Medicines & Healthcare products
Regulatory Agency

PHARMACOVIGILANCE
INSPECTION REPORT

Pharmacovigilance System Name: Advanz Pharma

MHRA Inspection Number: Insp GPvP 42590/37426818-0001

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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
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

Inspection type:	Statutory National Inspection
System(s) inspected:	Advanz Pharma Holdco Limited, [redacted]
Site(s) of inspection:	Remote
Main site contact:	[redacted] Advanz Pharma 15 rue du Bicentenaire 92800 Puteaux France Tel: [redacted] Email: [redacted]
Date(s) of inspection:	17- 19 February 2025 (Remote)
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted]
Previous inspection date(s):	11-14 December 2017 (Insp GPvP 42590/9386368-0004, Concordia International)
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU for maintenance of reference safety information and management of educational materials.
Products selected to provide system examples:	All UK-authorised products were within scope of the inspection
Name and location of UK QPPV:	[redacted] Advanz Pharma 15 rue du Bicentenaire 92800 Puteaux France Tel: [redacted] Email: [redacted]
Global PV database (in use at the time of the inspection):	[redacted] (commercially available)
Key service provider(s):	Pharmacovigilance services provided by APCER Medical information services provided by Universal Medica Group (UMG)
Inspection finding summary:	0 Critical findings 2 Major findings 6 Minor findings
Date of first issue of report to MAH:	15 May 2025
Deadline for submission of responses by MAH:	20 June 2025 29 August 2025 17 October 2025

Date(s) of receipt of responses from MAH:	19 June 2025 28 August 2025 14 October 2025
Date of final version of report:	20 October 2025
Report author:	[redacted] GPvP Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Advanz Pharma Holdco Limited (hereafter referred to as "Advanz Pharma") 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 UK and EU pharmacovigilance regulations and guidelines. In particular, reference was made to The Human Medicines Regulations 2012 as amended, Commission Implementing Regulation (EU) No 520/2012 and the EU good pharmacovigilance practices (GVP) Modules as modified by the guidance note 'Exceptions and modifications to the EU GVP that apply to UK MAHs and the licensing authority'.

The pharmacovigilance system, as described in [redacted] covered over [redacted] MAHs, [redacted] of which were UK MAHs (Mercury Pharma Group Limited, Mercury Pharmaceuticals Limited, Advanz Pharma Generics (UK) Limited, Amdipharm UK Limited, Focus Pharmaceuticals Limited, Correvio (UK) Ltd, Advanz Pharma Europe Limited, Cardiome UK Limited). The corporate headquarters were located in London, UK. Advanz Pharma's portfolio consisted of specialty generics, biosimilars, originator brands, and innovative medicines, and had a global reach in over [redacted] markets, including Europe, Australia, Canada and US, via affiliates and established partner networks. At the time of the inspection, Advanz Pharma held approximately [redacted] UK licenses- comprising of around [redacted] Category 2, and [redacted] Category 1 products).

A list of reference texts is provided at Appendix I.

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems as relevant to the management of reference safety information and educational materials and was performed remotely. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II). Personnel from Advanz Pharma were available throughout to participate in the inspection. The inspection was performed using interviews and document review.

B.3 Documents submitted prior to the inspection

The company submitted the UK PSMF (version [redacted] DLP: 31 December 2024, dated 22 January 2025) 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. Details of these additional requests is contained within the 'Advanz GPvP Document Request Sheet_05Feb2025' tracker. This tracker was also used for requesting of documents during the inspection.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. Minor amendments to the Inspection Plan that occurred during the inspection are highlighted using italic text in Appendix II.

A closing meeting was held remotely via teleconference to review the inspection findings on 20 February 2025. At the time of the closing meeting, some document requests remained outstanding. Final documents were provided to the inspectors post-inspection on 11 March 2025.

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

The last PV inspection had been conducted in December 2017 and pertained to Concordia International (Insp GPvP 42590/9386368-0004).

Within the past 7 years, Advanz Pharma had undergone significant organisational changes including company mergers in addition to product acquisitions.

- In late 2018 Concordia Healthcare Corp. rebranded as Advanz Pharma Corp.
- In early 2020 Advanz Pharma re-domiciled in the UK, and in May Advanz Pharma completed the merger with Correvio Pharma Corp., a speciality pharmaceutical company.
- In 2021 Cidron Aida Bidco, a subsidiary of Nordic Capital, acquired Advanz Pharma.
- In July 2022 Advanz Pharma completed acquisition of the non-US subsidiaries of Intercept Pharmaceutical, Inc, taking over its business in Europe, Canada and all other markets outside of the US.
- In November 2023 Pinnacle Biologics, based in the USA and previously managed as an independent entity, was fully integrated in Advanz Pharma's System.
- Between 2023 and 2024, Advanz Pharma had acquired various products from companies such as Janssen, Sanofi, Kyowa Kirin, and Beyer.

