Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Roche

MHRA Inspection Number: Insp GPvP 31/86087-0015

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
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
DIBD	Development International Birth Date
DSUR	Development Safety Update Report
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
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
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
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	EU Supervisory Authority Inspection
System(s) inspected:	Roche PSMF MFL644
Site(s) of inspection:	6 Falcon Way Shire Park Welwyn Garden City AL7 1TW
Main site contact:	[redacted] 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW [redacted] [redacted]
Date(s) of inspection:	14 – 18 May 2018
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	• PHV/2013/009: EU product-specific pharmacovigilance inspection for Avastin, Zelboraf, Bonviva and Bondronat ○ **Inspection site one:** 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK 29 – 31 October 2013 and 14 November 2013 ○ **Inspection site two:** Genentech Inc. 1 DNA Way, South San Francisco, California, 94080, US 18 – 22 November 2013 • GPvP 14878/86087-0007: MHRA national pharmacovigilance systems inspection: 16 – 20 January 2012 and 28 February – 01 March 2012 • GPvP 31/86087-0005, EMEA/INS/PhV/2009/02: EU product-specific pharmacovigilance inspection for RoActemra: 03 – 06 August 2009 • GPvP 31/86087-002: MHRA national pharmacovigilance systems inspection: 19 – 22 February 2007 and 11 June 2007 • 00031/0404: MHRA national pharmacovigilance systems inspection: 19 – 23 April 2004
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements

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Products selected to provide system examples:	As part of the inspection, documentation was examined for [redacted] amongst others.
Name and location of EU QPPV:	[redacted] Address and contact details as above
Global PV database (in use at the time of the inspection):	ARISg (version 4.24)
Key service provider(s):	• Tata Consultancy Services (TCS) are contracted to provide support with case processing, preparation of PBRERs, EU RMPs and addenda to clinical overviews, and ICSR data retrieval. • Parexel International Services are contracted to provide support with clinical safety reports, RMPs, signal detection and ICSR compliance monitoring, amongst other activities.
Inspection finding summary:	0 Critical findings 3 Major findings 1 Minor finding
Date of first issue of report to MAH:	22 June 2018
Deadline for submission of responses by MAH:	Initial: 27 July 2018 Follow-up: 16 August 2018
Date(s) of receipt of responses from MAH:	Initial: 27 July 2018 Follow-up: 14 August 2018
Date of final version of report:	03 September 2018
Report author:	[redacted] Senior Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Roche was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The inspection is also part of the EU plan for routine pharmacovigilance inspections of MAHs with centrally authorised products. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Regulation 726/2004/EC as amended, Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at Appendix I.

The Roche Group has two divisions; Diagnostics and Pharmaceuticals. Within the Pharmaceuticals division, the responsibility for most global PV activities is centralised in Product Development Safety and Risk Management (PDS). There are five main sites where global PV functions are undertaken; Basel, Beijing, Shanghai, South San Francisco and Welwyn. In addition, there are local operating companies which undertake local pharmacovigilance activities.

Roche holds centralised marketing authorisations for approximately 126 products covering 24 active substances. In addition, Roche holds approximately 37 national licences in the UK covering 16 active substances.

At the time of the inspection, the MHRA was the supervisory authority for Roche and was responsible for performing pharmacovigilance inspections as part of the EU plan for routine PV inspections of MAHs with centrally authorised products. In preparation for the exit of the UK from the European Union, Roche was in the process of transferring marketing authorisations for centrally authorised products, currently held by Roche Registration Limited, to a new legal entity in Germany, Roche Registration GmbH. As of 27 March 2018, the licence transfer was completed for products containing 15 of 24 active substances (Commission decision received). Commission decision was pending for products containing the remaining 9 of 24 active substances. In addition, Roche is relocating the position of the EU QPPV and the PSMF to Germany, effective 01 June 2018. Consequently, at the time of this inspection report, the Federal Institute for Drugs and Medical Devices (BfArM) is now supervisory authority.

B.2 Scope of the inspection

The inspection focused on risk management activities, including management of PASS, maintenance of product information, and additional risk minimisation activities and safety communication, and was performed at Roche's offices in Welwyn Garden City, Hertfordshire.

