Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Gilead Sciences International Limited

MHRA Inspection Number: GPvP 16807/123561-0007

151 Buckingham Palace Road London SW1W 9SZ UK
T 020 3080 6000 **E** gpvpinspectors@mhra.gsi.gov.uk www.mhra.gov.uk

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective Action Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
EMA	European Medicines Agency
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Updates Reports
QA	Quality Assurance
QPPV	Qualified Person for Pharmacovigilance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
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 and Statutory National Inspection
Name and address(es) of site(s) inspected:	Gilead Sciences International Limited Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT
Main site contact:	[redacted] Director Regulatory Compliance Gilead Sciences International Limited, Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT Email: [redacted] Telephone: [redacted]
Date(s) of inspection:	[redacted]
Lead Inspector:	
Accompanying Inspector(s):	
Previous inspection date(s):	31 October – 03 November 2011 (GPvP 16807-123561-003) 31 March – 03 April 2008 (GPvP 16807/123561-001) 07 - 10 June 2004 (GPvP 16807/0604)
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 PSURs were examined for the following centrally authorised products (CAPs): [redacted]
Name and location of EU/EEA qualified person for pharmacovigilance:	[redacted] Senior Director DSPH and EU QPPV Gilead Sciences International Limited, Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT
Global PV database (in use at the time of the inspection):	Argus version 7.0.3.1 (commercially available)
Key service provider(s):	Not applicable – all pharmacovigilance activities are performed by the MAH
Inspection finding summary:	0 Critical findings 2 Major findings 7 Minor findings
Date of first issue of report to MAH	18 May 2015
Deadline for submission of responses by MAH	19 June 2015, extended to 26 June 2015
Date(s) of receipt of responses from MAH	26 June 2015 11 September 2015

	25 September 2015
Date of final version of report	28 September 2015
Report author	[redacted] GPvP Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Gilead Sciences International Limited 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, for which the UK are the Supervisory Authority. 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 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.

Gilead Sciences International is an innovative pharmaceutical company specialising in the following therapeutic areas: HIV/AIDS, liver disease, oncology/inflammation, cardiovascular and respiratory disease. The company is headquartered in Foster City, California, with international commercial/clinical operations being led from Stockley Park, UK, and research and development from Abington, UK. In addition, there were additional affiliate offices throughout Europe, Australasia and South America.

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At the time of the inspection, the company held 13 UK marketing authorisations (MAs) obtained through centralised [redacted] and national [redacted] procedures. In addition, the company was the co-licensee with [redacted] for [redacted] a centrally authorised product.

B.2 Scope of the inspection

The inspection included a review of both local and global pharmacovigilance systems, and was performed at Gilead Sciences International Limited's offices in Abington, Cambridge. Personnel from Gilead's office in Foster City, California, attended the Abington site in order to participate in the inspection. Other staff from Foster City and Gilead's office in Ireland attended specific interviews by teleconference.

The inspection was performed using interviews and document review (including outputs from the global safety database and listings of medical information enquiries and product complaints). The inspection included a review of the roles and responsibilities of the EU/EEA Qualified Person responsible for pharmacovigilance. 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

The company submitted two Pharmacovigilance System Master Files (PSMFs) to assist with inspection planning and preparation: one for Gilead Sciences International Limited (version 6.0; dated: 02 September 2014) and another for [redacted] and Gilead Sciences Limited (version 6.0; dated: 02 September 2014). Specific additional documents were also requested by the inspection team and provided by the company, prior to the inspection.

These included: a list of pharmacovigilance-relevant UK SOPs; a line listing of worldwide case reports for UK authorised products; PSUR and DSUR schedules for UK authorised products and lists of ongoing interventional, non-interventional and investigator-initiated studies in the UK.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan (attached as Appendix II).

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

A closing meeting was held, to review the inspection findings, at Gilead's offices in Abington, Cambridge on 13 February 2015. A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

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

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

- A new EU/EEA Qualified Person for Pharmacovigilance (QPPV) had been appointed;
- Argus was upgraded to version 7.0.3.1 and was also updated to include Argus J functionality;
- A new case management process flow had been implemented.

In addition, since the previous inspection in 2011, new affiliate offices had been established in the following countries:

- EU: Belgium/Netherlands
- Non-EU: Brazil, Czech Republic, Hong Kong, Japan, Russia, Singapore, South Africa, South Korea, Taiwan

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: http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodPharmacovigilancePractice/Theinspectionprocess/index.htm

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 Signal Management

Requirements:

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

Directive 2001/83 EC as amended, Article 104 (2) (3(e)).

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 182 and 190.

Commission Implementing Regulation (EU) No. 520/2012, Article 21 (1).

GVP Module IX – Signal management.

Marketing Authorisation Holders are obliged to ensure that information on the benefits and risks of their products is evaluated on an ongoing basis, and appropriate action is taken in response to new information that impacts on the benefit-risk balance.

At the time of the inspection, the identification of new potential signals from ICSR data was limited to a qualitative review of individual cases and a quarterly review of a frequency report. The following deficiencies were noted:

Finding MA.1 a)

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The signal evaluation for [redacted] and leukopenia (dated January 2014) was considered to be inadequate and the following was noted:

- The review concluded that there was not enough evidence to confirm an association between [redacted] and the development of leukopenia. This was largely based on an assessment of 36 cases that concluded that "there was insufficient information to assess a relationship between the event and treatment with [redacted] These cases lacked information such as the outcome following dechallenge, white blood cell counts, medical history or concomitant medications."

  It was determined during the inspection that follow-up had not been performed for 24 of these 36 cases and the reason stated "no follow-up was identified as needed by Specialist nor reported from DSPH safety physicians."

