Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Torrent Pharma GmbH

MHRA Inspection Number: Insp GPvP 20658/13766-0003

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ABBREVIATIONS

ADR	Adverse Drug Reaction
CAPA	Corrective and Preventative Action
DCP	Decentralised Procedure
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
PIL	Patient Information Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred term
PV	Pharmacovigilance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOC	System organ class
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Re-inspection
System(s) inspected:	Torrent Pharma GmbH [redacted]
Site(s) of inspection:	Torrent Pharma UK Ltd. Nexus Building 4 Gatwick Road Crawley RH10 9BG United Kingdom
Main site contact:	[redacted]
Date(s) of inspection:	29 April – 02 May 2019
Lead Inspector:	[redacted]
Accompanying Inspector:	
Previous inspection date(s):	22 – 24 May 2012, 07 – 10 November 2017
Purpose of inspection:	Re-inspection to determine if appropriate action had been taken from the previous inspection and to review compliance with UK and EU requirements
Products selected to provide system examples:	As part of the general systems review, ADR reports were reviewed for all UK-authorised products and PSURs were examined for [redacted]
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	AER Database, version 6.3 (bespoke)
Key service provider(s):	Pharmacovigilance services provided by APCER Life Sciences Ltd.
Inspection finding summary:	0 Critical findings 6 Major findings 0 Minor findings
Date of first issue of report to MAH:	06 June 2019
Deadline for submission of responses by MAH:	19 July 2019; 20 September 2019
Date(s) of receipt of responses from MAH:	19 July 2019; 20 September 2019
Date of final version of report:	15 November 2019
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Torrent Pharma GmbH was selected for re-inspection as a result of one critical finding that was identified during the previous routine inspection of the MAH, performed on 07 – 10 November 2017. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the previous inspection. In addition, the inspection provided an opportunity to re-examine the overall compliance of the pharmacovigilance system 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.

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Torrent Pharmaceuticals Ltd (TPL), located in Ahmedabad, India, is the global headquarters of the Torrent Group (hereafter referred to as 'Torrent'). Torrent specialises in generic medicines and currently has over [redacted] products authorised in the UK, either nationally or via the MRP/DCP route. Torrent has a number of EU subsidiaries (collectively known as TPEU) which include:

- Torrent Pharma GmbH and Heumann Pharma GmbH & Co. Generica KG, both located in Nuremberg Germany and the central point for principal EU PV activities;
- Torrent Pharma UK Ltd. (TPUK).

The role of the EU QPPV has been outsourced to medwiss-extern GmbH & Co. KG based in Germany.

The majority of pharmacovigilance activities are outsourced to APCER Life Sciences with sites in India and the UK. This includes ICSR management, preparation of PSURs, preparation of risk management plans, literature searching and maintenance of the PSMF.

Activities carried out by Torrent in India with support from the affiliates in the UK and Germany include signal detection and management activities as well as the development and implementation of SDEAs. Local affiliates are also responsible for the implementation of additional risk minimisation measures, the identification and submission of safety variations and the submission of RMPs and PSURs to competent authorities.

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at Torrent's offices in Crawley, West Sussex. Personnel from Torrent and APCER attended the Crawley site in order to participate in the inspection. Personnel based in India from both parties participated in the inspection via teleconference.

The re-inspection provided the opportunity to review critical pharmacovigilance processes in more detail than the previous inspection which was hindered by the nature of the critical finding issued at that inspection.

The inspection was performed using interviews and document review (including outputs from the global safety database and listings of medical information enquiries and product

complaints). The systems reviewed during the inspection are highlighted in the pharmacovigilance inspection plan (attached as Appendix II).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version 08.00, date effective 26 February 2019) 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. Details of these requests are contained within document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the inspection plan. Minor amendments to the inspection plan that occurred during the inspection are highlighted using italic text in Appendix II.

A closing meeting was held to review the inspection findings at the Torrent offices in Crawley on 02 May 2019.

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 November 2017 the company had made the following changes to the pharmacovigilance system:

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- The QPPV changed from [redacted] to [redacted] in March 2018.
- All marketing authorisations previously held by Aptil Pharma Ltd. had been transferred to Torrent Pharma UK Ltd. as of 05 April 2019. Aptil was acquired by Torrent in 2014 as a UK MAH and all marketing authorisations had already been part of the Torrent pharmacovigilance system since then. It is planned that Aptil will be closed by the end of July 2019.
- Signal detection and management responsibilities will be outsourced to Sciformix Technologies Pvt. Ltd. as of June 2019.

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

During the previous inspection in November 2017, a critical finding was reported in relation to significant deficiencies across the following critical pharmacovigilance processes:

- Adherence to risk minimisation commitments and the update and maintenance of RMPs
- Authoring and submission of PSURs for UK-authorised molecules
- Submission of ICSRs for UK-authorised products
- Maintenance and communication of accurate product information

In addition, the critical finding contained aspects relating to Torrent's failure to address several deficiencies within the pharmacovigilance system despite being aware of them and to ensure appropriate oversight of the pharmacovigilance system.

At the time of re-inspection, some aspects of the critical deficiencies identified during the previous inspection had been addressed. However, major deficiencies relating to core pharmacovigilance processes and Torrent's ability to effectively manage and resolve self-identified non-compliances have still been identified.

C.4.2 Major findings

MA.1 Maintenance of 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 […].*"

When new information about the benefits and risks of a product become available it is often appropriate to make changes to reference safety information documents, such as SmPCs and PILs, so that healthcare professionals and patients are able to use the medicinal product correctly on the basis of full and comprehensive information.

The following finding was noted in relation to control and maintenance of reference safety information:

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Finding MA.1 a)

Torrent had failed to implement the updated PIL within 6 months following the approval of a grouped safety variation for [redacted] capsules ([redacted]). Out-of-date PILs had been released for [redacted] batches of [redacted] (various strengths) more than 6 months after the MHRA's approval of the variation on 14 December 2017. The last batches [redacted] containing the superseded PIL were released on 27 November 2018, 11.5 months after variation approval.

This was an isolated example as all safety updates approved by MHRA between 01 November 2017 and 01 April 2019 were reviewed during the inspection.

The [redacted] batches equated to over [redacted] packs of which almost [redacted] had been distributed for sale at the time of the inspection. The remainder was quarantined by Torrent following the inspection:

Product	Batch number	Batch size (packs)	QP Release date	Stock
[redacted]				

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As part of the variation the following information was added to the PIL:

- Section *1. What* [redacted] *is and what it is used for*:
  - Information about the new indication "peripheral and central neuropathic pain"

- Section *3. How to take* [redacted]
  - Dosage instructions for the use in peripheral and central neuropathic pain
  - Risk of fits associated with an overdose of the product

- Section *4. Possible side effects*:
  - Side effects "Jaundice (yellowing of the skin and eyes" (rare), "Liver Failure" and "Hepatitis (inflammation of the liver)" (both very rare).

MHRA published guidance (https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets) states that changes to labels, leaflets and packaging must be introduced within 3 to 6 months of variation approval so that it is ensured that the outdated labelling is not released to the market beyond this time.

Local procedure [redacted] *Artwork Generation & Maintenance* (revision 3, date effective 20 July 2018) reflected the MHRA's expectation in section 6.7.2 *What should a stakeholder notification consist of?* by stating that the implementation period is "usually 6 months" from approval.

Information on the affected [redacted] batches was passed to the MHRA Defective Medicines Report Centre (DMRC) as a notification of a defective medicine on 17 May 2019. The DMRC file number is [redacted] The decision of DMRC was that the quarantined stock of affected [redacted] batches may be distributed. Torrent was informed of this decision on 23 May 2019.

Should there be any batches containing the superseded PIL that have not yet been QP-released, a batch-specific variation must be submitted to and approved by MHRA prior to release. General guidance on the submission of variations is available on the MHRA website (https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation#major-variations-type-ii).

