Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: STADA Arzneimittel AG

MHRA Inspection Number: Insp GPvP 11204/19416019-0001

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
DCP	Decentralised Procedure
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSP	Patient Support Programme
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreement
SPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure

UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	STADA Arzneimittel AG (including affiliates) [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	27 – 28 July, 06 – 07 August 2020 This inspection was conducted remotely. An additional inspection day to review documentation was conducted on 18 August 2020.
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	8 – 11 July 2014 (GPvP 11204/310581-0002) 01 – 03 December 2009 (GPvP 11204/1310581-0001)
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the general systems review, the UK [redacted] Monitoring Service was reviewed (INN: [redacted]
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	VigiS3 (bespoke system)
Key service provider(s):	ICSR literature search services provided by Springer Healthcare.

	For activities carried out in the UK under the responsibility of the UK affiliate (Britannia): Medical information services provided by PrimeVigilance.
Inspection finding summary:	1 Major finding 6 Minor findings
Date of first issue of report to MAH:	15 September 2020
Deadline for submission of responses by MAH:	20 October 2020 10 November 2020 11 December 2020
Date(s) of receipt of responses from MAH:	20 October 2020 09 November 2020 11 December 2020
Date of final version of report:	14 December 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

STADA Arzneimittel AG was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Regulation (EC) No 726/2004 as amended, 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.

STADA Arzneimittel AG (STADA) is an international pharmaceutical company specialising in generic and non-prescription healthcare products. The overarching STADA Group is formed of affiliates in most EU and some non-EU countries, with the global headquarters in Bad Vilbel, Germany where the Global Pharmacovigilance Unit (GPU) is based. GPU is responsible for maintenance of the global PV system, all PV activities for corporate substances (those authorised in Germany or in at least two affiliates outside Germany) and RMP production for all STADA products. The PSMF is located in Germany and the supervisory authority responsible for conducting pharmacovigilance inspections on behalf of the EU is BfArM.

For regional or country affiliates, a Local Pharmacovigilance Unit (LPU) is set up to maintain and govern the local PV system. LPUs collect local ICSRs and carry out all PV activities for products authorised in only one affiliate outside Germany (local substances).

The LPU in the UK is Britannia, which was acquired by the STADA Group in 2007. Britannia is responsible for all PV activities for UK products and oversees the PV activities completed by Thornton & Ross (T&R). STADA acquired T&R in 2013 and an Associate Local Pharmacovigilance Officer (ALPO) at T&R works closely with the Local Pharmacovigilance Officer at Britannia to fulfil all PV responsibilities for products in the UK. T&R are also responsible for the PV activities conducted for the following UK marketing authorisation holders (MAHs), which sit within the T&R group: Internis Pharmaceuticals Ltd., Genus Pharmaceuticals Ltd. & Genus Holding Ltd., Nature Aid Ltd., L.C.M. Ltd., N.I. Ltd. and Zeroderma Ltd.

Within the UK, STADA currently holds a total of 284 MAs; 4 with STADA Arzneimittel AG as the MAH, and 280 MAs through the Group's UK affiliate MAHs. Of these 284 products, three have been centrally authorised, 90 via the DCP, 10 through the MRP and 181 via UK national procedures.

B.2 Scope of the inspection

The inspection included a review of the local UK and global pharmacovigilance systems and was performed remotely due to the COVID-19 pandemic. Personnel from GPU, Britannia (LPU) and T&R were available throughout the inspection to participate in ad hoc discussions held over video calls with inspectors.

The inspection was performed over four non-consecutive days in a two-week period using mainly document review (including outputs from the global safety database) supported by the ad hoc discussions with company personnel. Further detail can be found in the remote inspection plan (Appendix II).

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The scope of the inspection included collection and collation of ADRs at the UK affiliate level, management and reporting of ADRs (including a review of the global safety database), a review of the [redacted] Monitoring Service and oversight of the PV system by the QPPV.

It is recommended that risk management (including maintenance of reference safety information), ongoing safety evaluation and PSURs are subject to closer review during a subsequent pharmacovigilance inspection, as these areas were not reviewed during this inspection.

B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] effective from 09 April 2020) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection. This included all documented procedures governing the inspected topics, specific distributor agreements, line listings of ADRs for UK authorised products and specific documents related to the [redacted] Monitoring Service.

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 red italic text in Appendix II.

The inspection included a further inspection day than was initially planned, which was held on 18 August 2020 so that documents from the final request sheet could be reviewed.

