Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Bristol-Myers Squibb

MHRA Inspection Number: Insp GPvP 11184/108564-0006

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ABBREVIATIONS

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
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
MedDRA	Medical Dictionary for Regulatory Activities
NAP	Nationally Authorised Product
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC	EU Summary of Product Characteristics
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection
System(s) inspected:	Bristol-Myers Squibb [redacted]
Site(s) of inspection:	Bristol-Myers Squibb Pharmaceuticals Ltd. Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH
Main site contact:	[redacted]
Date(s) of inspection:	Onsite inspection conducted from 02 – 05 March 2020. Document review continued office-based and was concluded on 13 March 2020.
Lead Inspector:	Sophie Radicke
Accompanying Inspector(s):	Sarah Gomersal, Rory Littlebury, Dominic Nguyen-Van-Tam
Previous inspection date(s):	12 – 15 December 2005 and 06 – 07 February 2006; 25 – 27 January 2007; 08 – 11 February 2010
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, ADR reports were examined for all CAPs and UK NAPs. Specific PSURs were examined for [redacted] (both CAPs).
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Analytic and Worldwide Adverse Event Reporting and Evaluation (AWARE) version 6.0.11 (based on Argus, commercially available)
Key service provider(s):	Pharmacovigilance services provided by Accenture Safety database hosted by IQVIA Medical information services provided by ProPharma Group and PPD Medical Communications
Inspection finding summary:	0 Critical findings 3 Major findings

	3 Minor findings
Date of first issue of report to MAH:	24 April 2020
Deadline for submission of responses by MAH:	03 June 2020 03 July 2020
Date(s) of receipt of responses from MAH:	03 June 2020 03 July 2020
Date of final version of report:	20 July 2020
Report author:	Sophie Radicke *GPvP Inspector*

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Bristol-Myers Squibb 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 726/2004/EC 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.

Bristol-Myers Squibb Company (hereafter 'BMS') is a globally operating biopharmaceutical company with sites in more than 50 countries. There are 16 subsidiaries acting as marketing authorisation holders in the different EU countries.

Pharmacovigilance activities are conducted and coordinated by World Wide Patient Safety (WWPS) which is headquartered in New Jersey, USA. Responsibilities include AE report triage, oversight of pharmacovigilance service providers, literature review, development and maintenance of global PVAs and procedural documentation, compliance management and signal detection. The WWPS EU PV Office is located in Braine-l'Alleud, Belgium and supports EU-specific activities such as PSUR preparation and submission, and provides support of the EU QPPV who is based in France.

A Joint BMS-Accenture Pharmacovigilance Centre operates in Bangalore and Chennai, India and delegated activities include ICSR processing, generation of line listings from the safety database, literature review, support of signal detection activities and aggregate report writing.

The safety database AWARE is hosted by IQVIA and the vendor is responsible for the configuration of case management and reporting tools, and platform updates.

Medical information has been outsourced to PPD Medical Communications for the US and Latin America, and to [redacted] or Europe, Brazil, Canada, Middle East & Africa, Asia Pacific region, Japan and US.

BMS' product portfolio consists of CAPs and NAPs mainly in the following therapy areas:

- Oncology and haematology
- Immunology
- Antiviral and antibiotic drugs

The pharmacovigilance system is also shared with Bristol-Myers Squibb/Pfizer EEIG, the MAH of the CAP [redacted] Pharmacovigilance responsibilities for this product are described in a pharmacovigilance agreement between BMS and Pfizer, Inc. BMS' pharmacovigilance responsibilities for [redacted] include maintenance of the global safety database, ICSR processing and regulatory reporting in territories where BMS/Pfizer EEIG is the MAH, RMP preparation, signal management, preparation of aggregate reports and provision of the EU QPPV.

At the time of the inspection, the PSMF was located at the WWPS EU PV office in Belgium, therefore the Federal Agency for Medicines and Health Products (FAMHP) was the

Supervisory Authority responsible for conducting pharmacovigilance inspections on behalf of the EMA.