Root Cause Analysis

[redacted]

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Further Assessment
[redacted]
Corrective Action(s)
Not applicable
[redacted]
Preventative Action(s)
[redacted]

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[redacted]

MA.2 Quality Management System

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 8(3)
"*The quality system shall be based on all of the following activities: […]*
(d) quality improvements: correcting and improving the structures and processes where necessary."

Article 11
"*1. Specific quality system procedures and processes shall be in place in order to ensure the following: […]*
(e) effective communication by the marketing authorisation holder with the national competent authorities and the Agency, including communication on new risks or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;
(f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, […]."

Module I – Pharmacovigilance systems and their quality systems
I.B.6. Responsibilities for the quality system within an organisation
"*For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for: […]*
- identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary; […]".

I.B.11. Documentation of the quality system
"It is recommended that the documentation of the quality system also includes:
[…] records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified."

Module III – Pharmacovigilance inspections (Rev 1)
III.C.5. Role of marketing authorisation holders and applicants
"*Marketing authorisation holders with authorised products […] are subject to pharmacovigilance inspections (see III.B.1.). Therefore both have responsibilities in relation to inspections, including but not limited to the following: […]*

- to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings."

One aspect of the critical finding issued at the 2017 MHRA GPvP inspection related to a failure to address known deficiencies in the pharmacovigilance system (refer to MHRA 2017 finding CR.1 b). During the re-inspection, it was seen that the process to record and resolve non-compliances had been strengthened; however, the following findings were noted in relation to the adequate management and resolution of deficiencies in the pharmacovigilance system.

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Finding MA.2 a)

Torrent had failed to effectively resolve the deficiencies in relation to signal detection activities that had been self-identified prior to the 2017 inspection.

Torrent took signal detection activities in house in March 2017 and updated [redacted] *Global Identification And Evaluation Of Safety Signals* (version 05, date effective 31 May 2017) to assign molecules to a 6-month or 12-month frequency of signal detection. Each molecule was assigned a month when the signal detection activity would take place.

Due to insufficient resource in-house, signal detection activities were not delivered in line with [redacted] and Torrent initiated deviation D/MAY/18/021 on 08 May 2018. Relevant CAPA were agreed on 29 May 2018 and included that further resources would be hired to manage the process by 30 September 2018 and that signal detection for all molecules was to be performed by 30 April 2019. However, there was a delay in implementing the CAPA and the alternate target completion date (ATCD) for the CAPA was only signed during the inspection on 01 May 2019.

Therefore, at the time of the inspection, only 39 of the 98 molecules authorised in the UK had signal detection performed by the in-house team since March 2017. Consequently, Torrent had not met their obligation to "monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products" for 59 UK-authorised molecules in accordance with Directive 2001/83/EC as amended, Article 104(3)(e). A list of the 59 molecules for which no signal detection had been performed since March 2017 is included in Appendix III.

In addition, it was noted by inspectors that signal detection activities performed by the previous service provider [redacted] did not include all sources of data. The quarterly signal detection activity for the three molecules [redacted] (covering the period October 2015 to June 2016), [redacted] (covering the period October 2015 to September 2016) and cetirizine (covering the period October 2015 to September 2016) only included a review of literature articles for signal detection purposes. There was no evidence that a review of cases within the safety database or any other safety relevant information, such as reference product comparisons, had been reviewed.

Torrent stated during the inspection that further resource to conduct signal detection had been sourced as of 30 March 2019 when the pharmacovigilance service agreement with the service provider Sciformix Technologies Pvt. Ltd. had been signed. The project plan with the service provider, which was not yet effective at the time of inspection, indicated that signal detection activities for all EU-authorised molecules would be completed by 30 September 2019.

Post-inspection request: As the finding is in relation to the failure to effectively resolve deficiencies in the pharmacovigilance system, Torrent is requested to provide MHRA assurance in the resolution of the failings relating to this critical pharmacovigilance activity. The lead inspector will supervise the completion of these activities through post-inspection CAPA updates until signal detection has been completed and relevant actions have been taken for all UK-authorised molecules.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

[redacted]	

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[redacted]

Finding MA.2 b)

In relation to the corrective and preventative actions that were implemented following the 2017 MHRA inspection, examples of incomplete or ineffective corrective and preventative actions were identified:

i. At the previous MHRA inspection, it was identified that PSURs for [redacted] and [redacted] had not been submitted as stipulated in the EURD list (refer to 2017 MHRA inspection finding MA.2 a). As a corrective action, Torrent committed to submitting the two PUSRs on a national basis to MHRA. Torrent attempted to submit the PSURs directly to MHRA on 11 April 2018 and 12 April 2018, respectively; however, the submissions were rejected as the PSURs were not being submitted via the PSUR repository.

It is acknowledged that Torrent contacted the MHRA Information Processing Unit following the rejection and had not received a reply; however, the lead inspector was not informed of the issues when Torrent provided status updates on CAPA implementation on 16 April 2018 and 15 June 2018. On both instances, the corrective action was marked as complete with a completion date of 13 April 2018.

ii. To address findings CR.1 a) and MA.6 a) of the 2017 MHRA inspection, global SOP [redacted] *Oversight of Pharmacovigilance Process* (version 01, date effective 30 June 2018) was implemented to define the mechanism for continuous monitoring and oversight of the service provider and affiliates by the global PV team to ensure compliance of the pharmacovigilance system. The procedure stated in section 7.5 *Monthly Oversight of Affiliates* that each Torrent affiliate should provide a monthly report on PV-relevant activities to the global PV team.

However, there were gaps in the provision of monthly oversight reports from Torrent affiliates to the global PV team:

- EU and Russian affiliates: No monthly reports had been received from these affiliates since July 2018.
- Malaysian affiliate: The monthly reports for October and November 2018 were cumulatively provided to the global PV team along with the report covering December 2018 in January 2019.
- US affiliate: The monthly reports for the period from November 2018 to February 2019 were cumulatively provided to the global PV team along with the report covering March 2019 in April 2019.
- Brazilian affiliate: The monthly report for February 2019 was provided to the global PV team along with the report covering March 2019 report in April 2019.

Although responses had not been received from the affiliates, no deviations were

raised, or the issue escalated senior management to resolve the non-compliance with Torrent's procedure.

Root Cause Analysis

[redacted]

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Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 c)

There was a delay of five months in documenting the late submission of the [redacted] PSUR on 23 November 2018 in a deviation record, thus resulting in a delay to investigate the root cause and implement corrective and preventative actions. It was identified on 21 November 2018 that the [redacted] PSUR had not been submitted by the required deadline of 09 November 2018; however, deviation D/APR/19/13 was only initiated on 23 April 2019 and signed off by the quality team on 25 April 2019.

Global SOP PV-025 *Procedure for Identification, Investigation, Reporting and Escalation of Non-Conformance/Deviation for Pharmacovigilance System and CAPA tracking* (version 02, date effective 19 December 2018) stated in section 7.3.1 that "For deviations related to pharmacovigilance relevant activities which are handled at affiliated location, respective department […] shall initiate deviation in Torrent's PV Quality Management system within 05 business days from date of detection […]."

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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the EU countries.
[redacted]

Finding MA.2 d)
There was a lack of procedural documentation which governed the tracking of regulatory submissions at the UK affiliate. Recent changes to the structure of the team had led to the centralised allocation of workload (as opposed to individual staff being responsible for certain projects/ molecules) and this had led to a change of how the team tracked submissions to the regulatory authority. While it was seen that the process was in place, it had not yet been formally documented in a controlled procedure. As per Commission Implementing Regulation (EU) No. 520/2012, Article 11(1) it is required that procedures are in place which govern critical pharmacovigilance processes.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

MA.3 Management and Reporting of Adverse Reactions

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.5. Quality management
"*Competent authorities and marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as […], data coding, […].*

Data entry staff should be instructed in the use of the appropriate standards and terminologies […]."