Specific and recent changes relating to the management of reference safety information included the introduction of a validated Build-Operate-Transfer (BOT) tool utilising Robotic Process Automation (RPA), in [redacted] to make available the latest version of product reference documents (including SmPC, PIL) at a defined [redacted] location for company personnel. The BOT had been live since November 2024. Additionally, Advanz Pharma had adopted a new process step to publish the current SmPC/PIL via the company Medical Information website. The latter approach was being piloted at the time of the inspection-products had been selected based on enquiries received.

Of note, there had also been changes to the scope of work undertaken by PV service provider APCER Life Sciences Ltd. ('APCER'). Since 2008, end-to-end pharmacovigilance activities had been outsourced to APCER. However, in 2019, activities including medical information and case collation, PSMF maintenance, risk management plan (RMP) writing, periodic safety update report (PSUR) writing, signal detection and safety database management were brought in-house, and in 2020 QPPV support was also brought in-house. Since 2019, APCER performs case processing, ICSR submission, follow-up management, global literature review, in addition to deputy EU-QPPV, National Contact Person for UK (NCP) and local PV partner support.

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 that covers products authorised in respect of Northern Ireland which are graded as critical or major will be shared with the EMA, 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:

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

Commission Implementing Regulation (EU) No. 520/2012, Articles 11(1)(f)(g)

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01)
2.1.1. Submission of Type IA notifications
"*Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder.*"

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.4. Overall quality objectives for pharmacovigilance
"The overall quality objectives of a pharmacovigilance system are: […]
- *promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public;"*

Finding	**MA.1 a)**

Failures in the provision of up-to-date product information within packs were identified. Superseded product information was QP-certified beyond 6 months after the last acceptable date of QP-certification.

i. Delayed implementation was observed in relation to a Type IA_{IN} national variation submitted for [redacted] in order to update product information in relation to the risk of [redacted] in line with [redacted] Section 4 of the PIL and section 4.8 of the SmPC were updated.

The variation was submitted on 09 August 2023, and therefore the latest permissible date for QP certification of the superseded PIL ([redacted] was 09 February 2024 (6 months post submission[1]). However, a batch with the superseded PIL (batch no: [redacted] expiry date: April 2027; containing [redacted] ampoules- packs of 10x2 ampoules) was QP-certified on 11 June 2024, 4 months beyond the expected implementation deadline.

It was confirmed via documents received post-inspection that no other batches related to this product variation were impacted.

On 26 March 2025, the MAH notified the Defective Medicines Report Centre (DMRC) of the non-compliance in order to agree on any required actions. The MAH is

accordingly expected to devise and document, as part of their response, a CAPA plan that appropriately reflects the discussions with the DMRC.

ii. A second example was observed with a national Type IB safety variation [redacted] submitted for [redacted] The update to product information had been triggered by the MAH following periodic review during the company's harmonisation process, resulting in aligning the SmPC, outer packaging and label with the QRD template. Minor wording changes were observed only.

The variation was approved by the MHRA on 30 September 2022. The last batch of [redacted] batch no [redacted] expiry date: July 2025; containing [redacted] ampoules – packs of 10x2 ampoules) was manufactured in August 2022 and QP-certified on 29 September 2023 with the superseded PIL [redacted] This was 6 months later than the expected implementation due date[1].

No deviation was raised by the manufacturer [redacted] to account for the release of superseded artwork, nor was the deficiency made aware to the MAH. Advanz Quality team received monthly reports ('Artwork implementation compliance data') to oversee compliance of the manufacturers (CMOs), however, this deficiency was not flagged as the report reflected compliance of the timeliness for quarantining product materials as opposed to monitoring QP certification of batches.

It is acknowledged that, for this example, the nature of the changes did not appear to be significant in providing updated safety information. However, has been reported as a further example of out-of-date product information being utilised.

[1]The company is reminded that the MHRA allow a 3-to-6-month (maximum) grace period for the implementation of updated PILs into packs, unless otherwise specified. Day 0 is determined as the date of submission to the MHRA in the instance National Type IA(IN) variations, and the date of MHRA approval in the instance of National Type IB/II variations. Where the product is licensed under MRDCP, Day 0 is defined as the date of Reference Member State (RMS) approval for Type IA_{IN} and Type IB, and the date of RMS approval + 30 calendar days in the instance of Type II variations.

The MHRA published guidance: Medicines: apply for a variation to your marketing authorisation (dated 22 April 2024) https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation described that "[u]ntil further notice the variations classification guideline, which is a fundamental component of the operation of the variations system, will continue to apply to all types of variations."

Root Cause Analysis

[redacted]

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Preventative Action(s)
[redacted]

[redacted]

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

Finding	**MA.1 b)**

Advanz Pharma was not implementing Type IA_{IN} safety variations in line with regulatory expectations, resulting in delays of up to approximately 3 months in uploading updated product information to websites and communicating updates to relevant stakeholders.