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance systems and was performed at the BMS offices in Uxbridge, Greater London. Personnel from the UK and US attended the Uxbridge site in order to participate in the inspection. Where necessary, personnel from the US were also available via teleconference to participate in the 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).

Maintenance of reference safety information and the implementation of approved changes to the product information 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 [redacted]. dated 26 November 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 and B.

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.

Due to outstanding documentation, the inspection could not be completed during the onsite days (02 – 05 March 2020) and an interim closing meeting was held at the BMS office, Uxbridge on 05 March 2020 to summarise the inspection status and to provide preliminary feedback regarding the inspection findings. The inspection was concluded via office-based document review and a formal closing meeting was conducted via teleconference on 26 March 2020.

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

SECTION C: INSPECTION FINDINGS

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

Since the previous inspection in 2010 the company had made the following changes to the pharmacovigilance system:

- BMS divested the diabetes portfolio in 2013 and the portfolio of European over the counter products in 2018.
- The safety database changed from CARES, a bespoke database, to AWARE, a system based on Argus, on 08 December 2014.
- The Japan Safety Database was merged with AWARE on 21 October 2017.
- The EU QPPV changed from [redacted] to [redacted] MD in December 2018.
- A new system, Infinity, was introduced on 04 June 2019 to track and manage deviations, audits, product complaints and CAPA.
- At the time of the inspection, Empirica Signal was in the process of being replaced with PV Signal.

BMS acquired Celgene on 20 November 2019 with Celgene becoming a wholly owned subsidiary of BMS. During the integration phase, which is expected to be completed in Q3/Q4 2021, the two companies will maintain and operate separate pharmacovigilance systems, including separate QPPVs, PSMFs and safety databases. Nevertheless, the Head of WWPS is responsible for the overall pharmacovigilance activities of both BMS and Celgene products and one joint Senior Leadership team operates. In addition, the Medical Review Group covers the safety of both BMS and Celgene products and therefore has representatives from both entities depending on the type of product and related potential safety issue.

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 Management and Reporting of Adverse Reactions

Requirements:

Directive 2001/83/EC as amended, Article 107(1) stating that "*suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC.*" and Article 107(3).

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01), section 7.4 *SUSARs reported to the national competent authority (directly or indirectly through EVCTM)*

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.3. Follow-up of reports
"*[…] This is particularly relevant for monitored events of special interest, prospective reports of pregnancy (see VI.B.6.1. for guidance on the management of pregnancy reports), cases notifying the death of a patient, or cases reporting new risks or changes in the known risks.*"

VI.C.6.2.1.1. Adverse reaction data collected in the EudraVigilance Post-Authorisation Module
"*The adverse reaction reports collected in the EudraVigilance Post-Authorisation Module (EVPM) refer to unsolicited reports and solicited reports which do not fall under the scope of the Clinical Trials Directive 2001/20/EC […].*"

VI.C.6.2.1.2. Adverse reaction data collected in the EudraVigilance Clinical Trial Module
"*Only cases of suspected unexpected serious adverse reactions (SUSARs), related to investigational medicinal products (IMPs) studied in clinical trials which fall under the scope of Directive 2001/20/EC (see VI.C.1.1. for ICSRs management in clinical trials), should be submitted by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM).*"

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

Finding MA.1 a)

The MAH had submitted a number of ICSRs to the incorrect instance of EudraVigilance due to inconsistencies in completing the 'observe study type' field for cases with the same protocol ID in AWARE.

Since 08 December 2014, a total of 2573 ICSRs reported from 793 cases from clinical trials, individual patient use and other studies were incorrectly submitted to either EVHUMAN or EVCT. Just over 85% of these ICSRs were submitted to EVCT whereas they should have been sent to EVHUMAN in line with Directive 2001/83/EC, Article 107(1) and (3). The remaining ICSRs were incorrectly submitted to EVHUMAN, and not to EVCT in line with section 7.4 of CT-3.

The ICSRs presented 1.9% of all submissions for which the protocol number and/or code was completed in AWARE since 08 December 2014 and were associated with 84 different protocols.

[redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

[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)

The following deficiencies were identified in relation to the conduct of follow-up to request further information on adverse event reports and the documentation of this activity.

i. From a sample of 19 cases which required a targeted follow-up questionnaire (TFUQ) to be sent based on the reported events, there were seven serious, spontaneous, HCP confirmed cases for which the TFUQ was not sent.

- There were three cases [redacted] that reported either intestinal perforation or gastrointestinal perforation for [redacted] in combination with [redacted]

  Gastrointestinal (GI) perforation as a symptom of GI immune-related adverse reactions was listed as an important identified risk in the [redacted] EU RMP [redacted] dated 26 September 2019) for which a TFUQ was required.

- In addition, four cases reported for [redacted] did not have the TFUQ for "GI perforation" sent even though this was required as per the technical instruction *GPVE Individual Case Safety Report (ICSR) Processing Manual* (approved 03 November 2019), section F.3.12 *Targeted Letter*.

ii. The MAH used 'action items' in AWARE to initiate, track and document the conduct of follow-up activities to obtain further information regarding adverse event reports. As of 02 March 2020, there were approximately 3700 cases which were associated with late action items. Of these:

- There were around 2000 cases where a required action for follow-up had not been completed. Depending on the reporter type and adverse event, up to three follow-up attempts were made as specified *GPVE Individual Case Safety Report (ICSR) Processing Manual* (approved 03 November 2019), section F. *Letter & Action Item Conventions*.

  Of the 2000 cases, no follow-up attempt had been sent at all for 18 cases. 1655 cases required two follow-up attempts and 267 cases required three follow-up attempts and at least one of the follow-up attempts was not made for these cases.

- In addition, there were around 1700 action items relating to requests for follow-up which had been actioned but had not been updated in AWARE and thus appeared as overdue. *GPVE Individual Case Safety Report (ICSR) Processing Manual* (approved 03 November 2019) section C.13.2 *Action Items* stated "Open action items appear in the Worklist of the group/user who has responsibility for completing it. [...] C. COMPLETED: Enter date the action item was completed."

An analysis carried out by the MAH during the inspection indicated that there were delays of up to five years in either executing action items for follow-up or updating completed action items.