The following findings were noted in relation to management and reporting of adverse reactions:

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Finding MA.3 a)

There were deficiencies in the coding of reported events in the safety database. The line listing provided for the purposes of the inspection contained data extracted from the database at drug-event level including the MedDRA PT and SOC coded in the database for the reported event. A review of the line listing at PT level identified four event PTs that had been coded into three different SOCs for different cases:

PT	SOCs (primary SOC in *italic*)	Case ID
Dizziness	Cardiac disorders *Nervous system disorders* Vascular disorders	[redacted]
Neuroleptic malignant syndrome	General disorders and administration site conditions Injury, poisoning and procedural complications *Nervous system disorders*	[redacted]
Serotonin syndrome	Injury, poisoning and procedural complications Musculoskeletal and connective tissue disorders *Nervous system disorders*	[redacted]
Thrombotic thrombocytopenic purpura	*Blood and lymphatic system disorders* Skin and subcutaneous tissue disorders Vascular disorders	[redacted]

When searching for a low-level term (LLT) to code within the database, users were shown a selection screen which included all MedDRA LLTs which met the search criteria. Where an LLT had a primary and secondary SOC, the user was shown multiple rows, one per SOC. These rows were colour-coded to differentiate the primary from the secondary SOC; however, there were no instructions to detail which colours represented which SOC.

There were [redacted] other PTs which had been coded to more than one SOC within the database. This list was passed to the MAH for consideration of impact and is also presented

in Appendix IV.

During the inspection, Torrent were asked to perform a high-level impact assessment and confirmed that this coding error would impact on signal detection activities using signal frequency reports as these were coded by SOC. The threshold applied to the frequency reports was defined by the number of events received. If events were split across multiple SOCs, this might impact upon the MAH's ability to identify signals through the signal frequency reports.

In addition, this issue will impact upon the placement of PTs in PSUR cumulative summary tabulations and thus impair Torrent's ability to comply with Commission Implementing Regulation (EU) No. 520/2012), Article 11(1)(d) to ensure the quality, integrity and completeness of the information submitted on the risks of medicinal products.

Post-inspection request: As part of the responses to the inspection report, Torrent should conduct a full impact assessment in relation to the following:

- All signal detection activities that have been performed in-house since 01 March 2017 for UK-authorised molecules;
- All PSURs written and submitted for UK-authorised molecules since 01 January 2017.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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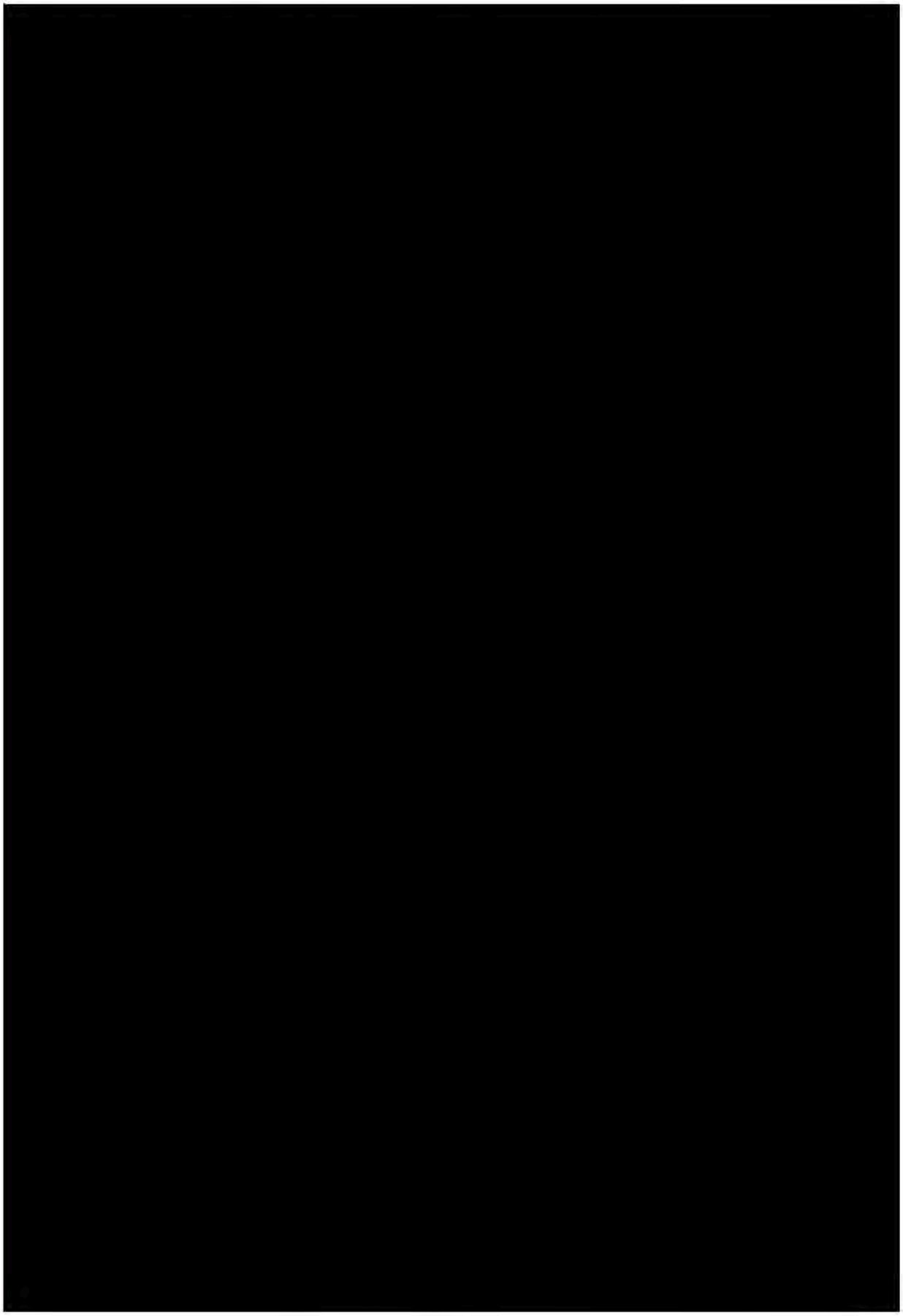