In the instance of internal notifications and electronic upload i.e. to the electronic medicines compendium (emc) and company websites (if applicable), Type IA_{IN} variations are expected to be implemented within 10 working days from the date of submission to the MHRA (in the instance of national procedures) or date of approval from the RMS (in the instance of MRDC procedures). The company, however, were waiting for the 'acceptance of notification' letter from the MHRA, before taking any action to implement Type IA_{IN} variations.

Details of the impacted variations were as follows:

i. [redacted] A national Type IA_{IN} variation was submitted on 13 March 2023 to the MHRA to update product information to recommend the use of [redacted] (as opposed to the previous guidance of [redacted] months), due to [redacted] in line with [redacted] This impacted section 4.6 of the SmPC and section 2 of the PIL. Key stakeholders such as APCER (case processing) and medical information were informed of the updated product information on 21 June 2023, and the updated PIL and SmPC were uploaded to the emc on 27 and 30 June 2023, respectively. Resulting in delays of approximately 3 months.

ii. [redacted]. A Type IA_{IN} variation under the mutual recognition procedure, to update product information around [redacted] (in line with [redacted]), received RMS approval on [redacted]. Sections 4.4,

4.5 and 4.9 of the SmPC and sections 2 and 3 of the PIL were updated as part of this procedure. Key stakeholders such as APCER (case processing) and medical information were informed of the updated product information on 17 August 2023, and the update PIL and SmPC were uploaded to the emc on 21 and 23 August 2023, respectively. Resulting in delays of nearly 2 months.

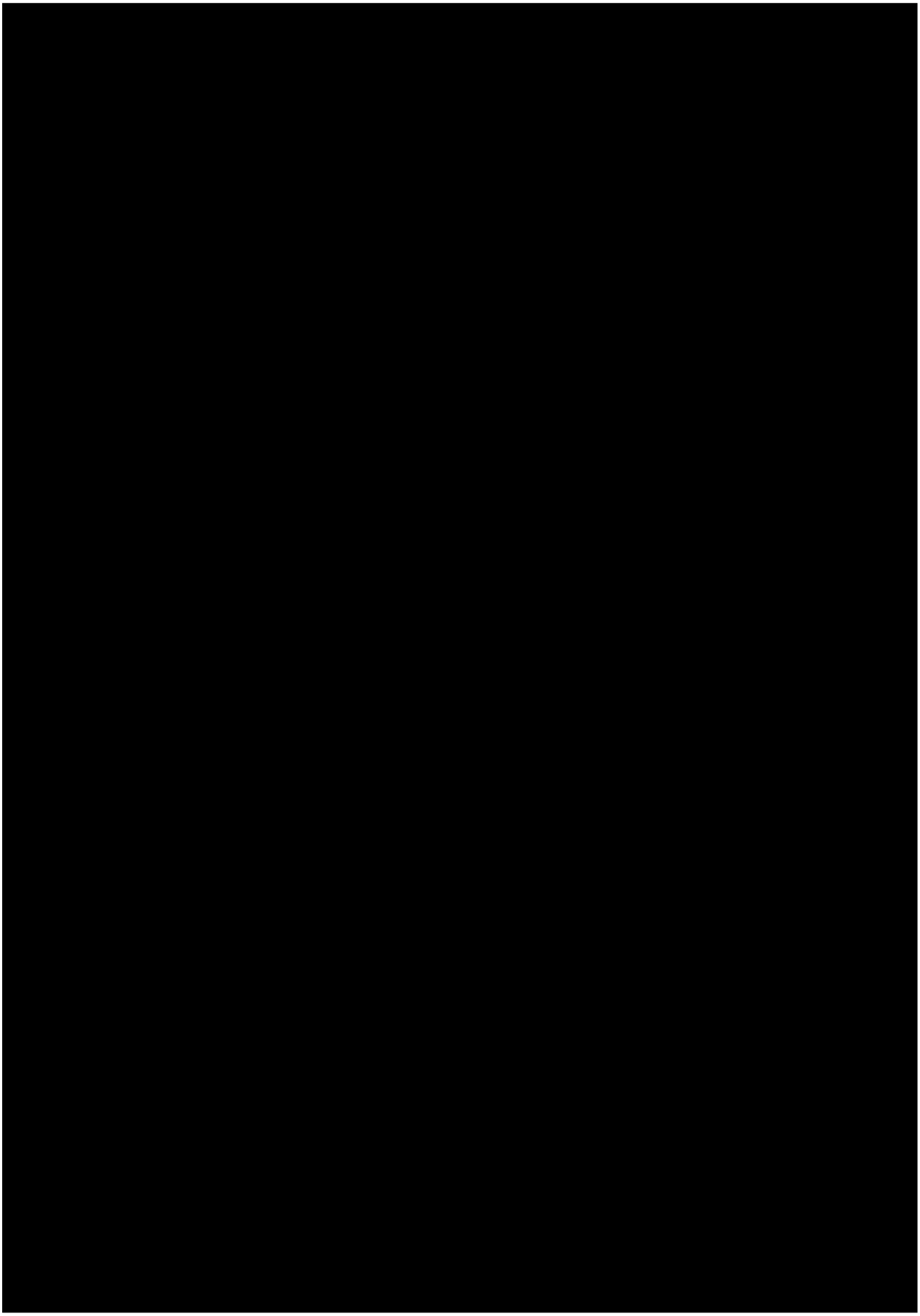
Advanz had already identified the late identification of RMS approval, and an email was circulated by Regulatory Affairs on 17 August 2023 (deviation [redacted] .

