Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Novartis

MHRA Inspection Number: Insp GPvP 101/1135-0016

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QA	Quality Assurance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Novartis PSMF [redacted]
Site(s) of inspection:	Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR
Main site contact:	[redacted] Novartis Pharma GmbH Blankreutestrasse 1 D-79108 Freiburg Office (D): + 49-(0)761-1304-309 Office (CH): +41-61 324 9055 Mobile (7x24): +49-172-654-4554 E-Mail [redacted]
Date(s) of inspection:	17 – 21 July 2017
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	UK systems re-inspection **Inspection no°:** GPvP 101-376165-0004 **Dates:** 19 – 23 August 2013 **Location:** Frimley, UK UK systems re-inspection **Inspection no°:** GPvP 101/376165-0003 **Dates:** 3 – 4 May 2011 and 28 – 30 June 2011 **Location:** Frimley, UK and Basel, Switzerland UK systems re-inspection **Inspection no°:** GPvP 101/376165-0002 **Dates:** 1 - 5 March 2010 **Location:** Horsham, UK CHMP re-inspection of [redacted] **Inspection no°:** EMA/INSP/PhV/2010/02 **Dates:** 13 - 16 July 2010 **Location:** Basel, Switzerland UK systems inspection **Inspection no°:** GPvP 101/376165-0001 **Dates:** 18 - 21 August 2008 & 11 Nov 2008 **Location:** Frimley & Horsham, UK Inspection of Licence Partner, Genentech **Inspection no°:** EMEA-INS-GCP-2008-08 **Date:** 15 - 18 September 2008

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	Location: US – Genentech site EMA triggered inspection - Lucentis® **Inspection no°:** EMEA-INS-GCP-2008-08 **Dates:** 29 September - 3 October 2008 **Location:** Basel, Switzerland
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, specific ADR reports and other documents were examined for [redacted] amongst other products.
Name and location of EU QPPV:	[redacted] Contact details as above.
Global PV database (in use at the time of the inspection):	ARGUS v7.0.5
Key service provider(s):	• Cognizant Technology Solutions contracted to provide case processing, data management and aggregate report preparation services. • Accenture contracted to provide case processing, literature screening and aggregate report preparation services. • PAREXEL newly contracted to provide aggregate report and risk management plan preparation services. • Quintiles contracted to provide case processing services (for Sandoz International GmbH). • ProPharma contracted to provide medical information services in the UK.
Inspection finding summary:	0 Critical findings 3 Major findings 6 Minor findings
Date of first issue of report to MAH:	18 August 2017
Deadline for submission of responses by MAH:	Initial: 22 September 2017 Follow-up: 01 November 2017 Follow-up: 30 November 2017
Date(s) of receipt of responses from MAH:	Initial: 22 September 2017 Follow-up: 01 November 2017 Follow-up: 24 November 2017
Date of final version of report:	24 November 2017
Report author:	[redacted]r

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Novartis 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.

The Novartis Group comprises three unique divisions:

- Novartis Pharmaceuticals and Novartis Oncology form the Innovative Medicines Division.
- Sandoz is the generic pharmaceutical division of Novartis and holds marketing authorisations (MA) for generic medicines and biosimilars.
- Alcon specialises in ophthalmology care, including eye care medicinal products, contact lens products and surgical devices.

Previously the Novartis business divisions had independent PV systems and corresponding PSMFs. However, since 2016 Novartis has been integrating the PV systems of Novartis Pharmaceuticals and Novartis Oncology ("PharmOnc"), Sandoz and Alcon into one PV system, under the umbrella of the newly created Global Drug Development (GDD) function. The integrated PV system, described in PSMF [redacted] (legacy PharmOnc PV system), came into effect as of 03 July 2017. Full completion of the integrated system was expected to occur in 2019, with harmonised processes and procedural documents across the three divisions, integration of additional IT platforms and migration of data. The pharmacovigilance organisation within Novartis is entitled 'Chief Medical Office (CMO) and Patient Safety', which reports into Novartis GDD.

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In March 2015, Novartis Pharma acquired GSK's oncology product portfolio and divested the vaccine portfolio (with the exception of the influenza vaccines) to GSK (see section C.1 for further details). The influenza vaccine portfolio has since been divested to Seqirus (a CSL company). GSK and Novartis have also entered into a Consumer Healthcare joint venture and GSK is providing the PV system for the products included within this joint venture (PSMF [redacted]

The status of the associated Novartis PSMFs can be summarised as follows:

Novartis:	PSMF [redacted] (active) (valid for all MAHs within Novartis Pharmaceuticals, Novartis Oncology, Alcon and Sandoz)
Novartis Vaccines:	PSMF [redacted] (retired)
Novartis Consumer Health:	PSMF [redacted] (retired)
Sandoz:	PSMF [redacted] (retired)
Alcon:	PSMF [redacted] (retired)

The Federal Institute for Drugs and Medical Devices (BfArM) in Germany, as the supervisory authority, is responsible for performing pharmacovigilance inspections of Novartis as part of the EU plan for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products. The last inspection of Novartis by BfArM was performed in April 2015.

B.2 Scope of the inspection

The focus of the inspection was on the activities conducted at a national level in the UK and those activities conducted globally that directly impacted the UK. The inspection was performed at Novartis's offices in Frimley, Surrey, and personnel from Basel, Switzerland and other CMO and Patient Safety global sites attended the Frimley site in order to participate in the inspection.