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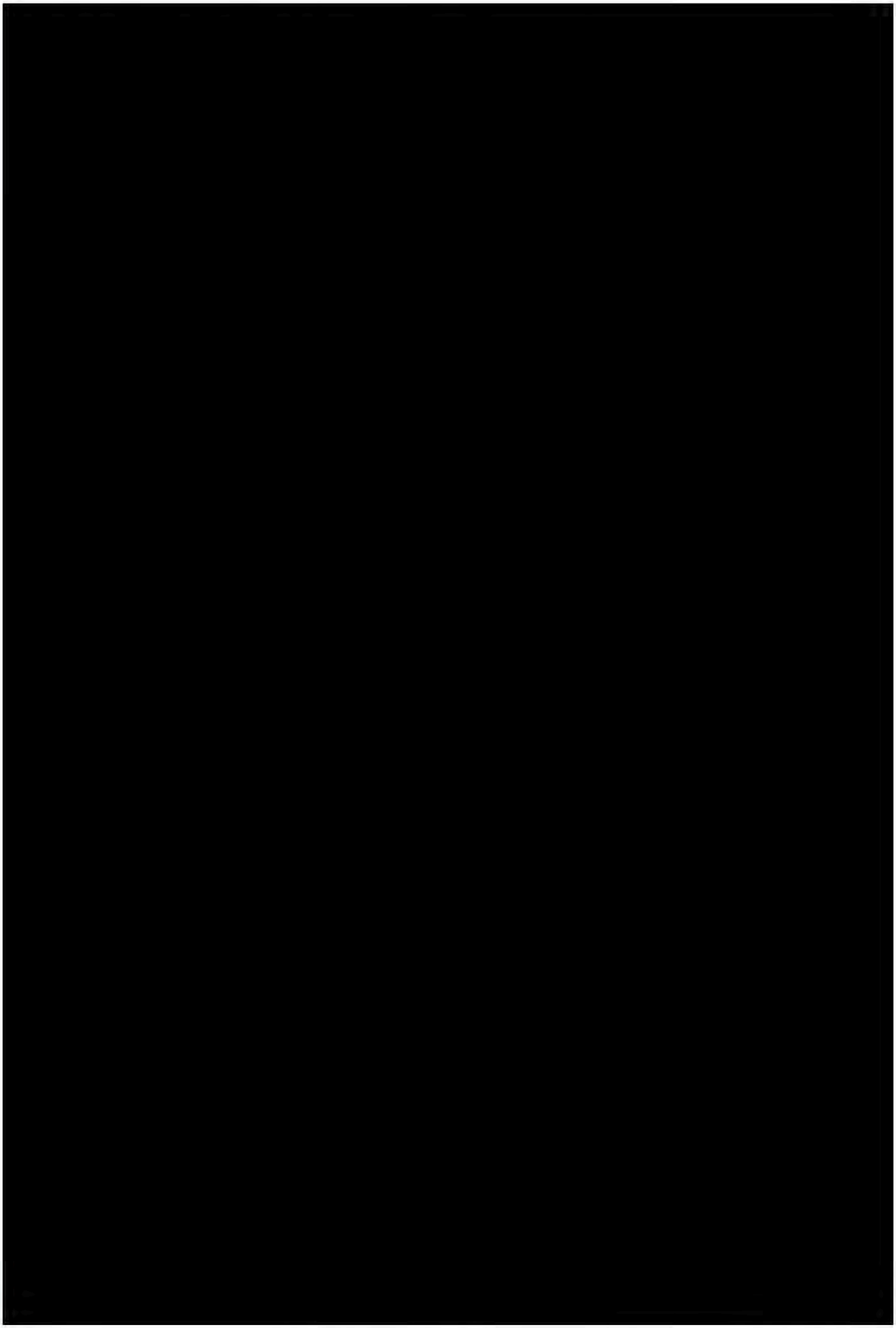

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

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Finding MA.3 b)
There were no procedures which governed the process of adding, changing or removing entries for the company products dictionary (CPD) used to code drugs in the safety database. Several examples were identified in the current CPD (dated August 2018) as well as the legacy CPD of misspelled active substances and where combination products had been entered using different standards. The examples have been included in Appendix V of the inspection report. As a result, there is the potential for cases to be missed when retrieving data from the safety database based on the active substance entered as a free-text search term in the search tool fur the purposes of signal detection and PSUR compilation. For signal frequency reports, global [redacted] *Global AER Database Operations and ICSR Processing Conventions* (version 7, date effective 17 September 2018) instructed users to "enter active substance name or multiple active substance names as well as combinations of both". The job aid for PSURs titled "Job Aid" (version 2.0, signed 16 July 2018) stated users should run a search for the active substance. For fixed combination products, users should run separate searches for both products and manually extract any cases for the combination product. **Post-inspection request:** As part of the responses to the inspection report, Torrent should consider the impact of having an uncontrolled product dictionary. The impact assessment should specifically include the number of cases attributed to the various spellings and standards used to describe the same active substance and address the impact this has had on signal detection activities and PSUR production.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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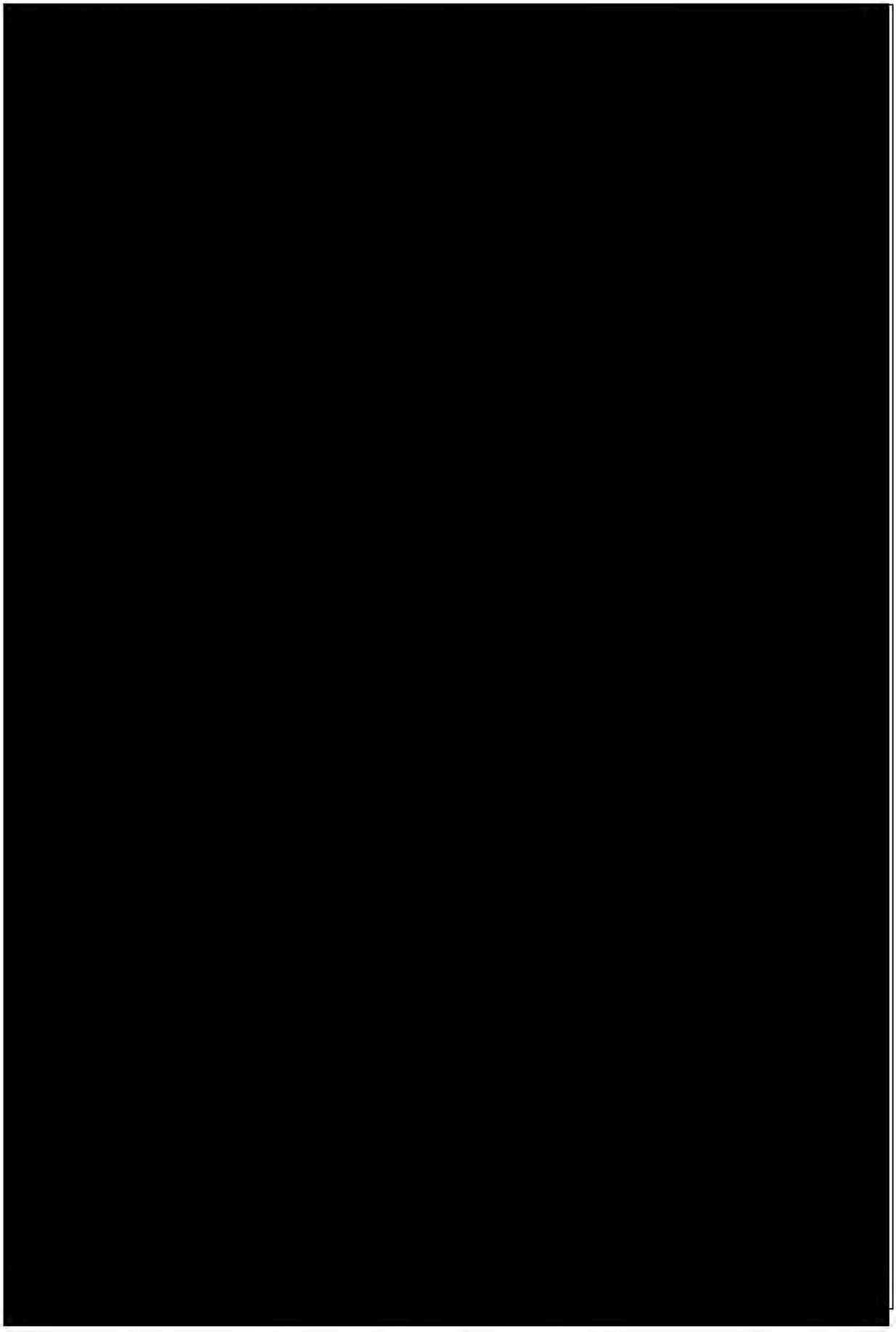

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

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MA.4 Signal Management

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 18(2)
"*Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database.*"

Article 18(3)
"*Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information.*"

Module IX – Signal management (Rev 1)
IX.C.3.2. Periodicity of monitoring
"*It is recommended to monitor EudraVigilance data at least every 6 months. A more frequent monitoring is recommended for active substances contained in medicinal products included in the additional monitoring list in accordance with Article 23 of Regulation (EC) No 726/2004 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS).*"

The EMA Signal detection in EudraVigilance pilot started on 22 February 2018 and MAHs are required to monitor EudraVigilance for signal detection purposes at least every 6 months for all products that are included in the pilot.

