into Section 4.4.

[redacted] Procedure for Safety Variations and Urgent Safety Restrictions [redacted], effective 27-May-2020 and [redacted] effective 05-Sept-2019) stated that the eMC should be updated within 10 calendar days of variation approval, in line with MHRA expectations.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.1 d)

There was one example of a variation which was submitted past the MHRA-expected maximum six-month deadline.

CMDh meeting minutes [redacted] published 13 December 2019, recommended that MAHs for [redacted] should submit variations to update Section 4.5 of the SmPC and Section 2 of the PIL with regards to an interaction with [redacted]. There was no recommended deadline included within the CMDh meeting minutes.

A variation for [redacted] was submitted by Bristol labs for [redacted] on the 12 August 2020, representing a delay of over two months from the maximum six-month deadline.

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Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

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[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).

APPENDIX II WEBSITE SCREENSHOTS

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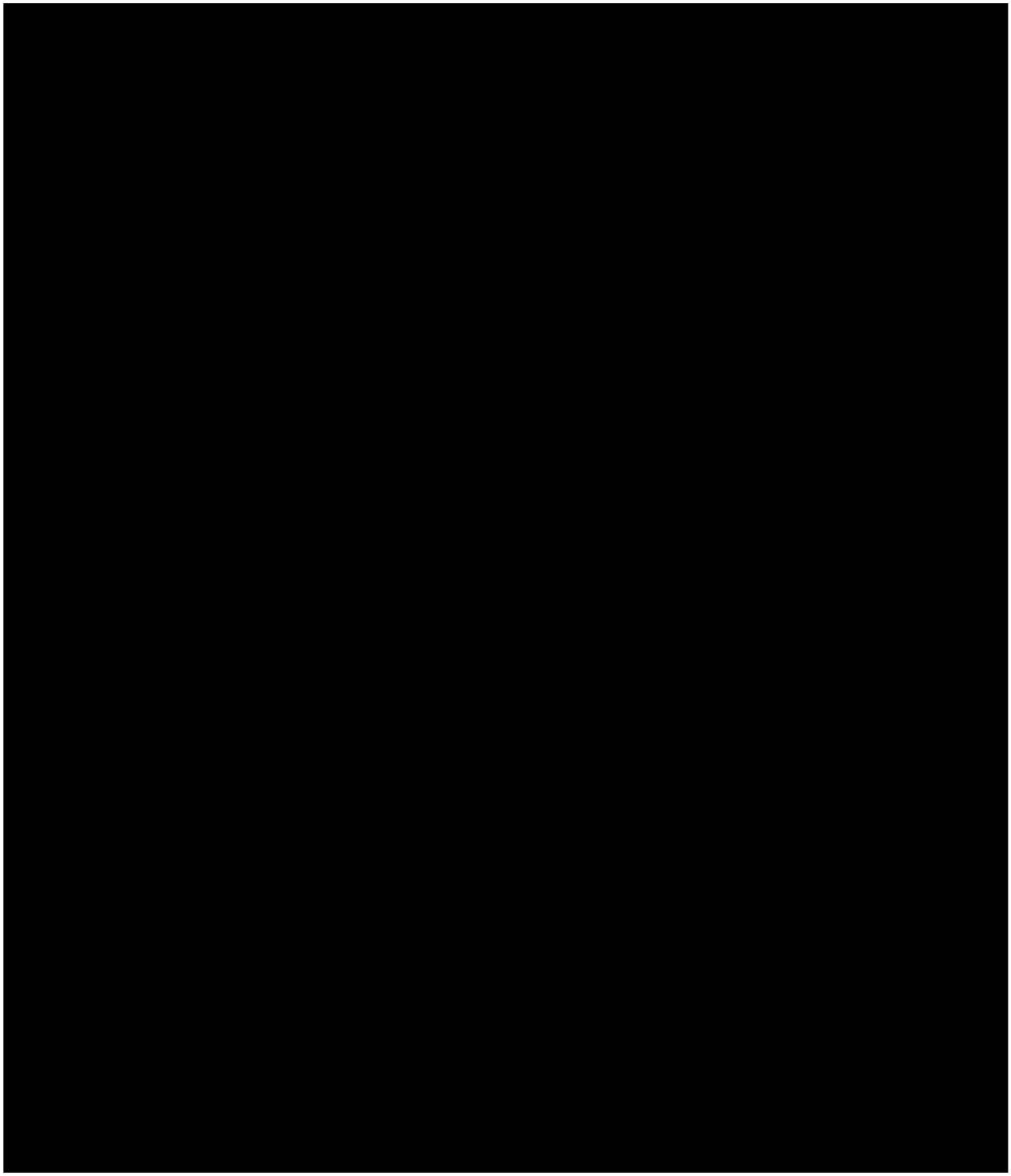