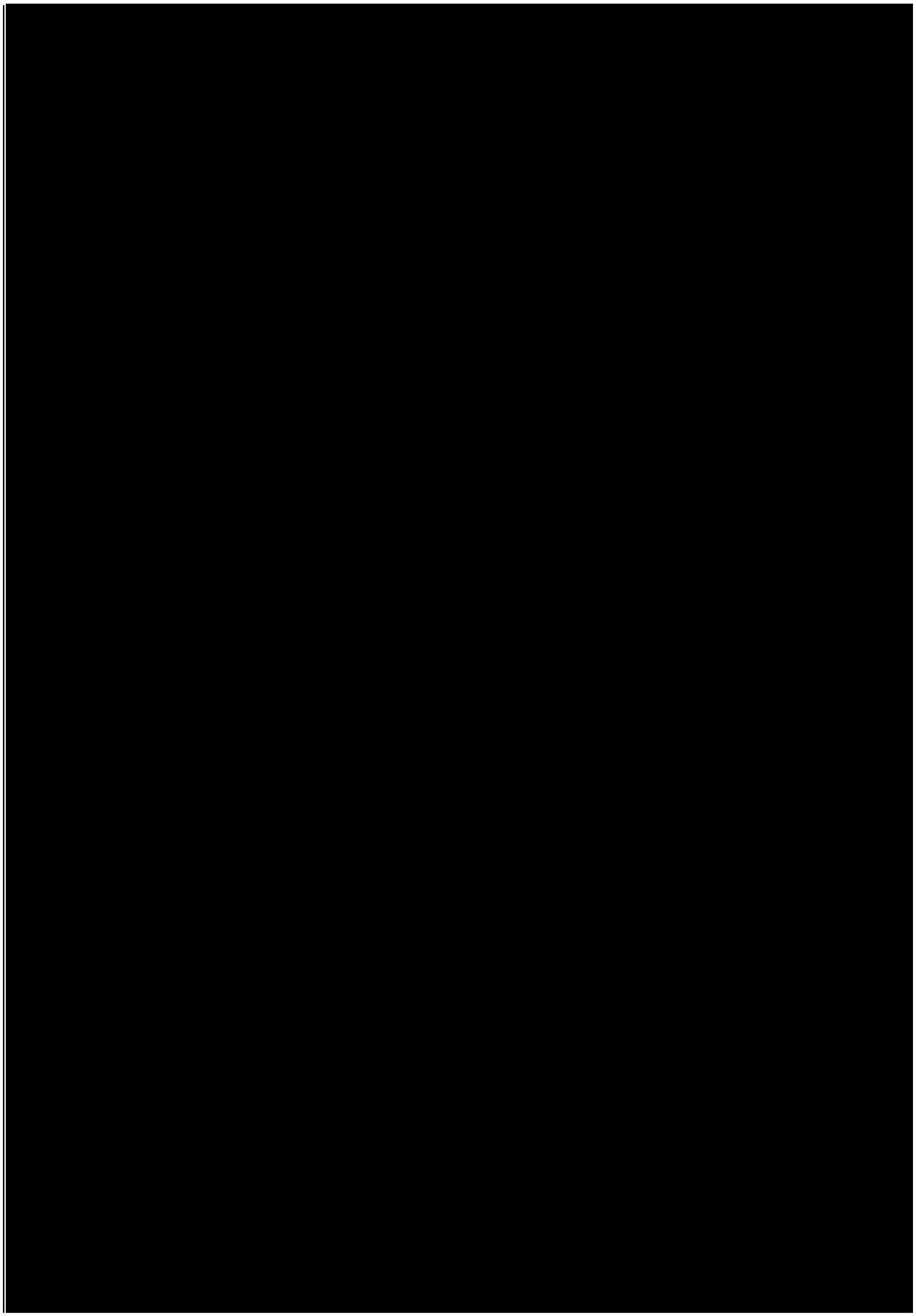
Post-inspection request: The MAH should address the following in their responses:
a) In relation to the first bullet point under ii., for the 18 cases for which no follow-up request was sent, please clarify the seriousness and report type of the cases. Please also specify whether the cases were reporting an outcome only (e.g. death or hospitalisation only) or were invalid cases.

b) In relation to the first bullet point under ii. for cases requiring two or three follow-up attempts, please confirm for how many cases the initial follow-up request was sent.
Root Cause Analysis
[redacted]

[redacted]

Further Assessment

[redacted]



[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]

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

MA.2 Biological Medicines

Requirements:

GVP Product- or Population-Specific Considerations II: Biological medicinal products
P.II.B.1.1.4. RMP part V "Risk minimisation measures"
"*As a general principle in order to improve traceability of biological medicines, all summaries of product characteristics (SmPCs) for biologicals (also with relevant appropriate wording in the package leaflets (PLs)) should include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file.*"

P.II.B.4. Signal management
"*In case of a signal any effort should be made to identify any common root cause such as batch.*"

"*Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological and important differences between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change).*"

"*Any signal should be evaluated in the context of batch-specific exposure data, including numbers/codes of delivered or sold batches, their size and the regions or countries where the respective batches have been delivered.*"

At the time of the inspection, the BMS portfolio included the following five products which were classed as biologicals:

[redacted]

The following findings were noted in relation to the specific requirements for signal management and the product information as described in GVP PII for biological medicinal products.

Finding MA.2 a)

The MAH did not have any processes which considered the requirements for signal detection and evaluation for biological medicines.

i. There was no process in place to identify differences in safety reporting between batches of the same product.

   While routine signal detection processes included criteria selected to identify potential product quality issues both in the Empirica database and in the product quality database TrackWise, there was no established process allowing for the detection of differences in safety reporting between batches of the same product. This was further exacerbated as the batch numbers associated with the cases which were flagged for review after triggering disproportionality criteria during routine signal detection were not available to reviewers in the Empirica system.

ii. Signals for biological products were not evaluated in the context of batch-specific exposure data. Procedure [redacted] *Work Instruction - Signal Detection and Management Manual* (effective 20 January 2020) outlined that the assessment and evaluation of a validated signal should be captured in a Signal Report. The Signal Report Model Document did not include any additional instructions for including batch-specific exposure data for biological medicines.