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Torrent's portfolio contained four UK-authorised molecules which were part of the signalling pilot. For two of the products, [redacted] and [redacted] the requirement for signal detection in EudraVigilance began in February 2018 with the start of pilot. The requirement to monitor EudraVigilance for [redacted] began in May 2018 when the marketing authorisation for [redacted] was approved in the UK. The fourth molecule included in the pilot, [redacted] received marketing authorisation in the UK in February 2019.

The following deficiency was seen in relation to Torrent's signal detection activities in EudraVigilance:

Finding MA.4 a)

Torrent did not monitor EudraVigilance for signal detection purposes for three out of four UK-authorised molecules [redacted] which were part of the EMA Signal detection in EudraVigilance pilot, until March 2019.

In March 2019, a 6-month report with the data lock point (DLP) of 28 February 2019 (covering the period from September 2018 to February 2019) was reviewed. Consequently, the data from February to September 2018 had not been reviewed for [redacted] and [redacted] and the data from May to September 2018 had not been reviewed for [redacted] as per Torrent's obligations.

Root Cause Analysis

[redacted]

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Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

MA.5 Collection of Safety Information

Requirements:

Directive 2001/83/EC as amended
Article 107(1)
"*Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.*"

Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.1. Collection of individual safety reports
"*Competent authorities and marketing authorisation holders should take appropriate measures to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources.*"

VI.B.4. Data management
"*When transfer of pharmacovigilance data occurs within an organisation or between organisations having set up contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.*"

At the previous MHRA inspection in 2017, significant deficiencies had been identified in relation to the collection of safety information from medical enquiries and to the mechanisms in place to ensure that all safety information was received from commercial partners. As a preventative action, Torrent had introduced a number of reconciliation activities between the global PV team, Torrent affiliates and commercial partners to ensure the receipt of all safety information; however, the following findings were identified in relation to the collection and collation of safety information:

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Finding MA.5 a)

Medical enquiry [redacted] was received by the UK affiliate on 17 September 2018 and contained the adverse event of "putting on weight" whilst taking [redacted] however, the report had not been sent to the global PV team and the service provider for entry into the safety database and reporting to EudraVigilance. The report contained the minimum reporting criteria and thus qualified for expedited reporting to EudraVigilance.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted].

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

Preventative Action(s)

[redacted]

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

Finding MA.5 b)

Periodic reconciliation of medical enquiries was not performed between the UK affiliate and the global PV team as per the local UK procedure [redacted] *Processing of adverse drug event reports from customers* (revision 03, date effective 26 May 2018) from 14 January 2019 to April 2019.

The SOP stated in section [redacted] *Reconciliation of safety information* that "TPUK will reconcile all safety information including AEs, other special situations, product complaints and medical enquiries forwarded to the Global PV Team with the latter on a weekly basis."

Prior to the inspection, Torrent reviewed all medical information enquiries received by the UK affiliate between 01 November 2017 and 25 April 2019 in relation to safety information. During the review, one medical enquiry [redacted] was identified, which had been received on 14 January 2019 and contained a report of vision problems for candesartan. The report was entered into the safety database on 25 April 2019 [redacted] As the report was received via an anonymous letter, no patient identifiers were available, and the case did not qualify for expedited reporting to EudraVigilance.

However, the cumulative review failed to identify all medical enquiries received during this period and which contained safety information that had not been reported (see finding MA.5 a).

No deviation was raised in relation to the missed weekly reconciliation of medical enquiries received by the UK affiliate from 14 January 2019 to April 2019 to investigate the root cause and implement corrective and preventative actions.

Root Cause Analysis

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[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.5 c)

Following a major finding at the 2017 MHRA inspection, Torrent initiated a project to implement SDEAs and/ or update technical agreements with commercial partners to ensure the transfer of all safety information. The following deficiencies were noted in relation to reconciliation activities between Torrent and distributors outside of the EU for products that were also authorised in the UK.

i. No retrospective reconciliation had been performed with the following distributors to ensure that all safety information had been received in the period prior to implementation of the respective SDEAs:

- [redacted] The distribution agreement had been in place since 07

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December 2017 and the SDEA became effective on 01 January 2019.

- [redacted] The distribution agreement had been in place since 01 August 2018 and the SDEA was signed on 25 October 2018.

ii. No reconciliation had taken place in February and March 2019 with [redacted] and [redacted] even though the SDEAs with both distributors stipulated a monthly reconciliation with Torrent.

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.5 d)

No responses had been received from the responsible persons for commercial partners in the following territories after reconciliation had been initiated by the global PV team on 22 October 2018, 02 February 2019 and 08 April 2019:

- UK
- Europe
- USA
- India and ROW

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For Brazil, no response had been received to the requests sent by the global PV team on 22 October 2018 and 02 February 2019.

Global [redacted] *Handling of Safety Data Exchange Agreements (SDEAs)* (version 04, date effective 03 May 2018) stipulated that a quarterly reconciliation between the global PV team and the responsible persons for commercial partners should take place so that the PV team had a complete list of all commercial partners with whom reconciliation was required. The completed Attachment 1 (undated) of [redacted] stated that information would be requested from representatives for the UK, Europe, USA, India and ROW, Brazil and Mexico.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

To perform a reconciliation with all the responsible counterparts related to existing partners.

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

Preventative Action(s)

[redacted]

[redacted]	

MA.6 Provision of information to enable supervision by national competent authorities

Requirements:

Regulation (EC) No. 726/2004 as amended
Article 57(2)
"*[…] For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union. To this effect the following measures shall be taken: […]*

(b) marketing authorisation holders shall, by 2 July 2012 at the latest, electronically submit to the Agency information on all medicinal products for human use authorised in the Union, using the format referred to in point (a);
(c) from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a)."

Commission Implementing Regulation (EU) No. 520/2012
Article 3
"*The pharmacovigilance system master file shall have an Annex containing the following documents:*
(1) a list of medicinal products covered by the pharmacovigilance system master file, including the name of the medicinal product, the international non-proprietary name (INN) of the active substance(s), and the Member State(s) in which the authorisation is valid; […]."

National competent authorities (NCA) have an obligation to supervise MAHs to ensure that legal requirements governing medicinal products are complied with. Information provided by MAHs to NCAs should be complete and accurate in order to facilitate the supervisory duty of the NCA. This could include information submitted to the database provided for in Regulation (EC) No. 726/2004 as amended, Article 57(1), or information included in the PSMF.

The following findings were noted in relation to provision of information to NCAs.

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Finding MA.6 a)

The following inaccurate data were noted in relation to the information submitted by the MAH to the Article 57 database:

i. The Article 57 database contained the following additional PSMFL numbers that were registered to different Torrent affiliates even though Torrent only had one PSMF in place [redacted]

- [redacted] – Heuman Pharma GmbH
- [redacted] – Torrent Pharma Ltd.

ii. Examples of UK-authorised products, for which Torrent Pharma UK Ltd. was the MAH, were identified in the Article 57 database which had been registered to the incorrect and/ or multiple PSMFL number(s) even though they were covered by the pharmacovigilance system registered under PSMFL 3393:

MA number	Product	Associated PSMFL number

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[redacted]

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]	

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Finding MA.6 b)
PSMF annex H (version 08.02, dated 24 April 2019) did not contain the following UK-authorised products: [redacted] All products received marketing authorisation from the MHRA on 14 March 2019 and were included in this pharmacovigilance system.
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]	

C.4.4 Comments

It was seen during the inspection that products with the same active substance, but which were authorised in different EU countries under different MAHs (e.g. different Torrent affiliates or Torrent and a co-licensing partner) and authorisation routes had separate RMPs with varying version numbers.

Torrent are reminded that in accordance with Commission Implementing Regulation, Article 30(2) the RMP is a document written at an active substance level and GVP V.B.3. states "It is recommended, where appropriate, that the RMP document includes all relevant medicinal products from the same applicant/marketing authorisation holder containing the same active substance(s)". If products are authorised in multiple territories and through different authorisation routes, it is expected that mechanisms are in place to align the RMPs across territories and procedures where possible.

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.