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).

The receipt, management and reporting of individual adverse drug reaction reports, and analysis and reporting of aggregate safety data - specifically signal management, periodic safety update reports and generation of other aggregate safety reports - were not reviewed

during this inspection. These topics will be reviewed during a subsequent pharmacovigilance inspection.

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B.3 Documents submitted prior to the inspection

The company submitted [redacted] to assist with inspection planning and preparation.

Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection; the detail of these requests is contained within document request sheets A and B.

B.4 Conduct of the inspection

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

A closing meeting was held to review the inspection findings at Roche's offices in Welwyn Garden City on 18 May 2018. A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

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

Since the previous MHRA inspection in 2013, the company had made the following changes to the pharmacovigilance system:

- The compliance and safety governance model had been strengthened through the introduction of the Medical Compliance Steering Committee, the Drug Safety Committee and the Global Labelling Committee. In addition, Roche had made enhancements to the quality management system, including the process for CAPA management, and introduced a model for global process ownership.

- The safety function (PDS) had been redesigned and there had been changes to key personnel, including the PDS Head, EU QPPV and the International PV (IPV) Head.

- New compliance roles within the Roche affiliates had been created, including RMP Implementation Coordinator and Market Research and Patient Support Programme (MAP) Lead.

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- Roche acquired the centrally authorised product, [redacted] from [redacted] in February 2015.

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 Post-authorisation safety studies

Requirements:

Regulation (EC) No. 726/2004 as amended, Article 28b (1).

Directive 2001/83/EC as amended, Article 107p.

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 201.

GVP Module I – Pharmacovigilance systems and their quality systems

I.C.1.3 (Role of the qualified person responsible for pharmacovigilance in the EU) *"In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV should include:*

- *being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the EU or pursuant to a risk management plan agreed in the EU;"*

GVP Module VIII – Post-authorisation safety studies (Rev 3)

VIII.B.2 (Study registration) *"The study protocol should be uploaded as soon as possible after its finalisation and prior to the start of data collection. […] Updated study protocols in case of substantial amendments, progress reports and the final study report should also be entered in the register (as soon as possible and preferably within two weeks after their finalisation)."*

VIII.B.4.3.2 (Final study report) *"The final study report should include the following information:*
10.6 Adverse events and adverse reactions: summary of all adverse events/adverse reactions collected in the study, in line with requirements described in GVP Module VI."

GVP Module VI – Management and reporting of adverse reactions to medicinal products (Rev 2)

VI.A.1.6 (Seriousness) *"Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered serious."*

ICH guideline E2F – Development safety update report

3.7 (Data in Line Listings and Summary Tabulations) *"Sections 7.1-7.3 of the DSUR should present important clinical safety information through:*

- *Interval line listings of the SARs that were reported to the sponsor during the period covered by the DSUR; and*
- *Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD."*

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.1 a)

There were errors identified in the presentation of serious adverse drug reactions (SADRs) in the [redacted] category 1 non-interventional PASS [redacted] clinical study report (CSR).

CSR section 9.6.1.2 (Serious Adverse Drug Reactions) stated *"Fifty-five patients (5.5%) experienced 78 SADRs"* and these were presented in Table 14.3-1 (Adverse Drug Reactions by MedDRA System Organ Class and Preferred Term). However, this was based on data derived from the clinical database, which included the investigator's seriousness assessment, and did not take account of non-serious adverse drug reactions that had been upgraded to serious during the MAH's seriousness assessment.

Examples of identified discrepancies between the CSR and the data in the global safety database included the following:

MedDRA Preferred Term (PT)	Serious ADRs presented in CSR Table 14.3-1 (case IDs)	Serious ADRs in the global safety database (case IDs)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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In total, 89 SADRs were present in the global safety database (based on the line listing provided in request D5) compared with 78 presented in the CSR, which has resulted in a 12% under-representation of SADRs in the CSR.

The cases listed above were reviewed by an MHRA scientific assessor and they concluded that the reports did not provide any additional information about the product that is not already known. Abnormal liver function tests (increased ALT and AST levels, total serum bilirubin increased in combination with increases of ALT and AST) is an important identified risk in the [redacted]EU RMP and is labelled in the EU SmPC. The cases of cardiac failure and cerebrovascular accident were confounded by multiple factors, including concurrent medical conditions. In addition, the individual cases above had been reported to the MHRA on an expedited basis. Due to these mitigating factors, this has been graded as a major rather than a critical finding.

