Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Celgene

MHRA Inspection Number: Insp GPvP 21752/2907930-0016

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PV	Pharmacovigilance
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreement
SmPC	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 Re-inspection
System(s) inspected:	Celgene [redacted]
Site(s) of inspection:	Remote inspection due to the COVID-19 pandemic
Main site contact:	[redacted]
Date(s) of inspection:	16 – 17 and 21 – 22 July 2020
Lead Inspector:	Rory Littlebury
Accompanying Inspector(s):	Sarah Gomersal
Previous inspection date(s):	• 22 – 24 January 2019 (GPvP on-site inspection) w/c 11-Feb-2019 (Two office-based inspection days) 12 March 2019 (GDP inspection) • 04 – 08 December 2017 (with seven remote inspection days between 2nd and 22nd January 2018) • 08 – 11 July 2013 • 21 – 24 April 2009 (UK) & 14 – 17 December 2009 (US) • 11 – 13 March 2008 (UK) & 31 March – 04 April 2008 (US)
Purpose of inspection:	Re-inspection to determine if appropriate action had been taken from the previous inspection and to review compliance with UK and EU requirements
Products selected to provide system examples:	The inspection focussed on the risk management systems in place for the [redacted] (all centrally authorised).
Name and location of EU QPPV:	[redacted] Contact details and address as above
Key service provider(s):	Medical writing services provided by Insight Medical Writing Ltd
Date of final version of report:	26 August 2020
Report author:	Rory Littlebury Senior GPvP Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Celgene was selected for re-inspection as a result of the critical finding that was identified during the previous inspection of the MAH, performed in January 2019. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the findings raised at the previous inspection. In addition, the inspection provided an opportunity to re-examine the overall compliance of the risk management system with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to the EU RMP and the communication between the MHRA and Celgene with regards to the risk management systems for [redacted]

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A list of reference texts is provided at Appendix I.

B.2 Scope of the inspection

The inspection focussed on the risk management systems for [redacted] and [redacted] Celgene, specifically the pregnancy prevention programmes (PPP), and was performed remotely. Personnel from Celgene participated in the inspection via videoconference.

The inspection focussed on a review of the systems and processes which were associated with the critical and major findings identified during the previous inspection.

The inspection was performed using interviews and document review. The scope of the inspection is highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

Future inspections should take into consideration the acquisition of Celgene by Bristol-Myers Squibb and the integration of the pharmacovigilance systems (see section C.1 of this report).

B.3 Documents submitted prior to the inspection

The company submitted pre-inspection documentation to assist with inspection planning and preparation. This included procedural documents associated with the pregnancy prevention programme and documentation supporting the conclusions reached in the [redacted] Celgene 2018-2019 audit report sent to the MHRA. This report contains data Celgene have collected from the pregnancy prevention programme and analyses its effectiveness.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan.

A closing meeting was held via videoconference on the 22 July to conclude the remote inspection.

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 OBSERVATIONS

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

Since the previous inspection in January 2019 the company had made the following changes to the pharmacovigilance system:

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- Several changes had been made to the [redacted] Celgene risk management system, specifically with regards to the self-audit process. Further details are in Section C.2.1 below.
- The acquisition of Celgene by Bristol-Myers Squibb had completed on the 20 November 2019. The pharmacovigilance systems remained separate, under two different [redacted] numbers, and with different EU QPPVs. There were plans to integrate the two systems into one. The project plan presented to the inspection team outlined a proposed pharmacovigilance system merger completion date of Q3 / Q4 2021.
- Celgene had been developing a proposal to align the risk management systems for all three [redacted] products. The proposal was planned to be submitted to the MHRA in September 2020.

C.2 Inspection findings

C.2.1 Critical findings

At the time of re-inspection, critical deficiencies relating to risk management identified during the previous inspection had been addressed and no further deficiencies associated with the risk management system were identified.

The critical deficiency reported at the January 2019 inspection was centred around Celgene's lack of oversight of the implementation of the PPP, specifically for institutions who were not providing any evidence that they had conducted an annual self-audit focused on determining whether the conditions of the PPP had been adhered to. Under the terms of the controlled distribution system, some institutions that were prescribing and dispensing [redacted] Celgene were required to audit a number of Prescription Authorisation Forms (PAFs) to determine whether the conditions of the PPP had been adhered to, and the self-audit results should be submitted to Celgene via a self-audit questionnaire for its oversight. Several institutions were identified who had not provided any information regarding PPP adherence to Celgene for two years.

Celgene had proposed CAPA to the MHRA in response to the findings raised at the January 2019 inspection; this included a commitment to review the reasons why some institutions registered to dispense [redacted] Celgene had not provided self-audit data. A company meeting was held at the MHRA's offices in Canary Wharf, London in October 2019 where the CAPA proposals were presented by Celgene regarding changes to the self-audit process, alongside the reasons for non-adherence to the self-audit process by some institutions. The proposed CAPA was further discussed and developed through submission of post-meeting questions by the MHRA to Celgene, before being accepted by the lead inspector on 19 November 2019. The agreed CAPA and the most recent [redacted] Celgene 2018-2019 audit report, dated 05 Jun 2020, submitted to the MHRA were reviewed in detail during the inspection.