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In relation to finding MA.2 a), the MAH provided progress reports on the completion of signal detection activities on 30 August and 30 September 2019. Additional information and records of signal detection activities were requested on 15 October 2019. These included the schedule for signalling activities, evidence of completed signal detection activities for [redacted] and [redacted] and the signal detection tracker, signal assessment reports and any further records demonstrating the actions taken for the respective identified signals for [redacted] and [redacted]. The MAH provided this information on 23 October 2019 and a follow-up call took place on 15 November 2019.

Following review of the provided documentation, it was noted that out-of-date reference safety information (RSI) was used for signal detection activities.

As an example, signal detection conducted for [redacted] on 04 June 2019 (covering the period 01 May 2018 to 30 April 2019) used the UK SmPCs for [redacted] Concentrate for Solution for Infusion [redacted] dated 26 March 2013) as the RSI. However, all three marketing authorisation licences were cancelled on 15 March 2019 following transfer of ownership from Aptil Pharma to Torrent. In addition, the SmPC had also been updated with safety information following a PRAC signal regarding osteonecrosis of the jaw in August 2018.

It is recommended that the MAH reviews its processes to ensure that the most recent Torrent RSI for the respective molecule is used for signal detection activities.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- 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).
- CPMP/ICH/3945/03: E2D “Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting”.
- CPMP/ICH/5716/03: E2E “Pharmacovigilance Planning”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 20658/13766-0003	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Torrent Pharma GmbH	**DATE**	29 April 2019
LOCATION	Nexus Building, 4 Gatwick Road, Crawley, RH10 9BG	**START TIME**	09:00 arrival for 09:30 opening meeting

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system and the quality system. The presentation should also include any changes to the pharmacovigilance system since the last inspection (other than CAPA from the previous inspection). *(approx. 20 minutes)*	[redacted]	[redacted]
ICSR management, including but not limited to • CAPA deliverables from the previous MHRA inspection, including case processing, assessment and submission to EMA • Database configuration *The live database should be made accessible during this session.*	[redacted]	
[redacted]		

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MHRA INSPECTION NUMBER	Insp GPvP 20658/13766-0003	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Torrent Pharma GmbH	**DATE**	30 April 2019
LOCATION	Nexus Building, 4 Gatwick Road, Crawley, RH10 9BG	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**

Sources of safety information, including but not limited to
• CAPA deliverables from the previous MHRA inspection, including
  ○ Medical information and product quality complaints
  ○ Literature
  ○ Safety data exchange with affiliates, licensing partners and distributors
• EVWeb
	[redacted]	[redacted]

Risk management, including but not limited to
• CAPA deliverables from the previous MHRA inspection, including
  ○ Update, maintenance and implementation of reference safety information
  ○ Maintenance of RMPs
  ○ Additional risk minimisation measures
• Signal detection and management
	[redacted]	[redacted]

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Section 43	***Oversight of the pharmacovigilance system**, including but not limited to*
	• *CAPA deliverables from the previous MHRA inspection, including*
	  ○ *QPPV and MAH oversight of the PV system, vendors and business partners*
	  ○ *Maintenance of the PSMF*
		[redacted]	[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 20658/13766-0003	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Torrent Pharma GmbH	**DATE**	01 May 2019
LOCATION	Nexus Building, 4 Gatwick Road, Crawley, RH10 9BG	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Quality management system, including but not limited to • Pharmacovigilance audits • Management of non-compliance through deviations and CAPA	[redacted]	[redacted]
Periodic safety update reports	[redacted]	

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MHRA INSPECTION NUMBER	Insp GPvP 20658/13766-0003	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Torrent Pharma GmbH	**DATE**	02 May 2019
LOCATION	Nexus Building, 4 Gatwick Road, Crawley, RH10 9BG	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review and ad-hoc questions	-	As required
Closing meeting	[redacted]	All welcome

APPENDIX III LIST OF MOLECULES WITH OUTSTANDING SIGNAL DETECTION

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APPENDIX IV LIST OF PTs ASSOCIATED WITH MORE THAN ONE SOC

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PT	SOC 1	SOC 2
[redacted]		

Section 43

PT	SOC 1	SOC 2
[redacted]		

Section 43

PT	SOC 1	SOC 2
[redacted]		

APPENDIX V MULTIPLE SPELLINGS OF DRUGS IN THE COMPANY PRODUCTS DICTIONARY

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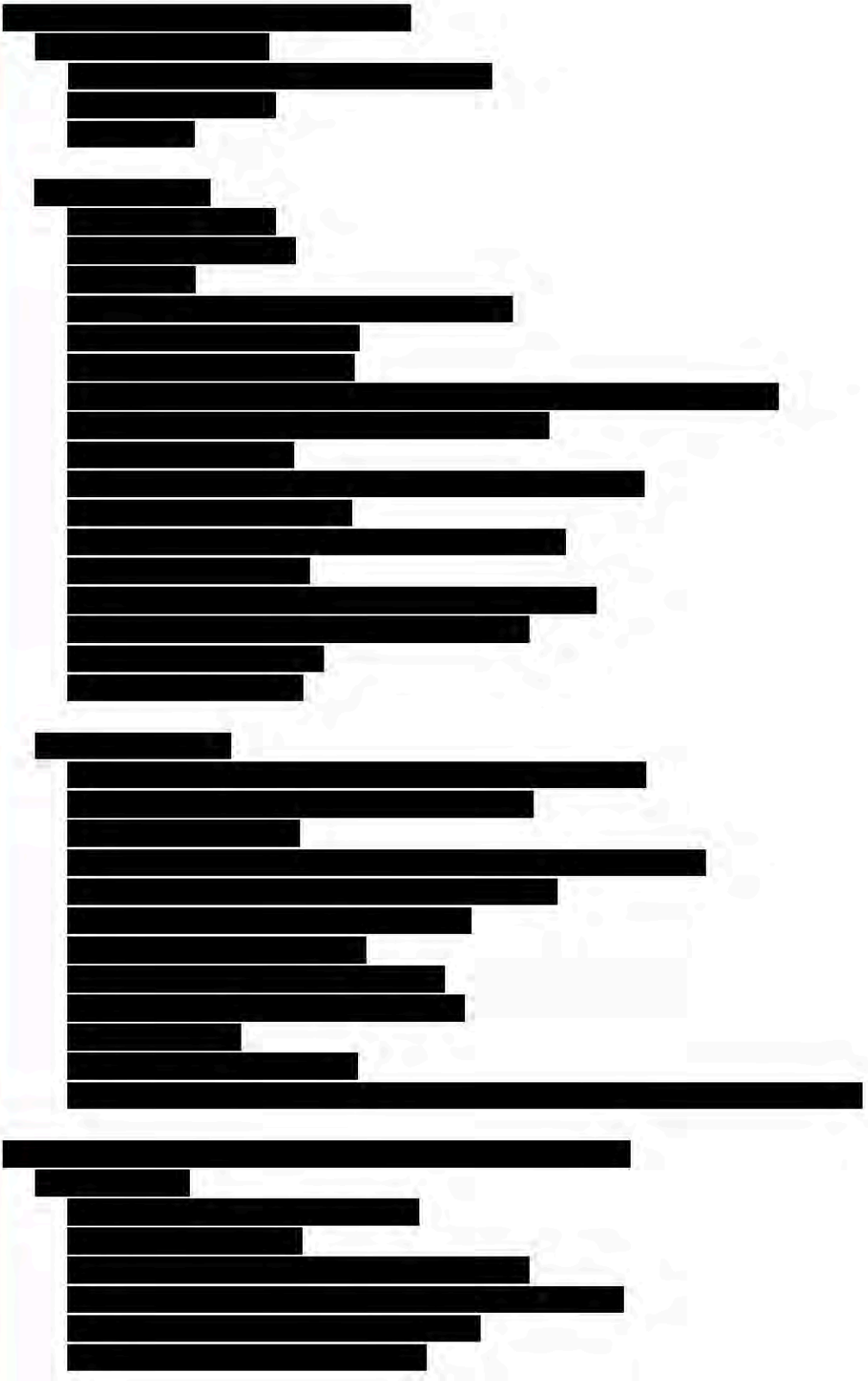