Specific activities within the scope of the inspection included:

- Transfer of pharmacovigilance data and activities for Oncology products following the GSK-Novartis transaction.
- Receipt of ICSRs from local sources, including patient oriented programmes (POPs), social and digital media, medical information enquiries and investigator-initiated trials.
- Reconciliation of safety data with third-parties.
- Processing, follow-up and reporting of ICSRs, with an emphasis on the role of Patient Safety in the UK Country Pharma Organisation (CPO).
- Set up and maintenance of locally managed pharmacovigilance agreements.
- Set up and management of locally managed non-interventional studies.
- Maintenance of UK authorised product information, e.g. SmPCs and PILs.
- Implementation of additional risk minimisation measures in the UK.
- Pharmacovigilance training for UK Patient Safety staff.
- Creation and maintenance of written procedures describing local pharmacovigilance activities.
- Mechanisms to monitor local pharmacovigilance processes and identify non-compliance, including audit.

The inspection was performed using interviews and document review (including outputs from the global safety database). The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

B.3 Documents submitted prior to the inspection

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The company submitted PSMF [redacted] which at the time was valid for all MAHs within Novartis Pharmaceuticals and Novartis Oncology. The company subsequently submitted PSMF [redacted] which was valid for all MAHs within Novartis Pharmaceuticals, Novartis Oncology, Alcon and Sandoz.

Specific additional documents were also requested by the inspection team and provided by the company, prior to the inspection. The details of these pre-inspection requests are contained within request sheets A – H.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the inspection plan.

Details of adverse reaction reports reviewed during the inspection for specific products are contained in the inspection notes.

The inspection was not completed during the onsite days (17 – 21 July 2017), although a closing meeting was held at Frimley, Surrey on 21 July 2017 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 further teleconference was held on 31 July 2017 to address some final points and to summarise the inspection status. A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Records, 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, the company had made the following significant changes to the pharmacovigilance system:

- In March 2015, Novartis Pharma acquired GSK's oncology product portfolio and divested the vaccine portfolio (with the exception of the influenza vaccines) to GSK. At day 1 of the transaction (02-Mar-2015), GSK continued to maintain the pharmacovigilance system for the oncology products, and all ICSRs, aggregate reports, RMPs and other safety deliverables were prepared using the data in the GSK global safety database. The safety database transfer from GSK to Novartis was completed on 19-Oct-2015 covering 11 products and, post data transfer, all pharmacovigilance activities transferred to Novartis. The safety database transfer from Novartis to GSK for all non-flu vaccines was completed on 16-Nov-2015.

- Since 2016, Novartis has been integrating the PV systems of Novartis Pharmaceuticals & Novartis Oncology, Sandoz and Alcon into one PV system (see section B.1 for further details).

- In August 2016, the transfer of Alcon's medicinal products portfolio to Novartis Pharmaceuticals commenced and transfer of marketing authorisations is proceeding across the globe for nearly all markets. By July 2017 it is anticipated that the UK Novartis Pharma portfolio will encompass all previous Alcon pharmaceutical drugs.

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- [redacted]as EU QPPV in September 2016.

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 at: https://www.gov.uk/good-pharmacovigilance-practice-gpvp#actions-after-the-inspection

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:

Regulation (EC) No. 726/2004 as amended

Article 28 (1).

Directive 2001/83/EC as amended

Article 107(1) *"Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study."*

Article 107(3).

GVP Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1)

VI.B.2 (Validation of reports) *"Only valid ICSRs qualify for reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the competent authorities to make sure that the minimum criteria for reporting are included in the reports".*

VI.B.7.1 (Reporting time frames) *"In general, the reporting of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by the national or regional pharmacovigilance centre of a competent authority or by any personnel of the marketing authorisation holder, including medical representatives and contractors."*

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

Finding MA.1 a)

There were examples of non-valid cases without identifiable patients that had been incorrectly reported to EudraVigilance. For example:

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- [redacted] a spontaneous US case fo[redacted] of multiple sclerosis relapse, received on 09-Jun-2017 and submitted to [redacted]on 21-Jun-2017. There were no patient identifiers in this case; however, "--" was recorded within the patient initials field in the global safety database, thus generating an automated

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submission to EudraVigilance via the in-built Argus reporting rules, despite being non-valid.

- [redacted] a spontaneous case from Japan for [redacted] of haematochezia and gastrointestinal haemorrhage, received on 17-Sep-2015. Novartis confirmed that *"The patient initials were entered with a dummy entry of XX as this is required for Japan to schedule/expedite the E2B file to PMDA as they require the field not to be blank according to local expediting requirement".* This entry in the patient initials field generated an automated submission to EudraVigilance on 28-Sep-2015.

It should be noted that these cases had not been reported to MHRA, due to manual interventions in the local reporting process employed by Patient Safety in the UK CPO.

Root Cause Analysis

[redacted]

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Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 b)
There were examples of valid ICSRs recorded within the UK Argus Affiliate module that had not been transmitted to the global safety database (Argus Core). The following two cases were identified out of a sample of 11 cases that had been initially assessed as non-valid and had not been transmitted to the safety database for processing. [Note: This sample of 11 was taken from 4871 reports received and assessed as non-valid in the period 02-Jan-2015 to 15-Jul-2017.] • [redacted] this was a [redacted] case with an initial receipt date of 07-Jul-2015, and events captured in Argus Affiliate on initial receipt were recorded as *"range of issues"*. • [redacted] this was a [redacted] case with an initial receipt date of 21-Oct-2016, and events captured in Argus Affiliate on initial receipt were recorded as *"Numberous side effects - not sufficient as an AE"* [sic]. Upon review of the source documents for these two cases during the inspection, the MAH confirmed that these cases were incorrectly assessed as non-valid, as adverse events had incorrectly not been identified during review of the source documents at the time of initial receipt. The cases were entered into Argus Core during the inspection and follow-up was subsequently initiated.

