From: s22
To: Recalls
Cc: s22
Subject: FW: TGA Enquiry - FW: Supervisory Risk Assessment & Draft Statement of Non Compliance GMP - Wasdell Europe Limited, Dundalk, Ireland [SEC=OFFICIAL]
Date: Monday, 8 April 2024 8:13:17 AM
Attachments: image003.png

Dear Recalls,

I have mistakenly sent the below email to Medsafe rather than TGA on Friday. Please accept my apologies for the error and the delay in response.

Please let me know if you require any further information.

s22

s22

Takeda Pharmaceuticals Australia Pty Ltd
s22 (mobile)
Email: s22 @takeda.com

From: s22 @takeda.com>
Sent: Friday, 5 April 2024 1:15 pm
To: Recalls <recalls@health.govt.nz>
Cc: s22 @takeda.com>; s22 @takeda.com>
Subject: RE: TGA Enquiry - FW: Supervisory Risk Assessment & Draft Statement of Non Compliance GMP - Wasdell Europe Limited, Dundalk, Ireland [SEC=OFFICIAL]

Dear s22

I am responding on behalf of s22 and thank you, for notifying Takeda of HPRA's statement of non-compliance pertaining to the manufacturer, Wasdell Europe Limited, IDA Dundalk Science and Technology Park, Mullagharlin, Dundalk Co. Louth, A91 DET0, Ireland. Takeda can confirm that, the following products **labelled and packaged** at Wasdell Europe Limited, Ireland are supplied in Australia.

Product
s22
Vyvanse 30mg 30 Caps Australia
Vyvanse 50mg 30 Caps Australia
Vyvanse 70mg 30 Caps Australia
Vyvanse 20mg 30 Caps Australia
Vyvanse 40mg 30 Caps Australia
Vyvanse 60mg 30 Caps Australia

s22 [redacted]

Takeda's request for consideration and action by TGA:

The GMP compliance issues at Wasdell Ireland, has triggered Supply Shortage in Australia for various strengths of VYVANSE (Medicines Shortage Notification references: MS-2023-NT-00980-1, MS-2023-NT-01341-1, MS-2023-NT-01486-1, MS-2024-NT-00004-1). After reviewing attachments included in TGA's email, Takeda is concerned about the potential non-inclusion of Takeda products (including s22 [redacted] and s22 [redacted] on the restricted GMP certificate that will be issued by HPRA to Wasdell Europe Limited noting the following text in the Supervisory Risk Assessment March 2024 (final v1):

> "After the issue of the SNC, anticipated to occur on the 6th May 2024, certification of batches produced at the site should only be performed for products that are included within the scope of a restricted GMP certificate. "(second dot point, p.6)
>
> "The HPRA proposes to issue a statement of non-compliance with GMP in relation to the Wasdell Europe Limited manufacturing site. In addition, the HPRA recommends that a restricted GMP certificate be issued to Wasdell Europe Limited to include those medicinal products that are deemed essential/critical for one or more markets and IMPs for supply to approved clinical trials." (second paragraph under section 5.0, p.7)

To remove the risk of potential medicine shortage of Takeda products in Australia, we respectfully request the TGA make a recommendation to the HPRA to include all strengths of VYVANSE, s22 [redacted] and s22 [redacted] (please see above Table) in the scope of the proposed Restricted GMP Certificate to ensure continuity of supply of these medicines to Australian patients.

Takeda's actions and communications to TGA

Takeda has been in communication with **TGA Compliance Section from June 2022** onwards regarding the on-going GMP compliance issues occurring at this site and have updated TGA of the actions taken by Takeda to mitigate the risks associated with the deficiencies found by the HPRA team to the Australian products. These communications include the following information:

> **Medical Risk Assessment**:
> Takeda considers the below products packed by Wasdell as medically critical for the following reasons:
>
> s22 [redacted]

s22 [redacted]

- Vyvanse is indicated as part of a comprehensive treatment program for attention deficit/hyperactivity disorder (ADHD) in adults, and for the treatment of children and adolescents with ADHD whose response to previous methylphenidate treatment was considered clinically inadequate.

Takeda's actions at the site:

- In consultation with HPRA, Takeda employed a contracted Person in Plant (PiP) model who oversees the manufacturing of every Takeda batch to provide assurances that Takeda products are manufactured in compliance with GMP.
- In addition to the PiP, an enhanced oversight model is in place, with Takeda personnel on site at the Wasdell facility.
- From March 2024, Takeda has employed an Operational Support Model where Takeda have engaged an agency to provide operational support over all Wasdell shifts for Takeda products.

Although the above will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP.

Please let me know if you require any further information.

Many thanks & regards

s22 [redacted]

s22 [redacted]
Takeda Pharmaceuticals Australia Pty Ltd
s22 [redacted] (mobile)
Email: s22 [redacted] @takeda.com

From: Recalls <Recalls@health.gov.au>
Sent: Wednesday, April 3, 2024 11:26 AM
To: s22 [redacted] @takeda.com>
Subject: TGA Enquiry - FW: Supervisory Risk Assessment & Draft Statement of Non Compliance GMP - Wasdell Europe Limited, Dundalk, Ireland [SEC=OFFICIAL]

Dear s22 [redacted]

We have recently become aware of the attached overseas statement of non-compliance pertaining to the manufacturer Wasdell Europe Limited. The ARTG suggests you may supply products by the manufacturer.
Can you please confirm if any of the affected devices have been supplied to Australia by COB 5/4/2024?
Kind regards,

s22 [redacted] **(she/her)**
Recall Officer – Recalls Section
Manufacturing Quality Branch
Medical Devices and Product Quality Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: s22 [redacted] | E: recalls@health.gov.au
Location: 27 Scherger Drive, Canberra Airport, ACT 2609
PO Box 100, Woden ACT 2606, Australia
The Department of Health and Aged Care ak owledges Firt Nations peoples as the Traditional Owners of Country throughout Aut ralia, and their o ntinuing o nnet ion to land, e a and o mmunity We pay our rep et s to them and their u ltures and to all Elders both pat and pre nt.

From: HPRA Inspections <inspect@hpra.ie>
Sent: Friday, March 22, 2024 6:23 AM
To: Recalls <Recalls@health.gov.au>; sante-rapid-alert-quality@ec.europa.eu; qdefect@ema.europa.eu; Recalls@apvma.gov.au; rapid.alert-alerte.rapide@hc-sc.gc.ca; Pgam@moh.health.gov.il; rapidalert@mhlw.go.jp; recalls.health.govt.nz <recalls@health.govt.nz>; rapidalerts@unicef.org; pics-rans@fda.hhs.gov; rapidalert@who.int
Subject: Supervisory Risk Assessment & Draft Statement of Non Compliance GMP - Wasdell Europe Limited, Dundalk, Ireland

Dear Colleagues,

As per EU Compilation of Union Procedures, please find attached a Supervisory Risk Assessment, product list and a draft statement of non-compliance with GMP related to the manufacturer, Wasdell Europe Limited, IDA Dundalk Science and Technology Park, Mullagharlin, Dundalk, Co. Louth, A91 DET0, Ireland.

Please advise HPRA at inspect@hpra.ie by 12th April if any shortages of essential medicines are anticipated in your country as a result of publishing the SNC on EudraGMDP.

Your sincerely,

s22 [redacted]

s22 [redacted]
Health Products Regulatory Authority | An tÚdarás Rialála Táirgí Sláinte
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. D02 XP77

****

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HPRA E-mail Disclaimer

****

Health Products Regulatory Authority Kevin O'Malley House Earlsfort Centre Earlsfort Terrace Dublin 2 Tel + 353 1 676 4971 www.hpra.ie

****

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****

From: s22
To: s22
Cc: s22
Subject: RE: VYVANSE lisdexamfetamine dimesilate 40 and 70mg capsules bottle - AUST Rs" 284020 and 199228 - Issues 814073, 814180 and 814615 [SEC=OFFICIAL]
Date: Friday, 2 August 2024 1:21:11 PM
Attachments: image001.png
image002.png
image003.jpg
Response to TGA request for Information Dated 12 Jul 2024 Final.pdf

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Dear s22

Attached here please find company's response document addressing TGA's request for information listed in your email of 12-Jul-2024 below.

Please contact s22 and me should you require any clarification or further information.

Thank you
Kind regards

s22

s22 – Oceania Cluster
Takeda Pharmaceuticals Australia Pty Ltd
Grosvenor Place, Level 39
225 George Street
Sydney NSW 2000 Australia
Mobile: +s22
s22 @takeda.com

From: s22
Sent: Thursday, July 25, 2024 11:42 AM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22
s22 @takeda.com>
Subject: RE: VYVANSE lisdexamfetamine dimesilate 40 and 70mg capsules bottle - AUST Rs' 284020 and 199228 - Issues 814073, 814180 and 814615 [SEC=OFFICIAL]

Dear s22

Many thanks for extending the due date.

Kind regards
s22

From: s22 @health.gov.au>
Sent: Thursday, July 25, 2024 11:39 AM

To: s22 @takeda.com>
Cc: s22 @health.gov.au>; s22
s22 @takeda.com>
Subject: RE: VYVANSE lisdexamfetamine dimesilate 40 and 70mg capsules bottle - AUST Rs' 284020 and 199228 - Issues 814073, 814180 and 814615 [SEC=OFFICIAL]

Dear s22

Due date for response is now 5 August. I may not be in the office on the 2 August.
Please email me if you anticipate further delays.

Regards

s22
Senior Evaluator
Adverse Event & Medicine Defect Section
Pharmacovigilance Branch

Phone: s22
Email: s22 @health.gov.au

Therapeutic Goods Administration
Location: 27 Scherger Drive Fairbairn ACT 2609
Australian Department of Health and Aged Care
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

From: s22 @takeda.com>
Sent: Thursday, July 25, 2024 11:15 AM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22
s22 @takeda.com>
Subject: RE: VYVANSE lisdexamfetamine dimesilate 40 and 70mg capsules bottle - AUST Rs' 284020 and 199228 - Issues 814073, 814180 and 814615 [SEC=OFFICIAL]

Dear s22

Thank you for your email. Takeda is working on the response to TGA's request and liaising with contract manufacturing sites for information required to comprehensively address TGA's questions. According to our assessment we will need more time for submission of company

response, to meet this end Takeda wish to request extending the response due date to 2-Aug-2024. I hope the TGA finds this to be acceptable.

I look forward to hearing from you.