- The evaluation was limited to ICSRs identified from the safety database. The evaluation did not reference the scientific literature (positive or negative results), or consider other sources of information. For example, it was identified by the Inspectors that both leukopenia and agranulocytosis were listed in a competitor SPC for the active [redacted]

  GVP module XI states: *'Signal assessment consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by marketing authorisation holders and competent authorities.'*

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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]	

Finding MA.1 b)
Invalid cases were not consistently considered in signal evaluations. The safety review template stated "If appropriate, review and include non-valid cases. If non valid cases are included in the review, include the following statement: In addition to the cases identified above, non-valid cases were also reviewed for any relevant information." It was described that the inclusion of non-valid cases in the evaluation would be determined based on the volume of valid information available for the review. If only a small number of cases had been reported, the invalid cases would be discussed; however, for signals involving a larger volume of cases to inform the conclusions non-valid cases could be omitted. This was not documented in any procedure. Furthermore GVP Module VI states *"Reports, for which the minimum information is incomplete, should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities."*
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 c)
The following delays were noted in the completion of signal management activities for the signal of Idela and pneumonitis: • This drug event pair was first detected at the Signal Detection (SD) meeting held on 09 December 2013 and assigned a priority 1 category (review to be presented to the Product Safety Committee (PSC) within 1 month). The signal was not discussed at the PSC until 07 March 2014, representing a delay of 2 months past the documented timeframe. • Following the PSC recommendation to add pneumonitis to the CCDS, this was not discussed at the (CLRC) until 26 August 2014, exceeding the 4 month documented timeframe. It is however, acknowledged that these delays had no impact, as the product was not authorised at that time (date of EU authorisation: 18 September 2014).
Root Cause Analysis

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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]	

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Finding MA.1 d)
The documented timeframes for the performance of signal management activities were not considered appropriate. SOP [redacted] (detection, evaluation and management of potential safety signals/issues, effective [redacted] allowed "Priority 2" signals (defined as a non life-threatening serious event or a non-serious event) 4 months for the initial signal work-up to be presented to the SD meeting and a further 2 months to be presented at the PSC. Therefore a signal of a serious adverse event could take up to 6 months from initial detection to confirmation. Further procedural delays regarding the timeframes for CCDS updates and variation approvals (as reported in finding MI.1 b)) could result in a new serious safety issue taking up to 13 months from detection to variation submission.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]

S43

[redacted]

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

Finding MA.1 e)

There was no routine cumulative review of adverse events received for the purpose of signal detection. The frequency reports created for the quarterly frequency review only included the number of cases received in the previous 2 year period.

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 MA.1 f)
A quarterly frequency review was performed using an output from the ARGUS safety database containing data for a two-year period; however, there were no documented criteria to trigger the identification of an event that is being reported more frequently.
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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[redacted]

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

Finding MA.1 g)
There were no documented criteria or quantitative / numerical thresholds in relation to the detection of new signals from ICSRs (for example, a trigger based on a number of events). Despite having a data set exceeding 145,000 individual cases, the MAH employed qualitative assessments performed by risk management scientists and physicians for the purpose of identifying new potential signals. Whilst it is acknowledged that the personnel performing this assessment are familiar with the products they are assessing and the indication they are treating, a qualitative assessment alone is not considered adequate to identify reporting trends and patterns in a data set of this size. GVP Module IX states: *'Statistical reports may be designed to provide tools for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering tools may facilitate the selection of ICSRs to be reviewed as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to the extent of usage of medicinal products and thus the potential public health impact.'* Due to the size of the Gilead dataset, it would be expected that some quantitative methods are utilised for signal detection purposes, which may include the use of defined thresholds.
Root Cause Analysis

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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.1 h)
The MAH had not demonstrated the effectiveness of their signal detection methodology. SOP-[redacted] *Detection, Evaluation and Management of Potential Safety Signals/Issues* (effective date: [redacted], section [redacted] stated "At least once a year, in the last quarter, performs a comparison of validated signals from regulatory agencies versus signals identified internally leading to CCDS changes to determine the effectiveness of signal detection activities." At the time of the inspection, this review had not been performed.

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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]	

MA.2 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.

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulations 187-188.

Commission Implementing Regulation (EU) No. 520/2012, Chapter V.

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

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

Finding MA.2 a)

Three third country ICSRs that met the criteria for expedited reporting were not reported to the MHRA. The table below provides further information regarding these cases and the reason for the error:

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Case ID	Country of Origin	Product	AE event terms	Reporter	Reason for non-submission
[redacted]	Japan	[redacted]	Fanconi Syndrome acquired; Blood phosphorus decreased; Drug resistance	Physician	Assessed incorrectly as invalid
[redacted]	Switzerland	[redacted]	Facial Paresis	Swissmedic	MHRA incorrectly entered as reporter
[redacted]	USA	[redacted]	Anaemia, Fatigue, Dyspnoea exertional, dizziness, palpitations, abdominal distention, swelling	Physician	Case initially incorrectly entered as invalid due to no identified country of origin

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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]	

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[redacted]

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

Finding MA.2 b)

In 2013 and 2014, there were multiple examples where Gilead failed expedited serious ICSRs within 15 days. The MAH had set themselves a tolerance target of 95% of all cases to be expedited within 15 days and in 2013 achieved an overall compliance of 89% and in 2014, 94%.

The majority of late submission cases to the MHRA were the result of late cases reported by vendors from market research and patient support programmes, as indicated in the table below:

Month/Year	Total no. of late cases	Reason for majority of late cases
June 2013	62	62 USA cases received late from [redacted] Access Programme (100% of the late cases)
July 2013	91	91 USA cases received late from [redacted] Access Programme (100% of the late cases)
April 2014	32	20 Canadian cases received late from Patient Support Programme (63% of the late cases)
September 2014	44	27 USA cases received late from [redacted] Access Programme (62% of the late cases)
October 2014	28	16 Spanish cases received late from Market Research Study (57% of the late cases)
December 2014	93	67 USA cases received late from [redacted] Access Programme (72% of the late cases)

It is acknowledged that each of these non-compliances was identified by the MAH during internal audit or through reconciliation processes and CAPAs have been implemented to address each individual issue; for example, evidence of communication with the MHRA was provided during the inspection regarding the low compliance figures from June and July 2013, in which the MAH stated the route cause was late receipt of cases from the [redacted] Access Programme, and identified that [redacted] call centre staff had not been trained to report death cases to Gilead Medical Information department. A CAPA was implemented which included training of staff, a re-write of contracts and implementation of reconciliation

activities.

