Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Max Remedies Limited

MHRA Inspection Number: Insp GPvP 20894/14038-0015

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ABBREVIATIONS

CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
NAP	Nationally Authorised Product
NCA	National Competent Authority
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
SmPC	EU Summary of Product Characteristics
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Max Remedies Limited (MFL1508)
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	Remote inspection conducted on 22 April, 06 May and 14 May 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	n/a
Previous inspection date(s):	02 December 2010
Purpose of inspection:	Triggered inspection of pharmacovigilance systems to review compliance with UK and EU requirements in relation to the maintenance of the reference safety information.
Products selected to provide system examples:	The product information, submission of safety variations and PIL into pack implementation was reviewed for nationally-authorised [redacted]
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Microsoft Excel (commercially available software).
Key service provider(s):	Not applicable – all pharmacovigilance activities are performed by the MAH.
Inspection finding summary:	1 Critical finding 3 Major findings 1 Minor findings
Date of first issue of report to MAH:	22 June 2020
Deadline for submission of responses by MAH:	27 July 2020 10 September 2020 10 November 2020
Date(s) of receipt of responses from MAH:	15 July 2020 19 August 2020 27 August 2020 28 October 2020
Date of final version of report:	29 October 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

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Max Remedies Limited was selected for inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme due to intelligence received by the Inspectorate from within the Agency that the product information of [redacted] was missing important safety information on metabolic acidosis and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in line with a CMDh recommendation published on 03 January 2018 following conclusion of procedure PSUSA/00010345/201702.

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.

Max Remedies Limited (hereafter 'Max Remedies') is a UK-based MAH and a subsidiary of [redacted] Brunel Healthcare. IVC Brunel Healthcare also owns a worldwide network of manufacturing sites. Max Remedies product portfolio is covered by the pharmacovigilance system operated by Brunel Healthcare Manufacturing Limited (hereafter 'Brunel'), a further subsidiary of [redacted] Brunel Healthcare. All pharmacovigilance activities are carried out by the QPPV and the QPPV back-up.

Products in the pharmacovigilance system include nationally authorised licences for loperamide, ibuprofen, paracetamol and paracetamol combination products for which Max Remedies is the MAH. The pharmacovigilance system also covers several licences for traditional herbal products for which Brunel is the MAH.

B.2 Scope of the inspection

The inspection included a review of the local (UK) pharmacovigilance systems and was performed remotely over 2.5 days on 22 April, 06 May and 14 May 2020. The inspection was predominantly performed via document review; however, personnel involved in pharmacovigilance and manufacturing activities were available via teleconference throughout the inspection for ad-hoc queries.

The inspection focused on routine risk management through the maintenance of authorised product information, i.e. SmPCs and PILs, and the quality management system supporting these activities. Topics in relation to data management, including the collection, collation and reporting of ICSRs, signal management and aggregate reporting 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 PSMF (v14.0, dated May 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. The detail of these requests is contained within document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Pharmacovigilance Inspection Plan (attached as Appendix II). 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 via teleconference on 14 May 2020.

On 15 May 2020, the MAH provided additional information regarding one of the findings reported in the closing meeting (see finding MA.2 a)).

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 2010, the company had made the following changes to the pharmacovigilance system:

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- In 2013, Max Remedies was acquired by [redacted], the owner of Brunel, and subsequently all pharmacovigilance activities were integrated into the Brunel pharmacovigilance system.
- In 2016 Brunel was acquired by [redacted] and a temporary agreement was in place to maintain Max Remedies pharmacovigilance activities within Brunel until 2017 when Max Remedies was also acquired by [redacted]
- The EU QPPV changed from [redacted] in October 2013.

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

CR.1 Periodic Safety Update Reports

Requirements:

Directive 2001/83/EC as amended
Article 23(3), stating that the MAH "*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.*"

Article 107b, describing the requirement to submit PSURs to the EMA

Article 107c, describing the frequency of PSUR submissions

Article 107g(2), stating that in "*the event of a variation, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a modification […].*"

EMA Post-authorisation procedural advice: questions and answers
Question 31. How shall I implement the outcome of a PSUSA procedure?
"*For PSUSAs of NAPs, for which a CMDh position was adopted by consensus or majority (EC Commission Decision), a timetable for submission of the variations which is applicable for all affected products, including those that are not listed in the annex to the decision, is published on the EMA website.*"

After a marketing authorisation is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long-term use, to confirm that the risk-benefit balance remains favourable. Periodic Safety Update Reports (PSURs) provide a comprehensive, concise and critical analysis of the current understanding of the benefit-risk profile of a product taking into account new or emerging information in the context of cumulative information on risks and benefits. The PSUR is therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of a product.