Kind regards

s22 [redacted]
s22 [redacted] – Oceania Cluster
Takeda Pharmaceuticals Australia Pty Ltd
Grosvenor Place, Level 39
225 George Street
Sydney NSW 2000 Australia
Mobile: s22 [redacted]
s22 [redacted]@takeda.com

From: s22 [redacted]@health.gov.au>
Sent: Friday, July 12, 2024 9:05 AM
To: s22 [redacted]@takeda.com>; s22 [redacted]@takeda.com>; s22 [redacted]@takeda.com>
Cc: s22 [redacted]@health.gov.au>
Subject: VYVANSE lisdexamfetamine dimesilate 40 and 70mg capsules bottle - AUST Rs' 284020 and 199228 - Issues 814073, 814180 and 814615 [SEC=OFFICIAL]

Dear Sir/Madam

The TGA has received reports regarding lack of efficacy and unexpected adverse reactions relating to Vyvanse products as referenced above.

Preliminary review of the TGA data (adverse event and complaint reports) has identified atypical trend, an increase in lack of efficacy reports in 2023 and 2024. The details of the recent 2024 reports are provided below.

s22 [redacted]

s22

Information required:

1. Please provide outcome of your assessment of the returned 70mg complaint product, including assessment of capsule appearance variation (as depicted in the photo provided by the patient).
2. Reporting trend of lack of efficacy for Vyvanse products (all strengths) in the last 7 years and assessment if there's an atypical trend in the last 2-3 years.
3. The details of the manufacturers of the complaint product batches referenced in this email and Vyvanse products (all strengths) currently in the AU market. Specifically, please provide details of the manufacturing sites of the active pharmaceutical ingredient (API) and Vyvanse dosage form (capsules), and if these have changed in the last 5 years.
4. If there is a current/pending GMP non-compliance issue for Vyvanse manufacturing sites which may be attributing to the current quality signal. If so, please provide details and outcome (if finalised)

My preliminary review of the TGA GMP compliance record identified there was insufficient evidence of GMP compliance at Wasdell Europe Ltd site. Therefore, on 4 July 2024, the TGA imposed condition on the current GMP clearance MI-2023-CL-05158-1 for Wasdell Europe Ltd (Id: 70336). The condition permitted only packaging labelling, secondary packaging, release for supply and testing (chemical and physical).

Please provide response by 26 July. If you have any questions regarding this issue, please contact me.

Regards

s22

Senior Evaluator
Adverse Event & Medicine Defect Section
Pharmacovigilance Branch

Phone: s22 [redacted]
Email: s22 [redacted] @health.gov.au

Therapeutic Goods Administration
Location: 27 Scherger Drive Fairbairn ACT 2609
Australian Department of Health and Aged Care
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

VYVANSE lisdexamfetamine dimesilate 70mg capsules bottle AUST R 199228
Batch no. 3217300C Expiry: Sep-2025

VYVANSE lisdexamfetamine dimesilate 40mg capsules bottle AUST R 284020
Batch no. 3216210A Expiry: Feb-2026

VYVANSE lisdexamfetamine dimesilate 40mg capsules bottle AUST R 284020
Batch no. 32234498B Expiry: Jul-2026

Responses to TGA Request for Information dated 12-Jul-2024

Reference Number: TGA Issues 814615, 814073 and 814180

01 Aug 2024

Response to TGA Request for Information Dated 12 Jul 2024

02 Aug 2024

Dear Sir/Madam,

Thank you for your recent reports, reference numbers **814073**, **814180** and **814615**, received at Takeda on 12th July 2024 regarding Takeda's products Vyvanse 70mg and Vyvanse 40mg.

Upon receiving the RFI from TGA Takeda have been able to identify Product Complaint cases which are associated with the TGA listed documents and a summary of the Investigations for the Individual complaints is listed below.

Takeda have completed the investigations into these reports and can conclude that there is no evidence that the manufacturing process has contributed to the issues identified.

Confirmation of Complaint Reports Received by Takeda

TGA Issue 814615 (Vyvanse 70mg):

Regarding the information provided to the TGA and directly to Takeda, Takeda have identified the initiated three (3) complaint records as related to the below communications in Takeda's Global Complaint Management System.

- PR 4407448 - Lack of Effect
- PR 4407296 - Suspected Tampering
- PR 4408411 - Product Appearance

TGA Issue 814073 (Vyvanse 40mg):
1 complaint record has been raised in Takeda's Global Complaint Management system;

- PR 4400629 – Lack of Effect

TGA Issue 814180 (Vyvanse 40mg):
1 complaint record has been raised in Takeda's Global Complaint Management system;

- PR 4435873 – Lack of Effect

Please note the lot number provided in the TGA Issue 814180 report , 32234498B does not align with a lot number in Takeda's systems. However, the lot number provided by the TGA closely matches another Takeda lot number 3221498B. This lot number is subsequently referenced throughout the rest of this document in relation to 32234498B reported by the TGA.
Lot number 3221498B has been released to the Australian market.

Takeda Complaint Investigation Summaries

Takeda Complaint Trending

Product Complaint Trending is used to indicate a potential quality issue with a batch or a trend emerging with a product that may warrant additional investigations, potential escalation, and possible corrective actions. s47 s47 [redacted]

- PR 4407448 (Vyvanse 70mg) - This is the second customer complaint received on Finished packaged lot 3217300C (bulk lot 3217300) for "Lack of Effect". No trend on the lot has been identified.

- PR 4407296 (Vyvanse 70mg) - This is the first customer complaint received on Finished packaged lot 3217300C (bulk lot 3217300) for "Suspected Tampering". No trend on the lot has been identified.

- PR 4408411 (Vyvanse 70mg) - This is the first customer complaint received on Finished packaged lot 3217300C (bulk lot 3217300) for "Product Appearance". No trend on the lot has been identified.

- PR 4400629 (Vyvanse 40mg) - This is the second customer complaint received on Finished packaged lot

3216210A (bulk lot 3216210) for "Lack of Effect". No trend on the lot has been identified.

- PR 4435873 (Vyvanse 40mg) - This is the third customer complaint received on Finished packaged lot 3221498B (bulk lot 3221498) for "Lack of Effect". No trend on the lot has been identified.

The batch production documentation for the primary 3 bulk lots revealed that the batches were manufactured according to specifications and GMP requirements and no atypical events were identified. There have been no changes to quality testing specifications affecting these lots. No quality issues were found that could have contributed to the reported issues.

Summary of Individual Complaint Report investigations

PR 4408411 (lot 3217300C) - Product – Appearance
An investigation was performed by the bulk manufacturing site, which included a review of the sample photograph by Patheon Cin QA. From the photo evaluation, as seen in photo the capsule appeared to be unlocked with misaligned print. The manufacturing processing controls prevent a capsule from proceeding through the Encapsulator opened / not locked, and to subsequently proceed through the check weigher without being rejected.

As part of the manufacturing process, operators perform a capsule appearance inspection on s47 [redacted] different time points. A total of s47 [redacted] capsules were examined. No defects were identified. Nothing unusual about the appearance of the capsules was observed. Lot 3217300 (bulk lot of **3217300C)** passed all quality checks and met specifications at the time of release. Based on the investigation there is no evidence of a material or manufacturing defect that could be correlated with the reported complaint.

PR 4407296 (lot 3217300C) - Suspected Tampering
Takeda Global Product Protection were notified about this report and reviewed all available information. As a result of this evaluation, they have confirmed this is an authentic Takeda lot 3217300C and no further investigation is required.

Bulk manufacturer Patheon Investigation Summary:
An investigation was performed by the bulk manufacturing site. On 04/15/2023 - 04/17/2023, Operations performed encapsulation via s47 [redacted].
Patheon identified no issues during API dispensing, blending, encapsulation, bulk packaging and release testing processes for bulk lot 3217300. Operators completed all security logs appropriately and per batch record instruction with no out-of-range excursions or losses documented.

From the photo review by Patheon CMO QA, the capsule appeared to be unlocked with misaligned print. A capsule cannot proceed through the Encapsulator opened or not locked, and subsequently proceed through the check weigher and not get rejected. Root Cause has been identified as not being related to the bulk manufacturing site.

Packaging CMO Wasdell completed the Investigation Summary:
The packing of this finished drug product batch was performed from 02 Jan 2024 to 07 Jan 2024. The batch packaging instructions include In-process checks (IPCs) which are carried out at set-up, start-up, and end of batch and at 30-minute intervals throughout the run of the batch. From the review of batch documents, all IPCs were satisfactory and there were no non-conformances noted during the packing of this batch. From a visual inspection of the photos provided, the capsule matches the required product specification and does not show any signs of tampering.

There were no issues identified in the packaging batch review that could be correlated to the reported complaint.

PR 4400629 (lot 3216210A); PR 4435873 (lot 3221498B) PR 4407448 (lot 3217300C); - Lack of Effect:

Review of the global safety database to check any additional adverse events related to the provided Lots/PRs revealed a total of 5 events. The details of the involved lots included 3 reports of LOE related to lot 3216210A (one 40mg with associated 2 PRs 4384593 and 4385281) and (2 with reported 40mg dose and one with unknown dose with PQC #4400629). The fourth report was related to lot 3221498B (40mg), and the 5th report was related to lot 3217300C (70mg) with PQC# 4416555). Only one (70mg) of the 5 reports was medically confirmed. Associated events were non serious and consistent with patient background conditions.

Each of the lots reported were manufactured, packaged and released in compliance with cGMP. No lot trends were noted. An investigation was performed on each batch and confirmed there were no issues or deviations noted during manufacturing that would result in subpotent drug product. All specifications were met at the time of release. In addition, the product's stability profile shows the product is stable when stored according to the labelled storage conditions over the established shelf life.

Based on the investigations performed and stability program for the product there is no evidence of events or atypical process behaviour that would contribute to lack of effect complaints.

TGA – Request for Information Responses:

1. **Please provide the outcome of your assessment of the returned 70mg complaint product, including the assessment of capsule appearance variation (as depicted in the photo provided by the patient).**

The complaint product subject to complaint report PR 4408411 lot 3217300C was returned to the DHL warehouse and Australian LOC Quality team member visually inspected the sample, taking additional photographs to assist in the complaint investigation

The Vyvanse 70mg capsules returned included a total of 27 capsules contained in the expected bottle presentation.
The appearance of all 27 capsules was consistent with the expected blue opaque body and pink opaque cap.
All 27 capsules had the text printed on the capsule 'S489' and '70mg' in black ink.
All 27 capsules were confirmed to be the same length and there was no evidence of tampering noted.
The product appearance was within the expected requirements specification and no concerns noted.

The photographs provided as part of the initial report were not represented as part of the physically returned product and cannot be confirmed to be from the same batch or bottle of product.

A visual assessment of the 3 capsules provided in the initial photographs were considered as part of the bulk manufacturing site investigation. The Patheon QA assessment confirmed that possible capsule manipulation was confirmed as observed, considering the capsule appeared to be consistent with an unlocked capsule with misaligned print. However, it was noted by the Bulk Manufacturer that a capsule cannot proceed through the Encapsulator process opened or not-locked, as the inbuilt manufacturing controls would ensure that the capsule is rejected.