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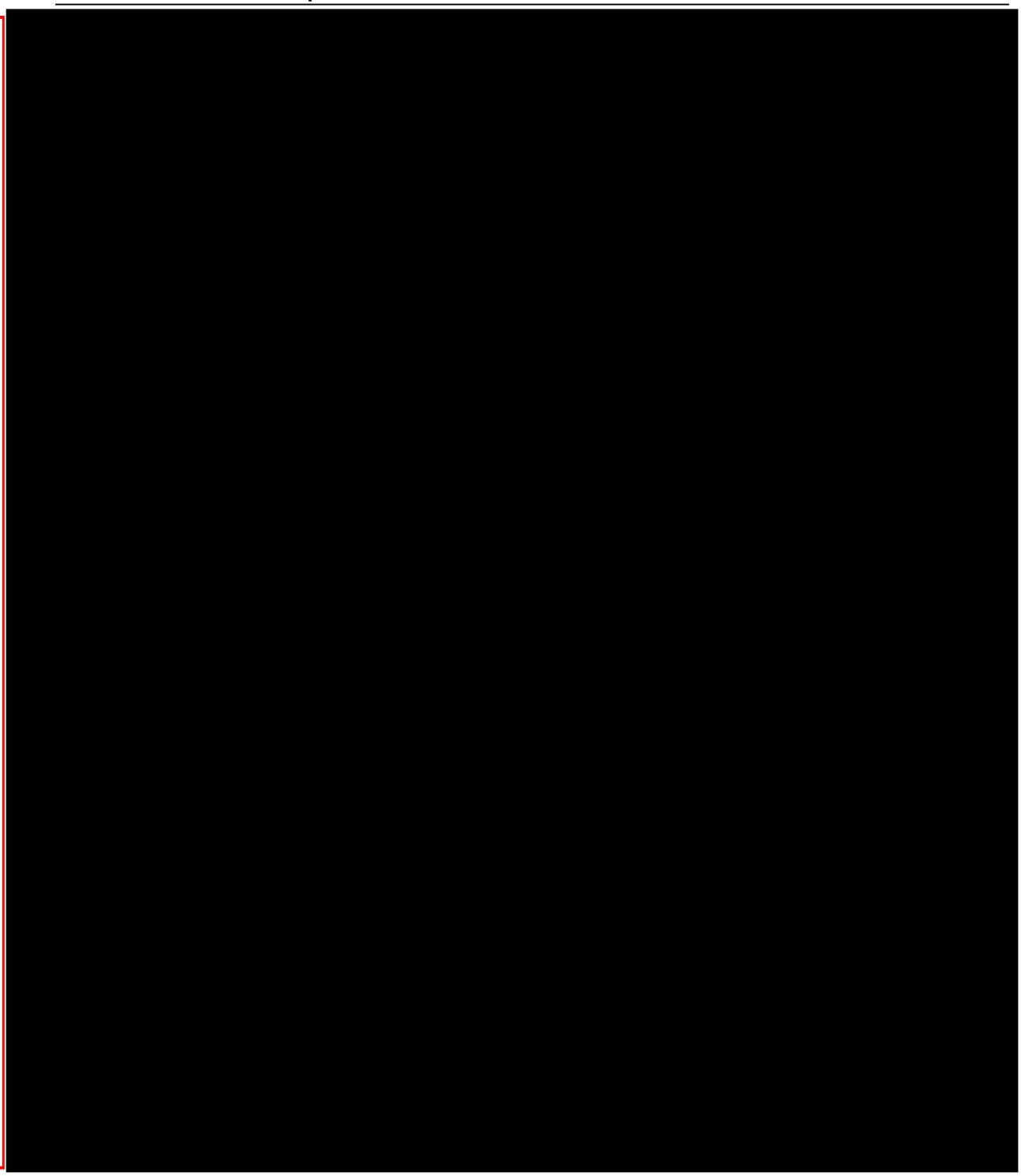

