Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Sanofi

MHRA Inspection Number: Insp GPvP 4425/18922628-0002

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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
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Sanofi – [redacted]
Site(s) of inspection:	410 Thames Valley Park Dr, Earley, Reading RG6 1PT
Main site contact:	[redacted]
Date(s) of inspection:	Office based inspection day on 09 December 2019 On-site days 10 – 13 December 2019
Lead Inspector: **Accompanying Inspector(s):**	[redacted]
Previous inspection date(s):	18 – 22 July 2016 (CHMP requested, ANSM led) 25 – 27 August 2015 16 – 19 December 2013 and 10 January 2014 07 – 09 January 2009
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	No specific products were selected for review, all UK authorised products were in scope of the inspection.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	PV-AEGIS – Customized version of Argus (commercially available)
Key service provider(s):	ICSR management provided by [redacted] Global literature review performed by [redacted]
Inspection finding summary:	1 Major finding(s) 3 Minor finding(s)
Date of first issue of report to MAH:	02 April 2020
Deadline for submission of responses by MAH:	13 May 2020
Date(s) of receipt of responses from MAH:	12 May 2020
Date of final version of report:	20 May 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Sanofi was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Regulation 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.

Sanofi is a global pharmaceutical company headquartered in Paris. The organisation contains five global therapeutic business units: Primary Care, China and Emerging Markets, Speciality Care, Vaccines and Consumer Health. These five business units are supported by the Global Pharmacovigilance Organisation (GPV). Governing bodies in the areas of Medical safety, compliance and quality maintain oversight of the business units. Sanofi had outsourced some pharmacovigilance activities, including ICSR processing and literature searching to Parexel and Cognizant.

Sanofi holds products authorised through the EU centralised route and the Supervisory Authority is Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM).

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems and was performed at Sanofi's offices in Reading, Berkshire. Personnel from Sanofi attended the site in order to participate in the inspection. Sanofi staff were also available via video and teleconference throughout the inspection.

The Supervisory Authority inspection of Sanofi was conducted in May 2019. The scope of this MHRA inspection was focussed on activities which impacted upon UK patients specifically (RSI and the management of risk management systems in the UK) and also PASS, which had not been covered during the Supervisory Authority inspection.

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

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B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 30 September 2019) 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.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan and included a scheduled office-based inspection day, which was held on 09 December 2019.

A closing meeting was held to review the inspection findings at Sanofi's offices on Friday 13 December 2019. Additional review was required after the onsite days, particularly in relation to pharmacovigilance data management, which resulted in document requests and office-based inspection after the onsite closing meeting. This review was completed on the 30 March 2020.

A list of the personnel who attended the closing meeting 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 2015 the company had made the following changes to the pharmacovigilance system:

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- The EU QPPV had changed from [redacted] (as reported in inspection GPvP [redacted]
- Four previously separate pharmacovigilance systems described in four PSMFs (Sanofi, Genzyme, Zenvita and Sanofi-Pasteur) had been integrated into a single global pharmacovigilance system operated by Sanofi and described in PSMF [redacted]
- An acquisition of the [redacted] had been completed and was integrated into the Sanofi pharmacovigilance system since July 2017.
- The Sanofi European Generics business had been divested to Zentiva, and since 30 September 2019 no pharmacovigilance agreements were in place between the two businesses.
- Sanofi had acquired [redacted]. The EU authorised product [redacted] was transferred into the Sanofi pharmacovigilance system.
- A license and collaboration agreement existed between Sanofi and Regeneron for the product [redacted] This product resides in Sanofi's PSMF [redacted] and Sanofi are responsible for conducting pharmacovigilance activities.
- The pharmacovigilance database was changed from an AERS system "AWARE" to a customised Argus model "PV-AEGIS" on 22 May 2018.