Ater completion of the encapsulation process the bulk capsules are packed for shipment in s47 s47 and shipped to the finished drug product packaging site (Wasdell Europe). The process for bulk packaging or finished drug product packaging is unlikely to have caused the unlocking of capsules.

2. **Reporting trend of lack of efficacy for Vyvanse products (all strengths) in the last 7 years and assessment if there's an atypical trend in the last 2-3 years.**

The Global product quality complaint data for the last three years for lack of effect has been reviewed. There have been no lot trends for the Australian market. Additionally, no safety signals for lack of efficacy for Vyvanse products (all strengths) have been reported in the last 7 years in Australia. LOE complaints were received at a frequency from Sweden, however, reporting rates considering exposure, concluded no increase. No increase in frequency or reporting rates were reported from Australia. Vyvanse and per the established safety profile of these products, this is not unexpected.

In September 2023 Takeda completed a Technical Evaluation of Vyvanse Capsules in response to an observed in Lack of Effect (LOE) Product Complaints. The purpose of this evaluation was to review recent quality and technical information related to the manufacture and release of Vyvanse capsules in response to a recent increase in global market product complaints of Lack of Effect (LOE).

s47 s47 . Along with many other attributes this review includes the drug substance content

(assay) of the Vyvanse drug product. s47 [redacted] which review the overall product quality and the continued verification of process performance, known respectively as the Annual Product Quality Review (APQR) and the Continued Process Verification (CPV) for which reports are compiled, reviewed and approved.

For this technical evaluation the APQR for the review period of 01 Mar 2021 through 28 Feb 2022 was reviewed which covers Vyvanse drug product batches manufactured/tested and dispositioned during the review period at Cincinnati and other manufacturing sites. All critical process parameters were operating in acceptable ranges and met specifications. The processes and analytical methods were confirmed to have remained in a validated state. A review was conducted of the commercial batch data as well as Annual Product Quality Reviews and Continued Process Verification reports for Vyvanse capsules drug product manufactured at the Patheon Cincinnati and other manufacturing sites. In all cases, the manufacturing process was found to be remaining in a validated state and all CQAs for released product met pre-determined specifications.

It can thus be concluded that the increase in market LOE complaints is not a result of any change in the quality of manufactured drug product at the approved manufacturing sites.

Two signals of lack of effect (LOE) from Sweden were evaluated covering the timeframe of 01 Jan 1990 through 31 Dec 2023 (signal number #716) and 01 Jan 2024 through 26 Feb 2024 signal number #749. Signal #716 was assessed as invalid and the signal #749 was refuted. Both signals included comparing all cases from all countries in the timeframes noted, with the comparison covering data for a 10-year period.

A third signal related to a product availability issue (signal No. #702) in which drug dependence analysis was discussed. This analysis was globally conducted including Australia and was also refuted.

3. **The details of the manufacturers of the complaint product batches referenced in this email and Vyvanse products (all strengths) currently in the AU market. Specifically, please provide details of the manufacturing sites of the active pharmaceutical ingredient (API) and Vyvanse dosage form (capsules), and if these have changed in the last 5 years.**

For the Vyvanse batches reported to the TGA the manufacturing Supply Chain is tabulated below:

TGA Reference No.	**814073**	**814180**	**814615**
Product Strength	Vyvanse 70mg Capsules	Vyvanse 40mgCapsules	Vyvanse 40mg Capsules
Manufacturing Date	**13 Apr 2023**	**22 Mar 2023**	**29 Aug 2023**
Expiry Date	**Sep 2025**	**Feb 2026**	**Jul 2026**
FDP Batch No	**3217300C**	**3216210A**	**3221498B (32234498B*)**
FDP Manufacturer	Wasdell Europe Limited IDA Dundalk Science and technology Park Mullagharlin Dundalk Co. Louth, Ireland	Wasdell Europe Limited IDA Dundalk Science and technology Park Mullagharlin Dundalk Co. Louth, Ireland	Wasdell Europe Limited IDA Dundalk Science and technology Park Mullagharlin Dundalk Co. Louth, Ireland
Bulk Packaged DP Batch No.	**3217300 (SAP Batch 12492530)**	**3216210 (SAP Batch 12492521)**	**3221498 (SAP 12623466)**
Bulk DP Manufacturer	s47 [redacted]		
API Vendor Batch No. (Takeda Batch No.)	**0000132755 (SAP 12407399)**	**0000132974 (SAP 12402098)**	**0000141589 (SAP 12516074)**
API Manufacturer	s47 [redacted]		

** Please note for the last complaint batch 32234498B is not a Takeda Batch number that is consistent with product manufactured at either manufacturing site. The nearest 40mg bulk batch found was 3221498. In case of a typo, this number has been used in the table.*

Response to TGA Request for Information Dated 12 Jul 2024

Takeda Australia Supply Chain for Vyvanse Products

Active Pharmaceutical Ingredient (API)

The API used in the manufacture of Australian Vyvanse range of products comes from following 2 sources which are both actively used.

- s47
-

Drug Product (DP)

The Bulk Drug Product (capsules) supplied to the Australian market are sourced from the following 2 manufacturing sites which are both actively used.

- s47
-

Finished Drug Product (FDP)

There are 2 registered Finished Drug Product manufacturing sites which are both actively used.

- Wasdell Europe Ltd, Dundalk, Ireland
- s47

Takeda confirms the only change related to the manufacturers of API, DP and FDP in the last 5 years has been the addition of s47 as a new site for DP/ FDP manufacture (TGA approval date 7-Sep-2022).

4. **If there is a current/pending GMP non-compliance issue for Vyvanse manufacturing sites which may be attributing to the current quality signal. If so, please provide details and outcome (if finalised)**

Takeda are not aware of any current or pending GMP non-compliance issues for the API (Lisdexamfetamine) manufacturing site s47.

Product Quality Reviews conducted over the time period associated with API manufactured as part of this investigation confirm that overall, the process is in control. All critical process parameters were operating within the acceptable ranges and met the specifications. There was no trend observed during the review period. There was no CAPA opened that was associated with critical in-process control or trend in analytical data.

Takeda are not aware of any current/pending GMP non-compliance issues for Vyvanse manufacturing at the bulk drug product manufacturer s47.

While there are GMP non-compliance issues at Wasdell which have resulted in a European Statement of Non-Compliance and a restricted GMP Licence at the site these are not attributable to the current quality signal. The GMP non-compliance issues have been mitigated as indicated in the risk assessments provided to the TGA previously.

The strategic product plan for Vyvanse Takeda has ceased finished drug product packaging at the Wasdell site and all future batches of Vyvanse for Australia are now being manufacture at s47.

Yours sincerely,

Market Surveillance Team

s47

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LIST OF ABBREVIATIONS

ND – not detected
LOQ – limit of quantification
TAMC – total aerobic microbial count
TYMC – total yeast mold count

s47 [redacted]

3.2.P.8.3 STABILITY DATA

Stability data is provided for commercial scale process performance qualification (PPQ) batches manufactured at s47 [redacted] Table 1 provides a batch overview. Analytical procedures utilized are as described in Section 3.2.P.5.2 and specifications applicable are as provided in Section 3.2.P.5.1.

Table 1 Batch Overview

Capsule Strength	Bulk Batch No.	Packed Batch No.	Batch Size Capsules (Blend Size)	Date of Manufacture	Drug Substance Manufacturing Site (TOB Batch No.)	Stability Start Date	Time Points Tested (Months)
20 mg	12182353	12239564	s47	January 2022	s47 (12033263)	18 Aug 2022	s47 (30°C/65%RH)
	12185503	12239566		January 2022	s47 (12041144)		s47 (30°C/75%RH)
30 mg	12191487	12266658		January 2022	s47 (12151666)		s47 (40°C/75%RH)
40 mg	12191581	12262019		January 2022	s47 (12151666)		
50 mg	12242494	12269369		April 2022	s47 (12234752, 12151666)		
	12248408	12269371		April 2022	s47 (12234752)		
70 mg	12190256	12263855		January 2022	s47 (12041144)		
	12191587	12263856		February 2022	s47 (12151666)		

Table 2 Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 12182353 (12239564) (30°C/65%RH)

s47

Table 3 Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 12182353 (12239564) (30°C/75%RH)

s47

[redacted]

Table 4 Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 12182353 (12239564) (40°C/75%RH)

s47

[redacted]

Table 5 Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 12185503 (12239566) (30°C/65%RH)

s47

[redacted]

Table 6 Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 12185503 (12239566) (30°C/75%RH)

s47

[redacted]

Table 7 Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 12185503 (12239566) (40°C/75%RH)

s47

[redacted]

Table 8 Lisdexamfetamine Dimesylate 30 mg Capsules; Batch 12191487 (12266658) (30°C/65%RH)

s47

[redacted]

Table 9 Lisdexamfetamine Dimesylate 30 mg Capsules; Batch 12191487 (12266658) (30°C/75%RH)

s47

[redacted]

Table 10 Lisdexamfetamine Dimesylate 30 mg Capsules; Batch 12191487 (12266658) (40°C/75%RH)

s47

[redacted]

Table 11 Lisdexamfetamine Dimesylate 40 mg Capsules; Batch 12191581 (12262019) (30°C/65%RH)

s47

[redacted]

Table 12 Lisdexamfetamine Dimesylate 40 mg Capsules; Batch 12191581 (12262019) (30°C/75%RH)

s47

[redacted]

Table 13 Lisdexamfetamine Dimesylate 40 mg Capsules; Batch 12191581 (12262019) (40°C/75%RH)

s47

[redacted]

Table 14 Lisdexamfetamine Dimesylate 50 mg Capsules; Batch 12242494 (12269369) (30°C/65%RH)

s47

[redacted]

Table 15 Lisdexamfetamine Dimesylate 50 mg Capsules; Batch 12242494 (12269369) (30°C/75%RH)

s47

[redacted]

Table 16 Lisdexamfetamine Dimesylate 50 mg Capsules; Batch 12242494 (12269369) (40°C/75%RH)

s47

[redacted]

Table 17 Lisdexamfetamine Dimesylate 50 mg Capsules; Batch 12248408 (12269371) (30°C/65%RH)

s47

[redacted]

Table 18 Lisdexamfetamine Dimesylate 50 mg Capsules; Batch 12248408 (12269371) (30°C/75%RH)

s47

[redacted]

Table 19 Lisdexamfetamine Dimesylate 50 mg Capsules; Batch 12248408 (12269371) (40°C/75%RH)

s47

[redacted]

Table 20 Lisdexamfetamine Dimesylate 70 mg Capsules; Batch 12190256 (12263855) (30°C/65%RH)

s47

[redacted]

Table 21 Lisdexamfetamine Dimesylate 70 mg Capsules; Batch 12190256 (12263855) (30°C/75%RH)

s47

[redacted]

Table 22 Lisdexamfetamine Dimesylate 70 mg Capsules; Batch 12190256 (12263855) (40°C/75%RH)

s47

[redacted]