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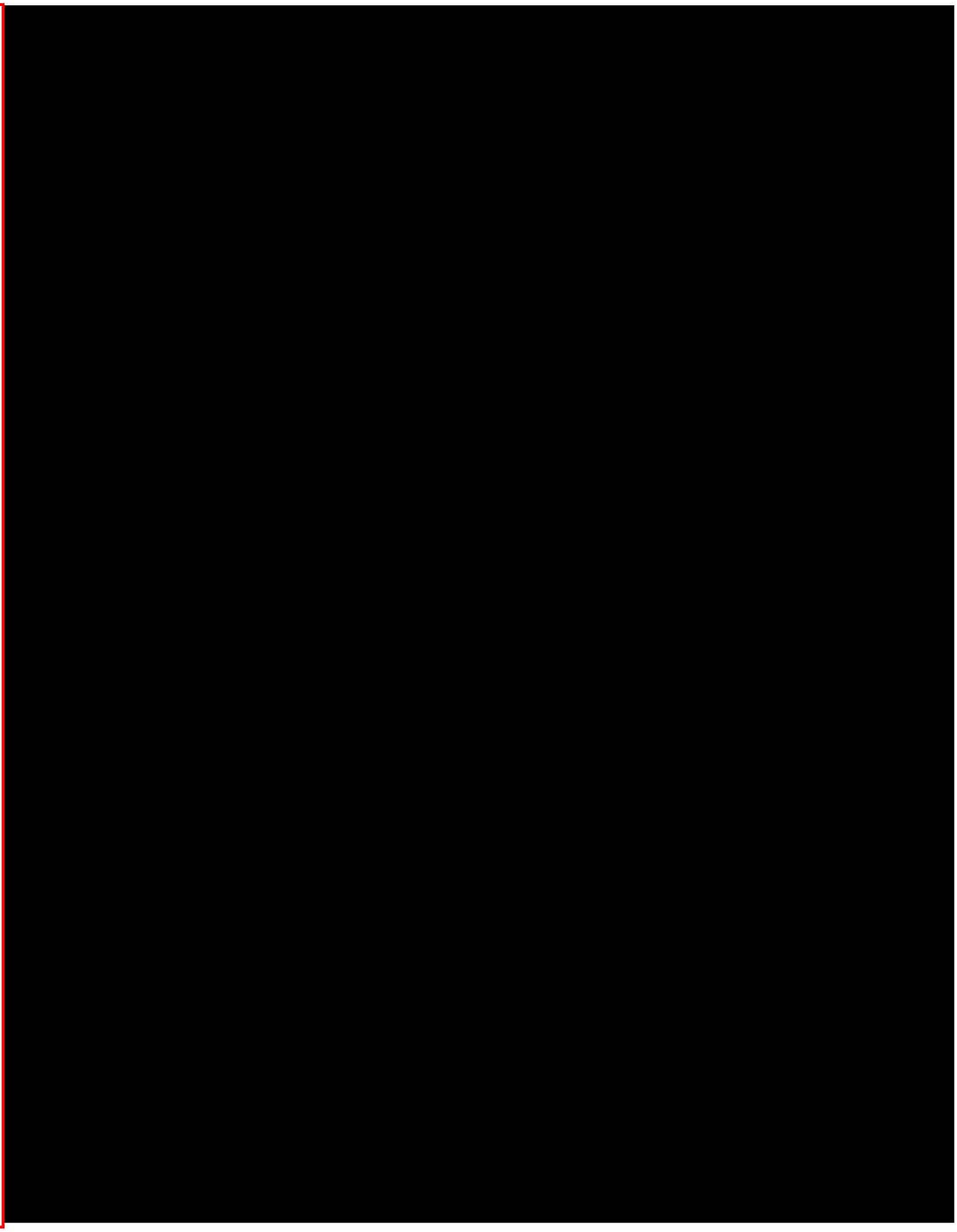

