Medicines & Healthcare products
Regulatory Agency

Bristol Myers Squibb GCP Inspection Report

Inspection No: INSP GCP 11184/108564-0010

Published 18 November 2024

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Inspection Summary

Inspection & Organisation Information	
Inspection Number	INSP GCP 11184/108564-0010
Purpose of Inspection	Statutory GCP CAPA Review Inspection
Type of Inspection	Remote
Organisation Inspected	Bristol Myers Squibb
Organisation Address	ARC Uxbridge, Sanderson Road, New Denham, Denham, Buckinghamshire. UB8 1DH
Organisation Type	Commercial Sponsor
Dates of Inspection	13 to 15 November 2024
Lead Inspector	[redacted] Inspector [redacted]
Date of Closing Meeting	13 to 15 November 2024

Inspection Report Version History (For Inspectorate Use Only)	
Inspection Report Date 01	18 November 2024
Response Receipt Date 01	18 December 2024
MHRA Review Date 01	02 January 2025
Response Receipt Date 02	10 January 2025
MHRA Review Date 02	10 January 2025

Inspection Close Date	10 January 2025

Inspections and Findings Selected for CAPA Review	
Year	2018
Inspection Reference	INSP GCP 11184/108564-0005

Relevant Critical Finding	Record Keeping/Essential Documents
Year	2020
Inspection Reference	INSP GCP 31296/2907930-0015
Relevant Critical Finding	Pharmacovigilance
Year	2020
Inspection Reference	INSP GCP 11184/108564-0007
Relevant Critical Finding	Pharmacovigilance

Background Information

Company Background

Bristol Myers Squibb (BMS) is headquartered in Princeton, New Jersey and has UK sites in Buckinghamshire (head office), Cheshire (business services) and the Wirral (pharmaceutical research institute).

BMS primarily focuses on oncology and immunology, looking to address unmet needs in rheumatology, gastroenterology, dermatology and neurology.

In January 2019, BMS announced it would acquire Celgene. In September 2021 the eTMF integration was completed (into BMS's [redacted] TMF) and in March 2022 a new safety database was implemented (both BMS and legacy Celgene into [redacted]).

Inspection Scope

This inspection was conducted to review CAPA for the selected findings, evidence of implementation and how it has been managed across the new QMS following the BMS acquisition of Celgene. The inspection was conducted remotely via document review only, without any interviews.

Previous inspections had identified several critical findings and these were in scope for this inspection (except a PV finding identified at the INSP GCP 11184/108564-0005 in 2018 as this was reviewed at the INSP GCP 11184/108564-0007 inspection in 2020).

No trials were selected as part of this inspection and therefore the TMF itself was not reviewed but eTMF Functional Area Metrics Summary from September 2024 were.

Definitions of Findings

Critical

a. Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:

   i. the rights, safety or well-being of trial subjects either has been or has significant potential to be jeopardised, and/or

   ii. the clinical trial data are unreliable and/or

   iii. there are a number of Major non-compliances (defined in (d) and (e)) across areas of responsibility, indicating a systematic quality assurance failure, and/or

b. Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (d) and (e)).

c. Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations.

Major

d. A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or

e. Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.

Other

f. Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.

Reference Texts

- UK Medicines Act 1968.
- The Human Medicines Regulations 2012, SI 1916 and the applicable statutory instruments including 2004/1031 (and subsequent amendments).
- ICH E6 'Note for Guidance on Good Clinical Practice'.
- Annex 13 to the EU Guide to Good Manufacturing Practice, 'Manufacture of Investigational Medicinal Products', July 2010.
- ICH E2A 'Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'.
- Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial ('CT-1') (2010/C 82/01).
- Communication from the Commission — 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).
- Heads of Medicines Agencies, Clinical Trial Facilitation & Coordination Group — Q&A Document: Reference Safety Information, November 2017 (RSI).

List of Common Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Product
CA	Competent Authority
CAPA	Corrective Action Preventive Action
CI	Chief Investigator
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CSV	Computer Systems Validation
CTA	Clinical Trial Authorisation or Clinical Trial Agreement
CTFG	Clinical Trial Facilitation Group
CTIMP	Clinical Trial of an Investigational Medicinal Product
CV	Curriculum Vitae
DE	Dose Escalation
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
eCRF	Electronic CRF
eCOA	Electronic Clinical Outcome Assessment
ePRO	Electronic Patient Reported Outcome
eTMF	Electronic Trial Master File
FIH	First in Human
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ISF	Investigator Site File/Investigator TMF
LPLV	Last Patient Last Visit
MAA	Marketing Authorisation Application
MHRA	Medicines and Healthcare products Regulatory Agency
MVR	Monitoring Visit Report