Table 23 Lisdexamfetamine Dimesylate 70 mg Capsules; Batch 12191587 (12263856) (30°C/65%RH)

s47

[redacted]

Table 24 Lisdexamfetamine Dimesylate 70 mg Capsules; Batch 12191587 (12263856) (30°C/75%RH)

s47

[redacted]

Table 25 Lisdexamfetamine Dimesylate 70 mg Capsules; Batch 12191587 (12263856) (40°C/75%RH)

s47

[redacted]

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Table 8 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 s47 Batch A60051A; s47 HDPE Bottles 19
Table 9 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A60051A; s47 HDPE Bottles 20
Table 10 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 s47 Batch 74678; s47 HDPE Bottles; Tested by s47 21
Table 11 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Batch A52898B; White/Dark Green Capsules; s47 HDPE Bottles 22
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Table 13 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Batch A60052A; White/Dark Green Capsules; s47 HDPE Bottles 28
Table 14 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch A60052A 29
Table 15 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 s47 Batch A52936B; s47 HDPE Bottles 30
Table 16 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules s47 Batch A52936B; s47 HDPE Bottles 33
Table 17 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 s47 Batch A60361A; s47 HDPE Bottles 36

Table 18 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, [redacted] Batch A60361A; [redacted] HDPE Bottles 38
Table 19 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; [redacted] Batch 74679; [redacted] HDPE Bottles; Tested by [redacted] 39
Table 20 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; [redacted] Batch A52938B; [redacted] HDPE Bottles 40
Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; [redacted] Batch A52938B; [redacted] HDPE Bottles 42
Table 22 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; [redacted] Batch A60363A; [redacted] HDPE Bottles 45
Table 23 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; [redacted] Batch A60363A; [redacted] HDPE Bottles 46
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1 STABILITY DATA

The stability data is provided for capsules, manufactured at s47 , s47 (formerly known as s47) located in s47 (s47). The stability data is used to support the proposed capsule shelf-life (Table 1).

s47

Table 1 Stability Batch Details

Dose (mg)	Packaged Batch Number	Batch Number	Date of Manufacture	Drug Substance Manufacturer, Batch Number	Batch Size	Packaging Details	Stability Start Date
20	A52605B	A52001	July 2009	s47 04090020	s47	s47 White Round 30 cc HDPE Bottle with PP child-resistant closure and induction seal	September 2009
	A59858A	A59468	January 2010	s47 A53796			March 2010
30	A52607B	A52607 (A52003)	July 2009	s47 04090020		s47 white round 30 cc HDPE bottle with PP child-resistant closure and induction seal.	September 2009
	A60051A	A60051 (A59466)	January 2010	s47 04090020			March 2010
	74678[a]	A98548E	August 2012	s47 1085			March 2013
40	A52898B	A52007	July 2009	s47 04090020		s47 White Round 30 cc HDPE bottle with PP child-resistant closure and induction seal	September 2009
	A60052A	A59469	January 2010	s47 A53796, A58645			March 2010
50	A52936B	A52936 (A52005)	July 2009	s47 04090020		s47 white round 30 cc HDPE bottle with PP child-resistant closure and induction seal.	November 2009
	A60361A	A60361 (A59472)	January 2010	s47 1037			March 2010
	74679[a]	AA0756B	August 2012	s47 1085			March 2013
70	A52938B	A52938 (A54595)	September 2009	s47 04090020		s47 white round 30 cc HDPE bottle with PP child-resistant closure and induction seal.	November 2009
	A60363A	A60363 (A59474)	January 2010	s47 1037, 1039			March 2010
	74680[a]	A97794B	August 2012	s47 1085			March 2013

[a] Packaged at s47 and tested at s47

Table 2 Stability Data for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch A52605B; Ivory Opaque/Ivory Opaque Capsules; s47 HDPE Bottles

s47 [redacted]

Table 2 Stability Data for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch A52605B; Ivory Opaque/Ivory Opaque Capsules; s47 HDPE Bottles

s47

[redacted]

Table 3 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch A52605B

s47

[redacted]

Table 3 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch A52605B

s47

[redacted]

Table 3 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch A52605B

s47

[redacted]

Table 4 Stability Data for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch A59858B; Ivory Opaque/Ivory Opaque Capsules; s47 HDPE Bottles

s47

Table 5 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch A59858B

s47

[redacted]

Table 6 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A52607B; s47 HDPE Bottles

s47

Table 6 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A52607B; s47 HDPE Bottles

s47

Table 6 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A52607B; s47 HDPE Bottles

s47

Table 7 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A52607B; s47 HDPE Bottles

s47

Table 7 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A52607B; s47 HDPE Bottles

s47

Table 7 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; [redacted] Batch A52607B; [redacted] HDPE Bottles

[redacted]

Table 7 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A52607B; s47 HDPE Bottles

s47

Table 8 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A60051A; s47 HDPE Bottles

s47

Table 9 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch A60051A; s47 HDPE Bottles

s47

Table 10 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 74678; s47 HDPE Bottles; Tested by s47

s47

Table 11 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Batch A52898B; White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 11 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Batch A52898B; White/Dark Green Capsules; s47 HDPE Bottles

s47

[redacted]

Table 12 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch A52898B

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[redacted]

Table 12 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch A52898B

s47

[redacted]

Table 12 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch A52898B

s47

[redacted]

Table 12 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch A52898B

s47

Table 13 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Batch A60052A; White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 14 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch A60052A

s47

[redacted]

Table 15 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch A52936B; s47 HDPE Bottles

s47

Table 15 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; [redacted] Batch A52936B; [redacted] HDPE Bottles

[redacted]

Table 15 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch A52936B; s47 HDPE Bottles

s47

Table 16 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules s47 Batch A52936B; s47 HDPE Bottles

s47

Table 16 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules s47 Batch A52936B; s47 HDPE Bottles

s47

Table 16 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules [redacted] Batch A52936B; [redacted] HDPE Bottles

[redacted]

Table 17 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch A60361A; s47 HDPE Bottles

s47

Table 17 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch A60361A; s47 HDPE Bottles

s47

Table 18 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, s47 Batch A60361A; s47 HDPE Bottles

s47

Table 19 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; [redacted] Batch 74679; [redacted] HDPE Bottles; Tested by [redacted]

[redacted]

Table 20 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A52938B; s47 HDPE Bottles

s47

Table 20 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A52938B; s47 HDPE Bottles

s47

Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A52938B; s47 HDPE Bottles

s47

Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A52938B; s47 HDPE Bottles

s47

Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A52938B; s47 HDPE Bottles

s47

Table 22 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A60363A; s47 HDPE Bottles

s47

Table 23 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A60363A; s47 HDPE Bottles

s47 [redacted]

Table 23 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch A60363A; s47 HDPE Bottles

s47 [redacted]

Table 24 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 74680; s47 HDPE Bottles; Tested by s47

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Table 3 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 3064285 8
Table 4 Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3064286 (Manufacturing Batch 3062970R); Ivory Opaque/Ivory Opaque Capsules 10
Table 5 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 3064286 12
Table 6 Stability Data for Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3074715 (Manufacturing Batch 3073462R); Ivory Opaque/Ivory Opaque Capsules; s47 [redacted] HDPE Bottles 14
Table 7 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch 3074715 16
Table 8 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 [redacted] s47 [redacted] Batch 3064287 (Packaged), 3062967R (Bulk); s47 [redacted] HDPE Bottles 19
Table 9 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 [redacted] Batch 3064287 (Packaged), 3062967R (Bulk); s47 [redacted] HDPE Bottles 21
Table 10 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 [redacted] s47 [redacted] Batch 3064288 (Packaged), 3062971R (Bulk); s47 [redacted] HDPE Bottles 23
Table 11 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules, s47 [redacted] Batch 3064288 (Packaged), 3062971R (Bulk); s47 [redacted] HDPE bottles 25
Table 12 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 [redacted] s47 [redacted] Batch 3074716 (Packaged), 3073463R(Bulk); s47 [redacted] HDPE Bottles 27
Table 13 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 [redacted] Batch 3074716 (Packaged), 3073463R(Bulk); s47 [redacted] HDPE Bottles 29

Table 14 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3065185 (Manufacturing Batch 3064650R); White/Dark Green Capsules; s47 HDPE Bottles 32
Table 15 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3065185 34
Table 16 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3065186 (Manufacturing Batch 3064651R); White/Dark Green Capsules; s47 HDPE Bottles 36
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Table 18 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3074717 (Manufacturing Batch 3073464R); White/Dark Green Capsules; s47 HDPE Bottles 40
Table 19 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3074717 42
Table 20 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 s47 Batch 3065145 (Packaged), 3063338R (Bulk); s47 HDPE Bottles 45
Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, s47 Batch 3065145 (Packaged), 3063338R (Bulk); s47 HDPE Bottles 47
Table 22 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 s47 Batch 3065146 (Packaged), 3063339R (Bulk); s47 HDPE Bottles 49
Table 23 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, s47 Batch 3065146 (Packaged), 3063339R (Bulk); s47 HDPE Bottles 51
Table 24 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 s47 Batch 3074719 (Packaged), 3073465R (Bulk); s47 HDPE Bottles 53
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Table 29 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules, s47 Batch 3065148 (Packaged), 3063337R (Bulk); s47 HDPE Bottles 64
Table 30 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 s47 Batch 3074720 (Packaged), 3073466R (Bulk); s47 HDPE Bottles 66
Table 31 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3074720 (Packaged), 3073466R (Bulk); s47 HDPE Bottles 68

LIST OF ABBREVIATIONS

NA	not applicable
ND	not detected
NMT	not more than
NR	not reported
RRT	relative retention time

Impurities

s47 [redacted]

1 STABILITY DATA

Stability data is provided for capsules, manufactured at s47 s47. The stability data is used to support the proposed capsule shelf-life (Table 1).