As an example, the Signal Report for pericardial disorders with [redacted] (dated 31 May 2018), identified through disproportionality analysis, did not include any exposure figures or batch data within the assessment or evaluation of the event.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.2 b)

There was no documented process for manufacturing changes for biological products to be communicated to those conducting signal detection activities to allow the detection of acute or serious new risks to be identified following such a change.

In addition, the MAH only provided limited evidence of this activity being conducted in the form of a general distribution list to the different BMS teams used to communicate the approval of a [redacted] variation for a manufacturing change of a biological product.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]	

Finding MA.2 c)
The current version of the EU SmPCs for the following biological products did not include prominent statements that the name and batch number of the administered product should be clearly recorded in the patient file. [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]	

MA.3 Quality Management System

Requirements:

Commission Implementing Regulation (EU) 520/2012, Article 8(4)
"*All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.*" (emphasis added)

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.6. Responsibilities for the quality system within an organisation
"*[…] 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; […].*"

GVP Module IV – Pharmacovigilance audits (Rev 1)
IV.B.2.4. Actions based on audit outcomes and follow-up of audits
"*The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.*

Upper management and those charged with governance, should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to upper management."

IV.C.2.1. Reporting by the marketing authorisation holder
"*Based on the audit findings, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented.*"

The following findings were noted in relation to the implementation of corrective and preventative actions (CAPA) from pharmacovigilance deviations and audits.

Finding MA.3 a)

Delays of up to 12 months were seen in formally agreeing and documenting CAPA plans and their due dates to address findings resulting from pharmacovigilance audits.

i. The audit of the co-marketing partner [redacted] was conducted from 04 to 06 February 2019 and the audit report was issued on 01 March 2019. At the time of the inspection, the CAPA plan wording and due dates for the finding relating to unclear language about responsibilities for pharmacovigilance activities included in the latest PVA signed between BMS and [redacted] had not yet been approved.

ii. The audit of the Italian BMS affiliate office [redacted] was conducted from 15 to 17 April 2019 and the audit report was issued on 15 May 2019. A proposed CAPA plan was submitted by the affiliate office on 30 May 2019; however, the CAPA wording and due dates for the finding relating to the management of local contracts and the contract clauses that relate to PV obligations and activities were not finalised until 20 January 2020 and had not yet been approved at the time of the inspection.

It is acknowledged that a number of proposed actions related to this finding were completed between 31 July and 29 October 2019 following discussion between the Italian affiliate and the Associate Director of Quality & Inspection Readiness in WWPS. Formal approval of the CAPA plan was requested by the affiliate office in July, September and December 2019.

A review of PSMF section 7.6 *Description of Open Corrective and/or Preventive Action Plans for Major/Critical Observations* (v33.0, dated 22 January 2020) also indicated that CAPA had not been formally agreed and documented for findings from the following audits at the time of inspection as the proposed CAPA due dates were blank:

[redacted]

The technical instruction [redacted] *Research & Development Audit Handbook* [redacted] date effective 15 March 2019) stated in Chapter 5, section B.2 *Follow-up with Auditees and Observation Owners* that "Responses and CAPA should be final and agreed with the lead auditor within 30 calendar days after receiving the initial audit report."

Root Cause Analysis

[redacted]

[redacted]

Further Assessment

[redacted]

[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)

Delays of up to seven months were seen in the implementation of CAPA proposed to address major and critical findings from pharmacovigilance audits. The following CAPA were not completed in line with their planned due dates:

i. [redacted] was an audit of the System for Screening of Websites Social Media Digital Media. The audit report was issued on 03 May 2019 and included a major finding relating to the [redacted] not listing all service providers performing moderation activities on behalf of BMS and a current list of digital agencies with whom BMS partners. The corrective action to send an email to collect this information was due to be completed by 20 July 2019, but the action had not yet been completed at the time of inspection (seven months later).