Max Remedies failed to submit PSURs for two active substances in its portfolio and this is considered to be a serious violation of applicable legislation and guidelines; consequently, a critical finding has been reported.

The finding was identified as the MAH had not submitted safety variations to implement the outcome of two PSUSA procedures (see finding CR.1 b)) and had stated during the inspection opening meeting that they were not notified of the procedure outcomes as they were not required to submit PSURs for any of their products.

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Finding CR.1 a)
Max Remedies had failed to author and submit the following PSURs for [redacted] and [redacted] • The PSUR for [redacted] due to be submitted in procedure [redacted] by 19 May 2017.

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In line with the 3-yearly PSUR submission cycle, the next PSUR was due to be submitted by 18 May 2020 (procedure [redacted]); however, at the beginning of the inspection the MAH had not yet authored or submitted this PSUR. The MAH subsequently prepared and attempted to submit the PSUR on 12 May 2020, but the PSUR was not yet included in the PSUR repository at the time of the closing meeting. Subsequently, the lead inspector advised the MAH to follow-up with the EMA and the PSUR was successfully submitted on 02 June 2020 before the procedure started.

- The PSUR for loperamide due to be submitted in procedure [redacted] by 29 August 2018.

At the time of the inspection, the MAH held three marketing authorisations for [redacted] and one marketing authorisation for [redacted] which were authorised under Article 10(c). They were thus not exempt from the requirement to submit PSURs in the EU.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

[redacted]	

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Finding CR.1 b)
Max Remedies had failed to submit variations to the MHRA to implement the outcome of PSUSA procedures for [redacted] • Following conclusion of procedure [redacted] the PRAC concluded that the product information for [redacted] should be varied to implement safety warnings regarding metabolic acidosis and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in SPC section 4.4 and 4.8 and the corresponding PIL sections. The outcome was published by CMDh on 03 January 2018 and the safety variation was due to be submitted by 21 February 2018. Max Remedies marketed the product [redacted] until December 2018. The omission was internally identified at the MHRA at the end of January 2020, following which the GPvP inspectorate issued a letter to the MAH highlighting the issue in February 2020. The MAH subsequently submitted a safety variation to MHRA to include the missing wording on 03 March 2020. • Following conclusion of procedure [redacted] the PRAC concluded that the SmPC section 4.4 and 4.9 for [redacted] should be varied to include additional warnings regarding QRS complex prolongation. The corresponding CMDh position was published on 13 March 2019 and the safety variation was due to be submitted by 15 May 2019. The omission was picked up by the MHRA assessor reviewing a different safety variation for loperamide submitted on 08 July 2019 to include PRAC recommended wording on Brugada syndrome. The assessor proactively included the missing wording of the PSUSA outcome as only the SmPC was affected and informed the MAH of this in the approval letter issued on 07 August 2019.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

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

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, 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.*"

Volume 2 EudraLex, Pharmaceutical Legislation: Notice to Applicants. Volume 2A - Procedures for marketing authorisation, Chapter 1 Marketing Authorisation (Revision 11, July 2019)
5.1.1 Continuous update of marketing authorisation
"*In this regard, marketing authorisation holders of marketing authorisations granted in accordance with Article 10 or 10c of Directive 2001/83/EC should introduce variations swiftly whenever the marketing authorisation of the reference medicinal product or of the "original" medicinal product is changed to address a safety or efficacy concern.*"

When new information about the benefits and risks of a product becomes 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 findings were noted in relation to control and maintenance of reference safety information.

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Finding MA.1 a)
The MAH did not amend the product information of its [redacted] licences in line with the outcome of an Article 31 referral [redacted] for [redacted] and [redacted] containing medicines that was published on 22 May 2015. The outcome of the referral included amendments to SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 to include updated safety wording on the small increased risk of cardiovascular problems associated with the use of high-dose [redacted] and on drug-drug interactions with aspirin. Associated changes were also required in PIL section 2 *What you need to know before you take […]*. The deadline for submission of the [redacted] variation by the MAH was 16 October 2015. At the time of the inspection, none of the Max Remedies [redacted] products were marketed; however, [redacted] was marketed in the UK from November 2015 to December 2018 and during this time the SmPC and PIL were missing the updated safety information.
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]

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

Finding MA.1 b)

Since November 2016, there was no process in place for comparison of the product information with that of the "original" medicinal product as a means of identifying whether the product information required update with new safety information as stipulated in Volume 2A - Procedures for marketing authorisation.