However, it is recommended that a more expansive CAPA should be considered to address recurring issues with non-interventional programmes, including patient support programmes.

Root Cause Analysis

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[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.2 c)
The ICSR reporting tool (dated 05 February 2015) included a requirement to submit lack of effect reports (serious and non-serious) to the MHRA. However, for the Gilead product portfolio, this was not required as per EU guidance. GVP Module VI.B.6.4 states *"in certain circumstances, reports of lack of therapeutic efficacy may require to be reported within a 15-day time frame (see VI.C.6.2.3.4. as regards electronic reporting in the EU). Medicinal products used in critical conditions or for the*

treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases."

Root Cause Analysis

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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.2 d)

There was no process for periodic reconciliation between [redacted] and Gilead affiliates to ensure all safety data had been received. It is acknowledged that an acknowledgement was sent to the affiliate upon receipt of a case; however, this was not considered to be sufficient to ensure that safety data is reconciled between Argus and the Affiliate Tracking System (ATS).

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 MA.2 e)
There was no written procedure governing the use of social media relating to Gilead products, including the identification of AEs, frequency of monitoring of social media platforms, reporting of AEs to Gilead/PV and quality checks to ensure all AEs are appropriately identified and reported. At the time of the inspection, Gilead managed a Twitter account through which adverse event data could be reported.
Root Cause Analysis
[redacted]

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[redacted]

Further Assessment

[redacted]

S43

[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 MA.2 f)

Deficiencies were identified in the follow-up of cases. For instance:

i. No follow-up request had been submitted for case [redacted] which was invalid as it contained no patient identifiers. This was identified as an isolated incident from a sample of 10 cases reviewed.

ii. At the time of the inspection, the MAH had in place documented timeframes for the completion of follow-up activities. When follow-up was required, a query would be raised in the ARGUS database. [redacted] stated that follow-up attempts would be actioned within the following timeframes:

- QPC 1: 12-15 days
- QPC 2: 15-20 days
- QPC 3: 20-30 days
- QPC 4: 12-15 days

At the time of the inspection the following follow-up attempts were outstanding, having exceeded the timeframes stated in the MAH Work Instruction, some of which having accrued delays of 2 months.

Case ID	QPC no.	Product	Event term	Date query opened	Date query due
[redacted]	QPC 2	[redacted]	Multi Organ Failure	20 Nov 2014	02 Dec 2014
[redacted]	QPC 2	[redacted]	Hepatic Failure	20 Nov 2014	02 Dec 2014
[redacted]	QPC 2	[redacted]	Anaemia	03 Dec 2014	16 Dec 2014
[redacted]	QPC 3	[redacted]	Vomiting	03 Dec 2014	16 Dec 2014
[redacted]	QPC 4	[redacted]	Cardiac Failure	10 Dec 2014	24 Dec 2014
[redacted]	QPC 3	[redacted]	Hot flush	09 Dec 2014	30 Dec 2014
[redacted]	QPC 2	[redacted]	Cryoglobulina	19 Dec 2014	02 Jan 2015
[redacted]	QPC 4	[redacted]	Drug abuse	29 Dec 2014	05 Jan 2015
[redacted]	QPC 2	[redacted]	Pneumonia	30 Dec 2014	12 Jan 2015

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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]

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[redacted]

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[redacted]

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

Finding MA.2 g)
The targeted questionnaire for [redacted] which became effective on 01 September 2014, to obtain additional information on cases involving diarrhoea/colitis, was not disseminated to local pharmacovigilance responsible persons (PRPs) until 19 December 2014. This resulted in no targeted questionnaire being sent for case [redacted] that was received in October 2014.
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.2 h)
Three cases for events that were on the Gilead 'Always Serious List' were classified by the company as non-serious: • Interstitial lung disease [redacted] • Blindness [redacted] • Malignant neoplasm [redacted] In addition it was also noted that this case was also incorrectly classed as invalid, yet patient identifiers were available. This case therefore was not reported to the authorities. It is noted that these cases were received prior to September 2013, when the Always Serious List was incorporated into ARGUS in order to generate automatic seriousness assessments. Therefore, future cases received for these events will be correctly entered as serious.
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]	

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Finding MA.2 i)

Discrepancies were identified in the listedness assessments recorded in the safety database for the event of 'hepatic function abnormal' for [redacted] This event was not listed in the CCSI; however, the following cases were assessed as listed:

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

It was explained that these cases were considered synonymous with the event term 'liver function test abnormal' which was listed within the CCSI. However, a number of other cases coding the term 'hepatic function abnormal' were assessed as listed. Whilst the listedness assessment no longer has any impact on regulatory submissions in the EU the MAH should be consistent in its approach to these assessments.