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]

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

Finding MA.1 b)

There were discrepancies between the [redacted] SAE data presented in the Annual Data Summary (ADS) of the MotHER pregnancy registry (dated 25-Apr-2017) and the SAE data recorded in the global safety database:

- ADS Table [redacted] (Maternal Serious/Targeted Adverse Events: Patients who received [redacted] only) listed two reports of pre-eclampsia. However, there was only one report of pre-eclampsia from this study in the safety database [redacted] The MAH confirmed that for one patient [redacted] the reported term was pregnancy-induced hypertension (PIH) / pre-eclampsia. The case processor assessed it as one event and entered only PIH (coded term 'Gestational hypertension') in the safety database. The MAH confirmed that the case will be corrected in the safety database to split the terms.

- ADS Table [redacted] listed two reports of arrested labour; however, there was only one report of arrested labour from this study in the safety database [redacted]. The MAH confirmed that for one patient [redacted] the reported event was arrest of descent. It was coded as PT 'Arrested labour' in the clinical database and as PT 'Abnormal labour' in the safety database.

These discrepancies could result in inconsistent presentation of data between the interim reports of this non-interventional PASS and other post-marketing reports, such as PSURs.

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]

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[redacted]

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

Finding MA.1 c)

There were examples of data discrepancies identified during the monthly reconciliation between the clinical and safety databases for [redacted] (PERUSE) that had not been resolved in a timely fashion, which could affect presentation of SAE/SAR data in DSURs.

- Case [redacted] was initially received on 15-Nov-2014. The PT 'Death' was recorded in the safety database but not in the clinical database and the reconciliation tracker indicated that a query was raised in August 2015; however, at the time of the inspection the query remained open. Upon request during the inspection, clarification was received from the service provider confirming that the event was due to disease progression and should not have been reported as an SAE. The MAH confirmed that a data correction will be performed to delete the event of 'Death' from the safety database upon receipt of source documents.

- Case 1[redacted] was initially received on 14-Oct-2013. The PTs 'Pleural effusion' and 'Dyspnoea' were recorded in the safety database, but 'Dyspnoea due to pleural effusion' was recorded in the clinical database. A query was initially raised in October 2015; however, at the time of the inspection the query remained open. Follow up information from site was received on 16-May-2018 (during the inspection) confirming that the final

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diagnosis was dyspnoea. The MAH confirmed that the event will be updated to 'Dyspnoea' as a single PT in both databases.

- Case [redacted] was initially received on 31-May-2017. PTs of 'Paraneoplastic syndrome' and 'Inappropriate antidiuretic hormone secretion' were recorded in the safety database but not in the clinical database. In addition, 'Diabetes insipidus' was recorded in the clinical database but not in the safety database. A query was initially raised in September 2017; however, at the time of the inspection the query remained open.

It was also noted that the field in the reconciliation tracker entitled 'Follow-up date' (column S) was not routinely populated.

The data lock point of the most recent [redacted] DSUR was 07-Jun-2017 and the line listings and cumulative summary tabulations in the report were generated from the safety database.

Root Cause Analysis

[redacted]

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

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

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Preventative Action(s)
[redacted]

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

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[redacted]

Finding MA.1 d)

There was no evidence of QPPV review of an interventional category 1 PASS protocol [redacted] This study was initiated in 2012, prior to product authorisation in the EU. Subsequently the study was agreed with PRAC as a category 1 PASS; however, there was no evidence of QPPV review and sign-off of the protocol.

It was noted that a deviation report [redacted] was raised on 03-May-2018, shortly prior to the inspection, in relation to the lack of QPPV review and sign-off of this protocol. It was also noted that two other deviations reports were initiated shortly prior to the inspection for lack of QPPV review and sign-off of PASS protocols [redacted] for study [redacted] for study [redacted].