PI	Principal Investigator
PIS	Patient Information Sheet
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person
RA	Regulatory Authority
R&D	Research and Development
REC	Research Ethics Committee
RMP	Risk Management Plan
RSI	Reference Safety Information
RWD	Real World Data
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SDR	Source Data Review
SmPC / SPC	Summary of Product Characteristics
SI	Sub-investigator
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TOPS	The Over-volunteering Prevention Scheme
UAT	User Acceptance Testing

Sponsor Inspection Findings

INSTRUCTIONS TO INSPECTED ORGANISATION

Inspection responses and any subsequent clarifications should be completed in the fields provided for each numbered finding. Please ensure there is a different row for each corrective and preventative action with the planned completion dates. Do not append any additional documentation or insert any file links. Please provide any other referenced documents as separate files.

No responses are required to any observations and recommendations.

1. Critical Findings

There were **no Critical findings** identified during this inspection.

2. Major Findings

There were **no Major findings** identified during this inspection.

3. Other Findings

There was **one Other finding** identified during this inspection relating to **Quality Assurance**.

3.1	**Quality Assurance**
3.1.1	At the previous inspection of Celgene (INSP GCP 31296/2907930-0015), it was identified that 'it was standard practice to assess 'lack of efficacy' events as 'expected', irrelevant of the terms that were listed in the RSI'. The CAPA commitment was to update [redacted] and provide training to impacted staff that 'only events explicitly stated in the RSI section of an IB or comparator RSI are considered expected, and events not listed in the RSI are considered unexpected for the purposes of regulatory reporting. Lack of efficacy, unless listed in the RSI, will be considered unexpected.' However, this CAPA had not been implemented: • [redacted] dated 29 July 2020 was updated to state that lack of efficacy/drug ineffective would be considered unexpected as per an IB but 'lack of effect, and similar PTs will be considered labelled for CCDS [Company Core Data Sheet], and local labels including SmPC and USPI [United States Package Insert] (as no drug is 100% effective), for both approved and unapproved indications'.

	• The current BMS process [redacted] dated 30 September 2024 was less clear on requirements but described that 'non-ADR' concepts (e.g. lack of efficacy) would be manually amended to 'labelled' and inspection document request 01 stated 'lack of efficacy would generally be considered expected for marketed product labels including SmPCs used as RSI for comparator products in clinical trials (as no drug is expected to be 100% effective in all patients), but be subject to reassessment based on medical judgment. For clinical trials using the IB as RSI, the approach of only considering events explicitly stated in the RSI as expected continues to be utilised. Events not explicitly stated in the IB RSI including lack of efficacy are considered unexpected.' *This finding has been defined as an 'other' as follow-up to inspection document request 01 confirmed that the BMS safety database contained no serious cases of lack of efficacy between 01 May 2020 and 12 November 2024 and therefore no cases of unreported SUSARs were identified.*

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	[redacted]
Preventative Action(s)	[redacted]
MHRA Review - 01	
[redacted]	

Inspected Organisation's Response - 02

[redacted]

MHRA Review - 02

Response accepted.

Observations and Recommendations

The were no observations and recommendations identified during this inspection.

Report Author:

[redacted]

[redacted] Inspector, [redacted] MHRA

Report Reviewer:

[redacted]

[redacted] Inspector, [redacted] MHRA

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.

Appendix I Summary of Activities

Inspected Organisation

Activity	Assessed			Comment
	Yes	Partial	No	
Analytical Laboratory			✓	
Archiving			✓	
BE/ BA Activities			✓	
Clinical Pathology Laboratory			✓	
Clinical Trial Reporting			✓	
Computerised Systems			✓	
Contracts & Agreements			✓	
Data Management			✓	
eCRF / Diaries / IVRS			✓	
IMP Management			✓	
Medical Affairs			✓	
Monitoring			✓	
Pharmacovigilance		✓		Review of CAPA and current procedures.
Project Management			✓	
Quality Assurance		✓		Review of CAPA.
Quality Systems			✓	
R&D Unit (Non-commercial only)			✓	
Regulatory Affairs			✓	
Statistical Analysis			✓	

Technical Facility (i.e. x-ray)			✓	
Training			✓	
Trial Master File/Essential Documents		✓		Review of CAPA and current procedures.
Other			✓	

Appendix II

Inspection Closing Statement

GCP INSPECTION STATEMENT

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Dates of Inspection	13 to 15 November 2024
Lead Inspector	[redacted] Inspector [redacted]
Date of Inspection Statement	13 to 15 November 2024

The organisation has provided corrective and preventative actions in response to the inspection report. These have been reviewed by the GCP Inspectorate and are considered acceptable. This inspection can be considered closed.

In summary:

There were no critical or major findings identified during this inspection.

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

Statement Issued by

[redacted]

[redacted] Inspector, [redacted], MHRA