iii. [redacted] Further to MA.1 a) i. key stakeholders such as APCER (case processing) and medical information were informed of the updated product information on 04 October 2023, and the updated PIL and SmPC were uploaded to the emc on 12 and 10 October 2023, respectively. Resulting in delays of over 1 month.

iv. [redacted] A national Type IA_{IN} variation was submitted on 14 October 2021 in response to the PRAC recommendation on the signal relating to [redacted] Key stakeholders such as APCER (case processing) and medical information were informed of the updated product information 15 November 2021. The company attempted to upload the PIL and SmPC to the emc on 02 December 2021. Whilst the PIL was successfully updated, the SmPC was not published until 20 January 2022, due to human error in completing the task. This resulted in delays of up to approximately 3 months. No deviation was raised for the delay.

Root Cause Analysis

[redacted]



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

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

Preventative Action(s)
[redacted]

[redacted]

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

MA.2 Additional risk minimisation measures

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulations 182 (2)(c), and (4)(c)(iii)

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.4. Overall quality objectives for pharmacovigilance
[…] promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public;

Finding MA.2 a)

Advanz Pharma had not adhered to the agreed implementation plan for the updated [redacted] HCP educational card (version [redacted] leading to a delay of 16 months in one element of the agreed implementation plan. The updated card received MHRA approval on [redacted] and the agreed implementation plan was as follows:

- One-time distribution of the hard-copy educational card to healthcare professionals within 6 months of approval.
- Upload of the card to emc shortly after approval
- Provision of the card in product packs from January 2023 onwards
- Provision of hard-copies to HCPs upon direct request

Specifically, Advanz Pharma had failed to implement the educational card into product packs from January 2023 onwards, as Advanz Pharma had QP-certified one batch ([redacted] expiry date: [redacted] batch size: [redacted] packs) on 28 December 2023,

which did not include the educational card in the pack. Instead, the first batch (batch no: [redacted], expiry date: [redacted]) containing the card was QP-certified on 07 May 2024.

Advanz Pharma had initiated an Article 61(3) (now regulation 267(4)) notification to the MHRA on 21 September 2023 to register the educational card mock-up with the MHRA. However, they were informed on 03 January 2024 and 14 February 2024 that the proposed change was not in the remit of such notification[2]. While it is acknowledged that Advanz had contacted the MHRA benefit-risk assessor on 28 September 2023 to make them aware of the submission and request an extension to the implementation timeline, this was only done 9 months after the agreed implementation date. In addition, the e-mail did not clearly explain that the card would not be supplied as part of the PIL or outer carton, as otherwise the assessor could have advised that this submission was not suitable.

As a mitigating factor, it was seen that the one-time distribution of the hard-copy educational card and upload to the emc were completed in a timely manner, so the information was available to HCPs via other routes.

[2]Advanz Pharma are reminded that guidance (including relevant contact details) for the submission and approval of additional risk minimisation measures to the MHRA is published: https://www.gov.uk/guidance/educational-materials-and-associated-distribution-plans.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 b)

There was a delay of 12 months in submitting the updated mock-up of the [redacted] carton to incorporate the new patient/carer reminder card to [redacted]. The educational materials were approved by the MHRA via a [redacted] worksharing initiative on [redacted] However, the MAH only contacted the benefit-risk assessor on 17 February 2021, 7 months later, to seek approval of the updated carton mock-up. The assessor advised the company on 26 April 2021 that the changes should be formally submitted via an Article 61(3) (now regulation 267(4)) notification for MHRA approval. The required submission was eventually made on 30 July 2021, which was accepted on [redacted]

The implementation plan agreed by the MHRA stated "*In addition to the postal distribution, companies will introduce an in pack patient reminder card. This will be either as a separate card or as a tear off strip at the end of the patient information leaflet. The in pack patient reminder card should be consistent with the hard copy. Implementation should start during 2020.*"

Since July 2020, two batches of [redacted] were QP-certified on 20 January 2021 (batch no: [redacted] expiry date: [redacted] batch size: [redacted] packs) and on 28 January 2021 (batch no: [redacted] expiry date: [redacted] batch size: [redacted] packs). The product is not currently marketed in the UK.