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]	

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Finding MA.2 j)

At the time of the inspection the MAH maintained two literature strategies depending on the authorisation status of a product. The development literature search would be initiated upon approval by a regulatory authority of the first clinical trial associated with the product. Articles identified via this literature search were used to support the marketing authorisation application (MAA). It was described that the post-marketing search would be updated to include the product brand name, following MAA approval. The following deficiencies were noted in relation to the literature search process:

i. There was a delay in the implementation of the post-marketing literature search strategy for [redacted]. The development search strategy had been conducted from November 2012 and the marketing authorisation approval was granted on 18 September 2014. However, the post-marketing search strategy (containing the product brand name) was not implemented until 26 September 2014.

ii. The work instruction [redacted] *Literature Review within* [redacted] (effective date: 30 July 2014) did not include a process for literature searching during the period where a product transitions from development to post-marketing, including applicable changes to search strategies.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

S43

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

Preventative Action(s)

[redacted]

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

Finding MA.2 k)

The MAH failed to correctly identify 12 ICSRs from a literature article retrieved via the weekly literature search. Article "Acute kidney injury caused by [redacted] and [redacted] coadministration" (Bickel et al.) was identified on 17 October 2013 and a single invalid case of acute renal failure and drug interaction [redacted] was entered onto the safety database.

Following review of the full article received on 22 October 2013, the case was re-assessed as valid by the literature reviewer. However, the case remained invalid in error in the safety database and further review of the case during the inspection on 11 February 2015 determined that the case needed to be corrected to add the patient identifier of 'adult' and create 12 additional valid cases that had not previously identified.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

S43

[redacted]

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

S43

Finding MA.2 l)

A number of errors in the data entry of ICSRs were noted:

i. The following invalid cases were assigned an incorrect case type in Argus. As they were missing patient identifiers, the cases should have been assigned the case type of 'Other'. This error would result in these cases being included in PSUR summary tabulations, despite being invalid cases:

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

ii. The following HCP-confirmed cases were entered onto Argus as 'consumer, non HCP':

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

All cases were either non-serious cases, unrelated or reporting a pregnancy exposure with no adverse event, and therefore there was no impact on regulatory reporting.

iii. A number of solicited consumer cases were missing the 'as determined causality' assessment. For example:

- [redacted] solicited USA consumer case,
- [redacted] solicited USA consumer case,
- [redacted] solicited USA consumer case,
- [redacted] Canadian solicited,consumer case.

GVP module VI states that solicited reports should have an appropriate causality assessment to determine whether they meet reporting requirement standards. Furthermore [redacted] *Global Safety Database Data Entry Conventions Manual* (effective date: not stated; revision 8) stated that this field should be populated for all valid cases. It is acknowledged, however, that all examples were non-serious and reported from consumers and so this deficiency has had no impact on regulatory reporting to the MHRA. .

Root Cause Analysis

[redacted]

S43

[redacted]

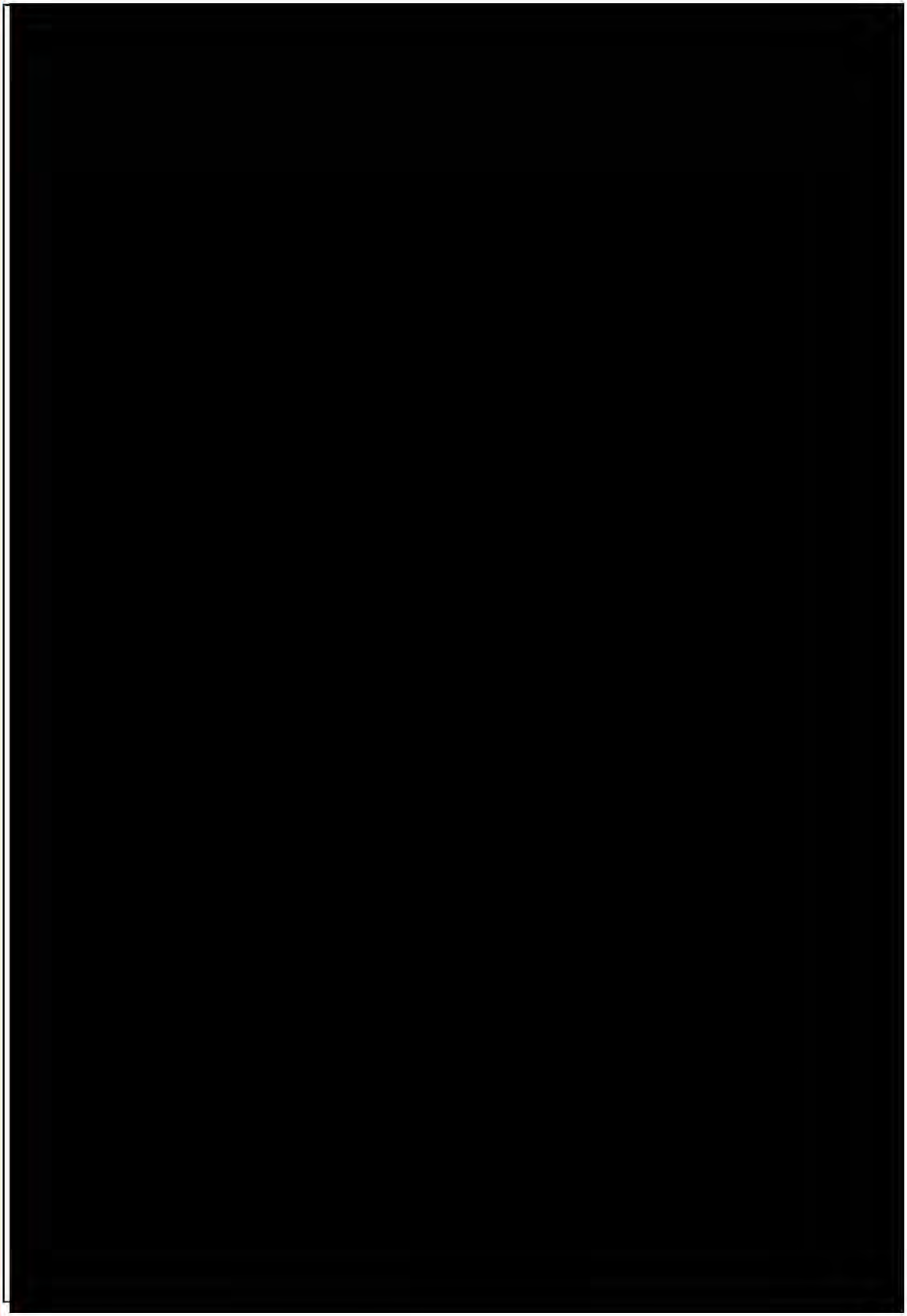
Further Assessment

[redacted]