A closing meeting was held to review the inspection findings via MS Teams on 07 August 2020 at 4.30 pm (UK time).

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 of STADA in 2009 and of T&R in 2014, the company had made the following changes to the pharmacovigilance system:

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- The QPPV had changed in June 2020 to [redacted] as the previous QPPV, [redacted] had retired.
- In 2014, Genus Pharmaceuticals was consolidated into a single company under Britannia Pharmaceuticals. All Genus products were transferred to T&R with the exceptions of [redacted] and the QMS from Genus formed the basis of the Britannia quality system.

Significant changes planned included a change to the Global Safety Database from VigiS3 to STADAvig in November 2020.

C.2 Definitions of inspection finding gradings

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

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

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

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

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

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

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

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

C.4.2 Major findings

MA.1 Maintenance of the PSMF

Requirements:

Commission Implementing Regulation (EU) No 520/2012,

Article 3, Content of the Annex to the pharmacovigilance system master file

'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;

...

(3) the list of subcontracts referred to in Article 6(2);

...

(5) a list of all scheduled and completed audits.'

Article 4, Maintenance

'1. The marketing authorisation holder shall keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, of technical and scientific progress and of amendments to Directive 2001/83/EC and Regulation (EC) No 726/2004.'

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Several deficiencies in the Annexes to PSMF [redacted] effective from 09 April 2020, were identified.

Finding MA.1 a)

Evidence was seen where information included in the Annexes to the PSMF was inaccurate or had not been updated to reflect the current status of agreements, marketing authorisations (MA) and completed audits:

i. Annex B-b 'Pharmacovigilance Agreements - United Kingdom', incorrectly included the following agreements between parties:

- [redacted] and T&R for [redacted] n the UK. T&R was not the MAH but only a distributor for this product in the UK.
- [redacted] and T&R for [redacted]. The distribution agreement was terminated on 13 March 2016.
- [redacted] was fully integrated with another distributor, [redacted] on 02 December 2019. There was an entry for [redacted] in this PSMF annex, but this entry related only to [redacted] No further reference to the products distributed by [redacted] were made (even though they were covered by [redacted].

ii. Annex H included [redacted] as an authorised product in the UK with [redacted] as the MAH. However the request to cancel the MA was submitted by the MAH on 15 November 2019 and was granted in November 2019 by the MHRA.

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iii. The audit report date for the audit conducted of [redacted] (a distribution partner) was incorrectly stated in PSMF section 10.
The audit (conducted between November 2019 to 15 January 2020) had a report date in the PSMF as 13 February 2019 which should have been 13 February 2020.

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]	

Finding MA.1 b)

Required information was not present in Annexes C and G:

i. Annex C-d 'Registries, surveillance or other support programmes United Kingdom, Britannia, T&R' did not list the following UK PSPs:
   - [redacted] (handled by Britannia nurses), active in the UK since 01 September 2008

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- [redacted] (outsourced to [redacted] agreement in place since 15 November 2019

ii. Annex G-a 'Completed and Scheduled Audits - United Kingdom, Britannia' did not include the audit of the [redacted] that took place in January and February 2019.

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 Periodic Safety Update Reports

Finding MI.1 a)
Adverse reactions included in PSUR summary tabulations were not presented in accordance with GVP Module VII.B.5.6. PSUR section "Data in summary tabulations", which states: *'The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH- E2A (see Annex IV). When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations.'* There was the potential that inaccurate data had been included in the summary tabulations as STADA were not assessing seriousness at an event level, only at case level. For PSUR summary tabulations, the serious/non-serious distinction was driven by the case level seriousness using logic built into the data retrieval program which may have led to incorrect designation of seriousness at event level. Recording of event level seriousness is possible as per ICH E2B(R2): *'Data Elements for Transmission of Individual Case Safety Reports A.1.5 Seriousness "[...] B.2.i.3 can be used to identify the seriousness of each reaction/event in accordance with the user guidance of the item'* During the inspection, this matter was raised with STADA who referred to ICH E2B(R3) which includes guidance on recording event level seriousness and is not yet mandatory. However, E2B(R3) is concerned with ICSR transmission, not presentation of adverse drug reactions in the PSUR. PSUR tabulations should be comparable across companies in order to facilitate meaningful assessment, and guidance on PSUR format (GVP Module VII) has been in place since 2 July 2012, which stipulates the serious/non-serious distinction for presentation of adverse reactions. It is further noted that during migration from vigiS3 to STADAvig, case level seriousness will be applied at an event level to all events contained in the case. However, for data entered directly into STADAvig, assessment of event level seriousness will be mandatory. This has the potential that, following implementation of STADAvig, PSURs will have a mixture of events where seriousness has been derived from case level seriousness and events where seriousness has been assessed at event level. STADA should make it clear to Assessors that this change to the database has occurred and that PSURs may be impacted.
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 MI.1 b)
PSUR No. 11 for [redacted] (DLP 19 November 2019) included exposure figures for a

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product in a territory which was not part of the PV system and where Britannia/STADA did not hold an MA for the product.