Notes to Specifications:

s47

Table 1 Stability Batch Details

Dose (mg)	Packaged Batch Number	Batch Number (Blend Batch Number)	Date of Manufacture	Drug Substance Manufacturer, Batch Number	Batch Size	Packaging Details	Stability Start Date
20	3064285	3062966R	October 2007	s47 04070042	s47	s47 White Round 30 cc HDPE Bottle with PP child-resistant closure and induction seal	February 2008
	3064286	3062970R	October 2007	s47 04070042			February 2008
	3074715	3073462R	May 2009	s47 04090008			June 2009
30	3064287	3062967R	October 2007	s47 04070042		s47 white round 30 cc HDPE bottle with PP child-resistant closure and induction seal.	February 2008
	3064288	3062971R	October 2007	s47 04070042			February 2008
	3074716	3073463R	May 2009	s47 04090008			June 2009
40	3065185	3064650R	January 2008	s47 3059173		s47 White Round 30 cc HDPE bottle with PP child-resistant closure and induction seal	February 2008
	3065186	3064651R	January 2008	s47 3059173			February 2008
	3074717	3073464R	May 2009	s47 3073846			June 2009
50	3065145	3063338R	October 2007	s47 04070043		s47 white round 30 cc HDPE bottle with PP child-resistant closure and induction seal.	February 2008
	3065146	3063339R	October 2007	s47 04070043			February 2008
	3074719	3073465R	May 2009	s47 04090007			June 2009
70	3065147	3063336R	October 2007	s47 04070043		s47 white round 30 cc HDPE bottle with PP child-resistant closure and induction seal.	February 2008
	3065148	3063337R	October 2007	s47 04070043			February 2008
	3074720	3073466R	May 2009	s47 04090007			June 2009

Table 2 Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3064285 (Manufacturing Batch 3062966R); Ivory Opaque/Ivory Opaque Capsules

s47

[redacted]

Table 2 Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3064285 (Manufacturing Batch 3062966R); Ivory Opaque/Ivory Opaque Capsules

s47

[redacted]

Table 3 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 3064285

s47

[redacted]

Table 3 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 3064285

s47

[redacted]

Table 4 Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3064286 (Manufacturing Batch 3062970R); Ivory Opaque/Ivory Opaque Capsules

s47

[redacted]

Table 4 Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3064286 (Manufacturing Batch 3062970R); Ivory Opaque/Ivory Opaque Capsules

s47

[redacted]

Table 5 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 3064286

s47

[redacted]

Table 5 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules; Batch 3064286

s47

[redacted]

Table 6 Stability Data for Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3074715 (Manufacturing Batch 3073462R); Ivory Opaque/Ivory Opaque Capsules; s47 HDPE Bottles

s47 [redacted]

Table 6 Stability Data for Lisdexamfetamine Dimesylate 20 mg Capsules; Packaged Batch 3074715 (Manufacturing Batch 3073462R); Ivory Opaque/Ivory Opaque Capsules; s47 HDPE Bottles

s47 [redacted]

Table 7 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch 3074715

s47

[redacted]

Table 7 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch 3074715

s47

[redacted]

Table 7 Dissolution Profile for Lisdexamfetamine Dimesylate 20 mg Capsules, Batch 3074715

s47

[redacted]

Table 8 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3064287 (Packaged), 3062967R (Bulk); s47 HDPE Bottles

s47

Table 8 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3064287 (Packaged), 3062967R (Bulk); s47 HDPE Bottles

s47

Table 9 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3064287 (Packaged), 3062967R (Bulk); s47 HDPE Bottles

s47

Table 9 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3064287 (Packaged), 3062967R (Bulk); s47 HDPE Bottles

s47

Table 10 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3064288 (Packaged), 3062971R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 10 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3064288 (Packaged), 3062971R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 11 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules, s47 Batch 3064288 (Packaged), 3062971R (Bulk); s47 HDPE bottles

s47

Table 11 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules, s47 Batch 3064288 (Packaged), 3062971R (Bulk); s47 HDPE bottles

s47 [redacted]

Table 12 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3074716 (Packaged), 3073463R(Bulk); s47 HDPE Bottles

s47

Table 12 Stability Data for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3074716 (Packaged), 3073463R(Bulk); s47 HDPE Bottles

s47

Table 13 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3074716 (Packaged), 3073463R(Bulk); s47 HDPE Bottles

s47 [redacted]

Table 13 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3074716 (Packaged), 3073463R(Bulk); s47 HDPE Bottles

s47 [redacted]

Table 13 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 30 mg Capsules; s47 Batch 3074716 (Packaged), 3073463R(Bulk); s47 HDPE Bottles

s47 [redacted]

Table 14 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3065185 (Manufacturing Batch 3064650R); White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 14 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3065185 (Manufacturing Batch 3064650R); White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 15 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3065185

s47

[redacted]

Table 15 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3065185

s47

[redacted]

Table 16 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3065186 (Manufacturing Batch 3064651R); White/Dark Green Capsules; s47 HDPE Bottles

s47

[redacted]

Table 16 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3065186 (Manufacturing Batch 3064651R); White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 17 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3065186

s47

[redacted]

Table 17 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3065186

s47

[redacted]

Table 18 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3074717 (Manufacturing Batch 3073464R); White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 18 Stability Data for Lisdexamfetamine Dimesylate 40 mg Capsules; Packaged Batch 3074717 (Manufacturing Batch 3073464R); White/Dark Green Capsules; s47 HDPE Bottles

s47 [redacted]

Table 19 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3074717

s47

[redacted]

Table 19 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3074717

s47

[redacted]

Table 19 Dissolution Profile for Lisdexamfetamine Dimesylate 40 mg Capsules, Batch 3074717

s47

[redacted]

Table 20 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch 3065145 (Packaged), 3063338R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 20 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch 3065145 (Packaged), 3063338R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, s47 Batch 3065145 (Packaged), 3063338R (Bulk); s47 HDPE Bottles

s47

Table 21 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, s47 Batch 3065145 (Packaged), 3063338R (Bulk); s47 HDPE Bottles

s47

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s47 [redacted]

Table 22 Stability Data for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch 3065146 (Packaged), 3063339R (Bulk); s47 HDPE Bottles

s47

Table 23 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules, s47 Batch 3065146 (Packaged), 3063339R (Bulk); s47 HDPE Bottles

s47

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s47

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s47

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s47 [redacted]

Table 25 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch 3074719 (Packaged), 3073465R (Bulk); s47 HDPE Bottles

s47

Table 25 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch 3074719 (Packaged), 3073465R (Bulk); s47 HDPE Bottles

s47

Table 25 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 50 mg Capsules; s47 Batch 3074719 (Packaged), 3073465R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 26 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3065147 (Packaged), 3063336R (Bulk); s47 HDPE Bottles

s47

Table 26 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3065147 (Packaged), 3063336R (Bulk); s47 HDPE Bottles

s47 [redacted]

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s47 [redacted]

Table 27 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules, s47 Batch 3065147 (Packaged), 3063336R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 28 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3065148 (Packaged), 3063337R (Bulk); s47 HDPE Bottles

s47

Table 28 Stability Data for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3065148 (Packaged), 3063337R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 29 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules, s47 Batch 3065148 (Packaged), 3063337R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 29 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules, s47 Batch 3065148 (Packaged), 3063337R (Bulk); s47 HDPE Bottles

s47

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s47

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s47 [redacted]

Table 31 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3074720 (Packaged), 3073466R (Bulk); s47 HDPE Bottles

s47 [redacted]

Table 31 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3074720 (Packaged), 3073466R (Bulk); s47 HDPE Bottles

s47

Table 31 Stability Dissolution Profile for Lisdexamfetamine Dimesylate 70 mg Capsules; s47 Batch 3074720 (Packaged), 3073466R (Bulk); s47 HDPE Bottles

s47

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1 STABILITY SUMMARY AND CONCLUSION

1.1 Studies Conducted

Lisdexamfetamine dimesylate capsules are manufactured at s47 ., located in s47) and s47 Manufacturing Services, s47 (formerly known as s47 located in s47 North Carolina (s47). Stability studies have been set up at both manufacturers in accordance with ICH Q1A and Q1B (photostability).

Stability studies have been conducted at 25°C/60%RH, 30°C/65%RH and accelerated studies conducted at 40°C/75%RH. Long-term testing of lisdexamfetamine dimesylate capsules stored in bulk at 25°C/60%RH or warehouse conditions (19°C to 25°C/30% to 60%RH) has been performed to support bulk storage of capsules. In-use stability testing of lisdexamfetamine dimesylate capsules stored at 25°C/60%RH in open containers and photostability of lisdexamfetamine dimesylate capsules have also been conducted.

The capsules used in the stability studies were manufactured according to the formulation described in Section 3.2.P.1. s47 s47 s47 (batch 74678, 30 mg and batch 74680, 70 mg manufactured at the s47 site). s47 s47

A summary of the studies performed and the data available to date is provided in Table 1 through Table 7.

1.1.1 Study Methodology and Specification

Stability batches are tested for s47 s47

Table 1 Stability Studies for Lisdexamfetamine Dimesylate Capsules Manufactured at [redacted]; Stored in HDPE Bottles/Polypropylene Cap ([redacted] 30 cc)

Packaged Batch Number (Bulk Batch Number)/Capsule Strength	Batch Size (Capsules)	Date of Manufacture	Stability Start Date	Time Points Tested (Months)		
				25°C/60%RH	30°C/65%RH	40°C/75%RH
3064285 (3062966R)/20 mg	[redacted]	October 2007	February 2008	[redacted]		
3064286 (3062970R)/20 mg		October 2007	February 2008			
3074715 (3073462R)/20 mg		May 2009	June 2009			
3064287 (3062967R)/30 mg		October 2007	February 2008			
3064288 (3062971R)/30 mg		October 2007	February 2008			
3074716 (3073463R)/30 mg		May 2009	June 2009			
3065185 (3064650R)/40 mg		January 2008	February 2008			
3065186 (3064651R)/40 mg		January 2008	February 2008			
3074717 (3073464R)/40 mg		May 2009	June 2009			

Table 1 Stability Studies for Lisdexamfetamine Dimesylate Capsules Manufactured at s47 [redacted]; Stored in HDPE Bottles/Polypropylene Cap (s47 [redacted], 30 cc)

Packaged Batch Number (Bulk Batch Number)/Capsule Strength	Batch Size (Capsules)	Date of Manufacture	Stability Start Date	Time Points Tested (Months)		
				25°C/60%RH	30°C/65%RH	40°C/75%RH
3065145 (3063338R)/50 mg	s47 [redacted]	October 2007	February 2008	s47 [redacted]		
3065146 (3063339R)/50 mg		October 2007	February 2008			
3074719 (3073465R)/50 mg		May 2009	June 2009			
3065147 (3063336R)/70 mg		October 2007	February 2008			
3065148 (3063337R)/70 mg		October 2007	February 2008			
3074720 (3073466R)/70 mg		May 2009	June 2009			

s47 [redacted]

Table 2 Stability Studies for Lisdexamfetamine Dimesylate Capsules Manufactured at s47 , Stored in HDPE Bottle/Polypropylene Cap s47 30 cc)

Packaged Batch Number (Bulk Batch Number)/Capsule Strength	Batch Size (Capsules)	Date of Manufacture	Stability Start Date	Time Points Tested (Months)		
				25°C/60%RH	30°C/65%RH[a]	40°C/75%RH
A52605B (A52001)/20 mg	s47	July 2009	September 2009	s47		
A59858A (A59468)/20 mg		January 2010	March 2010			
A52607B (A52607)/30 mg		July 2009	September 2009			
A60051A (A60051)/30 mg		January 2010	March 2010			
74678 (A98548E)/30 mg[b]		August 2012	March 2013			
A52898B (A52007)/40 mg		July 2009	September 2009			
A60052A (A59469)/40 mg		January 2010	March 2010			
A52936B (A52936)/50 mg		July 2009	November 2009			
A60361A (A60361)/50 mg		January 2010	March 2010			
74679 (AA0756B)/50 mg[b]		August 2012	March 2013			
A52938B (A52938)/70 mg		September 2009	November 2009			
A60363A (A60363)/70 mg		January 2010	March 2010			
74680 (A97794B)/70 mg[b]		August 2012	March 2013			