As a mitigating factor, the [redacted] coordinated a hard-copy mailer consisting of a HCP cover letter and patient cards to approximately [redacted] healthcare professionals that was distributed in August 2020. In addition, Advanz Pharma uploaded the patient/carer card to the emc on 03 August 2020, so the information was available to HCPs and the public via these routes.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Preventative Action(s)

[redacted]

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

C.4.3 Minor findings

MI.1 Provision of information to the licensing authority

Finding MI.1 a)
The following deficiencies were identified with respect to information presented in the UK PSMF [redacted] (DLP: 31 December 2024, dated 22 January 2025). i. The PSMF metrics/KPIs did not present an accurate and complete view of compliance in regard to safety variation submissions. Examples were identified where rejected (and subsequently late) submissions were reflected as 'on time', and where non-compliance to internal timeframes were not reflected accurately in the PSMF. a. A type IB safety variation for [redacted], resulting from PSUSA, was due on and submitted by 22 February 2024. The variation was rejected due to technical issues (PL number incorrect) and resubmitted on 05 March 2024. The submission was considered as 'on time' and presented as compliant in PSMF Annex F. The company stated that rejected submissions were not reflected in the PSMF and would be reflected as 'on time' once the re-submission was made even if the original deadline for submission was passed. The regulatory affairs team measured the quality of regulatory submissions, via KPIs, that were presented on a monthly basis. Rejected submissions would be highlighted during these meetings. Of the evidence provided (safety variation and RFI meeting minutes, and the internal communications shared by the regulatory team), it could not be verified that the QPPV was informed of the delay in successfully submitting the variation on time due to the rejected submission. b. Overdue (per internal timeframes) variation submissions were not reflected in PSMF Annex F5a *'Compliance figures for submission of routine safety variations in UK'*, where dedicated columns presented compliance in relation to internal and external timeframes. All months in 2024 reflected 0 late submissions according to either internal deadlines, or authority deadlines.

As an example, safety variations for [redacted] were due to be submitted 120 days following the date of decision on [redacted] however, as of the time of the inspection, had not yet been submitted. The updates were triggered as part of the harmonisation process, and according to the tracked change documents provided, related to sections 4.2, 4.4- 4.9, 5.1- 5.3 of the SmPCs. The changes were still under assessment and no change control had yet been raised. This variation would be submitted beyond the company-determined timeframes of 120 calendar days, but no deviations were recorded to account for the delay.

Furthermore, this variation was recorded as 'on time' in the safety variation log despite exceeding company timeframes. The safety variation log formed the basis of QPPV oversight and was used to inform discussions during the weekly safety variation and RFI meetings.

ii. Annex H.2 *List of Products with Specific Safety Monitoring (RMPs with additional risk minimisation measures)* did not include accurate and up-to-date information:
   i. ~~The entry for [redacted] did not include any information regarding the implementation of agreed educational materials in the UK, e.g. publication on emc and hard-copy distribution via mail.~~
   (Lead Inspector note 04Aug2025: Following review of inspection evidence, this element of the finding has been removed from the inspection report.)
   ii. The entry for [redacted] indicated that the "*patient reminder card will be the part of patient information leaflet (tear and use from the PIL) which will be provided along with the packs*"; however, it was not specified since when the card had been provided as part of the PIL.
   iii. The entry for [redacted] stated that "*HCP cards have been implemented as component with [redacted] pack from the batches released from January 2023*", but as described in finding MA 2.a), the card was not included in UK packs until May 2024. In addition, the MAH was incorrectly stated as [redacted] the EU MAH of the corresponding centrally authorised product, rather than [redacted] the UK MAH.

iii. Annex G6 *List of ADVANZ PHARMA Schedule for Internal Pharmacovigilance Audits* included incomplete information regarding the date the audit report was issued following the conduct of the Risk Management Plan audit on 27 July 2023. The annex only stated the date the audit report was completed with CAPA (03 November 2023); however, it was not detailed that the initial report was shared with the MAH on 26 September 2023.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

[redacted]

Preventative Action(s)

[redacted]

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

Finding MI.1 b)

The notification of the [redacted] marketing status to the MHRA was delayed by two years, as the MAH only informed the MHRA on 10 December 2024 that the product had not been marketed since 30 October 2022.

Conflicting information regarding the marketing status was also received before and during the inspection, as PSMF Annex H1 (version [redacted] DLP 22 January 2025) listed the product as marketed; however, an updated version (DLP 09 February 2025), provided as part of a pre-inspection document request on 12 February 2025, listed the product as not marketed. In response to other document requests during the inspection, the product was then declared as marketed again due to the product being available intermittently due to stock supply issues.

The last batch of [redacted] was QP-certified on 28 January 2021 (batch no: [redacted] expiry date: [redacted]

In accordance with HMR 2012 regulation 73, MAHs must notify the licensing authority if the product to which the authorisation relates is to be withdrawn from the market in the United Kingdom (whether temporarily or permanently). The notification must be given before the beginning of the period of 2 months ending with the date on which the product is to be withdrawn from the market unless it is not reasonably practicable to do so.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]

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

MI.2 Deviation management

Finding MI.2 a)

There were delays and improper grading of a deviation relating to the availability of product information for UK authorised products via the emc.