A 'Distribution, development, commercialisation & supply agreement' (dated 22 June 2015) and a 'Licence agreement' (dated 15 June 2016) were in place between [redacted] These specified that [redacted] would supply [redacted] with the active ingredient [redacted] for development of a product for the US market.

[redacted] was not the MAH for the US finished product and the product was not included within PSMF Annex H. Therefore, the following PSUR sections incorrectly included exposure data from the US and was not in accordance with GVP Module VII.B.5.2. PSUR section "Worldwide marketing authorisation status":

'This section of the PSUR should contain a brief narrative overview including: date of the first authorisation worldwide, indications(s), authorised dose(s), and where authorised.'

- Table 1 Overview of Authorisations of Medicinal Products per Country: the US was inappropriately listed for [redacted]
- Section 5.2. Cumulative and Interval Patient Exposure from Marketing Experience: interval sales data was listed for the US as [redacted] which was included in the cumulative sales data.

It is important that exposure figures are accurate so that PSURs are reviewed in the context of true exposure figures and availability of the product.

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

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

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[redacted]

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

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MI.2 Patient Support Programmes

Britannia has operated a patient support programme (PSP) for [redacted] since 2008, which involves nurses providing patient and healthcare provider (HCP) support. This includes providing training and treatment initiation services to patients with Parkinson's disease that had been selected by their HCP to start [redacted] treatment.

At the time of the inspection approximately 1200 patients at just over 100 prescribing centres were enrolled in the programme. Nurses documented all patient contacts in the PATHFINDER system, which also included a specific section to document adverse events.

Several deficiencies were observed around the procedural documentation for processes governing the [redacted] PSP.

Finding MI.2 a)

There was limited evidence of robust mechanisms in place to ensure that all adverse events received via the [redacted] PSP were correctly identified and forwarded to the Britannia LPU for processing.

i. The reconciliation process between LPU and the nurse manager was not formally documented in a procedure. [redacted] PV Information Processing and Monitoring ([redacted] effective from 22 July 2020) included details of reconciliation for product technical complaints and medical enquiries but no description of how this would be handled for PSPs. This has been graded as a minor finding as evidence was seen that confirmed reconciliation activities were being completed for PSP cases.

ii. The company stated that the nurse manager conducted random quality checks of the patient notes in PATHFINDER. However, this process was not documented in any procedures. Evidence was requested to show the first time these quality checks were completed and the company provided logs reportedly covering the checks for May-July 2019 but these were undated.

iii. There was no procedural documentation in place which described the process of documenting patient contacts and the reporting of adverse events in PATHFINDER prior to 03 June 2019, when [redacted] 'Nurses in [redacted] Therapy' was first issued.

STADA is reminded that as per GVP Module VI.B.5. Quality management:
'*Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system.*'

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

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[redacted]

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

Preventative Action(s)
[redacted]

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

MI.3 Management and reporting of ICSRs

ICSRs received by UK affiliates were forwarded to the LPU, Britannia, for processing and entry into the Global Safety Database. The LPU documented all ICSRs in a local tracking case log within one working day of receipt and assigned a local case number into the tracker before sending the case to GPU for approval.

If information significant for the validation or scientific evaluation of the case was missing from the ICSR, follow-up was carried out by Britannia so that necessary information could be added to the case. Follow-up attempts were tracked and documented on the local case tracking log and any new follow-up information was forwarded to GPU.

Finding MI.3 a)

There were delays of up to four months until requests for follow-up information were sent out by the LPU from the date of ADR receipt.

- Case [redacted] received on 19 September 2019: This case reported pruritus and pregnancy exposure with [redacted] was received from a sales representative. No follow-up attempt was made until almost four months later on 10 January 2020 to obtain the patient's contact details so that further information regarding the outcome and status of pregnancy could be obtained.