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[redacted]

APPENDIX VI PTS PRESENTED IN MORE THAN ONE SOC IN PSUR SUBMITTED (SINCE 01-JANUARY-2017 UNTIL 30-APRIL-2019)

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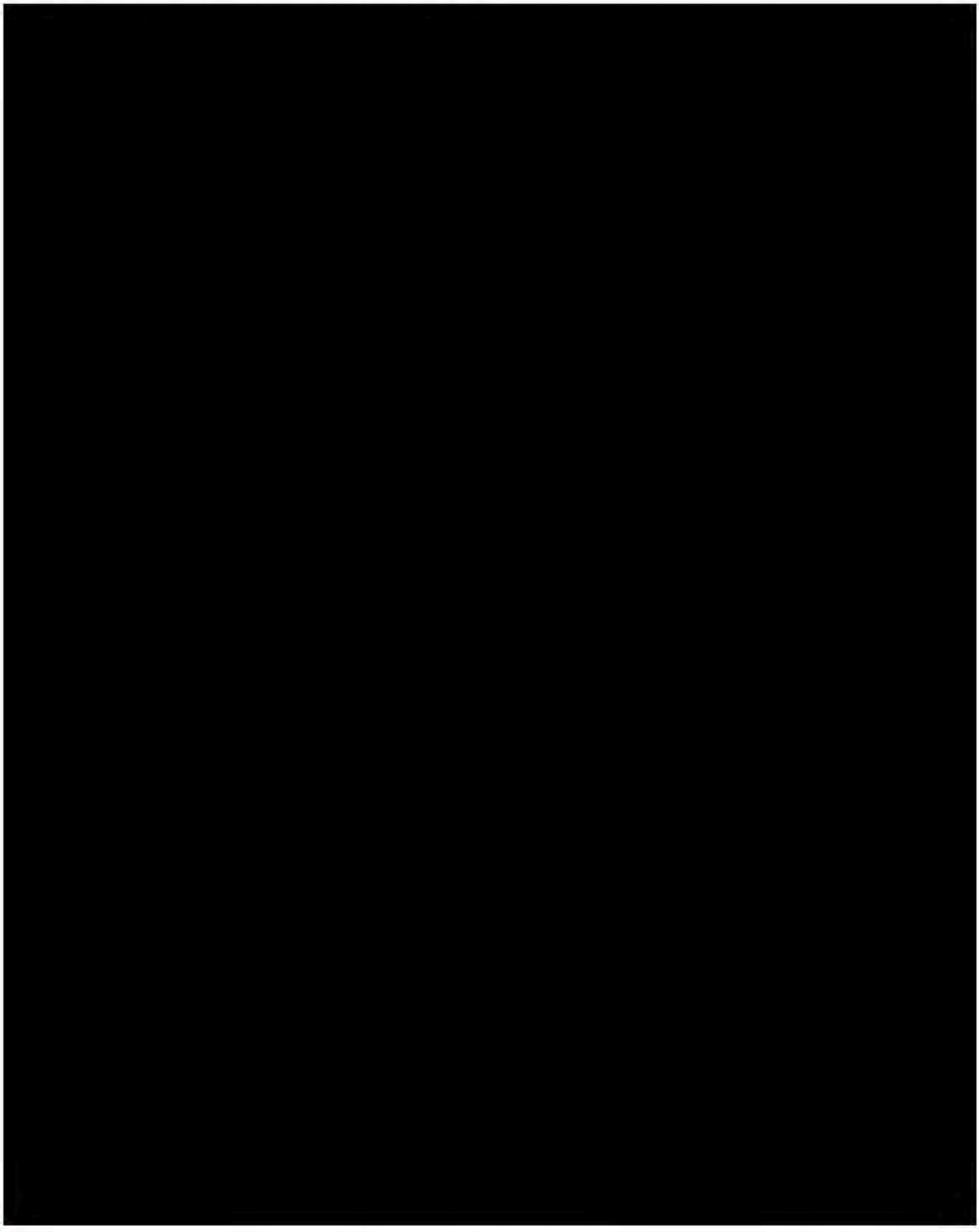

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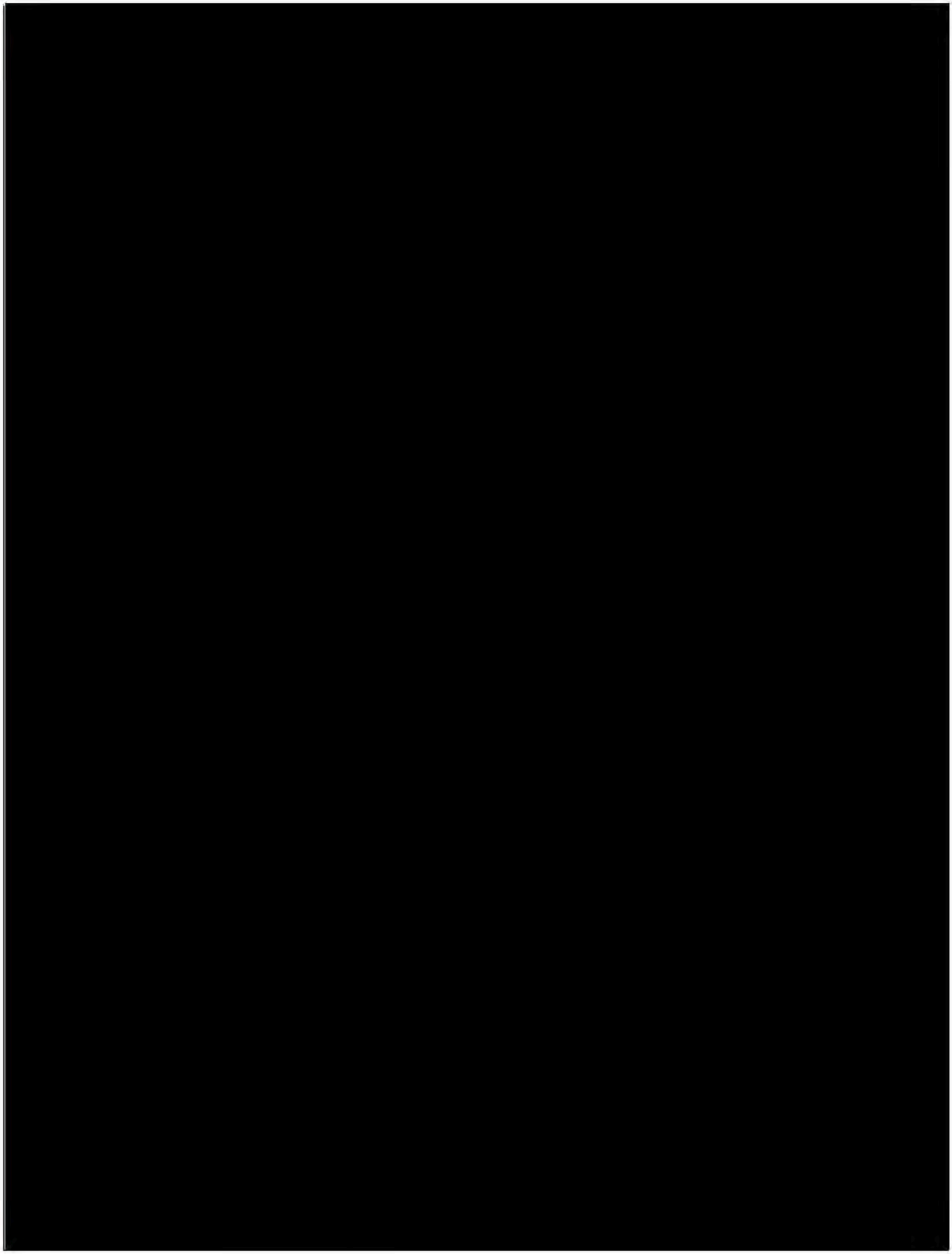