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

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

Preventative Action(s)
[redacted]

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

Finding MA.1 c)

A serious UK [redacted] initially received on 21-Jul-2016 with reported events of atrioventricular block second degree, neuroendocrine tumour and death, had not been reported on an expedited basis to the MHRA in accordance with EU reporting requirements.

The MAH confirmed that the initial report was non-valid due to a lack of patient identifiers; however, despite the fact that follow-up information received on 14-Nov-2016 included the patient's initials, a report was not scheduled to the MHRA in error.

Whilst it is acknowledged that this was the only missed report to MHRA identified by the inspector out of multiple cases sampled, following targeted interrogation of a line listing from the global safety database, cardiac disorders are included in the [redacted] as important identified and potential risks. Therefore, this fatal report could represent important information for this product.

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.2 Risk Management System

Requirements:

Regulation (EC) No. 726/2004 as amended

Article 21 (1).

Directive 2001/83/EC as amended

Article 104 (2) and (3)(c) *"As part of the pharmacovigilance system, the marketing authorisation holder shall: operate a risk management system for each medicinal product".*

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916)

Part 11 Pharmacovigilance, Regulation 182(c).

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)

XVI.B.6 (Quality systems of risk minimisation measures) *"These records, the RMP and the associated risk management systems, as well as any documents on risk minimisation measures may be subject to audit or inspection".*

A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions. Risk management is applicable to medicinal products at any point in their lifecycle. The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

The following findings were noted in relation to risk management systems:

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Finding MA.2 a)

Novartis had failed to adequately fulfil an RMP commitment to implement additional risk minimisation measures for [redacted] specifically relating to the distribution of educational materials in the UK.

i. The [redacted] included a commitment to provide educational materials to healthcare professionals (HCP) that included instructions on the dosing regimen, in order to minimise the risk of medication errors. The MHRA had agreed the materials, which included two types of patient adherence/dosage cards, the patient information leaflet and a cover letter explaining the pack and re-affirming the black triangle status of the product. The agreed distribution plan for the UK consisted of an initial mailing of the materials in February 2016, and subsequent yearly mailings in February 2017 and February 2018, to haematology doctors, haematology nurses and pharmacists (the mailing list reviewed on inspection was just under 2,000 names and addresses).

   The MAH had performed a mailing of the educational materials in February 2016,

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however the February 2017 mailing had not been performed.

ii. The agreed distribution plan outlined that, for the subsequent mailings in February 2017 and February 2018, any HCPs who had requested educational materials in the year between mailings would be added to the mailing list. However, the current mailing list did not include the following HCPs who had requested educational materials since the initial mailing in February 2016:

Ref	Date of request	Name	Occupation	In mailing list?
[redacted]	04/05/2016	[redacted]	Clinical Nurse Specialist	No
[redacted]	05/05/2016	[redacted]	Haematology Pharmacist	No
[redacted]	06/10/2016	[redacted]	HCP, unknown	No
[redacted]	15/11/2016	Phone request - Unknown	Unknown	The request was from Guernsey and there were no Guernsey postcodes in the mailing list.

It is acknowledged that the second mailing was not performed, as per the finding raised under point i. However, even if it had been performed, the above HCPs would not have received the materials as they had not been added to the mailing list. It should also be noted that for reference [redacted](above), there were no additional records retained of the request. Therefore, there was no specific address in Guernsey to be added to the current mailing list fo[redacted]educational materials.

Root Cause Analysis

[redacted]

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Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

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[redacted]

Finding MA.2 b)

Deficiencies were identified with regards to the distribution of [redacted] patient reminder cards in accordance with the distribution plan agreed by the MHRA.

The distribution plan (sent to MHRA on 16-Sep-2015) outlined the following:

- Patient reminder cards will be sent to Trust pharmacies ordering in the last 12 months with a covering letter requesting that the card is passed onwards to treating HCPs.
- The letter will notify HCPs to contact Novartis medical information for further copies, as required.
- The reminder card will also be sent to any additional Trust pharmacies that order [redacted] in the future.

There was evidence that in December 2015, patient reminder cards were sent to Trust pharmacies who had ordered [redacted] within the previous 12 months. However, the MAH did not send out any further patient reminder cards until June 2016, covering orders placed in the period January to June 2016. A retrospective 6-monthly mailing of the cards is not considered to be an appropriate way to fulfil the obligation to send reminder cards to any additional Trust pharmacies that order [redacted] in the future.

In addition, when records of the June 2016 mailing were requested during the inspection, only a distribution list used for the mailing was provided and there was no evidence that the actual mailing had taken place.