- Case [redacted] received on 12 June 2020: These cases reported two patients who experienced severe dizziness three to four weeks after treatment with [redacted] The first follow-up attempt (which included an attempt to obtain patient identifiers) was conducted on 15 June 2020 but no further follow-up attempt was made until during the inspection, almost two months later on 6 August 2020.

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- Case [redacted] received 13 May 2020: This case reported diarrhoea and vomiting via the [redacted] No follow-up attempt to obtain further information regarding the outcome of these ADRs was made until during the inspection, almost three months later on 06 August 2020.

- Case [redacted] received 21 May 2020: This case reported "Nodules to abdomen, arms and legs with [redacted]" for [redacted] via the UK PSP. No follow-up attempt to obtain further information regarding the outcome was made until during the inspection, over two months later on 06 August 2020.

Each of the above cases met the required criteria for follow-up as stated in the Britannia procedure [redacted] PV Information Processing and Monitoring ([redacted] effective from 15 February 2019 and version 10 effective from 22 July 2020). However, the time taken to send requests for follow-up were not in compliance with this procedure, which stated the below:

"- When no answer is received the reporter should be reminded at the latest every 4 weeks
- Dependent on the ICSR seriousness shorter reminder intervals may be required
- Usually, the reporter will be contacted up to 3 times.[...]
- ICSRs about drug exposure during pregnancy are followed up until the outcome of pregnancy is known. The reporter is contacted within 6 weeks after the expected delivery date; an outcome of pregnancy form ([redacted] should be completed. Further follow up should be carried out at 6 months post birth"

The MAH is reminded of GVP Module VI which states:

'When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy [...], cases notifying the death of a patient, or cases reporting new risks or changes in the known risks.'

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]

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[redacted]

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

MI.4 Reference Safety Information

Finding MI.4 a)

Safety information published on the Britannia sponsored [redacted] was not up to date with the current approved product information for [redacted].

Specific ADRs and information from the SPC section 4.4 Special warnings and precautions for use were listed on the website. However, the information in the 'Warnings and Precautions' section on the website was missing the following information which had been present in the SPC for [redacted] since 17 October 2016:

"Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with [redacted] Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS."

This has been graded as a minor finding as the website included links to the current SPCs published on the EMC for [redacted]

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[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 MI.4 b)

STADA was unable to provide any evidence that demonstrated the medical information service provider (PrimeVigilance) was informed of updated product information following regulatory approval of the below safety variations:

- [redacted] this variation was approved on 07 October 2019 to update the safety warnings in SmPC section 4.2 and 4.4 regarding the use in the elderly and risk of falls in-line with PSUSA outcome [redacted]
- [redacted]: this variation was approved on 19 February 2018 to include new information regarding the outcome of a 24-month randomised, double-blind Phase IV study in SmPC section 5.1.
- [redacted] products: this variation was approved on 22 February 2018 to include headache as a new adverse drug reaction in SmPC section 4.8.

Britannia's [redacted] Medical Information and Master Summary of Product Characteristics [redacted] effective from 18 May 2020) stated the following in section 9.2:
"If changes to the SPC or PIL are made, PrimeVigilance must be provided with

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updated copies by the Britannia…
Send the product information as PDF electronic files within 5 days of approval of the change".

The requirement to inform PrimeVigilance of updated product information was also reflected in T&R procedures: [redacted] [redacted] Instructions on Using the data Package for PrimeVigilance Medical Information [redacted] effective from 01 November 2018) stated in section 3:

"PrV [PrimeVigilance] and Local Pharmacovigilance Unit … will be notified of any changes to a SmPC with two working days, following its upload onto the eMC website".

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[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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MI.5 Maintenance of the Article 57 database

Finding MI.5 a)

At the time of inspection, the QPPV details in the Article 57 database had not been updated for several products following the appointment of a new QPPV, [redacted] on 01 June 2020.

Per GVP Module II.B.2.2., changes to the QPPV should be updated in the Article 57 database immediately and no later than 30 calendar days.

However, a search of the Article 57 database (conducted 18 August 2020, almost 2 months after the change in QPPV) for [redacted] still showed the previous QPPV [redacted] for some products, examples have been provided below:

[redacted]

Evidence was seen that STADA was taking action to update the database and that the QPPV oversight of the system was maintained; therefore, this finding has been graded as minor.