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 under 'Inspection outcomes' at: https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp

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 Reference Safety Information

Requirements:

Directive 2001/83/EC as amended

Paragraph 40 *"The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information."*
Article 23(3) *"The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge"*

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

Finding MA.1 a)

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One batch of [redacted] was QP certified and released with an outdated patient information leaflet (PIL) past Sanofi's compliance date and the MHRA expected six-month deadline from approval. The outdated PIL did not include significant safety information present in the latest approved version.

Batch [redacted] had been QP certified on the 31 January 2019, with a copy of the previous PIL. The updated PIL [redacted] should have been in batches from the Sanofi compliance date of 07 January 2019, and the MHRA expected six-month deadline of 11 January. The variation which included the updated PIL [redacted] was approved on 11 July 2018.

Sanofi's internal deadline was outlined in [redacted] "Production of regulatory text and artwork for submission and subsequent implementation" [redacted] effective from 03 September 2019) stated: *"New artwork should be implemented into manufacturing packaging runs as soon as practically possible, but within 6 months of a variation approval (subject to manufacturing runs) unless the HA dictates an earlier implementation date. No stock may be QP released using old artwork after 6 months following the approval of new artwork, unless this has been agreed in advance with the relevant HA."*

Guidance published by the MHRA states that once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months:
https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets.

The updated PIL contained additional safety related information, including a warning and

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information about concomitant use whilst taking [redacted] or related drugs.

The MAH had identified this whilst compiling information for the inspection and raised deviation [redacted] The MAH committed to contacting the MHRAs Defective Medicine Reporting Centre (DMRC) regarding this batch of product. This was reviewed by DMRC [redacted] and no further action was required.

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 MA.1 b)

There were examples where outdated product information was available on the electronic Medicines Compendium (eMC) and company-sponsored websites. The examples identified did not include significant changes to product information, but together illustrate a weakness in process.

Examples included:

a) Sanofi published product information on the eMC. One example was found where the product information was not the latest approved version. The most recently approved SPC for [redacted] was dated the 15 October 2019, however the version on the eMC was dated 31 July 2014. There were changes to sections 4.4, 4.5 and 4.5, and changes in line with the QRD template in the latest version.

Sanofi's procedural document [redacted] "Production of regulatory text and artwork for submission and subsequent implementation [redacted] stated "*electronic versions of the updated SmPC and PIL will be placed on the eMC or medicines.ie within 10 working days of HA approval."*

b) A company sponsored website [redacted] contained out of date PILs and SPCs for three [redacted] licences:

i. [redacted] dated 28 April 2017 and PIL dated February 2017 were available on the website, current versions were dated 08 April 2018 (SPC) and August 2018 (PIL). Safety changes included removal of a sentence from section 4.2, layout updates to section 4.8 and the document was brought in line with the QRD template.

ii. [redacted] dated 28 April 2017 and PIL dated February 2017 were available on the website, current versions were dated 26 July 2019 (SPC) and July 2019 (PIL). Safety changes included removal of a sentence from section 4.2, layout updates to section 4.8 and the document was brought in line with the QRD template.

iii. [redacted] dated 28 April 2017 and PIL dated February 2017 were available on the website, current versions were dated 28 August 2019 (SPC) and July 2019 (PIL). Changes included a layout change to section 4.8 and an update to section 6.3 regarding storage instructions once opened in respect to microbial contamination.

c) A company website containing product information for HCPs and patients for [redacted], contained prescribing information (PI) that was based on a previous version of the SPC. The PI referenced on the website had been updated in December 2018 but the SPC for [redacted] had been updated in September 2019. No significant changes were identified between the versions of the SPC and PI.

d) The HCP and patient focussed website for [redacted]

included a copy of the SPC which was not the most recently approved version. The SPC on the website was dated the 28 June 2019, whereas the currently approved version was dated the 06 September 2019. The latest version included minor updates to section 6.3 and included a change of MA Holder information. This was corrected during the inspection.

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e) Previous versions of PILs for [redacted] containing products were identified on a product website [redacted] This website provides patients with product information about the medication, including a patient guide, patient card and PILs for the licence numbers [redacted] The changes to the updated PILs did not include any safety-related information.