The CAPA was not completed despite repeated reminders sent to the finding owner on 27 September, 19 November and 19 December 2019, a meeting with the finding owner on 28 January 2020 and escalation to the Tier 2 PV Quality Council in October 2019 and February 2020.

ii. [redacted] was a system audit of Post-Authorisation Safety Studies (PASS). The audit report was issued on 04 July 2019 and reported a critical finding in relation to the applied definition of PASS, the classification of studies as PASS and their review by the QPPV. Corrective action CA.4 for this finding to review why certain studies were missing from the PSMF was due to be completed by 30 September 2019 but was only completed on 10 January 2020 with a delay of 3.5 months.

The finding owner was contacted by the quality team on 19 November 2019, 06 December 2019 and 19 December 2019, but no response was received.

Root Cause Analysis

[redacted]

[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 c)
There was an example of ineffective and incomplete preventative actions associated with the incorrect transfer of data from the medical information database ATHENA into the safety database AWARE. CAPA record [redacted] (raised on 23 April 2019) described the CAPA for an issue identified when cases from ATHENA were transferred into AWARE. The root cause identified that when changes had been made to add fields into the AE form residing within ATHENA, it had inadvertently hard-coded a change into the form as well. This hard-coded change resulted in any entry into the "gender" field being populated within AWARE as "MALE". The preventative action for this issue detailed a comparison exercise to be completed after all further changes to ensure the accuracy of all fields. CAPA record [redacted] (raised on 20 August 2019) described the CAPA for another issue which had occurred following a change to the AE form within the ATHENA system. On this occasion the change had inadvertently resulted in any value of "UNKNOWN" entered into the "consent for follow-up" field in ATHENA being populated in AWARE as "No". The MAH had written corrective actions for this issue but had not raised any preventative actions and had not determined whether the preventative actions raised in [redacted] had been

ineffective or proposed any further or additional preventative actions. The MAH should consider how it will be ensured that future changes to the ATHENA system, including the planned upgrade, do not result in changes to the mapping of fields when data is transferred into AWARE.
Root Cause Analysis
[redacted]

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

C.4.3 Minor findings

MI.1 Additional risk minimisation measures

Finding MI.1 a)
No date of revision was included in the UK Eliquis patient alert card (PAC) that was supplied to patients via product packs along with the patient information leaflet. A review of the batch certification records, and the regulatory document management system GAME showed that the PAC supplied in packs corresponded to the version most recently approved by the EMA. [redacted] Addendum I – Educational materials, section [redacted]. Add I.4. states "for version control [...] the date of last revision of the text (i.e. the approval date of the material by the applicable national competent authority) in the format of "<month> <year>" should be provided on the first and the last page".
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

[redacted]

Preventative Action(s)
[redacted]

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

MI.2 Pharmacovigilance System Master File

Finding MI.2 a)

The following audits were not listed in PSMF Annex G2 *Rolling 5-year List of Completed Audits* [redacted] dated 06 February 2020) even though associated audit findings were included in section 7.6 *Description of Open Corrective and/or Preventive Action Plans for Major/Critical Observations*:

Audit reference	Audit description	Audit report date
[redacted]	[redacted]	06 October 2019
[redacted]	[redacted]	27 November 2019
[redacted]	[redacted]	04 November 2019

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

[redacted]

Corrective Action(s)
[redacted]
[redacted]
[redacted]
Preventative Action(s)

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

MI.3 Management and Reporting of Adverse Reactions

Finding MI.3

There were approximately 100 adverse reactions reported for UK-authorised products for which the adverse event received date was left blank in AWARE. The MAH confirmed that the respective reactions would have therefore been missed from the interval section in the PSUR summary tabulations and only appeared in the cumulative section of the relevant PSUR.

A breakdown of the number of adverse reactions with blank adverse event received date by product is shown in the table below. All of these reactions met the criteria for inclusion in the PSUR summary tabulations.