It is noted that from July 2016, Novartis had entered into an agreement with [redacted] a distribution partner, to stock the patient reminder cards along with the product, and an automated system picked both items together when an order for [redacted] was received. The MAH had oversight of the total numbers of cards and orders fo[redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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

Finding MA.2 c)

Novartis had published educational materials on the electronic Medicines Compendium (eMC) website, to facilitate access by HCPs and patients. There was no documented timeline described in any procedural document for updating the eMC following the approval of updated educational materials and delays were noted in updating eMC with revised versions of materials.

i. On 06-Feb-2017, updated educational materials for [redacted] were agreed by the MHRA. The updated materials included the Preparation and Injection Guide, Healthcare Professional Guide and patient alert cards for the indications Cryopyrin-Associated Periodic Syndromes (CAPS), Still's disease (including Systemic Juvenile Idiopathic Arthritis (SJIA)) and Gouty Arthritis. Changes to the materials included information regarding Still's disease and included the risk associated with the use of live vaccines in new-borns exposed to canakinumab in utero.

   The agreed distribution plan included uploading copies of the updated documents on the eMC, replacing the previous versions which were already published. The materials were not updated on the eMC until 05-May-2017, 88 days after the materials had been agreed by the MHRA.

ii. The [redacted] educational materials were updated to include the

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extension of the idiopathic thrombocytopenia purpura (ITP) indication for paediatric use and updated guidance on food interactions, and the revised materials were agreed by the MHRA on 07-Nov-2016. The distribution plan agreed with MHRA stated:

"Key Milestones: All materials will be available on the eMC website following MHRA approval. Novartis Medical Information will have all materials available to supply on request."

However, the eMC was not updated until 23-Nov-2016, 16 days after the materials had been agreed by the MHRA. It is acknowledged that this is a minor delay; however, the eMC was the only mechanism for communication of these materials in the UK, as the MHRA had agreed that a proactive mailing direct to HCPs was not required.

UK Regulatory Affairs was responsible for submitting materials for review by the MHRA and for uploading agreed materials onto the eMC (where required). Procedural document SOP-[redacted] 'UK CPO Review & Approval of Promotional & Non-Promotional Material' [redacted] tated only that materials should be updated in a "timely manner"; no actual timeline was specified. It is expected that product information, including educational materials, published on external medicines compendia and company websites, are uploaded within 10 working days of acceptance by the Agency.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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

MA.3 Non-interventional Studies, including Post-Authorisation Safety Studies

Requirements:

GVP Module VI – Management and reporting of adverse reactions to medicinal products

VI.A.2.4 (Seriousness) *"As described in ICH-E2A, a serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect."*

GVP Module VIII – Post-authorisation safety studies

VIII.B.6 (Data protection) *"For non-interventional PASS imposed as an obligation, the marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information […]. This provision should be also followed for PASS required in the risk management plan agreed in the EU or conducted voluntarily in the EU."*

A PASS is defined in Directive 2001/83/EC as amended, as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

The following findings were noted in relation to PASS:

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Finding MA.3 a)

Case [redacted] received from [redacted] (a 5-year observational paediatric PASS), included a serious adverse event of renal tubular disorder, which did not appear within Table 12-7 'Serious adverse events with suspected relationship to study drug, by primary SOC and preferred term' in section 12.3.2 'Serious adverse events', within the final study report (dated 23-Oct-2015).

The rationale provided by Novartis for why the SAE did not appear in the final study report was that the seriousness was not reported. However, the initial source document was an SAE report form and included a seriousness criterion of 3, which was defined as "involved or prolonged inpatient hospitalisation". The follow-up information dated 23-Jan-2013 confirmed that the patient was hospitalised from 18-Jan-2012 to 20-Jan-2012. The reporter also indicated on the SAE form that there was a reasonable possibility that the study treatment caused the event.

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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 MA.3 b)

There was an example of where a PASS protocol had not been adhered to with regards to site monitoring visits.

Afinitor (everolimus) PASS [redacted](A phase IV multicentre, open-label, non-interventional study of postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer treated with [redacted] in combination with [redacted]…]) was a locally managed UK-only PASS. Section 9.8 of the protocol[redacted] under the heading 'Site Monitoring', stated:

"During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, adherence to the protocol and Good Clinical Practice, progress of enrolment, and to ensure study treatment is being dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits."

There was no evidence of any site visits having been conducted during the study, instead only telephone monitoring had been performed.

Whilst there was evidence of some information recorded in the eCRF being verified by the data management service provider, Syne Qua Non, through requesting source documentation from the sites, this was only where queries existed with the information recorded in the eCRF. As a result, there was limited source data verification using patient records, to ensure the completeness and accuracy of the information reported from the

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study.

This study was listed in Part III.4.4 (Stated additional pharmacovigilance activities) of the [redacted] and the final study report was in draft at the time of the inspection.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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

C.4.3 Minor findings

MI.1 Management and Reporting of Adverse Reactions

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

Finding MI.1 a)

There were some issues identified in relation to event-level seriousness assessment, as per the MAH's internal procedural guidance on the assignment of seriousness classification.

Novartis utilised a list of important medical events (NVS-IME) to facilitate the assessment of seriousness at event level. The instructions for the use of the NVS-IME list in [redacted] 'Working Practice for Seriousness Criteria Assessment' [redacted] were stringent; section 4.2 stated that:

"For events that were originally reported as non-serious that have been upgraded because the event is included in the NVS-IME list, may only be downgraded again to non-serious by the medical reviewer if the "downgrade" is included in the PGD [product guidance document] for the product. Any "downgrade for IME specified events" must be clearly documented in the PGD [product guidance document] *for the product".*

i. [redacted] a non-interventional study case concerning [redacted] and the event of *"progression of Alzheimer's disease"* reported by the investigator, which had been coded to a MedDRA Preferred Term (PT) of 'Dementia Alzheimer's type' (serious per NVS-IME list), had been assessed as non-serious. The company stated that the rationale for assessing the event as non-serious was because it was a report of disease progression and not new onset of disease. This assessment was not in line with [redacted] as there was no information contained within the Lucentis PGD to justify the downgrade.