In the examples above, there were no instances of significant safety messages being unavailable on product websites as a result of not updating the RSI to the latest version. However, information available on company websites should be reviewed once product information has been updated and the most recently approved versions should be available.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

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

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[redacted]

C.4.3 Minor findings

MI.1 ICSR Management

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Finding MI.1 a)
Sanofi were extracting data from the global safety database by using the AEGIS Product Family Name field. [redacted] (where a record represents one drug product included within a case), covering [redacted] distinct product names were identified which did not have the Product Family Name completed. Sanofi described two root causes: data entry errors or that re-coding of the drug when processing follow-up information received from EudraVigilance was not correctly completed and had resulted in blank product family names. Events from these cases would be missing from downstream pharmacovigilance activities which include signal detection and aggregate reports such as PSURs. This has been graded as minor due to small number of cases which had these errors when compared to the size of the global safety database.
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]	

MI.2 Post Authorisation Safety Studies

Finding MI.2 a)
The protocol for [redacted] "A prospective multicenter observational post authorization safety sub-registry to characterize the long-term safety profile of commercial use of [redacted] in adult patients with [redacted] was not uploaded to the EUPAS Register, ENCePP. Sanofi supplied version [redacted] of the protocol in the pre-inspection documentation, dated 11 September 2018. GVP Module VIII.B.2. states: *"Non-interventional PASS should be registered in the EU PAS Register before the study commences or at the earliest possible date, for example if data collection had already started for a study included in the risk management plan. The study protocol should be uploaded as soon as possible after its finalisation and prior to the start of data collection."*
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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[redacted]

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

MI.3 Record Management

Finding MI.3 a)
Regulatory text/Artwork tracking forms, used by Regulatory Affairs to manage and track the required activities during the review and approval process of updates to product information (including draft mock-ups, current versions of the text and evidence of approval) were unavailable for the following variations: • [redacted] –submitted 15 March 2017, approved 11 July 2018 • [redacted] – submitted 26 February 2018, approved 11 February 2019

In response to the inspection document request, the company raised a deviation and committed to expanding the search of the archive boxes to establish if there are any other missing archived files.

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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]	

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- 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”.
- EMA/CHMP/ICH/135/1995: E6 (R2) “Guideline for good clinical practice”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1 (onsite)
PHARMACOVIGILANCE INSPECTION OF	Sanofi	**DATE**	10th December 2019
LOCATION	410 Thames Valley Park Drive, Reading, RG6 1PT	**START TIME**	09:00 arrival for 09:30 opening meeting

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system and the quality system *(approx. 20 minutes)*		[redacted]
Document Review		
Lunch		

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Sources of UK Safety Data, including but not limited to: - Medical information - Product Quality complaints - Solicited sources of information	[redacted]	[redacted]
[redacted]		

MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Sanofi	**DATE**	11th December 2019
LOCATION	410 Thames Valley Park Drive, Reading, RG6 1PT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Post Authorisation Safety Studies, including but not limited to: - The set-up and management of Post Authorisation Safety Studies EUPAS12423 and EUPAS11998 have been selected for review during this inspection.	[redacted]	[redacted]
LUNCH	-	-

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Risk Management systems in the UK, including but not limited to: - Additional risk management activities being performed in the UK - Effectiveness measures of risk management systems	[redacted]	[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Sanofi	**DATE**	12th December 2019
LOCATION	410 Thames Valley Park Drive, Reading, RG6 1PT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Reference Safety Information, including but not limited to: - Pre-submission processes - Post-approval pathways, including dissemination of updated product information	[redacted]	[redacted]
LUNCH	-	-
This afternoon is reserved for ad-hoc queries in all areas		Interviewee(s) as required.

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MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Sanofi	**DATE**	13th December 2019
LOCATION	410 Thames Valley Park Drive, Reading, RG6 1PT	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
This day is reserved for ad-hoc queries		Interviewee(s) as required.
Inspectors meeting	-	Inspectors only
Closing meeting	-	All welcome