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]	

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[redacted]

Finding MA.1 e)

The protocol for [redacted] section 8.7 (Data Management) stated *"The CRO will follow standard procedures for ensuring accurate data entry, including performing an audit (i.e., a comparison of data on paper to data in the database) of a subset of data entered."* However, an audit of data entered into the Electronic Data Capture (EDC) system for this study had not been conducted as per the protocol.

The Data Management Plan [redacted] conflicted with the study protocol as section 15.0 (Quality Management Activities) stated *"Data Quality Audits are not applicable to the [redacted] Project"*.

It is acknowledged that the Data Entry Guidelines for study [redacted] section 5 (Site and method of data entry) described the data entry QC process, which included a 100% comparison of the entered data by a second Data Administrator.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 f)

The CSR for [redacted] was dated 16-Feb-2018; however, the results were not posted to the EU PAS Register until 10-May-2018, approximately 10 weeks outside of the recommended two-week timeframe stated in GVP Module VIII. In addition, the latest version of the protocol [redacted] was not posted to the register.

Root Cause Analysis

[redacted]

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1. For study [redacted] the last data collection/ extraction was in Jul-2017. The CSR was signed in Feb-2018 and the results were uploaded on 10-May-2018 to the EU PAS Register, which was in line with Roche Global: Clinical Study Disclosures SOP [redacted] The date of upload diverged from the recommended two-week time period mentioned in Module VIII, since the point of reference for Roche was not the finalization date of the report, but the date of last data collection/extraction. As such, the current Roche process is not aligned with GVP Module VIII.

2. For [redacted] the latest version of the protocol [redacted], was implemented prior to the 11-Apr-2017 update to the Global: Clinical Study Disclosures SOP [redacted], which added the requirement for Roche to upload NI-PASS protocols to the EU PAS register. Retrospective uploading to the EU PAS register of protocols approved prior to 11-Apr-2017 was not required as part of this SOP update.

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]	

MA.2 Maintenance of product information and safety communication

Requirements:

Regulation (EC) No. 726/2004 as amended, Article 16 (3).

Directive 2001/83/EC as amended, Paragraph 40 and Article 23 (3).

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 5 Marketing Authorisations, Regulation 76.

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 summaries of product characteristics (SmPCs), patient information leaflets (PILs) and investigator's brochures (IBs), so that healthcare professionals, 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 the maintenance of product information and the communication of safety information in marketing materials:

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Finding MA.2 a)

The [redacted] core data sheet (CDS) was updated to include changes to safety information on 14-Apr-2016 (version 7.0); however, a variation to implement the corresponding changes in the EU SmPC was not submitted until 06-Apr-2017 (approximately one year later) (company reference [redacted]

There were multiple changes to the CDS between version 6 (November 2014) and version 7, including a new dosage form with accompanying instructions, and updated text on use in patients with renal or hepatic impairment. Specifically,

- in renal impairment, information on the lack of dosage adjustment in mild to moderate impairment was changed to mild impairment only, and to reflect caution in use in severe renal impairment, with accompanying pharmacokinetic data;
- in hepatic impairment, data to reflect the results of studies provided the basis for adjusted text on dosage in relation to hepatic function;
- the section on undesirable effects from clinical trials was tabulated to include occurrence (percentage and frequency terms).

The company had initially assigned a target date for submission of a variation to update the SmPC and PIL of October 2016, which would have been an acceptable timeframe. In addition to the delay in the submission of the variation, the company claimed to have identified the delay in October 2016 but only internally approved a revised submission target date in March 2017, approximately six months later. The issue was not handled as a deviation (per SOP [redacted] 'Deviations and Corrective Actions and Preventive Actions'), rather as an 'ad hoc extension' approved without record in the Global Labelling Committee (GLC) minutes, but via e-mail with the GLC Chairperson.

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Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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[redacted]

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

Finding MA.2 b)

There was evidence of abbreviated prescribing information (API) which was not updated in a timely manner after a safety update to the [redacted] SmPC had been approved.