ii. [redacted] a consumer case received via a patient support programme concerning [redacted] and the reported event of nephrolithiasis (serious per NVS-IME list). The company stated that the event had been classified as non-serious as *"Nephrolithiasis seems to be an incidental finding and there is no evidence of immediate intervention necessary to prevent life threatening consequences",* as it had been identified following a routine ultrasound for an ovarian cyst. This assessment was not in line with [redacted] as there was no information contained within the [redacted] to justify the downgrade. In addition, the fact that it was an incidental finding should not influence the assessment of seriousness.

iii. [redacted] a case reported from a HCP via a patient support programme concerning [redacted] and the reported event *"dysdiadochokinesis on the left upper limb",* which was coded to the PT of 'cerebellar syndrome' (serious per NVS-IME list). The company stated that the symptoms reported for cerebellar syndrome were *"typical MS symptoms and no worsening or aggravation of the events was reported. Hence event was assessed non-serious".* This assessment was not in line with [redacted] as there was no information contained within the [redacted] to justify the downgrade, and the rationale provided is rather an assessment of causality.

iv. [redacted] a case reported by a consumer via a patient support

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programme concerning [redacted] and the reported event *"suppresses her immune system"*, which was coded to the PT of 'immunosuppression' (serious per NVS-IME list). The company stated that, as the event term used was *"a consumer reported term used when describing a self-reported upper respiratory tract infection"* the event was coded but considered non-serious by the safety physician. This assessment was not in line with [redacted] as there was no information contained within the [redacted] to justify the downgrade. In addition, the ICSR seriousness criterion should not be downgraded from serious to non-serious if the receiver disagrees with the seriousness reported by the primary source.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MI.1 b)

A review of the risk of multiple sclerosis (MS) rebound effect following cessation of [redacted] therapy had been ongoing by the PRAC since September 2016. The MAH had submitted for regulatory assessment a cumulative review of all relevant data from all sources on a potential rebound effect, and in the assessment report prepared by the PRAC Rapporteur in March 2017 concerns were raised around whether cases describing this event had been coded appropriately, in order to facilitate the detection of this safety signal.

"Rebound effect" or "rebound phenomenon" is usually referred to when a medication is discontinued, and there is a re-emergence of symptoms (either absent or controlled while taking the medication) which are now worse (in frequency and/or severity) than pre-treatment levels (i.e., the baseline).

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All [redacted] cases in the safety database where a PT of 'multiple sclerosis' had been coded, as well as several cases of disease progression, condition aggravated and similar, were reviewed during the inspection to assess whether they represented a report of rebound effect or rebound phenomenon. One case out of the 15 sampled appeared to contain a report of neurological worsening with severe lesions in the brain following [redacted] cessation [redacted] Polish CT case).

It is acknowledged that the event of rebound syndrome is not a fully defined syndrome and discussions are continuing with EMA on the classification of this event. However, there was no evidence that further information was sought from the investigator to assess whether this was a case of MS rebound. In addition, the limited information in the internal product guidance document and the study protocol (as outlined below) did not facilitate identification of this potential case of MS rebound.

- The company's internal product guidance document for [redacted] included guidance on the coding of cases of rebound effect in section 4.6, which stated that:

  "CT / NIS cases: Cases of MS relapse/CNS lesion/disease progression/rebound reported in clinical studies should follow conventions determined in the protocol."

- The protocol for the study from which the SAE in [redacted] was reported [redacted] did not contain any event-specific conventions regarding the reporting of SAEs (section 7.2), including for reporting of suspected MS rebound cases.

Root Cause Analysis

[redacted]

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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 c)
A communication to the Pharmacovigilance Operations team responsible for managing ICSRs regarding a known database issue was not disseminated in a timely manner. It was identified following the migration of the ICSR data from GSK to Novartis for the

oncology products that, when a non-significant follow-up/correction is performed on a case for the first time, the "Auto Schedule Later" checkbox gets automatically ticked upon locking the case, which results in regulatory reports being generated for the non-significant follow-up/correction for previously reported cases.

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The issue was raised on 19-Oct-2015 but a communication to the Pharmacovigilance Operations team was not sent until 14-Jul-2017, shortly prior to the inspection. The communication instructed staff to uncheck the "Auto Schedule Later" checkbox immediately post locking the case to prevent erroneous scheduling of reports. It was also noted that an associated update to MAP chapter 16 was in the approval stage at the time of the inspection.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

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[redacted]

Preventative Action(s)

[redacted]

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

Finding MI.1 d)

The following minor case processing errors were identified and were not considered to be systemic issues upon review of the dataset provided in inspection request B5.

i. Clinical trial case, [redacted] did not have an associated protocol ID number. The MAH stated that this was due to an error during processing of non-significant follow-up information and therefore there was no impact on expedited reporting. However, the MAH should consider whether there has been any other impact on aggregate reporting or other down-stream pharmacovigilance activities.

ii. The following cases did not have a case level seriousness assigned, even though events within the cases had been coded as non-serious. The MAH should consider whether there has been any impact on aggregate reporting or other down-stream pharmacovigilance activities.

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The cases were corrected by the MAH during the inspection.