Corrective Action(s)

[redacted]

S43



S43

[redacted]

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

Preventative Action(s)

[redacted]

S43

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

C.4.3 Minor Findings

MI.1 Regulatory Affairs

When new information about the benefits and risks of a product become available it is often appropriate to make changes to reference safety information documents, such as summaries of product characteristics (SPCs) and patient information leaflets (PILs), so that healthcare professionals or patients 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:

Finding MI.1 a)

The following deficiencies were noted in the timeframes governing the submission of safety variations:

i. The date that the MAH identified as the "day zero" for the measurement of safety variation submission compliance was not considered wholly appropriate. The date taken was that of the CCDS effective date, rather than the date that the PSC confirmed a new signal and made the recommendation to update the CCDS.

S43

SOP-[redacted] *Procedure for the authoring, review, approval and distribution of developmental core safety information and company core data sheets* (effective date: 09 July 2014) describes a timeframe of 4 months between the Product safety Committee (PSC) decision date and Core Labelling Review Committee (CLRC) approval. Therefore the "day zero" used to calculate the timeliness of safety variation submission could be up to 4 months after a signal confirmation and decision to update the CCDS.

ii. Following the effective date of the CCDS, SOP-[redacted] allowed up to 90 days (category 2 updates) or 180 days (category 3 updates) for safety variations to be filed. As a result, the total time from the decision date to update the CCDS and variation submission could exceed the expected timeframes of 6 months (category 2 updates 7 months, category 3 updates 10 months).

iii. There was no documented timeframe to describe the finalisation of the updated CCDS following a CLRC decision. It was noted during the inspection that in practice this occurred within a week of the CLRC meeting.

Only one example of a delay was identified from the samples examined during the inspection (reported as finding MI.1.b).

Root Cause Analysis

[redacted]

S43

[redacted]

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

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

Preventative Action(s)
[redacted]

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

S43

[redacted]

Finding MI.1 b)
A delay of 7 months from the confirmation of a safety issue by the PSC to variation submission was identified during the inspection. Following a Drug Monitoring Committee meeting on 04 April 2013, two clinical studies [redacted] and [redacted] were terminated due to significant efficacy and safety observations. This information was presented as late breaking information in the [redacted]n PSUR dated 09 May 2013. These signals were further discussed at the Product Safety Committee (PSC) on 14 May 2013, and the decision taken to update the CCDS with the safety and efficacy findings from these studies. The updated CCDS was not approved by the Core Labelling Review Committee (CLRC) until 04 October 2013 (~5 months after the signal confirmation) and a variation submitted on 20 December 2013 (~7 months after the signal confirmation)." It was acknowledged that these activities were performed in line with the documented timeframes in place at the MAH at the time of the inspection (refer to finding MA.1 d)).
Root Cause Analysis
[redacted]

S43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

S43

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

MI.2 Auditing of the Pharmacovigilance System

The following findings were noted in relation to quality assurance auditing of the pharmacovigilance system:

Finding MI.2 a)	
At the time of the inspection, there was no formalised risk assessment for the scheduling of pharmacovigilance audits of patient support programmes and market research programmes. It was acknowledged that the MAH had undertaken such audits, based on an informal assessment of risk (and in response to a request from the FDA); however, the risk based assessment had not been formalised or documented.	
Root Cause Analysis	
[redacted]	
Further Assessment	
[redacted]	
Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	

S43

S43

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

S43

Finding MI.2 b)

Delays were identified in the issue of an audit report following the conclusion of a pharmacovigilance audit.

SOP[redacted] *Audit Completion* (effective date: [redacted] stated that audit reports are to be completed within 30 days (calendar) following the last day of the audit. During the inspection, a number of delays were identified in the issue of an audit report following the conclusion of a pharmacovigilance audit. It was acknowledged that a number of these reports were in association with an increased number of audits of US Speciality Pharmacies, performed in the latter part of 2014 following an FDA inspection request. It was described that the reason for the delay in issuing these reports was associated with the increased strain on available audit resource.

However there were some additional examples of delayed audit reports that were not associated with Speciality Pharmacies.

Audit number	Audit end date	Audit report date	Days late (number of days post 30 days)
[redacted] Affiliate (South Korea)	30-Apr-2014	09-Jun-2014	10
[redacted] Affiliate (Canada)	12-Jun-2014	24-Jul-2014	12
[redacted] Affiliate (UK)	12-Jun-2013	24-Jul-2013	12
[redacted] DSPH (Aggregate reports)	13-Dec-2013	03-Feb-2014	22
[redacted] DSPH (Case processing)	02-Jul-2013	23-Aug-2013	22
[redacted] Distributor Pharmacovigilance Agreement[redacted]	02-Feb-2014	28-Apr-2014	55

Root Cause Analysis

[redacted]

S43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

S43

[redacted]

Finding MI.2 c)
An example was identified where no response had been received from an auditee 19 months after the audit report had been issued. An audit of the distributor [redacted] was performed in June 2013 and the report issued to the distributor in July 2013. Whilst attempts had been made to obtain a response from the distributor (23 August 2013; 09 September 2013; 04 February 2014; 14 November 2014), at the time of the inspection, a response had not been received. Evidence of escalation of the issue to the management team was provided during the inspection but this did not happen until 22 January 2015. Furthermore, the audit did report significant audit findings including a lack of a documented pharmacovigilance system.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

S43

[redacted]

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

Preventative Action(s)
[redacted]

S43

[redacted]