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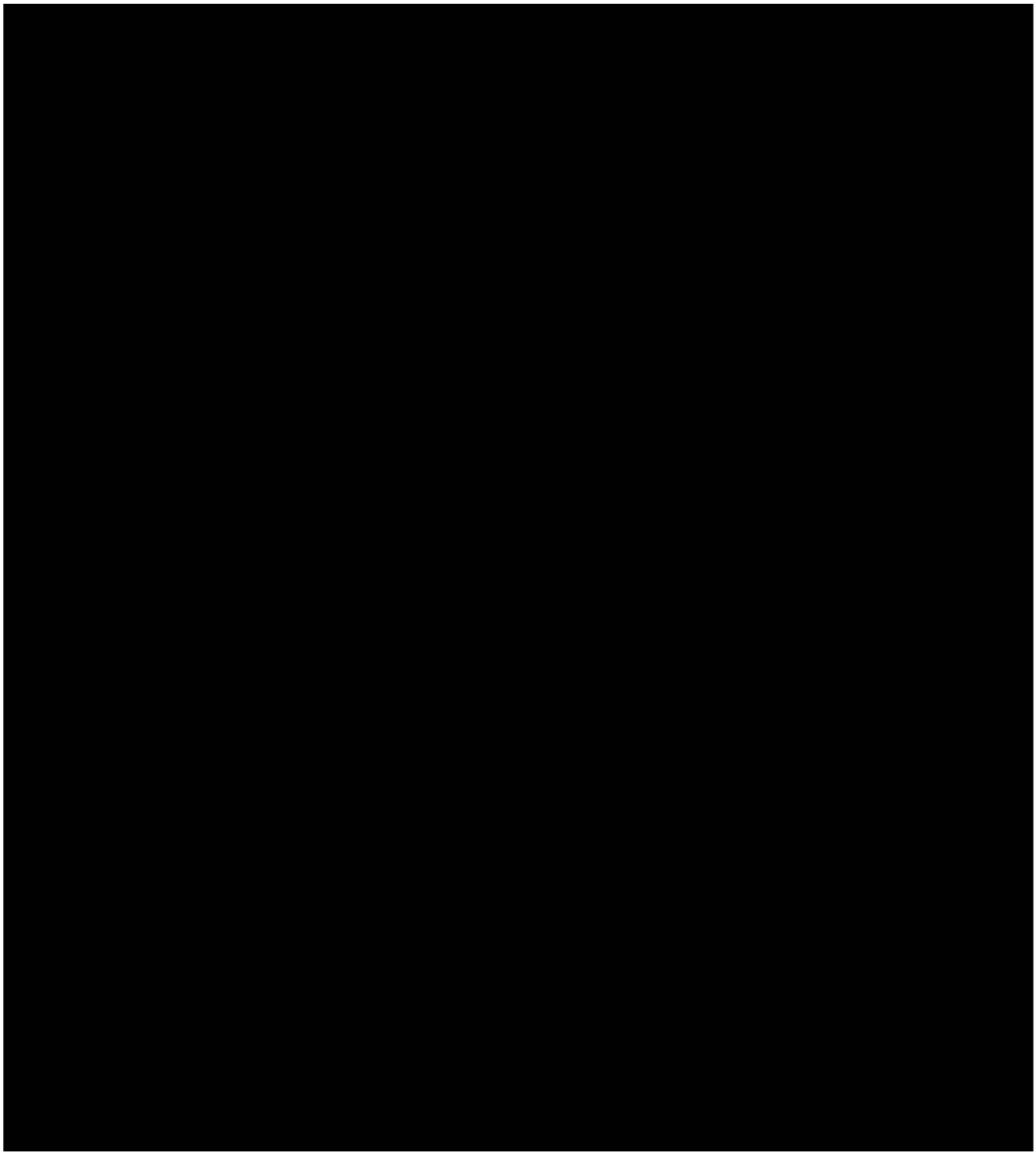

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[redacted]

APPENDIX III PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Bristol Laboratories	**DATES**	09 - 10 August 2020 14 - 16 September 2020
LOCATION	Remote inspection	**START TIME**	09:00 on all days

Inspection plan (N.B. the plan may be subject to change in the lead-up to, or during, the inspection)

The scope of the inspection will include the following topics:

- **Reference Safety Information**
  - To include signal detection, validation, evaluation and tracking

- **Additional Risk Minimisation Measures (aRMMs), including Post-authorisation Safety Studies**
  - Management, oversight and implementation of UK educational materials
  - Management and oversight of Post-authorisation Safety Studies

- **Periodic Safety Update Reports**
  - Scheduling, accuracy and submission of reports

Wednesday 09 September 2020 – Thursday 10 September 2020 (Days 1 – 2):

An opening meeting will be held by videoconference on Wednesday 09 September at 9.00am (BST), which will be led by the lead inspector. The agenda will be as follows:

- Review of the scope and arrangements for the inspection
- Company presentation by Bristol Labs to provide an overview of the company, pharmacovigilance system and quality system. The presentation should last no longer than 20 minutes.

The remainder of the inspection will consist of remote document review, written requests and ad hoc video/telephone clarifications with subject matter experts as required. Please provide a designated contact point who can assist with any ad hoc questions from the inspectors or arrange calls between inspectors and subject matter experts if required.

Monday 14 September 2020 – Wednesday 16 September 2020 (Days 3 – 5) (Inspection did not extend into Wednesday 16 September)

Remote document review, written requests and ad hoc queries from inspectors where necessary.

A closing meeting will be held via videoconference on Wednesday 16 September (timing to be confirmed) during which feedback on the inspection will be provided to the company. The closing meeting was held on Tuesday 15th September.

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Bristol Laboratories are requested to complete the below with the names and job titles of the designated contact point and those staff who will be dialling in to the opening meeting.

Designated contact point:

[redacted]