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)

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MI.2 Regulatory Affairs

When new information about the benefits and risks of a product becomes available it is often appropriate to make changes to reference safety information documents, such as SmPCs, PILs and investigator's brochures (IBs), so that HCPs, patients or trial subjects are able to use the medicinal product correctly on the basis of full and comprehensive information.

The following findings were noted in relation to control and maintenance of reference safety information:

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Finding MI.2 a)

There were some examples of discrepancies with no documented justification between the CCDS and the EU SmPCs for [redacted] which were products acquired from GSK in 2015. The details of the discrepancies are included in Appendix III.

These were mainly differences in the known frequencies of specific event terms; however, there was an example of a missing term in section 4.8 (Undesirable effects) of the [redacted] SmPC; specifically, the term Torsade de Pointes, which was included in the [redacted] CCDS. However, it is acknowledged that this medical concept was included in section 4.4 of the SmPC.

[redacted]

Root Cause Analysis

[redacted]

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[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

[redacted]

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

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Preventative Action(s)

[redacted]

[redacted]

Root Cause Analysis

[redacted]

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[redacted]

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[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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Deliverable(s)	Due Date(s)

Preventative Action(s)

Deliverable(s)	Due Date(s)

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[redacted]

Finding MI.2 b)

A variation to update safety and pharmacogenomic information in the [redacted] EU SmPC had been approved on 22-Mar-2016. The variation was to add information into section 4.4 (Special warnings and precautions) and section 5.1 (Pharmacodynamic properties) regarding an increased risk of ALT elevations in certain populations, and to add contraception information in the pregnancy and lactation section. The eMC was not updated with the approved SmPC until 26-Sep-2016, a delay of over six months.

It is expected that product information published on external medicines compendia and company websites, is updated within 10 working days of receipt of approval.

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]	

MI.3 Pharmacovigilance Audit

The following finding was identified in relation to the risk assessment process for the purposes of pharmacovigilance audit planning:

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Finding MI.3 a)

The planning of pharmacovigilance audits was undertaken by the global Compliance and Audit group, in accordance with SOP [redacted] Annual UQAP Audit Planning' [redacted] The frequency of audits of business partners was defined based on a risk assessment. However, there was no defined process to identify and risk assess all local pharmacovigilance business partners (excluding POP vendors) relevant to the UK, for consideration for inclusion in the global audit schedule.

It was stated that high risk business partners identified due to poor performance are notified to the global Quality Assurance department via the CPO; however, there was not a systematic process to ensure that a suitable risk assessment was performed for all pharmacovigilance activities that had been delegated to another organisation.

As an example, there had been no documented risk assessment of the following UK business partners for the purposes of audit planning:

Name	Type of agreement
[redacted]	Co-promotion agreement
[redacted]	Co-promotion agreement
[redacted]	Outsourcing of PV activities
[redacted]	Outsourcing of PV activities
[redacted]	Outsourcing of PV activities

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]	

MI.4 Pharmacovigilance System Master File

The following finding was identified in relation to the PSMF:

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Finding MI.4 a)
Alloga, a UK distribution partner, was not listed within annex B.9.7 (Service providers and commercial arrangements on local level for EU/EEA countries) o[redacted]of the PSMF, which was provided to the MHRA prior to the inspection. This was subsequently queried by the inspector and the business partner was added to annex B.9.7.a (Pharma service providers and commercial arrangements on local level for EU/EEA countries) of PSMF version 15.1.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

MI.5 Record Management

The following finding was identified in relation to the management of pharmacovigilance records:

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Finding MI.5 a)
Source documents for case [redacted] specifically for the initial version of the case [redacted] and three follow-up versions [redacted] could not be retrieved from archive to be provided to the inspection team.
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]	

MI.6 Written Instructions

The following findings were identified in relation to written procedures, including lack of a documented process for provision of educational materials and a deviation from a written procedure:

Finding MI.6 a)
There was no documented process which supported the provision of educational materials to HCPs and patients, following ad hoc requests directed to the Novartis medical information function. Educational materials were available for several products authorised in the UK to fulfil additional risk minimisation commitments. In practice, requests for educational materials received by the medical information function were directed to the respective Business Franchise assistant, who would place an order with the third-party mailing distributors to organise delivery.
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]	

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Finding MI.6 b)
The PASS assessment form [redacted] (Cardiac monitoring of D2406 patients) had not been reviewed or approved by the EU

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QPPV, or deputy, prior to the study commencing, which was not in accordance with written procedures.

SOP [redacted] 'PASS requirements for Clinical Studies' [redacted] Section 4.1.1 outlined that a PASS assessment form should be completed, reviewed and signed by the EU QPPV, or deputy, for global or regional studies, to document the EU QPPV approval of the PASS classification prior to the study starting [redacted] also indicated that the form should be signed by the EU QPPV prior to the study starting:

"If the study PASS Assessment is Yes, send a copy of form and Study Concept sheet to: eu-eea.qp@novartis.com for EU QPPV approval and is included as part of the documentation for the Study Concept review and then archived with the study documentation".

The PASS assessment form for study [redacted] (first patient, first visit 29-Sep-2014) was not sent to the EU QPPV for review and approval until 16-Jun-2015. The form was sent to the EU QPPV again on the 16-Oct-2015, as there had been no approval received by the Clinical Scientific Director. The form was ultimately signed by the deputy QPPV on the 19-Oct-2015, over a year after the study had begun.