Generic Name	Number of events	Examples of serious reaction MedDRA PTs with blank adverse event received date
[redacted]	[redacted]	Pneumonia, sepsis
[redacted]	[redacted]	Death, haemorrhage, intracranial haematoma
[redacted]	[redacted]	Caesarean section
[redacted]	[redacted]	Death, haemorrhage urinary tract
[redacted]	[redacted]	Haematuria
[redacted]	[redacted]	Bone marrow toxicity, haemophagocytic lymphohistiocytosis, hypopituitarism
[redacted]	[redacted]	Bone marrow toxicity, metastatic renal cell carcinoma, pneumonitis, sclerema
[redacted]	[redacted]	Anaphylactic reaction, haematemesis, shock haemorrhagic

During the inspection, the MAH stated that an in-line QC validation would be implemented as an additional quality check to the AWARE safety database at the end of Q1 2020. These quality validation checks would include event receipt date along with several other field validations. The system would populate an error message while the case was in workflow if the event receipt date was blank OR future receipt date, which would prompt users to correct this field while the case was in workflow.

Post-inspection requests:

a) The MAH should list in their response the PSUR(s) in which the adverse reactions were not included in the interval section but only in the cumulative section of the summary tabulation.

b) The MAH should comment in the further assessment on the effects of missing event received date on any other regulatory or scientific documents (bespoke or otherwise) apart from PSURs.

c) In addition, the MAH should clarify in the further assessment whether the adverse reactions without an adverse event receipt date would have been included in signal detection activities.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

[redacted]

Corrective Action(s)	
[redacted]	
[redacted]	

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

C.4.4 Comments

1. During the inspection it was noticed that the MAH had some difficulties in extracting data from the safety database in a timely fashion and in a usable format. The MAH is encouraged to review this in consideration of their capacity to provide safety data to health authorities at short notice, for example for urgent requests.

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.
- Guideline on good pharmacovigilance practices (GVP).
- Directives 2001/20/EC and 2005/28/EC in relation to Clinical Trials.
- 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.
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/135/1995: E6 (R2) "Guideline for good clinical practice".
- Eudralex Volume 10, Chapter II: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT3'), June 2011.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 11184/108564-0006	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Bristol-Myers Squibb	**DATE**	02 March 2020
LOCATION	Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DH	**START TIME**	09:00 arrival for a 09:30 start

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 may also include information on any relevant ongoing remediation work in the pharmacovigilance system. *(approx. 20 minutes)*	SR	All welcome [redacted]

		[redacted]
Document collation and review		
LUNCH		
Collection and collation of safety data I, including but not limited to • Medical information • Product quality complaints • Social media • Distribution and license partners	SR	Interviewee(s): [redacted]

		[redacted]
Collection and collation of safety data II, including but not limited to • Patient support programmes • Expanded access programmes • Market research programmes • Non-interventional studies and investigator-initiated studies	RL	[redacted]

		[redacted]

N.B. The Inspection Plan may need to be amended during the inspection.

SG – Sarah Gomersal; RL – Rory Littlebury; DN – Dominic Nguyen-Van-Tam; SR – Sophie Radicke

MHRA INSPECTION NUMBER	Insp GPvP 11184/108564-0006	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Bristol-Myers Squibb	**DATE**	03 March 2020
LOCATION	Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DH	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
ICSR management, including but not limited to • Data entry, coding assessments and submission to EudraVigilance • Follow-up activities • Quality assurance and vendor oversight	DN	[redacted]

LUNCH		
Signal management, including but not limited to • Signal detection, validation, evaluation and tracking • Consideration of requirements for biologicals	RL	[redacted]
Additional risk minimisation measures, including but not limited to • Submission, maintenance and distribution of UK educational materials • Effectiveness of risk minimisation measures	SR	[redacted]

Quality Management System	*SR*	[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 11184/108564-0006	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Bristol-Myers Squibb	**DATE**	04 March 2020
LOCATION	Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DH	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Periodic safety update reports	SG	[redacted]
Ad-hoc session regarding distribution of patient alert cards in packs	*SR*	[redacted]
LUNCH		
Document review and ad-hoc questions	-	As required

MHRA INSPECTION NUMBER	Insp GPvP 11184/108564-0006	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Bristol-Myers Squibb	**DATE**	05 March 2020
LOCATION	Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DH	**START TIME**	09:00

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