The non-compliance was identified on 31 January 2022 and reported inconsistencies between the documents available on emc versus the current labelling documents. A reconciliation was performed between the emc and [redacted] for UK-authorised product labelling documents, from which [redacted] products were determined to be impacted, [redacted] of which were marketed products. The inconsistencies included out-of-date product information being available on the emc and/or products that were no longer marketed and therefore should have been removed from the emc according to company processes. Between December 2022 and June 2023 corrections were made to the emc. From the evidence provided it was unclear why it took nearly 18 months to assess the issue and to subsequently take action, i.e. complete all corrections to the emc.

Deviation [redacted] was formally opened on 17 August 2023, after emc had been corrected, and closed 09 January 2024. The deviation was initially categorised as major but was downgraded to minor, based on corrective and preventative actions having already been put in place, by the time of the deviation being formally reviewed and reported. The MAH is reminded that the grading of findings should consider the actual impact and non-compliance at the time of occurrence and should not be amended based on actions taken by the company after identification. Notably, given that the deviation was reported as minor it would have also not been visible in the PSMF.

This has been graded as a minor finding based on a review of the management of other deviations which suggested that the mismanagement of this particular deviation was an isolated issue.

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 Record management

Finding MI.3 a)
Advanz did not have independent documentary evidence of the hard-copy distribution of the 'Appropriate use of [redacted] guide (version [redacted]. The MAH contracted with Wilmington Healthcare on 13 December 2021 to identify relevant recipients according to the MHRA-agreed target audience and to organise the hard-copy mailer. While Advanz Pharma followed up with Wilmington Healthcare to confirm the distribution status on 10 January 2022, they only received an email back stating that the mailing was dispatched on 05 January 2022, without any further evidence that the mailing had occurred. It is acknowledged that some letters were returned to the Advanz Pharma London office as the recipient was not known at the address, therefore providing passive confirmation that the mailing had occurred.
Root Cause Analysis
[redacted]

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

Finding MI.3 b)
Inaccuracies were identified with the information presented in the company's safety variation log. The company's safety variation log indicated that the variations were 'approval awaited' i. [redacted] Type IB variation [redacted] (change control (CC) number: [redacted] submitted on 24 December 2021, had received approval from the MHRA on [redacted] Evidence received post-inspection indicated that despite the information within the safety variation log, the company had implemented the variation within expected timeframes. Internal stakeholders were informed on 28 January 2022, the emc was updated on 01 February 2022, and the superseded PIL was last QP-certified into batches on 30 March 2022. ii. [redacted] Type IA variation [redacted] (CC number: [redacted] had been submitted on 14 October 2021. As explained during inspection, no MHRA approval is given for a national Type IA variation. The company had received acknowledgement from the MHRA on 11 November 2021, which was subsequently circulated to stakeholders that same day. Refer to MA.1 b) for further information on the timeliness of implementation. This has been graded a minor finding since it did not reveal that the MAH had missed to implement the variations, and was rather a documentation error.
Root Cause Analysis
[redacted]

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

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

Finding MI.3 c)
The MAH maintained a schedule (the 'Harmonisation schedule') to define the timing for the periodic review of product information, and, where applicable, included details of the relevant reference medicinal product to be used. The Harmonisation schedule 2023-2025 stated that the reference medicinal product for [redacted] was 'Not applicable', yet the company had correctly aligned the product information to [redacted] with the most recent harmonisation completed in July 2024.
Root Cause Analysis

[redacted]

Further Assessment
[redacted]

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

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

Finding MI.3 d)
The Global Signal Schedule for UK molecules incorrectly stated that the [redacted] signal detection frequency ("C", annual) was due to aRMMs not having been implemented. However, this was incorrect as the annual frequency was determined due to the low number of ICSRs (1 in 2024).
Root Cause Analysis
[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]

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

MI.4 Reference Safety Information

Finding MI.4 a)

[redacted] Type IB variation [redacted] submitted on 12 March 2024, received approval from the RMS [redacted] on [redacted]. The company indicated that since they had not received any formal approval letter from the MHRA (Concerned Member State, CMS) that they had not updated their [redacted] area (archiving the previous product information), nor notified relevant stakeholders in relation to the updated UKSPC/PIL.

This has been graded as minor, since at the time of receiving approval, and as of the date of the inspection, the product was not marketed, and therefore no immediate action in terms of implementing the variation was expected. Nevertheless, the company should ensure that documentation remains up to date in case of changes to the marketing status of the product.

Post inspection request- the company is requested to perform further assessment to determine if any other records indicated as 'awaiting approval' have received approval and therefore action(s) are required by the company.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Preventative Action(s)

[redacted]

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

MI.5 Written Procedures

Finding MI.5 a)

Procedural documentation did not describe the scenario in which the reference medicinal product was cancelled. Verbally it was stated that "*the MAH picks up the latest approved reference document of other generic available on EMC. If in scenario ADVANZ reference product is last updated we compare the documents within UK and EU territories, QRD updates and excipient guidelines updates*".