A Type II safety variation for the CAP [redacted] (variation numbe [redacted] which included an update to the dosing recommendations for patients with renal impairment, received the positive CHMP opinion on 08-Dec-2017 and was published on the electronic Medicines Compendium (eMC) on 19-Dec-2017. The API was only updated on 16-Feb-2018 (approximately two months later) (document ID: [redacted] 2)) to include the new dosage recommendations. Promotional material that included out of date API had been distributed, as follows:

- [redacted] Patient Pack Briefing for Healthcare Professionals [redacted] which described the items available to patients in the patient pack and the means to access them (related to photosensitivity risk of [redacted], was certified on 12-Jan-2018, issued to field staff on 25-Jan-2018 (later withdrawn on 15-Feb-2018) and was subsequently distributed to HCPs. The Patient Pack Briefing incorrectly contained the June 2017 API and therefore did not correctly reflect the warnings on use in renal impairment.

- A Pharmacist's Letter [redacted] was created on 22-Jan-2018 with a "Date of first use" of 30-Jan-2018 and included the previous API (dated June 2017); thus, it did not include the updated dosing information. The letter was distributed to sales representatives on 30-Jan-2018 and was available for use from that date.

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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]	

MA.3 Pharmacovigilance system master file

Requirements:

Regulation (EC) No. 726/2004 as amended, Article 21 (1).

Directive 2001/83/EC as amended, Article 104 (3(b)).

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 182.

GVP Module II – Pharmacovigilance system master file (Rev 2)

II.B.4.3 (Sources of safety data) *"For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorisation holder through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight."*

II.B.4.4 (Computerised systems and databases) *"The location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the PSMF".*

II.B.4.8 (Annex to the PSMF) *"The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation:*
- *the type of procedure for authorisation and procedure number (e.g. centrally authorised, nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure);*
- *the Rapporteur country or Reference Member State;*
- *the presence on the market in the EU [DIR Art 23(a), REG Art 13(4)];*
- *other (non-EU) territories where the product is authorised or on the market."*

Every MAH should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorised medicinal products. Details of the system should be recorded in a PSMF, which should be permanently available for inspection. The following findings were noted in relation to the PSMF:

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Finding MA.3 a)

The following issues were identified with regards to the product list in PSMF Annex H3 (List of Roche EU products):

i. Annex H3 for both versions of the PSMF submitted for inspection [redacted] incorrectly listed the following:

- [redacted] UK marketing authorisations [redacted] were listed as valid and marketed, whereas the authorisations were cancelled effective 31-Jan-2018 (following transfer of ownership). These authorisations should not have appeared as 'valid' in the March 2018 PSMF.

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- [redacted] UK marketing authorisations [redacted] were listed as valid and not marketed, whereas these authorisations were cancelled in 2014.

The MAH explained during the inspection that the Annex H3 content was generated from the XEVMPD content of the EMA Article 57 database and not the company's product registration database (GPRS). A review of the GPRS and XEVMPD data was conducted by the MAH in February 2017, nonetheless the discrepancy for the clonazepam authorisations (appearing as 'deregistered' in GPRS and 'Valid' in XEVMPD) was not highlighted or corrected.

During the inspection, the MAH stated that future PSMF product lists would be generated using the GPRS data. However, a review of the submissions and current accuracy of all EU/EEA authorisations appearing in the Article 57 database should be conducted.

ii. The marketing status for products with centralised licences in PSMF Annex H3 was not presented for each territory in the EU. "N/A" was entered in the column entitled 'Authorisation Status Detail'.

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]	

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[redacted]

Finding MA.3 b)

PSMF Annex C2 (List of Interventional and Non-Interventional Studies (Ongoing)) was inaccurate with regards to the classification of PASS and PAES. The following discrepancies were noted during inspection preparation:

- [redacted] (PERUSE) was a category 1 PASS in the RMP and a specific obligation in Annex II of the marketing authorisation (MA) but was classified as 'Non-PASS/PAES' in PSMF Annex C2.
- [redacted] (APHINITY) was a PAES in the RMP and a specific obligation in Annex II of the MA but was classified as 'Non-PASS/PAES' in PSMF Annex C2.
- [redacted] (BERNIE) was a category 3 PASS in the RMP but was classified as 'Non-PASS/PAES' in PSMF Annex C2.
- [redacted] was classified as 'PASS Imposed Category 1' in PSMF Annex C2 but was a category 3 PASS in the RMP.
- [redacted] was classified as 'PASS Imposed Category 2' in PSMF Annex C2 but was a category 3 PASS in the RMP.