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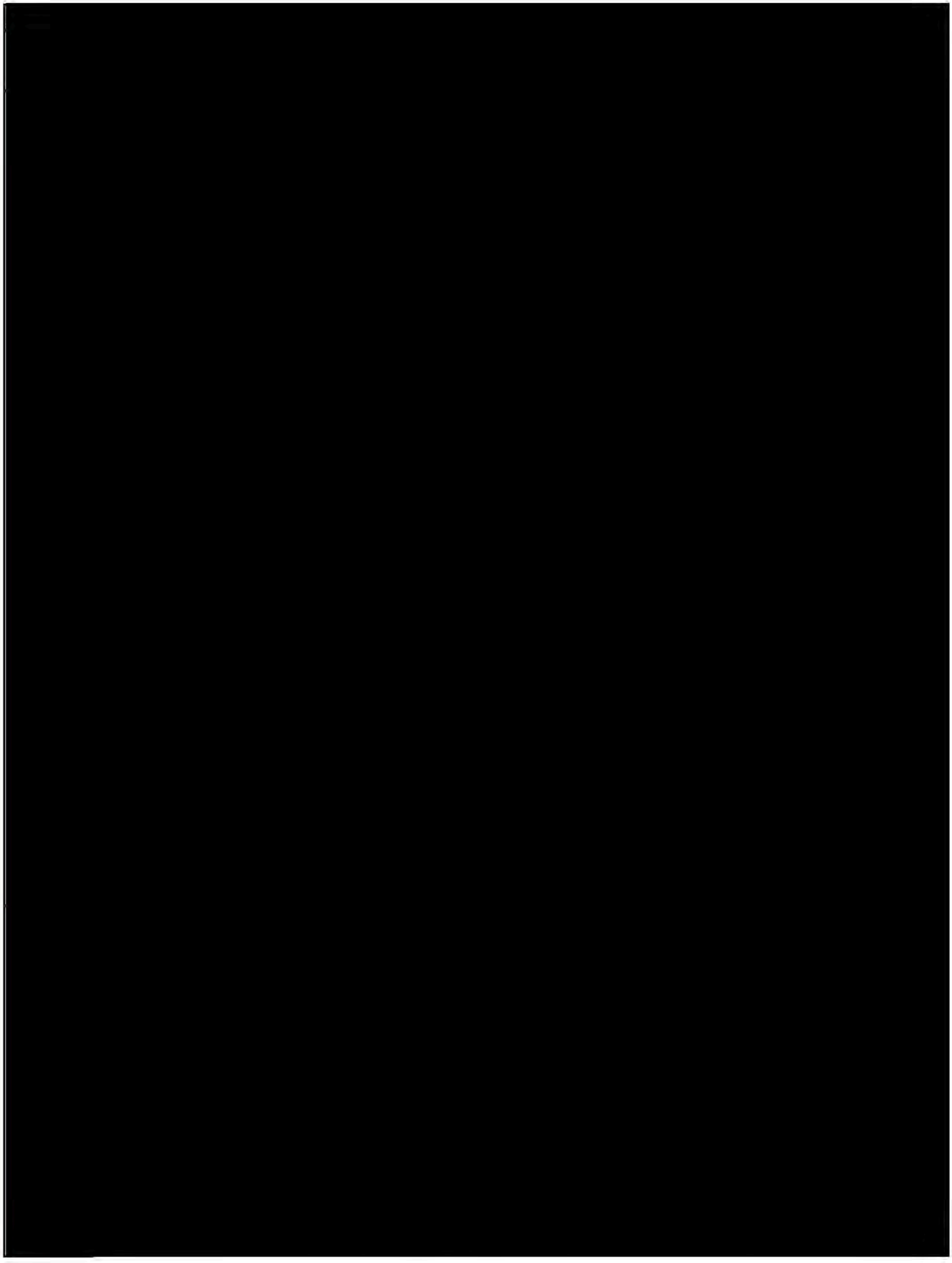

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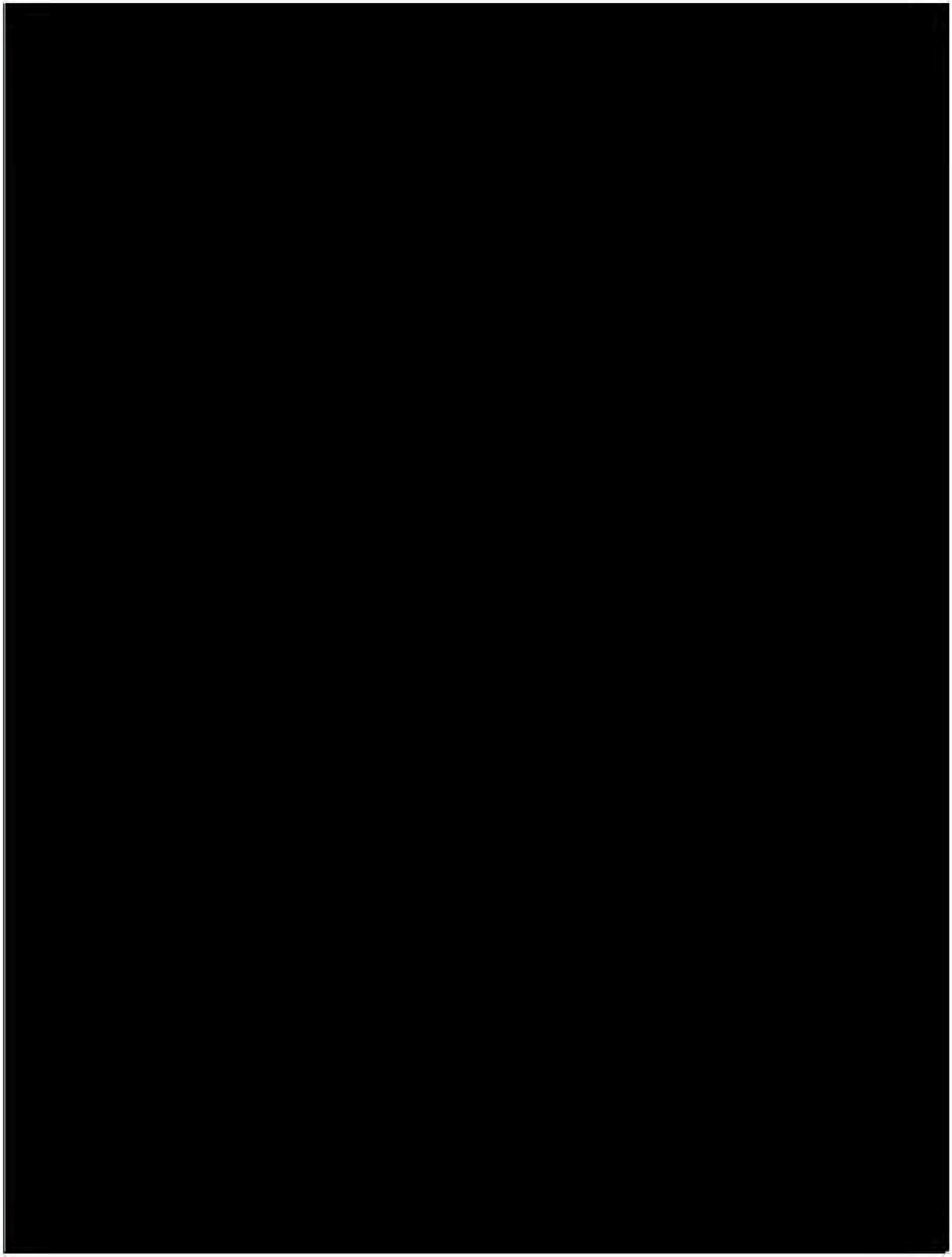

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