It is reminded that where the MAH updates the product information to align with another reference medicinal product, a Type II variation must be submitted to the agency, and the MAH should continue to align with the selected reference medicinal product for future updates.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	**Due Date(s)**

[redacted]

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

Finding MI.5 b)
There was no written procedure outlining the version control of hard-copy educational materials to ensure that only the current versions were distributed by the Medical Information team in the London office. Medical Information were responsible for sending hard copy materials if requested by HCP and patients, either directly or via the Advanz commercial staff. The MAH verbally stated during the inspection that no requests for hard-copy educational materials had been received in the past three years.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

[redacted]

Finding MI.5 c)
Monthly reconciliations between the RMP team and APCER as well as the RMP team and the Medical Information team were not described in any procedural documentation. Advanz described that these reconciliations were implemented in February 2024 and April 2024, respectively, to ensure that those teams have access and are aware of the latest approved versions of Targeted Follow-up Questionnaires (APCER) and educational materials (Medical Information).
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 Pharmacovigilance Audits

Finding MI.6 a)
The auditors who conducted the Risk Management Plan audit on 27 July 2023 did not have sufficient knowledge, skills and abilities relating to auditing principles, procedures and techniques as required by GVP IV.B.3.1.2. While the CVs and training records indicated proficiency in knowledge and experience of pharmacovigilance requirements and activities, the auditors did not appear to have received any training and/or qualifications specific to the principles and techniques of audits.

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]	

C.4.4 Comments

1. Inconsistencies were observed in the recording of dates within deviation reports. Specifically, the fields used to capture dates were not well-defined in order to ensure appropriate representation of the date recorded. For example, deviation [redacted] (described in finding MI.1) was identified on 31 January 2022, as verbally stated by the company. According to the deviation report this date was reflected in the field 'date occurred', which could instead be interpreted as the date on which the non-compliance occurred. On this occasion, the deviation accounted for multiple non-compliances, nevertheless, it would be important for the company to consider the clarity of the deviation record forms and review the current company guidance to ensure consistency and accurate interpretation of the records.

   Of note, during the inspection, the inspectors did not request nor review available guidelines, if any, for the creation and maintenance of deviation records within the quality management system. Hence, this observation is presented as a comment regarding the deviation records as opposed to the underlying process.

   MAH Response: [redacted]

2. Inaccuracies were identified with the safety variation listing provided to the inspectors to provide end-to-end understanding of the implementation of safety variations submitted since January 2022. This impeded progress of the inspection as the inspectors spent additional time clarifying discrepancies.

   Dates provided in Document Request [redacted] (Safety variation listing) were discrepant from the documentation provided in relation to PIL implementation (Document Request [redacted] Specifically, the last batch with superseded information QP-certified into packs dates were reflected as:

   - [redacted]
     - DR [redacted] 07-Jul-2023
     - DR [redacted] 24-Mar-2023
   - [redacted]
     - DR [redacted]: 03-Jul-2023
     - DR [redacted]: 29-Sep-2023
   - [redacted]
     - DR [redacted]: 02-Feb-2024

- DR[redacted]: 11-Dec-2023

MAH Response: [redacted]

3. PSMF Section 7.7 incorrectly described that "Annex F8 – *Metrics for the adherence to Relevant RMP requirements or other commitments related to MA describes the commitments and status of those commitments.*"; however, information regarding the implementation of RMP commitments such as aRMM were included in Annex H.2 *List of Products with Specific Safety Monitoring (RMPs with additional risk minimisation measures)*. PSMF Annex F8 predominantly included only information on TFUQs (with the exception of [redacted]. The MAH is recommended to consider improving the clarity of the content in relation to RMP commitments.

MAH Response: [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

- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916) as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**INSPECTOR(S)**	[redacted] (lead inspector), [redacted]
PHARMACOVIGILANCE INSPECTION OF	Advanz Pharma	**DATES**	17- 19 February 2025

This inspection will primarily focus on a review of the Risk Management processes, including but not limited to:

- The identification of safety updates, submission of safety variations and the implementation of updated product information.
- The maintenance and implementation of educational materials.

Please be prepared to provide live demonstrations of any relevant databases/IT systems.
N.B. The Inspection Plan may be subject to change before and during the inspection.

Monday 17 February 2025 (Day 1)

- An opening meeting will be held by videoconference at **09:30** (GMT), which will be led by the lead inspector. The agenda will be as follows:

1. Review of the scope and arrangements for the inspection.
2. Brief presentation by Advanz Pharma (~20 minutes max.) with an overview of the company and pharmacovigilance system. The presentation should focus on the topic listed for inspection and any relevant ongoing remediation work in the pharmacovigilance system.

- An interview session to discuss the management and maintenance of Reference Safety Information (RSI) will be held **11:00- 12:30** (GMT). This will involve discussion of pre-submission processes and post-approval pathways for safety variations, including dissemination of updated product information and the introduction of PILs into packs, in addition to the methods for quality assurance and oversight.

- An interview session to discuss the management and implementation of Educational Materials will be held **14:00- 15:00** (GMT). This will involve a discussion on the submission, maintenance and distribution of UK educational materials, in addition to compliance oversight.