An audit of NIS/PASS including ICSR management was conducted in May-2017 and a finding was identified that relevant activities were not correctly and consistently classified as PASS, and that for a particular study [redacted] there were PASS classification discrepancies across the EU RMP, Clinical Trial Management System (CTMS) and PSMF. One of the corrective actions was as follows: *"Each SSL* [Safety Science Leader] *of products with an EU RMP and for which Roche is the MAH in the EEA to check and confirm that all post-approval studies captured in the PV Plan of the EU RMP are appropriately identified as PASS in MDMS/CTMS. Deadline: 31Oct2017."* However, discrepancies in PASS categorisation remained at the time of the inspection in the Clinical Trial Management System and consequently in PSMF Annex C2.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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[redacted]

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

Finding MA.3 c)

There were examples of computerised systems used for critical pharmacovigilance activities that should be described in the PSMF section on computerised systems.

- Signal Tracking At Roche (STAR) – used to track signal management activities.
- Global Product Regulatory System (GPRS) – used to collate the status of authorisations worldwide, track commitments to NCAs, track core data sheet changes and changes to SmPCs and PILs centrally and by the majority of affiliates for their local submissions (UK use TrackWise) and used to retain documentation relating to the approval of prescribing information updates and correspondence with the authorities.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.3 d)
The key performance indicators (KPIs) presented in PSMF Annex F1A (List of Performance Indicators and Results) that were used to monitor compliance with regards to the maintenance of authorised product information included 'CDS triggered mandatory updates of Summary of Product Characteristics (SmPC) submitted to Health Authorities on time – EEA'. There was no KPI that included externally triggered SmPC updates, e.g. those requested by national competent authorities, referral outcomes, etc. GVP Module II.B.4.6 requires that the PSMF contains an overview of the methods used to ensure timeliness of safety variation submissions compared to internal and competent authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted. Associated KPIs should be included in the PSMF Annex.
Root Cause Analysis
[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]	

C.4.3 Minor findings

MI.1 Additional risk minimisation measures

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. The majority of safety concerns are addressed by routine risk minimisation measures. Exceptionally, for selected important risks, routine risk minimisation may be considered insufficient and additional risk minimisation measures may be deemed necessary.

The following findings were noted in relation to the implementation of additional risk minimisation measures. There are no significant concerns regarding Roche's management of additional risk minimisation measures in the UK and therefore these findings have been graded as minor, despite some breaches of GVP Module XVI Addendum I.

Finding MI.1 a)

GVP Module XVI Addendum I – Educational materials, section Add I.3 states that a detailed implementation plan for educational programmes should be submitted to NCAs with the following information:

- target population(s);
- dissemination method (e.g. paper, e-mail, via social media, learned societies and/or patient associations, publication on websites);
- time point when dissemination is anticipated to start and frequency of further disseminations;
- estimated date of launch or date of start of the marketing of the product (in the case of a new marketing authorisation).

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Examples were identified where the implementation plan submitted to the MHRA for educational programmes was not compliant with GVP Module XVI Add I:

i. Following the addition of the giant cell arteritis (GCA) indication to the [redacted] licence, educational materials were submitted to the MHRA for approval. An email dated 03-Oct-2017 contained the following updated materials:

   - Adult rheumatoid arthritis (RA)/GCA combined IV/SC HCP Brochure (clean and highlighted changes)
   - Adult Step-by-Step Dosing and Administration Guide RA/GCA (clean and highlighted changes)
   - Combined Patient Alert Card (clean and highlighted changes)
   - GCA Patient Brochure (new)

   The implementation plan described within the email did not contain the required details and simply stated:

   "Upon approval, the educational materials will be distributed to applicable Healthcare Professionals and updated on the eMC website."

   Subsequently, on 13-Mar-2018, the patient brochure required updating due to identification of an error regarding concurrent use with live attenuated vaccines. The communication to the MHRA did not include any implementation plan and the MHRA

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assessor had to request information regarding how these materials would be made available to healthcare professionals (email dated 11-Apr-2018).