[a] Also stored at 30°C/75%RH, tested at s47 .
[b] Product packaged at Wasdell and stability testing conducted at s47

Table 3 Stability Studies for Bulk Lisdexamfetamine Dimesylate Capsules, Manufactured at s47 [redacted]

Batch Number/Capsule Strength	Batch Size (kg)	Date of Manufacture	Stability Start Date	Time Points Tested (Months)
				25°C/60%RH
3052604/20 mg	s47 [redacted]	July 2006	February 2007	s47 [redacted]
3054868/30 mg		September 2006	February 2007	
3054916/70 mg		October 2006	February 2007	

Table 4 Stability Studies for Bulk Lisdexamfetamine Dimesylate Capsules, Manufactured at s47 [redacted]

Batch Number/Capsule Strength	Batch Size (kg)	Date of Manufacture	Stability Start Date	Time Points Tested (Months)
				25°C/60%RH
3066098/30mg	s47 [redacted]	October 2007	June 2008	s47 [redacted]
3066100/50mg		October 2007	June 2008	
3066101/70mg		October 2007	June 2008	

Table 5 Stability Studies for Bulk Lisdexamfetamine Dimesylate Capsules, Manufactured at s47 [redacted]

Batch Number/Capsule Strength	Batch Size	Date of Manufacture	Stability Start Date	Time Points Tested (Months)
				25°C/60%RH
A52605/20 mg	s47 [redacted]	July 2009	September 2009	s47 [redacted]
A52898/40 mg		July 2009	September 2009	
A52936/50 mg		July 2009	November 2009	
A52938/70 mg		September 2009	November 2009	

Table 6 In-Use Stability Studies for Lisdexamfetamine Dimesylate Capsules, Manufactured at s47 , Stored in HDPE Bottles (s47 30 cc)

Batch Number/Capsule Strength	Batch Size	Date of Manufacture	Stability Start Date	Time Points Tested (Days)
				25°C/60%RH, Open Storage
3074716/30 mg (Packed from lot 3073463R)	s47	May 2009	March 2011	s47
3074719/50 mg (Packed from lot 3073465R)		May 2009	March 2011	
3074720/70 mg (Packed from lot 3073466R)		May 2009	March 2011	

Table 7 Photostability Studies for Lisdexamfetamine Dimesylate Capsules, Manufactured at s 47 , Stored in HDPE Bottles (s 47 , 30 cc)

Batch Number/Capsule Strength	Batch Size	Date of Manufacture	Stability Start Date	Condition/Time Points Tested
3069657/20 mg (Packed from lot 3062966R)	s47	October 2007	October 2008	s47
3069659/30 mg (Packed from lot 3062967R)		October 2007	October 2008	
3069660/40 mg (Packed from lot 3064650R)		October 2007	October 2008	
3069661/50 mg (Packed from lot 3063338R)		October 2007	October 2008	
3069662/70 mg (Packed from lot 3063336R)		October 2007	October 2008	

1.2 Packaging

Stability testing is presented on lisdexamfetamine dimesylate capsules packaged in 30 cc HDPE bottles with a s47 fill. For certain markets, the product will be packed as a s47 fill in 30 cc HDPE bottles. The stability data provided for the capsules as s47 , in 30 cc HDPE

bottles is s47 [redacted]

1.3 Discussion of Results

1.3.1 Bulk Stability Testing

Data is provided in:

- Section 3.2.P.8.3 s47 [redacted] Bulk Stability
- Section 3.2.P.8.3 s47 [redacted] Bulk Stability

s47 [redacted]

The data s47 [redacted] shows that all results are within specification. The stability data from each study indicates that the product may be stored in bulk for up to 12 months prior to packaging.

1.3.2 In-Use Stability Testing

Data is provided in Section 3.2.P.8.3 s47 [redacted] In-use Stability.

In-use stability testing of lisdexamfetamine capsules has been performed in accordance with EMA guidance CPMP/QWP/2934/99 for medicinal products stored in multi-dose containers. Samples from one batch each of s47 [redacted] strengths of capsules were tested. The capsules selected were from batches approximately s47 [redacted] old which had been stored at 25°C/60%RH for s47 [redacted] prior to initiating the in-use stability test. The data generated on the s47 [redacted]

Samples were stored at 25°C/60%RH in open containers for s47 [redacted] and were tested after s47 [redacted]

The data after open storage for s47 [redacted] and s47 [redacted] shows that all results are within specification. The demonstrated stability of the product indicates that no additional labelling for in-use shelf-life or storage conditions is required.

1.3.3 Photostability

Data is provided in Section 3.2.P.8.3 s47 [redacted] Photostability.

The photostability of batches of lisdexamfetamine dimesylate s47 [redacted] and s47 [redacted] capsules manufactured and packaged at s47 [redacted] was evaluated in accordance with ICH Q1B s47 [redacted]

Samples from one batch of each strength of capsules were subjected to a light chamber analogous to the s47 [redacted] Current ICH guidelines specify a minimum light exposure of 1200 Klux and an integrated near ultraviolet energy of not less than 200 watt-hours/square meter. s47 [redacted]

s47 [redacted] The samples were all tested for s47 [redacted] and the results evaluated against the specification in Section 3.2.P.5.1.

Th s47 [redacted] indicates that no significant change in the assay or degradation profile occurs following photolytic stress. The s47 [redacted] were also within specification. The lisdexamfetamine dimesylate capsules can be considered stable to light.

1.3.4 Long-Term Stability Studies

Data is provided in:

- Section 3.2.P.8.3 Stability Data s47 [redacted]
- Section 3.2.P.8.3 Stability Data s47 [redacted]

s47 [redacted]

1.3.4.1 Appearance

All lisdexamfetamine dimesylate stability batches manufactured at s47 [redacted] and s47 [redacted] conformed to the specification for appearance at all storage conditions.

1.3.4.2 Assay

All lisdexamfetamine assay results are within the specification range s47 [redacted] of label claim for all batches and storage conditions.

The assay results for all batches from both s47 [redacted] and s47 [redacted] at the long-term storage condition (25°C/60%RH) are within the specification limits at all time points s47 [redacted]

The assay results for batches stored at the intermediate storage condition (30°C/65%RH) are within specification for up to s47 [redacted] at both s47 [redacted] and s47 [redacted] A s47 [redacted]

At the accelerated condition (40°C/75%RH), s47 [redacted]

A graphical representation of the assay results observed on stability at the long-term storage condition (25°C/60%RH) is provided in Figure 1 and Figure 2 for s47 [redacted] and s47 [redacted] respectively. Statistical analysis of the data s47 [redacted]

The stability trends for the product are well characterized based on the product knowledge gained since the first global approval of lisdexamfetamine dimesylate capsules in 2007. Since that time, the stability data has reproducibly shown the same trend in assay over time. The trend for the batches included in this dossier is representative of the known behaviour of the product.

s47 [redacted] has been approved in the US since 2007, as s47 [redacted]

s47 [redacted]

This data observed on the pivotal clinical batch is representative of drug product data at s47 [redacted] when stored at 25°C/60%RH long term stability condition, and is considered qualified through the Sponsor's clinical studies. Hence, the safety and efficacy.

The quality of the product is ensured, through monitoring of the assay against the proposed specification and the related substances specifications throughout the s47 [redacted] shelf-life at the long-term condition of 25°C/60%RH.

Figure 1 Assay Stability Trend Plot for s47 [redacted] **Batches**

s47 [redacted]

Figure 2 Assay Stability Trend Plot for s47 Batches

1.3.4.3 Related Substances

There are no trends observed in the amount of the identified impurities s47 s47 found in any of the stability samples at any of the conditions. This supports that these are s47 . There are no significant changes in the level of s47 found in samples of lisdexamfetamine dimesylate capsules stored for up to s47 at 25°C/60%RH and 30°C/65%RH; and at 40°C/75%RH for up to s47 at both s47 and s47

All results for s47 for batches stored at the long-term condition (25°C/60%RH), are within specification for up to s47 . s47

There are no significant changes in the levels of the s47 with time.

At the intermediate storage condition (30°C/65%RH), s47 [redacted] The results for both manufacturing sites show similar trends.

At the accelerated storage condition (40°C/75%RH), s47 [redacted] The results for both manufacturing sites show similar trends.

s47 [redacted]

1.3.4.4 s47 [redacted]

All s47 [redacted] results for lisdexamfetamine dimesylate batches manufactured at s47 [redacted] s47 [redacted] and s47 [redacted] conformed to specifications at all stability time points tested. No trends observed in the s47 [redacted] with either storage time or condition.

1.3.4.5 s47 [redacted]

All s47 [redacted] results for lisdexamfetamine dimesylate batches manufactured at s47 [redacted] s47 [redacted] and s47 [redacted] conformed to specifications at all stability time points and for all conditions tested.

s47 [redacted]

1.4 Overall Conclusion

Satisfactory long-term stability data has been generated for lisdexamfetamine dimesylate capsules stored at 25°C/60%RH for up to s47 [redacted] for both s47 [redacted] and s47 [redacted] batches. This data supports the proposed s47 [redacted] shelf-life.

Satisfactory data has been generated to support in-use stability, photostability and bulk storage of capsules.

1.5 Proposed Storage Conditions and Shelf-Life

The proposed shelf-life is s47 when stored in HDPE bottles.

The recommended storage conditions are “Do not store above 25°C”, included on the proposed labeling.

1 STABILITY SUMMARY AND CONCLUSION

1.1 Studies Conducted

A study is being conducted to obtain long-term stability data for s47 s47 on batches manufactured at s47 , s47 to support its registration as a manufacturing site for lisdexamfetamine dimesylate capsules.

s47

Stability testing of batches from commercial scale process performance qualification (PPQ) at s47 follow the stability protocol as described in Table 1. An overview on batches being studied is provided in Table 2.

s47

Table 1 Stability Studies on PPQ Batches

Interval (Months)	Test Condition
	s47
Initial	X, M

s47

Table 2 Batch Overview

Capsule Strength	Bulk Batch No.	Packed Batch No.	Batch Size Capsules (Blend Size)	Date of Manufacture	Drug Substance Supplier (TOB Batch No.)	Stability Start Date	Time Points Tested (Months)
20 mg	12182353	12239564	s47	January 2022	s47 (12033263)	18 Aug 2022	s47
	12185503	12239566		January 2022	s47 (12041144)		
30 mg	12191487	12266658		January 2022	s47 (12151666)		
40 mg	12191581	12262019		January 2022	s47 (12151666)		
50 mg	12242494	12269369		April 2022	s47 (12234752, 12151666)		
	12248408	12269371		April 2022	s47 (12234752)		
70 mg	12190256	12263855		January 2022	s47 (12041144)		
	12191587	12263856		February 2022	s47 (12151666)		

1.2 Study Methodology and Specification

Stability batches are tested for s47 s47 Analytical procedures are provided in Section 3.2.P.5.2 and specifications are provided in Section 3.2.P.5.1.