N.B. Optional breaks will be offered, should interview sessions last longer than anticipated.

The remainder of the inspection (days 2 – 3) will consist of remote document review, written requests and ad hoc video/telephone clarifications with subject matter experts (SMEs) as required. Please provide a designated contact point who can assist with any ad hoc questions from inspectors or arrange calls between inspectors and SMEs as required.

Tuesday 18 February 2025 (Day 2)
Inspectors will conduct review of documents received. No formal meetings will be held on this day but we do ask that MAH contacts are available via MS Teams chat in case any further requests or questions are made by the Inspection team.

- *09:00- 10:00 – Document Request* [redacted] *and* [redacted] *Company participants:* [redacted]
- *12:00- 13:00 –* [redacted] *checklist. Company participants:* [redacted]

Wednesday 19 February 2025 (Day 3)
Continued review of documents received. MAH is advised to ensure SMEs remain available for ad hoc discussions if required.
A closing meeting will be held via videoconference on 19 February 2025 (timing to be confirmed) during which feedback on the inspection will be provided to the company. All relevant personnel are welcome to attend the closing meeting.

- *10:15- 10:45 - Document Request* [redacted] *Clarification. Company participants:* [redacted]
- *15:00- 15:30- Clarification of various topics (Implementation of Variations (Type IA, MRDCP), PSMF Metrics,* [redacted] *Company participants:* [redacted]

Closing meeting (Thursday 20 February 2025)
The closing meeting was held at 10:00. Closing meeting attendees are documented in Advanz_Pharma_GPvP_Closing_meeting_attendance_record_Feb-2025.docx.pdf.

Company contact details
Advanz Pharma should complete the below with the names and job titles of the designated contact point, subject matter experts and those staff who will be dialing in to the opening meeting, and interview sessions on Day 1.

Please note that ADVANZ PHARMA attendees and SMEs will be working and available during the 3 days of inspection on GMT timezone.

Designated inspection contact point:
[redacted] Global QPPV-Director Patient Safety, [redacted]
[redacted] Associate Direct Patient Safety, [redacted]

Subject matter experts (by topic):

Opening meeting attendees:
[redacted] (Chief Medical Officer), [redacted]
[redacted] (Global Director - Patient Safety), [redacted]
[redacted](Global QPPV – Director Patient Safety), [redacted]
[redacted] (Associate Director - Patient Safety), [redacted]
[redacted] (Director Quality & PVQA), [redacted]
[redacted] (Director – Global Clinical Development), [redacted]
[redacted](Vice President – Medical Affairs), [redacted]
[redacted] (Vice President – Medical Affairs), [redacted]
[redacted] (Director – Global Health Compliance), [redacted]
[redacted] (Vice President – Global Regulatory Affairs), [redacted]
[redacted] (Head - Regulatory Affairs, UK & Ireland), [redacted]
[redacted](National Contact Person for Pharmacovigilance in the UK), [redacted]

Interview Session attendees:
- **Maintenance of Reference Safety Information (RSI):**

[redacted](Associate Director Patient Safety), [redacted]
[redacted] (Senior Executive Patient Safety), [redacted]
[redacted] (Senior Executive Patient Safety), [redacted]
[redacted] (Specialist - Regulatory Affairs UK), [redacted]
[redacted] (Sr. Manager - Regulatory Affairs UK & Ireland), [redacted]
[redacted] (Director, Medical Information), [redacted]
[redacted] (Global QPPV - Director Patient Safety), [redacted]
[redacted] (Global Director – Patient Safety), [redacted]
[redacted] (Director Quality & PVQA), [redacted]
[redacted] (Specialist – PVQA), [redacted]
[redacted](Specialist - Artwork Implementation), [redacted]

- **Management and implementation of Educational Materials:**

[redacted] (Specialist Patient Safety), [redacted]
[redacted] (Associate Director Patient Safety), [redacted]
[redacted] (Manager Patient Safety), [redacted]

[redacted] (Global QPPV – Director Patient Safety), [redacted]
[redacted] (Global Director – Patient Safety), [redacted]
[redacted] (Medical Advisor - UK & Ireland), [redacted]
[redacted] (Head of Hospitals - S&M – UK), [redacted]

Closeout meeting attendees:
[redacted] (Chief Medical Officer), [redacted]
[redacted](Global Director - Patient Safety), [redacted]
[redacted] (Global QPPV – Director Patient Safety), [redacted]
[redacted] (Associate Director - Patient Safety), [redacted]
[redacted] (Director Quality & PVQA), [redacted]
[redacted] (Director – Global Clinical Development), [redacted]
[redacted] (Vice President – Medical Affairs), [redacted]
[redacted] (Vice President – Medical Affairs), [redacted]
[redacted] (Director – Global Health Compliance), [redacted]
[redacted](Vice President – Global Regulatory Affairs), [redacted]
[redacted] (Head - Regulatory Affairs, UK & Ireland), [redacted]
[redacted] (National Contact Person for Pharmacovigilance in the UK), [redacted]