Roche contacted the MHRA again on 18-Apr-2018 requesting agreement that the materials need not be pro-actively sent out, but instead a letter would be sent to HCPs notifying them of an update to the materials, which would be made available via the eMC. Again, the email communication to the MHRA did not include all required information regarding this implementation plan and the assessor had to request when this letter would be distributed to HCPs informing them of the update (email dated 18-Apr-2018).

ii. The [redacted] educational materials, which included dosing guidelines and Interstitial Lung Disease (ILD) awareness and management strategies, were submitted to the MHRA for approval on 28-Jul-2016. The implementation plan, as follows, did not include the method of dissemination:

"This Educational material once approved will be distributed within 60 days to oncologists, oncology nurses, oncology HCPs and Pharmacists".

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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[redacted]

Finding MI.1 b)
The [redacted] educational programme included brochures for healthcare professionals which provided information regarding efficacy and safety. There were two versions of these materials available for the different approved indications; one brochure covered the juvenile indications (systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis) and the other brochure covered the RA and GCA indications. An error in the juvenile brochure was identified; on page 11, under the heading "Hepatic transaminases", there was a statement recommending that ALT and AST levels are monitored *"every 4 or 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter".* This statement related to the RA and GCA indications only. Following discussions between the inspector and an MHRA assessor during the inspection, the MAH is requested to delete this statement and submit updated materials to the MHRA for approval.
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]	

Finding MI.1 c)
There was no evidence that educational materials had been provided to sites that had ordered product prior to the formal print-run of the materials. The Tecentriq educational materials, which included a patient alert card and an information brochure for healthcare professionals, were not formally available for dissemination at the time the product was launched onto the UK market (launch date was 05-Oct-2017, materials were ready for printing and shipping on 11-Oct-2017). The Medical Marketing Manager for the product initiated a communication to the sales team to request notification of any orders between the launch date and the print date, in order to pro-actively send ad hoc copies of the materials to ensure they would be available for prescribers and patients. Two orders were received during this period, but there was no evidence retained to confirm that the ad hoc materials had been posted to the sites.

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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]

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

[redacted]

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Finding MI.1 d)
The MAH was routinely uploading approved educational materials (initial and updated versions) to the eMC as a method of dissemination to relevant stakeholders. The Risk Management Plan Implementation Coordinator (RMP IC), who was responsible for ensuring the materials were sent to UK Regulatory Affairs along with a form [redacted] 'GBR: Request Form to Publish, Update or Withdraw Risk Minimisation Materials on the eMC'), described that upload to the eMC would occur within 60 calendar days from MHRA approval (in line with the timeline for dissemination of hard-copy materials outlined in [redacted] (GBR: The Implementation of Risk Management Plans in the UK and Malta, [redacted] Whilst the requirement to submit educational materials for upload to the eMC was outlined in [redacted] there were no documented timeframes as described by the RMP IC.
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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[redacted]

Finding MI.1 e)
The Medical Information function had a role in the ad hoc dissemination of educational materials upon request, either via direct hard-copy mailing or through placing an order for materials from the distributor [redacted] for delivery. There was no approved procedural document within the quality management system which detailed this process. The process was described in the Medical Information Handbook (V2.2.); however, this was not a controlled document and there was no evidence of medical information staff having trained on the document.
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]	

C.4.4 Comments

1. Since March 2018, Roche is no longer reporting suspected adverse reactions from clinical trials for non-investigational medicinal products (non-IMPs) to the concerned marketing authorisation holder.

   It is acknowledged that the 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') states *"While the legal obligations contained in the rules on pharmacovigilance as set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply (see section 2) to adverse reactions to IMPs or non-IMPs, in cases where the non-IMP is an authorised medicinal product, investigators and sponsors are encouraged to report suspected adverse reactions to the non-IMP to national competent authorities or to the marketing authorisation holder."* [Emphasis added]

2. Case [redacted] was a Health Authority (HA) report received by Roche regarding a patient taking [redacted] who had a positive pregnancy test but subsequently suffered a spontaneous abortion.