1.3 Packaging

The product may be packed as a s47 fill or s47 fill in s47 HDPE bottles. The stability data collected and provided for the capsules as s47 fill in s47 HDPE bottles s47 s47 HDPE bottles, as the s47 s47 Details related to the container closure system are provided in Section 3.2.P.7.

1.4 Discussion of Results

1.4.1 s47 and Accelerated Stability Studies

The data available to date is provided in Section 3.2.P.8.3 Stability Data and individual parameters discussed below.

1.4.1.1 s47

All lisdexamfetamine dimesylate stability batches conformed to the specification for s47 for all time points at all storage conditions tested.

1.4.1.2 s47

The s47 for all batches available to date at the s47 storage conditions are within the specification limits. s47 s47 s47 . All results were still within specification.

The stability trend for s47 for batches manufactured at s47 is similar to product manufactured at the approved manufacturing site at s47 and is representative of historical product quality.

The quality of the product is ensured, through monitoring of the assay against the approved specification.

1.4.1.3 s47

There are no trends observed s47 s47 found in any of the stability samples based on long-term data available to date. Further, there are no significant changes in the s47

All results for s47 obtained for batches stored at the s47 s47 are within specification s47

s47 All results were within specification. There is similar behaviour of batches produced at the approved manufacturing site at s47

At the s47
s47
s47 with similar behaviour of batches produced at the approved manufacturing site at s47

The trend for the batches manufactured at s47 is representative of the historical product quality.

1.4.1.4 s47

All s47 results for lisdexamfetamine dimesylate batches available to date conformed to specifications at all storage conditions tested.

1.4.1.5 s47

All s47 results for lisdexamfetamine dimesylate batches available to date conformed to specifications at all storage conditions tested.

1.4.1.6 s47

All batches conformed to the specifications for s47 .

1.5 Overall Conclusion

Long-term s47 stability data has been generated for lisdexamfetamine dimesylate capsules s47 . The data and trends are in alignment with historical results and therefore, supports the proposed s47
s47

1.6 Proposed Storage Conditions and Shelf-Life

The proposed shelf-life is s47 when stored in the approved packaging configuration as per Section 3.2.P.7. The recommended storage is "Do not store above 25°C.

Takeda Risk Assessment (Version 6)
Supply of Products to Australia and s47 Market

BACKGROUND

The Wasdell site in Dundalk, Ireland, is a primary and secondary packaging site of oral solid dosage forms and has been operational since July 2019.

A for-cause GMP and Controlled Drugs inspection of Wasdell was conducted by the Irish HPRA from s47 to s47 The objective was a general GMP-GDP inspection and to review the implementation of CAPAs of previous HPRA inspections.

The most recent HPRA inspection cited a critical GMP observation for the deficiencies related to the pharmaceutical quality system.

PRODUCTS IN SCOPE

Australia and s47

Product Name	Product Strength	ARTG No.	s47
s22			
Vyvanse lisdexamfetamine dimesilate	50 mg capsules bottle 50 mg capsules bottle 60 mg capsules bottle 70 mg capsules bottle 70 mg capsules bottle	199226 N/A 284021 199228 N/A	s47
s22			

PURPOSE

The purpose of this risk assessment is to review how the risks associated with the critical and the other inspection findings have been, or will be, either avoided or mitigated for Takeda products packaged prior to and after the last HPRA inspection of Wasdell. It also provides a medical risk assessment for impact to patient if product is not available.

MEDICAL RISK ASSESSMENT

Takeda considers the below products packed by Wasdell as medically critical for the following reasons:

s22 [redacted]

- Elvanse/Vyvanse is indicated as part of a comprehensive treatment program for attention deficit/hyperactivity disorder (ADHD) in Adults, and for the treatment of children and adolescents with ADHD whose response to previous methylphenidate treatment was considered clinically inadequate. Multiple other trade names are available for methylphenidate (in the EU).

s22 [redacted]

RISK ASSESSMENT / MITIGATION

Seven major classes of deficiencies have led to one critical HPRA observation summarized as Senior Wasdell management have not ensured that an effective pharmaceutical quality system was in place.

Takeda wants to emphasize that:

- Wasdell do not manufacture exclusively for Takeda.
- HPRA have not suspended Wasdell's license. HPRA observations apply to Wasdell as a site, without taking into account the mitigating actions Takeda have taken to date.

The risk of all HPRA observations have been assessed as per ICH Q9 (see attachment 1 - Takeda risk assessment, taking Takeda mitigation into account). Attachment 1 lists all observations, Wasdell's assessment and Takeda's assessment. Whereas the HPRA observations and Wasdell's input applies to all Wasdell products, Takeda's assessment only applies to the Takeda products, which clarifies the difference in risk level between the HPRA, Wasdell and Takeda.

For quick reference, the seven classes of deficiencies leading to the critical observation and Takeda's mitigating actions are described below:

1. **Absence of evidence that Wasdell had implemented their remediation programme strategy.**

   Takeda Mitigation:

   Takeda employs on-site senior consultants to support the implementation of Wasdell's CAPAs. Previous critical HPRA observations included Controlled Drugs (CD) observations. In alignment with the HPRA Takeda focused this resource on CD observations. Related CD CAPA actions have been satisfactorily closed. After the inspection the HPRA granted a 6 month extension of the CD license instead of the previous monthly extension. Takeda's consultant resource will now focus on implementing the GMP related CAPAs.

   Takeda always has a Person in Plant (PiP) (see also section on Quality Oversight Model) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP.

2. **The informed Interim Head of Quality had not undertaken action for omitted QC checks.**
3. **Deficient QC arrangements with risk of approval of wrong bulk for production.**
4. **Deficient Materials management, goods' receipt and supplier management activities.**

   Takeda Mitigation:

   The QC check performed at Wasdell are not analytical testing, but visual checks performed on incoming materials. Full release testing is performed before the bulk is shipped to Wasdell. Takeda QP's certify the imported bulk before packaging at Wasdell begins. Takeda has oversight and responsibility of all suppliers providing capsules and tablets to Wasdell. Takeda has confidence in the incoming materials being provided to Wasdell through its supplier quality management process including auditing.

5. **Deficient personnel and organizational arrangements.**

   Takeda Mitigation:

   In agreement with the HPPA Wasdell are not permitted to run more than four out of the ten packaging lines at any one time.

   Takeda employees (approximately 10 consultants) provide onsite support for Wasdell. Activities supported include deviations, HPRA remediation and batch review. Takeda staff and SMEs are frequently on site to provide support to Wasdell.

   Takeda's PiP oversees the manufacturing of every Takeda batch to provide assurances that Takeda product is manufactured in compliance with GMP.

6. **Deficient line clearance/cleaning process.**

Takeda Mitigation:

All line clearance/cleaning steps are verified by the PiP and provide approval to Wasdell prior to production continuing. If not completed to the satisfaction of the PiP, Wasdell repeat the line clearance/cleaning.

7. **Deficient approach to data integrity (DI).**

Takeda Mitigation:

HPRA observations regarding DI were related to the Warehouse and incoming QC checks. Takeda considers the Production Area higher risk and has deployed PiP's in production. When occasional DI infringements are detected by the PiP, deviations are initiated, and appropriate action is taken by Wasdell including disciplinary action. No fraudulent or malicious intent was perceived in these instances but were rather caused by lack of training and awareness. With the PiP oversight of Takeda batches and the PiP verification of critical activities, the potential risk to the product and patient is reduced.

QUALITY OVERSIGHT MODEL

As a result of a previous critical audit finding in November 2022, Takeda's oversight of Wasdell operations was increased. Since December 2022 Takeda products were manufactured under Takeda's enhanced oversight model including Person-in-Plant (PiP)* to provide assurances that Takeda products are packaged in compliance with GMP without relying exclusively on Wasdell's oversight. As has always been the practice, Takeda continue to approve all deviations prior to disposition. This model includes:

- Increased presence of Takeda personnel on site
- Increased Takeda support for deviations investigations
- Full batch record review
- Implementation of Person in Plant

The PiP's are senior quality external consultants employed by Takeda to oversee manufacture of Takeda's products. They are empowered to stop the packaging line if they identify a risk to the quality of Takeda's product.

Over the period up to May 2023 the PiP oversight had increased to cover approximately 56hours/week and includes oversight of critical activities such as line set up, line clearance and IPCs.

Takeda's enhanced oversight model provided assurance that the products packaged at the site had been produced in compliance with GMP. Such assurance was based on the unannounced, random presence of Takeda personnel or PiP, executing their independent oversight by relying on Takeda's pharmaceutical system.

In the period between May 2023 and Sep 2023 Takeda had further enhanced the model to a full oversight. This further enhancement was done in consultation and agreement with the HPRA and remains in place. The enhancements include:

- Increased PiP oversight to 84hours/week over 7 days
- Introducing stage gates for critical activities where manufacturing cannot progress until these are verified by the PiP (line clearance/cleaning, machine set up and reconciliation).

Any anomaly observed by the PiP are immediately highlighted to senior Wasdell staff, is communicated by email to Takeda, is summarized in a weekly report which is then discussed with Takeda QA and QP.

Takeda remains confident that the full oversight model, designed in consultation with the HPRA, was sufficiently effective for batches made prior to the last HPRA inspection and continues to be so.

*Note: the role of the Takeda PiP referred to in this document is to provide independent supervision of the packaging operations at Wasdell Dundalk and to identify, document and report to Takeda any practices that may impact on Takeda's responsibility for compliance with GMP and controlled drugs legislation. The PiP is empowered to stop packaging operations if they observe unsatisfactory practices, and ensure immediate remedial action is taken. Every batch packed for Takeda has three stage gates which do require an in-depth verification step and approval by the PiP prior to continuation of the batch. Those are after line cleaning, after line set up and loading and after reconciliation. Non-conformances with line cleaning result in re-cleaning. Non-conformances spotted during production may result in actions such as stop the line, segregation of part or the entire batch. (See also attachment - 2 PiP Oversight/Guidelines for Wasdell.)

EXIT STRATEGY (confidential)

The Tech Transfer of Vyvanse was initiated in 2020 and is planned to be completed by end of March 2024. After that date Wasdell will no longer pack Vyvanse.