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[redacted]

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[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

Section 43

[redacted]

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

MI.6 The quality management system

The following minor findings were noted in relation to compliance management processes and training of personnel for pharmacovigilance:

Finding MI.6 a)
STADA explained in writing that the timeframes associated with developing CAPA from audit findings depended on the nature of the finding and CAPA itself; however, there was an example of an unacceptably long timeframe to develop CAPA following major audit findings. Further to MA.1 a), the anticipated date of resolution for three major findings from the audit of [redacted] was given as 30 June 2020 in PSMF version [redacted] However, at the time of inspection no CAPA plans had been finalised and it was noted that the MAH only contacted [redacted] regarding this matter on 21 July 2020, 5 months since the audit was completed. The guidance in GVP Module IV.B.2.4. states that: *"Corrective and preventive actions to address critical and major issues should be prioritised."* A delay of 5 months to develop a CAPA to address the major findings does not demonstrate prioritisation in line with this guidance.
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]

[redacted]	

Finding MI.6 b)
Two examples were identified where staff had not completed the annual pharmacovigilance refresher training, which was a requirement as per [redacted] Pharmacovigilance

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Requirements Training (version 5 effective from 27 September 2017). Neither a Senior Key Account Manage[redacted] nor an [redacted] nurse [redacted] completed their refresher training 2019.
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

1. **Provision of information to inspectors:** During the inspection, inspectors requested a list of company-sponsored websites. The provided list included the website https://thebritniapharmuk-ltd.com. However, when the inspector queried the contact details provided on this website, personnel from the MAH clarified that this was a counterfeit website they had been aware of since June 2020 and that it was not associated with Britannia. The MAH should ensure that correct and complete information is provided to inspectors.

2. **Cases from EudraVigilance:** Following the May 2020 SA inspection, a finding was given in relation to downloaded cases from EudraVigilance. STADA confirmed that when STADAvig goes live in November 2020 these cases will be added to the new database but will still be excluded from PSURs, which is not in compliance with GVP

Module VII. STADA should ensure that the data in PSURs is presented appropriately in accordance with GVP VII.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

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

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- 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	TBC	**DATES**	Inspection day 1: 27 July 2020 Inspection day 2: 28 July 2020 Inspection day 3: 06 August 2020 Inspection day 4: 07 August 2020
PHARMACOVIGILANCE INSPECTION OF	STADA Arzneimittel AG	**START TIME**	09:00 on all days
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:

- **Collection and collation of adverse drug reactions at the UK affiliate level**
- **Management and reporting of ADRs (including a review of the global safety database) at the UK affiliate and corporate level**
- **Processes and management of the UK [redacted] monitoring service**
- **Oversight of the PV system by the QPPV**

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Monday 27 July 2020 (day 1)

An opening meeting is proposed for 09:00 on the morning of day 1 by videoconference (VC) which will be led by the lead inspector. This will include a:

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

2:00 pm [redacted] Monitoring Scheme: Presentation by the MAH (20 min), questions from inspectors

4:00 pm: QPPV oversight discussion [redacted]

The remainder of the day 1 will consist of remote document review and further document requests will be submitted throughout the course of the day. 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.

Tuesday 28 July 2020 (day 2)

Day 2 of the inspection will consist of remote document review and discussions with company personnel may be required. Please ensure that subject matters experts are available and indicate any times personnel may be unavailable that day. The lead inspector will liaise with the designated contact point to arrange ad hoc discussions as required.

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9:00 am: [redacted] ad hoc discussion [redacted]

2:00 pm: Case processing discussion ([redacted]

3:00 pm: SDEAs and PVAs discussion [redacted]

3:30 pm: [redacted] Monitoring Scheme discussion [redacted]

4:00 pm: LPO and APLO discussion [redacted]

A call or VC will be held with the QPPV or delegate on day 2 (time to be confirmed) to indicate the end of the first phase of the inspection and to confirm the plan for inspection day 3.

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

Thursday 06 August 2020 (day 3)

Review of documents provided for batch 2 and discussion of ad hoc queries from the inspector.

Friday 07 August 2020 (day 4)

Review of documents provided for batch 2 and discussion of ad hoc queries from the inspector.

9:30 am: Discussion for document request O [redacted]

11:15 am: Discussion for document request N4 ([redacted])

3:30 pm: Discussion for document request Y [redacted]

The inspection will finish with a closing meeting VC on day 4 (time to be confirmed) when feedback will be provided from the inspection.

STADA should complete the below with the names and job titles of the designated contact point and those staff who will be dialling in to the opening meeting.

Designated contact point:

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[redacted]

Subject matter experts (by topic):

ADR collection and management UK:

[redacted]

Opening meeting attendees:

[redacted]