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]	

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C.4.4 Comments

1. The Novartis convention for recording events in the global safety database allowed the capture and classification of both diagnoses and of signs and symptoms, where reported. For cases received from interventional studies, MAP Chapter 8 [redacted] section 8.6.2 ('Event coding conventions for interventional trial cases including incidental findings') stated: "*Do not code typical symptoms reported by investigator in section 8 as adverse events when it is beyond reasonable doubt that they are linked to a diagnosis reported in section…*"

   There was no similar guidance for the coding of definitive and provisional diagnoses and associated signs and symptoms from post-marketing cases.

   GVP Module VI.C.6.2.2.3 states that: "*In practice, if a diagnosis is reported with characteristic signs and symptoms, the preferred option is to select a term for the diagnosis only and to MedDRA code it in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'*".

   It is recommended that the MAP is updated to include guidance for the coding of definitive and provisional diagnoses and associated signs and symptoms from post-marketing cases, in accordance with GVP Module VI and MedDRA Points to Consider.

2. It was noted that Novartis had recently identified some UK POPs and social media programmes that had not been communicated to Patient Safety in the UK CPO, despite requirements to do so within SOP [redacted] 'CPO UK Procedure for UK Management of Patient Oriented Programs and POPSystem (POPsys)' [redacted] and SOP [redacted] 'Collection of Adverse event reports from Novartis Social Media Programs and Listening programs' [redacted]. The following programmes had not been communicated and therefore had not been entered into POPsys (the database for recording and tracking these types of programmes). As a result, these programmes had not been subject to audit risk assessment or inclusion in the PSMF.

Deviation Number	Description	Programme start date	Identification date
[redacted]	Social media listening activity.	16 January 2017	11 April 2017
[redacted]	Virtual detailing project undertaken for [redacted]	18 November 2015	12 May 2017
[redacted]	A patient case study involving [redacted]	06 March 2017	31 May 2017

It is acknowledged that the MAH had identified these deficiencies prior to the inspection and raised deviations. It was also noted that programmes had been put on hold, where necessary, and Novartis had conducted retrospective reconciliation activities with third-parties. However, as it was described that these discrepancies had been identified by chance through conversations or receiving an AE from an unknown programme, Novartis should consider additional quality assurance activities to ensure the timely communication of these types of programmes to Patient Safety. The MAH should perform a further assessment to determine whether any further UK programmes have not been communicated to Patient Safety.

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) Modules.
- 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".
- CPMP/ICH/287/95: E2B (M) "Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports" and ICH E2B(R2) "Maintenance of the Clinical Safety Data Management: Data Elements For Transmission Of Individual Case Safety Reports".
- EMA/CHMP/ICH/544553/1998: E2C (R2) "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".
- 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.
- CHMP/313666/05: "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

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APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	GPvP 101/1135-0016	**LEAD INSPECTOR**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Novartis Pharmaceuticals and Novartis Oncology	**INSPECTION TEAM**	[redacted]
LOCATION	Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR		
DATES	17 July 2017 to 21 July 2017		

Day 1, 17 July 2017, arrival 09:00 for 09:30 opening meeting

Opening Meeting
Review of scope of inspection and inspection plan

[redacted]

[redacted] **Attendees**

[redacted]

Global Attendees

[redacted]

The rest of day one is reserved for document review by the inspection team. There may be ad-hoc interview sessions requested during the day.	
Day 2, 18 July 2017, 09:00 start time **The day will consist of document review and ad-hoc interview sessions as defined by the inspection team.**	
Inspection room 1 **Topic 1 – Local sources of safety data** This topic includes but is not limited to: - Medical information enquiries and product complaints - Social and digital media - Legal - Sales representatives - Licensing partners - Managed access programmes - Patient oriented programmes - Interventional and non-interventional studies - Investigator initiated studies	**Local interviewees:** [redacted]

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Inspection room 1 **Topic 2 – Local management of ICSRs (clinical and post-marketing) by UK Country Patient Safety** This topic includes but is not limited to: - Data entry and preliminary case assessments - Follow-up activities - Expedited reporting to MHRA - Quality assurance activities	[redacted]
Inspection room 2 **Topic 1 – Transfer of pharmacovigilance data and activities for Oncology products following the GSK-Novartis transaction** This topic includes but is not limited to: - Migration of case reports into Novartis ARGUS global safety database - Transfer of aggregate safety reports and ongoing signals - Management of ongoing/pending safety label changes - Transfer of ongoing studies	[redacted]

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	Third-party interviewee: **Uwe Trinks**, Foresight Group (TC)
Day 3, 19 July 2017, 09:00 start time **The day will consist of document review and ad-hoc interview sessions as defined by the inspection team.**	
Inspection room 1 **Topic 1 – Routine risk minimisation, including the maintenance of local labels** This topic includes but is not limited to: - Communication of CDS updates to COs - Local labelling maintenance - Post-approval implementation	[redacted]

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Inspection room 2

Topic 1 – Local implementation of risk management plan commitments

This topic includes but is not limited to:

- Implementation of additional pharmacovigilance activities listed in the pharmacovigilance plan
- Implementation and tracking of additional risk minimization measures
- Use of the CoSTA application

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Day 4, 20 July 2017, 09:00 start time **The day will consist of document review and ad-hoc interview sessions as defined by the inspection team.**	
Inspection room 1 **Topic 1 – Quality management system** This topic includes but is not limited to: - Management of procedural documents relevant to UK Country Patient Safety - Training of UK Country Patient Safety staff - Mechanisms to monitor pharmacovigilance processes and identify non-compliance, including audit, key performance indicators and oversight of UK-specific service providers - Management of deviations, non-compliances and CAPA	[redacted]
Day 5, 21 July 2017, 09:00 start time	
This day is reserved for document review by the inspection team. There may be ad-hoc interview sessions throughout the day as defined by the inspection team. The inspection will end with a closing meeting, to which everyone is invited.	