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

Finding MI.2 d)
A risk assessment of distribution partners was completed by the Regulatory Compliance group in February 2013, and assigned distribution partners a risk score that was then categorised as High (601 – 1000), Medium (251-600) or Low (40-250) risk. It was noted that all distributors scored between 280 and 560 and therefore all considered medium risk. As a result, the risk assessment was limited in its value in aiding the prioritisation of distributor audits for pharmacovigilance purposes (a separate risk assessment was performed in relation to GDP responsibilities). It was described during the inspection that the MAH were considering adapting this risk assessment, to address the point raised above.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

S43

[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

S43

Finding MI.2 e)	
There was an example where a distributor scored more highly than others and was not prioritised for audit. [redacted] scored 520 in the risk assessment, however was not scheduled for audit in 2013 or 2014, despite scheduling distributors with lower scores for audit (for example [redacted] (480 - scheduled July 2014) [redacted] (480 - scheduled July 2014).	
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.3 Periodic Safety Update Reports

Periodic Safety Update Reports (PSURs) provide analysis of the current understanding of a product. The following findings were noted in relation to PSURs:

Finding MI.3 a)
To inform their PSUR scheduling the MAH checked the EURD list on a six-monthly basis. As the list is updated on a monthly basis, it is possible that changes to the frequency cycle or DLP might be missed. It is therefore expected that MAHs to check the EURD list on a monthly basis to ensure that PSUR scheduling remains accurate. No errors were identified in PSUR scheduling during the inspection.
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]	

S43

MI.4 Non-interventional Programmes

The following findings were noted in relation to non-interventional programmes:

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Finding MI.4 a)
There was no documented procedure for the management of compassionate use programmes for authorised medicinal products. It is noted that there was an SOP for managing requests for access to investigational medicinal products: SOP-[redacted] *Request for Access to Investigational Medicinal Products via Expanded Access Programs.*
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]	

S43

Finding MI.4 b)
There was no prescriber agreement implemented with the requesting physician for a compassionate use supply of [redacted] The request was received on 06 July 2014 from [redacted] Israel, via the local distributor (patient initials BT). The request was approved on 10 July 2014 by Gilead Medical Affairs and supply of [redacted] was started on 03 August 2014. SOP[redacted] *Interfaces Between* [redacted] *and* [redacted] *Functional Areas for the Management of Pharmacovigilance Activities* (effective date: [redacted] section 5.3.4.2 states that Clinical Operations/Medical Affairs personnel manage the request, including preparation of the prescriber agreement.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

S43

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

MI.5 Pharmacovigilance System Master File

Every marketing authorisation holder 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 pharmacovigilance system master file (PSMF), which should be permanently available for inspection. The following findings were noted in relation to the PSMF:

S43

Finding MI.5 a)
At the time of the inspection, the MAH was maintaining two Pharmacovigilance System Master Files: one covering the products authorised to Gilead Sciences International and the other to cover the joint venture product [redacted] (MAH: BMS Gilead Sciences). It was determined during the inspection that the pharmacovigilance system and processes used for [redacted] were the same as that used for the Gilead portfolio. As a result, the MAH should maintain a single PSMF to cover a single pharmacovigilance system.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

S43

[redacted]

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

Finding MI.5 b)

The updated PSMF, which was provided upon request of the Inspection Team, did not include the most up-to-date information.

At the time of the inspection, the MAH was updating the PSMF on a quarterly basis. Prior to the inspection the inspection team made a request for an updated PSMF, including annexes, to be provided on day 1 of the inspection (09 February 2015). However, the PSMF provided was dated 17 December 2014 and the dates of some of the Annexes were prior to this date. For example, Annex G *Quality System* was dated 28 November 2014. As a result, the information provided to the Inspectors was not sufficiently comprehensive to facilitate the conduct of the inspection. For example:

- The product list in Annex H was not comprehensive and did not contain products that had been recently authorised [redacted](authorisation date 17 November 2014) and [redacted](authorisation date: 18 September 2014)).
- The list of completed audits was not up-to-date resulting in additional document requests having to be made.

Whilst it is considered acceptable to routinely update the PSMF on a quarterly basis, the MAH is reminded that there is requirement to provide an up-to-date PSMF within 7 days of a Competent Authority request.

Root Cause Analysis

[redacted]

S43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

S43

Finding MI.5 c)	
The Antiretroviral Pregnancy Registry, relevant to [redacted] was not listed in PSMF Annex C *Sources of Safety Data*.	
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 Medical Information

The provision of information to healthcare professionals and consumers is part of providing an effective scientific service, as well as part of the pharmacovigilance system to ensure all adverse drug reactions reported to the MAH are collected and collated. The following findings were noted with respect to the Medical Information function:

Finding MI.6 a)
The contract with Professional Information (effective date: May 2012) did not include the provision for the exchange of occupational exposure and off-label use. At the time of the inspection, Professional Information were providing an out-of-hours medical information service, in addition to a full medical information service on select days.
Root Cause Analysis
[redacted]
Further Assessment

S43

[redacted]

S43

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

Finding MI.6 b)

The following deficiencies were noted in [redacted] *Medical information request handling process in EMEA Medical Affairs department* (effective date: 11 July 2012):

i. Section 5.6.1.3 described the requirement to transfer special situations reports to drug safety. However, this omitted cases of occupational exposure and off-label use. It was described during interview that off-label use cases that have been confirmed to involve a patient would be forwarded to drug safety. Whilst there was limited information in the corresponding Global SOP SOP[redacted] *Medical Information Request Handling* (effective date: 02 [redacted] A presentation delivered to Medical Affairs personnel [redacted] – Safety Information Reporting – Medical Affairs – Global version[redacted], provided very specific advice on how to deal with off-label use cases.

ii. Section 5.6.2 stated "If a medical information request relates to or includes an AE, the following details must be recorded.