At the time of the inspection, Max Remedies held one product licence for [redacted] ~~and three product licences for paracetamol~~ [redacted] ~~which were~~ *was* authorised under Article 10(c) (informed consent application) and were marketed in the UK *and for which the "original" medicinal product was still authorised. It is noted that the product information of this product was aligned with that of the "original" medicinal product.*

~~A comparison of the SmPC and PIL of the marketed product~~ [redacted] ~~with the product information (dated 25 November 2019) of~~ [redacted] ~~was carried out the inspector. The review identified that the following information was missing in the product information of the Max Remedies product:~~

- ~~drug-drug interaction with chloramphenicol in SPC section 4.5 *Interaction with other medicinal products and other forms of interaction*~~

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- ~~methemoglobinemia in SPC section 4.8 *Undesirable effects*~~

[redacted] ~~was chosen for comparison as this product was used by the MAH as the comparator prior to November 2016. The product licence of the original medicinal product~~ [redacted] ~~had been cancelled.~~

Note added by lead inspector on 27 October 2020: This finding was amended following consultation with the MHRA Vigilance and Risk Management of Medicines Division and Licensing Division to remove the example for paracetamol. As the "original" medicinal product for these licences granted under Article 10(c) was cancelled, the MAH is not required to choose a different medicinal product with which to align the product information of their products. The excluded examples appear now as struck through in the finding. Text added for context appears in italic.

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

Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	[redacted]
[redacted]	[redacted]

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[redacted]

Finding MA.1 c)
There was a slight delay of 26 days in the submission of a safety variation for [redacted] to the MHRA to implement PRAC recommended wording on serious cardiac events in SmPC section 4.4 *Special warnings and precautions* for use, 4.9 *Overdose* and 5.3 *Preclinical safety data* and corresponding sections in the PIL. The PRAC recommendation was published on 04 April 2017 and the variation was to be submitted within two months, i.e. by 04 June 2017, but the MAH only submitted the variation on 29 June 2017. During the inspection, the MAH stated that they had identified the PRAC recommendation at the beginning of May and that this was the date from which they had calculated the deadline for variation submission.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

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[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MA.2 Record management

Requirements:

Commission Implementing Regulation EU No. 520/2012
Article 12
"*1. […] Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents […].*" (emphasis added)

"*2. […] Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires.*"

Competent Authorities may request source data relating to pharmacovigilance activities extending over some period of time. The authorities need to know that the data can be accessed, will be readable and can be easily retrieved. The following deficiencies relating to record management were noted.

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Finding MA.2 a)

During the inspection Max Remedies was unable to provide the records showing that the MHRA was contacted and had agreed to an extension of the deadline beyond 31 December 2016 to implement the updated PIL and labelling of [redacted] products which included the optimised posology for paediatric patients.

MAHs of [redacted]-containing products were instructed by the MHRA to submit a [redacted] variation by 30 September 2016 to amend the relevant marketing authorisations in line with the optimised posology for paediatric patients. The updated product information was to be incorporated in packs at the next production run and by 31 December 2016 at the latest.

Max Remedies submitted the relevant [redacted] variation within the required deadline and the variation was granted on 14 December 2016. At the time, Max Remedies marketed several GSL [redacted] products [redacted] and between 31 December 2016 and 14 June 2017 a total of 3,552,528 packs in 65 batches containing the superseded dosage recommendations were QP-certified.

Only a day after the closing meeting, the MAH provided the e-mail records showing that the MHRA had been contacted and extension had been agreed until 14 June 2017 to implement the PIL and labelling stating the updated dosage recommendation in packs.

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.2 b)
The MAH did not have any records which detailed the legal basis of application for their products. Consequently, this impacted on Max Remedies' ability to determine whether

PSURs were required for their products (see finding CR.1 a)) and to submit the correct information on their products in the Article 57 database (see finding MA.3 a)).
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]	[redacted]

MA.3 Provision of information to enable supervision by national competent authorities

Requirements:

Commission Implementing Regulation (EU) No. 520/2012, Article 3(1)

GVP Module II – Pharmacovigilance system master file (Rev 2)
II.B.4.8. Annex to the PSMF
"*An annex to the PSMF shall contain the following documents:*
- *A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s), and the Member State(s) in which the authorisation is valid […].*"

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)."

The Human Medicines Regulations 2012

Regulation 73 Obligation to notify placing on the market etc

"*(3) The holder of a UK marketing authorisation must notify the licensing authority if the product to which the authorisation relates is to be withdrawn from the market in the United Kingdom (whether temporarily or permanently).*

(4) A notification under paragraph (3) must be given before the beginning of the period of two months ending with the date on which the product is to be withdrawn from the market unless it is not reasonably practicable to do so."