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The changes to the [redacted] self-audit process implemented since the January 2019 inspection are outlined below:

- The follow-up procedures for non-responders now included responsibilities for the Customer Care team to reach out to non-responding institutions, and methods of communication now included telephone calls, alongside reminder letters.
- Celgene had developed a prioritisation for institutions, which resulted in them being classified as high risk or low risk. High risk institutions were those that had ordered or received product either during the reporting period, or six months prior to the annual [redacted] Celgene audit report period. Low risk institutions did not meet these criteria. High risk institutions were prioritised for follow-up over low risk institutions.
- Celgene had introduced a process whereby institutions that did not respond to Celgene with self-audit data would no longer be eligible to receive [redacted] Celgene under the terms of the controlled distribution system. If institutions wished to continue receiving [redacted] Celgene, then the outstanding data would have to be supplied to Celgene.
- The process for clarifying discrepancies on the PAFs identified during self-audit had changed. This now included discrepancies for males as well as for women of child-bearing potential (WCBP), and now included a set number of follow-up attempts with associated timeframes.
- The process for managing non-adherence to the PPP identified during self-audit had changed and was now conducted in real-time upon receipt of the self-audit questionnaire. Celgene was categorising non-adherence as either confirmed or unconfirmed following attempted communication with the pharmacy. Non-adherence letters are now sent within two business days.
- The re-training for non-adherent pharmacies was now scheduled with an increased frequency, occurring every two months. Non-adherent pharmacies were followed-up and invited to attend training more regularly and, if pharmacies did not attend, an escalation process was now in place.
- Institutions which had reported non-adherence to the terms of the PPP for consecutive years are now identified from the self-audit data. Non-adherent institutions are invited for re-training.

C.2.2 Comments

Celgene may wish to review the process regarding pharmacies who have been de-registered due to not submitting self-audit data and wish to re-register.

At the current time, procedural document [redacted] "Registering Pharmacies and Physicians participating in the PPP for [redacted] (UK and Ireland)" [redacted] effective 13 Dec 2019) mandates that any missing data is required prior to re-registration. However, this could be supplemented further by outlining the specific information / data which is missing, alongside information about the institution at the time of de-registration. This may include the data which has not been provided to Celgene, which triggered de-registration, the classification of risk (either high or low) together with the amount of product supplied to the institution over the reporting period.
As re-registration may not occur for a number of years this information would assist in re-registering the institution quickly, allowing product to be supplied.

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.

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Celgene have adequately addressed the issues identified at the previous MHRA GPvP Inspection in January 2019. No additional responses are required at this time. The risk management system for all [redacted] products is considered to be in general compliance with applicable legislation at this time.

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. The acquisition of Celgene by Bristol-Myers Squibb and the planned merger of systems should be taken into consideration.

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).

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DATES**	16 – 17 July 2020 Follow-up days: w/c 20 July 2020
PHARMACOVIGILANCE INSPECTION OF	Celgene	**START TIME**	09:00
LOCATION	Remote inspection	**INSPECTION TEAM**	Rory Littlebury Sarah Gomersal
Inspection Plan			

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The inspection will focus on the remedial actions taken since the January 2019 GPvP Inspection of Celgene, in regards to the critical finding concerning risk management.

Specifically:

1. The changes to the [redacted] self-audit process, including the management of non-adherence.
2. The management of institutions who have not responded to the most recent self-audit.
3. The management of data from institutions who have responded to the most recent self-audit.

The inspection may also include other elements of the risk management system.

The inspection is intended to be performed through document review, with documents being supplied to the inspection team by close of business on 15th July 2020. Further document requests will be submitted through the course of the 16th and 17th of July and will be reviewed w/c 20th July 2020. There may be documents requested prior to the 15th July, and this will be made clear on the initial document request sheet.

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An opening meeting is proposed for 09:00 on the 16th July. This will allow an opportunity to discuss any inspection logistics. Celgene are also asked to provide a presentation which outlines the status of the CAPA from the previous inspection, and also outlines the current status of the acquisition of Celgene by BMS, in particular focused on the plans for the pharmacovigilance system.

Following the opening meeting, a separate presentation with appropriate SMEs is requested to outline the changes which have been made to the [redacted] self-audit process, and the actions which have been taken to collate and analyse the self-audit data which has been used for the [redacted] audit report dated 04-June-2020.

There will be a closing meeting on the final day of the inspection, envisaged to be Wednesday 22nd July, but this may change depending on the status of the inspection at this point.

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Celgene are asked to provide the names and job titles of those staff who will be available:

1. Opening meeting

[redacted]

2. Presentation of changes to [redacted] self-audit

[redacted]

3. Inspection host and other mailboxes which Celgene wish document requests and ad-hoc queries to be sent to

[redacted]