- Identifiable reporter

- Identifiable patient
- A suspect drug
- A suspected reaction"

It did not describe what should be done, should these four criteria not be available. (Again it was described during interview that these non-valid cases would be transferred to drug safety). It was however, noted that the global SOP [redacted] describing the provision of a medical information service and adverse event collection (effective date: [redacted] provided clear guidance on what to do should the 4 criteria not be available.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

S43

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

MI.7 Risk Management Systems

Finding MI.7 a)

During the inspection a delay was identified in the update of risk management plan (RMP) educational materials following a variation approval to update the SPC and PIL with strengthened information regarding the risks communicated in the educational materials. For example:

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i. A variation to update the [redacted]SPC with adapted recommendations regarding renal monitoring and further information regarding renal adverse events received a positive CHMP opinion on 24 July 2014 and final linguistic approval on 20 August 2014. Consequent updates to the educational materials communicating these risks were not submitted to the MHRA for approval until 14 January 2015, a delay 5 months following final approval of the updated wording.

ii. On the 23 August 2012 the CHMP adopted version 12 of the [redacted]RMP and the outcome communicated to the MAH on the 29 August 2012. In this communication the MAH were asked to consider updates to the RMP educational material to incorporate further information regarding renal toxicities. Updates to the RMP educational materials were not submitted to the MHRA for approval until 04 February 2013, a delay of approximately 6 months following the CHMP request.

iii. It was also noted that there was no documented timeframe for the update of educational materials (where applicable) following variation approval.

This has been graded as a minor finding as it is acknowledged that there is currently no published guidance stipulating the timeframes for incorporating new and relevant safety information into educational materials that form part of the risk management plan, following approval of safety updates to authorised product information. This specific issue was raised with the MHRA Vigilance and Risk Management of Medicines division for consideration, who agreed that the time elapsed between the final linguistic approval and submission of the updated educational materials was too long. The issue regarding the lack of documented guidance was also raised and a request raised with the Rapporteur for GVP Module XVI for inclusion in a subsequent revision of the module.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

S43

[redacted]

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

C.4.4 Comments

S43

i. At the time of the inspection, the PSUR for [redacted] was on a six-monthly reporting cycle within the EU, as stated in the EURD list. During the inspection, the company explained that, from August 2015, annual PBRERs would be required to be submitted to the US FDA and therefore planned to submit an annual PBRER, which locks on 26 August 2016, to EU authorities in place of a six-monthly PSUR covering the period 27 February 2016 – 26 August 2016.

ICH E2C (R2) states "*In situations when an MAH is preparing PBRERs on both a six-monthly and annual basis for different regulatory authorities, the regulatory authority requiring a PBRER on a six-month cycle may accept PBRERs containing 12-month interval data. MAHs should discuss the acceptability of this approach with the relevant regulatory authority(ies).*"

ii. Discrepancies were noted in the frequencies of adverse events presented in the Company Core Data Sheet (CCDS) (revised: 21 October 2014) and the Summary of Product Characteristics (SPC) (revised: July 2014) for Stribild. The following discrepancies were identified:

Event Term	Frequency stated in CCDS (21 October 2014)	Frequency stated in SPC (July 2014)
Depression	very common	uncommon
Suicide ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness)	common	uncommon
Insomnia	very common	common
Renal failure	common	uncommon
Fatigue	very common	common

The company explained that frequencies for each document were calculated differently: the frequencies in the CCDS were based on treatment emergent adverse events (TEAEs) regardless of the causal relationship evaluated by clinical study investigators; the frequencies in the SPC were based on TEAEs considered to be related to the drug by investigators. It is noted that SPCs contain the latter as a result of a CHMP request.

The company should consider documenting the reason for this deviation from the CCDS.

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.
- Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use, September 2008.s
- 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".
- 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".
- CHMP/ICH/309348/2008: E2F "Development safety update reports".
- CPMP/ICH/135/95: E6 (R1) "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: GPvP INSPECTION PLAN

MHRA INSPECTION NUMBER	GPvP 16807/123561-0007	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Gilead Sciences International Limited	**DATE**	09 February 2015
LOCATION	Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT	**START TIME**	10:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting • review of scope of inspection and inspection plan • overview of the company and pharmacovigilance system, including significant changes implemented since last inspection *(presentation by MAH to be no longer than 20 minutes)*	RC	All welcome [redacted] VP, Drug Safety & Public Health (DSPH) [redacted] Senior Director, EU QPPV, DSPH [redacted] Senior Director, Standards, Collaborations and Systems (S&C) DSPH [redacted] Senior Director, Medical Surveillance & Coding (MSC) DSPH [redacted] Senior Director, Operations, DSPH [redacted] Director, S&C, DSPH [redacted] Manager, S&C, DSPH [redacted] Senior Director, Regulatory Compliance [redacted] Director, Regulatory Compliance

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Receipt and handling of medical information enquiries and product quality complaints	RW	Interviewee(s): [redacted], Director, Medical Information [redacted] Associate Manager, Medical Information [redacted] Associate Director, Quality [Cork] [redacted] Safety Specialist, DSPH [redacted] Administrative Coordinator, DSPH [redacted], Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
Document Review	-	Inspectors only
LUNCH	-	-
Case receipt and processing • management of spontaneous cases, including coding, evaluation, follow-up and submission • management of regulatory authority cases • management of clinical trial cases ***From 15:30 due to staff availability:*** • literature searching and review *(The review and monitoring of websites/digital media will be covered in a separate session on the afternoon of Day 2.)*	CL	Interviewee(s): [redacted], Senior Safety Specialist, Operations, DSPH [redacted] Safety Specialist II, Operations, DSPH [redacted] Associate Director, Medical Surveillance and Coding (MSC), DSPH [redacted] Safety Spec, Operations, DSPH [redacted] Manager, Operations, DSPH [redacted] (Manager, Literature Services, DSPH [Foster City] [redacted] Manager, Lit Resources, DSPH [Foster City] [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)

Document Review	-	Inspectors only

Please note:

- Relevant SOPs, working practices, training records, CVs and job descriptions should be made available to the inspection team.
- Other documents will be requested during the inspection.
- The Inspection Plan may need to be amended during the inspection.