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 provided in response to requests made in the context of an inspection or a post-authorisation measure, 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.

Finding MA.3 a)
The Article 57 database listed the incorrect information on the legal basis of application for the following product licences. The entries stated that the products were licensed under Article 10(1) (generic application); however, they were licensed under Article 10(c) (informed consent application):

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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]	

Finding MA.3 b)

PSMF Annex H *List of Licenced Medicines and Traditional Herbal product held by Brunel Healthcare Manufacturing Limited* (v14.0, dated May 2019) incorrectly included the product [redacted] even though the licence was cancelled on 11 June 2019. The product licence was also still listed in the Article 57 database at the time of the inspection.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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

Finding MA.3 c)
The MAH had not communicated the change in marketing status of [redacted] from 'marketed' to 'not marketed' to MHRA after the last batch of product was QP-certified in December 2018. The marketing status in the MHRA internal system stated the product was marketed since 26 October 2015.
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.4.3 Minor findings

MI.1 Maintenance of the Reference Safety Information

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Finding MI.1
There was a discrepancy between work instruction [redacted] *Product Licence Safety Information* (v5, date of issue December 2018) and PSMF Annex F *Pharmacovigilance System Performance* (v14.0, dated May 2019) in relation to the timeline from identification of the need to update the product information with new safety information and submission of the variation to MHRA. [redacted] Appendix 1 *Flowchart for Product Information Approval* stated that variations would be prepared and submitted to the NCA within a timeline of five weeks; however, the flow charts in PSMF Annex F stated variations would be submitted within four days (if no artwork changes were required) or 60 days (if artwork changes were required).
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]	

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 aspects of the pharmacovigilance system reviewed during this inspection will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

In relation to critical findings CR.1 a) and CR.1 b), Max Remedies is requested to proactively notify the GPvP Inspectorate (gpvpinspectors@mhra.gov.uk) of the successful submission of upcoming PSURs where required for their products. In addition, Max Remedies should also notify the GPvP Inspectorate after the PSUR final assessment report becomes available to confirm whether a safety variation to update the product information is required and when the relevant variation(s) will be submitted.

Following successful receipt of adequate evidence, the lead inspector recommends 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).
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 20894/14038-0015	**DATES**	Inspection day 1: 22 April 2020 Inspection day 2: 06 May 2020 *Inspection day 3: 14 May 2020*
PHARMACOVIGILANCE INSPECTION OF	Max Remedies Limited	**START TIME**	09:00 on day 1 09:00 on day 2 *09:00 on day 3*
INSPECTOR	[redacted]		

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

This inspection will be focused on the maintenance of Reference Safety Information (including but not limited to the identification of safety updates, submission of safety variations and the implementation of updated product information).

Wednesday, 22 April 2020 (day 1)

An opening meeting will be held at the start of the inspection by teleconference (TC) on Zoom on the morning of day 1 which will be led by the lead inspector. The agenda will be:

- Review of the scope and arrangements for the inspection
- Brief presentation by Max Remedies (20 min maximum) with an overview of the company and pharmacovigilance system. The presentation should focus on the topic listed for inspection and any relevant ongoing remediation work in the pharmacovigilance system.

The remainder of the inspection will consist of remote document review. Interview sessions with company personnel are not intended. However, please provide a designated contact point who can assist with any ad hoc questions from the inspector or arrange calls between inspector and subject matter experts if required. Alternatively, queries may be addressed through written communication.

A TC will be held with the QPPV or delegate at the end of day 1 to indicate the end of the inspection day (4.50 pm) and to confirm the plan for inspection day 2.

If required, a 2nd batch of document requests will be submitted at the end of day 1. Documents should be provided by **COB on 05 May 2020**.

Section 40 & 43

Wednesday, 06 May 2020 (day 2)
Review of documents provided for batch 2 and discussion of ad hoc queries from the inspector.

TC with [redacted] (Qualified Person) and [redacted] (EUQPPV) to discuss various queries.

~~*The inspection will finish with a closing meeting TC at the end of day 2 (time to be confirmed) when feedback will be provided on any non-compliance.*~~

Thursday, 14 May 2020 (day 3)

Review of 3rd batch of documents requested. A closing meeting TC was held at the end of day to provide feedback on the observed non-compliances.

Max Remedies should complete the below with the names and job titles of the designated contact point and those staff who will be joining the opening meeting.

Designated contact point: [redacted], Regulator Affairs Manager, email: [redacted]

Opening meeting attendees: [redacted]