   Based on the information in the initial version of the HA report, Roche created two cases; one for the mother with "pregnancy" coded (case [redacted] and one for the foetus with "drug exposure in utero" and "congenital anomaly" coded (AE [redacted] There was no information in the initial case which suggested that a congenital anomaly had occurred, although the CIOMS seriousness criteria of "congenital abnormality/birth defect" had been selected in the HA report. The inspector confirmed post-inspection that a follow-up report had been received by the MHRA, which confirmed the spontaneous abortion; however, a follow-up report had not been sent to MAHs. The MHRA will correct the case to change the seriousness criteria, incorporate the follow-up information and re-send to relevant MAHs.

3. There was a content omission identified in the RMP for [redacted] page 318. The following sentence associated with the liver safety concerns had not been completed:

   "Healthcare Provider Brochure

   To inform and provide guidance to healthcare providers on…"

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 Supervisory Authority inspection is performed as part of the routine EU programme of pharmacovigilance inspections of MAHs with centrally authorised products.

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.
- Directives 2001/20/EC and 2005/28/EC in relation to Clinical Trials.
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- CHMP/ICH/309348/2008: E2F "Development safety update reports".
- EMA/CHMP/ICH/135/1995: E6 (R2): "Guideline for good clinical practice".
- Eudralex Volume 10, Chapter II: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT3'), June 2011.
- CHMP/313666/05: "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 31/86087-0015	**LEAD INSPECTOR**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Roche	**INSPECTION TEAM**	[redacted]
LOCATION	6 Falcon Way Shire Park Welwyn Garden City AL7 1TW		
DATES	14 – 18 May 2018		

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Day 1, 14 May 2018, arrival 09:00 for 09:30 opening meeting

Opening Meeting
Review of scope of inspection and inspection plan

Company Presentation (max 30 minutes)
Overview of the company and pharmacovigilance system, and significant changes to the PV system since the 2013 MHRA inspection

[redacted]

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Inspection room 1 **Topic 1 – Additional risk minimisation measures (aRMMs) and safety communication** This topic includes but is not limited to: - Educational programmes - Pregnancy prevention programmes - Dear Healthcare Professional Communication - Evaluating the effectiveness of aRMMs - Emerging Safety Issues	
Local RMP Implementation	[redacted]
Local Regulatory - Ad-hoc	[redacted]
PLATO Reporting - Ad hoc	[redacted]
Erivedge and Roaccutane Pregnancy Prevention Programmes	[redacted]
Day 2, 15 May 2018, 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 – Post-authorisation safety studies (PASS)** This topic includes but is not limited to:	[redacted]

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- PASS classification, inventory and registration - Receipt, assessment and reporting of cases from PASS - Generation of interim and final study reports - MAH oversight of PASS, including monitoring, safety data reconciliation and audit **Specific products and studies will be selected prior to the inspection and notified to Roche, in order to provide the MAH with the opportunity to consider availability of relevant staff. Study specific questions can be addressed in separate interview sessions.**	[redacted] *Additional colleagues will be made available for interview as needed.*
PASS Classification, inventory and registration	[redacted]
Management of cases from PASS / Reconciliation	[redacted]

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Study MO28047 - **Study Monitoring** - **Data quality checking as per the EDC study specification document**	[redacted]
CTMS Demo	[redacted]
PASS GPRS Demo	[redacted]
Inspection room 2 **Topic 1 – Maintenance of authorised product information** This topic includes but is not limited to: - Identification of safety updates and variation submission - Implementation of updated and approved SmPCs and PILs	[redacted] *Additional colleagues will be made available for interview as needed.*
Artworks	[redacted]
XEVMPD	[redacted]

Day 3, 16 May 2018, 09:00 start time The day will consist of document review and ad-hoc interview sessions as defined by the inspection team.
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.
RMM [redacted]
RMM - Medical Information [redacted]
RMM - [redacted] PPP [redacted]
MotHER and Interim Reports [redacted]
Signal Mgmt and Product Info Mgmt [redacted]
[redacted]

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Day 4, 17 May 2018, 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.
[redacted]**PPP Demo** [redacted]
PIM/Signal Mgmt [redacted]
Audit (PASS) [redacted]
QP Oversight of Updated PI to eMC [redacted]K
[redacted]

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Day 5, 18 May 2018, 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.**
[redacted]**discussion** [redacted]
Closing Meeting [redacted]