[redacted]

MHRA INSPECTION NUMBER	GPvP 16807/123561-0007	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Gilead Sciences International Limited	**DATE**	10 February 2015
LOCATION	Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Ongoing safety monitoring and Risk Management Plans • signal detection • risk management	CL	Interviewee(s): [redacted] Associate Director, MSC, DSPH [redacted] Associate Director, MSC, DSPH [redacted] Director, Regulatory Affairs [redacted] Associate Manager, Regulatory Affairs [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
LUNCH	-	-
To start at 13:00 due to staff availability **Case receipt and Processing *(continued from Day 1)*** • monitoring of websites and digital media	CL	Interviewee(s): [redacted] Public Affairs (standby) [US East Coast] [redacted] Director, Marketing [Foster City] [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
From 15:30 due to staff availability	KT	Interviewee(s):

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Non-interventional sources of safety data • non-interventional studies • patient support/assistance programmes (PSPs/PAPs) • compassionate use programmes *(The processing of cases will be covered in the Case Receipt and Processing session on the Afternoon on Day 1.)*		[redacted] Senior Director DSPH and EU QPPV [redacted] Associate Director, S&C, DSPH [redacted] Director, Medical Information [redacted] Medical Director, UK [redacted] Clinical Operations [Foster City] [redacted] Senior Clinical Trial Management Associate, Clinical Operations [Foster City] [redacted] Director, Clinical Research [Foster City] [redacted] Clinical Programme Manager [redacted] Senior Clinical Programme Manager [redacted] Director Patient Support Services [Foster City] [redacted] Director, S&C, DSPH [Foster City] (PAPs) [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
Interventional clinical trials • initiation and management of clinical trials • management of investigator-initiated studies *(The processing of cases will be covered in the Case Receipt and Processing session on the Afternoon on Day 1.)*	KT	Interviewee(s): [redacted] Associate Manager, Operations, DSPH [redacted] Associate Director, Medical Surveillance and Coding (MSC), DSPH [redacted] Associate Manager, S&C, DSPH [redacted] Sr Safety Spec, Operations, DSPH [redacted] Director, Clinical Operations [Foster City] [redacted] Medical Director, UK [redacted] Manager, Regulatory Affairs

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		[redacted] Associate Director, CCF [Foster City] [redacted] Senior Manager, CCF [redacted]n, Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
Document Review	-	Inspectors only

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MHRA INSPECTION NUMBER	GPvP 16807/123561-0007	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Gilead Sciences International Limited	**DATE**	11 February 2015
LOCATION	Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
PSUR and DSUR production and submission	RC	Interviewee(s): [redacted] Associate Director, MSC, DSPH [redacted] Senior Manager, Regulatory Affairs [redacted] Manager, Regulatory Affairs [redacted] Contractor, Regulatory Operations [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
Contracts and agreements • licensing partners • distributors • external service providers	KT	Interviewee(s): [redacted] Senior Director, DSPH, S&C [redacted] Associate Manager, DSPH, S&C [redacted] Director, Legal [redacted] Director, Regulatory Compliance (Inspection Coordinator)
LUNCH	-	-
Quality Management System	RW	Interviewee(s):

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• pharmacovigilance policies/procedures • pharmacovigilance training • auditing of pharmacovigilance activities • document retention and archiving • maintenance of the PSMF		[redacted] Senior Director, DSPH, S&C [redacted] Director, S&C, DSPH [redacted] Associate Manager, S&C, DSPH [redacted] Manager, DSPH, S&C, DSPH [redacted] Associate Manager, S&C, DSPH [redacted] Manager, Quality Document and Training Administration (QDTA) [redacted] Director Regulatory Compliance [redacted] Senior Director, Regulatory Compliance
From 15:30 due to staff availability **Control and maintenance of reference safety information, including core safety information, SPCs and PILs** • internal and external triggers • review process • variation submission • implementation, including websites and artwork	RC	Interviewee(s): [redacted] Associate Manager, Regulatory Affairs-UK [redacted] Director, Regulatory Affairs [redacted] Director, Regulatory Affairs [Foster City] [redacted] Associate Manager, Medical Information [redacted] Manager, Supply Chain or Alternative Cork Nominee [Cork] [redacted] Director, Regulatory Affairs [redacted] Manager, Regulatory Affairs [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
Document Review	-	Inspectors only

MHRA INSPECTION NUMBER	GPvP 16807/123561-0007	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Gilead Sciences International Limited	**DATE**	12 February 2015
LOCATION	Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Roles and responsibilities of EU/EEA Qualified Person for Pharmacovigilance (QPPV)	RC	Interviewee(s): [redacted] Senior Director DSPH and EU QPPV [redacted] Senior Director, DSPH, S&C (Observer) [redacted] Director, Regulatory Compliance (Inspection Coordinator)
Ad hoc questions and clarifications	ALL	
Document review	-	Inspectors only
LUNCH	-	-
Document review	-	Inspectors only
Inspectors meeting	-	Inspectors only

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MHRA INSPECTION NUMBER	GPvP 16807/123561-0007	**DAY**	5
PHARMACOVIGILANCE INSPECTION OF	Gilead Sciences International Limited	**DATE**	13 February 2015
LOCATION	Flowers Building, Granta Park, Abington, Cambridge, CB21 6GT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review	-	Inspectors only
Ad hoc questions and clarifications	ALL	
LUNCH	-	-
Document review	-	Inspectors only
Inspectors meeting	-	Inspectors only
Closing Meeting	RC	All welcome

* Please note that only Roisín Cinnéide and Rebecca Webb will be attending on Day 5.