APPENDIX III DIFFERENCES BETWEEN CCDS AND EU SMPCS

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[redacted]

CCDS line	SmPC section	Nature of discrepancy
296 - 302	4.4. First paragraph under Thrombotic/ Thromboembolic complications in SmPC:	Number of patients experiencing thromboembolic/thrombotic events (TEEs) in study is different in SmPC compared to the CCDS. 38/955 & 6/484 vs 31/955 & 5/484.
396 - 403	4.7	CCDS states that there have been no studies to investigate the effect on driving performance, while the SmPC states that it has negligible influence on the ability to drive and use machines.
445	4.8	Pharyngitis listed as 'common' in CCDS, 'uncommon' in SmPC (ITP study population).
446	4.8	Urinary tract infection listed as 'common' in CCDS, 'uncommon' in SmPC (ITP study population).
448	4.8	Nausea listed as 'very common' in CCDS, 'common' in SmPC (ITP study population).
449	4.8	Diarrhoea listed as 'very common' in CCDS, 'common' in SmPC (ITP study population).
450	4.8	Dry mouth listed as 'common' in CCDS, 'uncommon' in SmPC (ITP study population).
451	4.8	Vomiting listed as 'common' in CCDS, 'uncommon' in SmPC (ITP study population).
453	4.8	Cataract listed as 'common' in CCDS, 'uncommon' in SmPC (ITP study population).
474	4.8	Abdominal pain was observed in paediatric studies. For all other ADRs identified in paediatric studies a diamond is next to the term in section 4.8 of the SmPC. No diamond is present for abdominal pain to indicate this.
550	n/a	Post marketing data section in CCDS not covered in SmPC, including the term 'thrombotic microangiopathy with acute renal failure'.

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[redacted]

CCDS line/page	SmPC section	Nature of discrepancy
211 - 215	4.4	Number of patients experiencing hepatotoxic ADRs in studies is different in the CCDS compared to SmPC. 2% in CCDS and 2.8% in SmPC (the cumulative frequency of severe liver injury at 1 year of treatment), 8% in CCDS and 10.3% in SmPC (cumulative frequency in DQA1*02:01 and DRB1*07:01 allele carriers).
Page 12	4.8	Hyperbilirubinaemia and hepatotoxicity listed as 'uncommon' in CCDS, 'common' in SmPC

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[redacted]

CCDS page	SmPC section	Nature of discrepancy
Page 6	4.4	Decreases in LVEF reported in 16/142 patients in CCDS, with 2/40 in Placebo arm. Different numbers in SmPC - 15/140 and 1/39.
Page 6	4.4	14/16 subjects had concurrent hypertension in CCDS, with 13/15 in SmPC
Page 6	4.4	Arterial thrombotic events: Angina not included in warning about arterial thrombotic events observed in studies in the SmPC
Page 9	4.5	Co-administration of pazopanib 800mg with paclitaxel - result in 26% in paclitaxel AUC in CCDS. Different value (25%) in SmPC
Page 12	4.8	Anorexia appears under a footnote associated with decreased appetite in section 4.8 of SmPC, 'very common' in CCDS (RCC study)
Page 12	4.8	Transient ischaemic attack listed as 'common' in CCDS, 'uncommon' in SmPC (RCC study)
Page 12	4.8	QT prolongation and Torsade de Pointes not listed as ADRs identified in RCC study in 4.8 of SmPC. 'Electrocardiogram QT prolonged' is present under investigations, but is listed as an 'uncommon' ADR, while QT prolongation is common in CCDS. (RCC study)
Page 12	4.8	Venous thrombotic events listed as 'uncommon' in CCDS, and 'common' in SmPC (RCC study)
Page 12	4.8	Cerebral haemorrhage and haematuria not listed in SmPC (RCC study)
Page 13	4.8	Alopecia listed as 'common' in CCDS, 'very common' in SmPC (RCC study)
Page 13	4.8	Palmar-plantar erythrodysaethesia syndrome listed as 'common' in CCDS, 'very common' in SmPC (RCC study)
Page 13	4.8	Rash listed as 'common' in CCDS, 'very common' in SmPC (RCC study)
Page 13	4.8	Proteinuria listed as 'common' in CCDS, 'very common' in SmPC (RCC study)
Page 13	4.8	Asthenia listed as 'very common' in CCDS, 'common' in SmPC (RCC study)
Page 12	4.8	Anorexia and Weight decreased not included as ADRs identified in STS trials in SmPC (listed as very common in CCDS)
Page 12	4.8	Myocardial infarction listed as 'common' in CCDS, 'uncommon' in SmPC (STS trials)
Page 13	4.8	Anorexia listed as 'very common' in CCDS, 'common' in SmPC (STS trials)
Page 13	4.8	Palmar-plantar erythrodysaethesia syndrome listed as 'very common' in CCDS, 'uncommon' in SmPC (STS trials)

Page 13	4.8	Myalgia listed as 'very common' in CCDS, 'common' in SmPC (STS trials)
Page 13	4.8	Musculoskeletal pain listed as 'very common' in CCDS, 'common' in SmPC (STS trials)
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