In 2023 Takeda has identified alternative packaging sites for all remaining Takeda products packaged by Wasdell. The Tech Transfers are on-going. The last Wasdell production runs for Intuniv and Agrilyn are currently planned by end of Jun 2024.

CONCLUSION

Takeda recognizes the criticality of the observations made by the HPRA and continues to partner with the regulator in order to manage and minimize the impact of the situation as it unfolds. In this Risk Assessment the risks/benefits have been carefully considered and effective mitigations have been implemented to enable continued supply of Quality product to the impacted Global markets.

Takeda's enhanced, full oversight model was aligned with the HPRA in 2023. The current enhanced oversight model provides assurance that Takeda products continue to be packaged in compliance with GMP and with appropriately managed risk to product quality and patient safety.

The (confidential) exit strategy, which is being implemented in phases, and which constitutes Takeda's long-term strategy, will eliminate the manufacturing risks associated with Wasdell Dundalk from the estimated date of Q4 2024 onwards.

Takeda remains in constant communication with the HPRA in relation to Wasdell.

ATTACHMENTS

Attachment 1: Takeda risk assessment, taking Takeda mitigation into account
Attachment 2: PiP oversight – Guidelines for Wasdell

SIGNATURES:

Name Title	Signature/Date
Author: s22 s22	DocuSigned by: s22 Signer Name: s22 Signing Reason: I am the author of this document Signing Time: 07-Mar-2024 | 04:54:10 JST 72EE59E308024F2EB1C161FCFB1C88F4
Approver: s22 s22	DocuSigned by: s22 Signer Name: s22 Signing Reason: I approve this document Signing Time: 06-Mar-2024 | 20:13:37 GMT 0F2F743FCEAA4726B22AC77B0BB3763D

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
	Pharmaceutical Quality System		
s47			
		Low	It is acknowledged that for Wasdell in general this observation bears at least a medium risk. For Takeda products however, the risk is assessed as low because Takeda employs on-site senior consultants to support the implementation of Wasdell's CAPAs. Previous critical HPRA observations included Controlled Drugs (CD) observations. In alignment with the HPRA Takeda focused this resource on CD observations. Related CD CAPA actions have been satisfactorily closed. After the inspection the HPRA granted a 6 month extension of the CD license instead of the previous monthly extension. Takeda's consultant resource will now focus on implementing the GMP related CAPAs. Takeda always has a Person in Plant (PiP) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP.
		Low	
		Low	
		Low	
		Low	
		Low	It is acknowledged that for Wasdell in general this observation bears at least a medium risk. For Takeda products however, the risk is assessed as low because The QC check performed at Wasdell are not analytical testing, but visual checks performed on incoming materials. Full release testing is performed before the bulk is shipped to Wasdell. Takeda QP's certify the imported bulk before packaging at Wasdell begins. Takeda has oversight and responsibility of all suppliers providing capsules and tablets to Wasdell. Takeda has confidence in the incoming materials being provided to Wasdell through its supplier quality management process including auditing.
		Low	Takeda considers the Production Area higher risk and has deployed PiP's in production. Any issue observed by the PiP that requires a deviation is immediately escalated by the PiP within Wasdell and communicated to Takeda. Takeda then follows up on the status of the deviation.

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47 [redacted]	[redacted]	Low	For every rejected batch of Takeda product at Wasdell, Takeda raises a CAPA to track destruction of the batch. Prrior to loading the line for packing a Takeda batch, the PiP reviews the starting materials brought in by the warehouse. In addition Full release testing is performed before the bulk is shipped to Wasdell. Takeda QP's certify the imported bulk before packaging at Wasdell begins. Takeda has oversight and responsibility of all suppliers providing capsules and tablets to Wasdell. Takeda has confidence in the incoming materials being provided to Wasdell through its supplier quality management process including auditing.
[redacted]	[redacted]	Low	
[redacted]	[redacted]	Low	
[redacted]	[redacted]	Low	
[redacted]	[redacted]	Low	
[redacted]	[redacted]	Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47 [redacted]	[redacted]	Low	
		Low	Although the complete DP batch number consists of 3 parts (xxxxx-yyyy-zz), the last 2 parts together (-xxxx-zz) uniquely identify the batch, regardless of the strength.
		Low	For Takeda products the risk is assessed as low because The QC checks performed at Wasdell are not analytical testing, but visual checks performed on incoming materials. Full release testing is performed before the bulk is shipped to Wasdell. Takeda QP's certify the imported bulk before packaging at Wasdell begins. Takeda has oversight and responsibility of all suppliers providing capsules and tablets to Wasdell. Takeda has confidence in the incoming materials being provided to Wasdell through its supplier quality management process including auditing. For every rejected batch of Takeda product at Wasdell, Takeda raises a CAPA to track destruction of the batch. Prrior to loading the line for packing a Takeda batch, the PiP reviews the starting materials brought in by the warehouse.
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details** **(applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments** **(applies only to Takeda products)**
Critical			
s47	[redacted]	Low	
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	HPRA Deficiency Details (applies to ALL Wasdell products)	TAKEDA Risk Assessment (applies only to Takeda products)	TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)
Critical			
s47 [redacted]	[redacted]	Low	
		Low	
		Low	For Takeda products the risk is assessed as low because The QC checks performed at Wasdell are not analytical testing, but visual checks performed on incoming materials. Full release testing is performed before the bulk is shipped to Wasdell. Takeda QP's certify the imported bulk before packaging at Wasdell begins. Takeda has oversight and responsibility of all suppliers providing capsules and tablets to Wasdell. Takeda has confidence in the incoming materials being provided to Wasdell through its supplier quality management process including auditing. For every rejected batch of Takeda product at Wasdell, Takeda raises a CAPA to track destruction of the batch. Prrior to loading the line for packing a Takeda batch, the PiP reviews the starting materials brought in by the warehouse.
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	HPRA Deficiency Details (applies to ALL Wasdell products)	TAKEDA Risk Assessment (applies only to Takeda products)	TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)
s47 [redacted]	[redacted]	Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47 [redacted]	[redacted]	Low	
		Low	Although observartions related to QC are assessed as low risk, from a holistic point of view, this observation could occur in production, and hence the Medium risk. As mitigating actions Takeda has a PiP onsite to provide oversight of manufuring of Takeda products. At any given time, s47 [redacted] s47 are allowed to run to limit the impact of resources. If issues are detected, the PiP checks the training status of the concerned employee and has the authority to stop an impacted line and segregate Takeda product. Without PiP on-site, Wasdell is not allowed to progress Takeda product.
		Low	
		Low	
		Low	
		Low	This document will not impact the quality of the products.

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47	[redacted]	Low	This document will not impact the quality of the products.
		Low	All line clearance/cleaning steps are verified by the PiP and provide approval to Wasdell prior to production continuing. If not completed to the satisfaction of the PiP, Wasdell repeat the line clearance/cleaning.
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	HPRA Deficiency Details (applies to ALL Wasdell products)	TAKEDA Risk Assessment (applies only to Takeda products)	TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)
Critical			
s47 [redacted]	[redacted]	Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	HPRA observations s47 were related to the Warehouse and incoming QC checks. Takeda considers the Production Area higher risk and has deployed PiP's in production. When occasional DI infringements are detected by the PiP, deviations are initiated, and appropriate action is taken by Wasdell including disciplinary action. No fraudulent or malicious intent was perceived in these instances but were rather caused by lack of training and awareness. With the PiP oversight of Takeda batches and the PiP verification of critical activities, the potential risk to the product and patient is reduced.
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	HPRA Deficiency Details (applies to ALL Wasdell products)	TAKEDA Risk Assessment (applies only to Takeda products)	TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)
Critical			
s47		Low	
		Low	
		Low	
MAJOR DEFICIENCY			
s47			

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47	[redacted]	Low	Apart from artwork changes, due to packaging operations only, changes with regulatory impact are not expected. Where artowrk requires an update, changes originate at Takeda, and tracked to implementation in Takeda's CC system. In addition Takeda products are QP certified by Takeda after a full batch record review, including a review of the artwork samples from the beginning, middle and end of package a Takeda batch. The Takeda PiP will spot changes and query them.
		Low	Apart from artwork changes, due to packaging operations only, changes with regulatory impact are not expected. Where artowrk requires an update, changes originate at Takeda, and tracked to implementation in Takeda's CC system. In addition Takeda products are QP certified by Takeda after a full batch record review, including a review of the artwork samples from the beginning, middle and end of package a Takeda batch. The Takeda PiP will spot changes and query them.
		Low	Wasdell does not package clinical trial material for Takeda.
		Low	
		Low	
		Low	This observation is for a non-Takeda product. Where artwork requires an update, changes originate at Takeda, and tracked to implementation in Takeda's CC system. In addition Takeda products are QP certified by Takeda after a full batch record review, including a review of the artwork samples from the beginning, middle and end of package a Takeda batch.
		Low	
		Low	
		Low	Takeda is exiting Wasdell, no changes to Takeda artwork will be implemented at Wasdell.
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	Takeda always has a Person in Plant (PiP) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP.
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47	[redacted]	Low	
		Low	Wasdell does not provide batch certification services to Takeda. Takeda does a full batch record review and batch certification of every Takeda batch.
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	Since this major observation was made by the HPRA, Wasdell CAPA actions related to controlled drugs have been closed, a full and satisfactory controlled drug stock take was done and reported to the HPRA. The HPRA has granted a 6 month extension of the CD license instead of the previous monthly extension. The Feb stock verification was intitiated in Feb.
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	This observation was related to a non-Takeda product and is not applicable to Takeda.

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47		Low	Takeda always has a Person in Plant (PiP) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP and such observations are expected to be detected by the PiP.
		Low	Takeda always has a Person in Plant (PiP) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP. Aftersetting up and loading the line Wasdell is required to obtain approval from the PiP to continue packaging of a Takeda batch. As part of the verifications the PiP walks the line with the engineer and controls the machine settings.
		Low	
		Low	
		Low	
		Low	
		Low	
	Production		
s47			
		Low	Takeda always has a Person in Plant (PiP) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP and such observations are expected to be detected by the PiP.
		Low	Takeda always has a Person in Plant (PiP) overseeing manufacturing of every Takeda batch. Although this will not address the HPRA observations without a fully implemented remediation plan, it ensures that Takeda products are manufactured in compliance with GMP and such observations are expected to be detected by the PiP.

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47			
		Low	s47 which had no impact on the executed cleaning validation.
		Low	A formal risk assessment to be performed by Wasdell has been agreed with the HPRA. It is believed by Wasdell that there is currently no impact however the risk assessment will remedy any issue.
		Low	The form on s47 has been reviewed and updated. Currently no impact has been concluded.
		Low	s47 Further assessment is being undertaken by Wasdell to clarify any items highlighted by the HPRA.
		Low	The analytical verification utilised as part of the cleaning validation process is considered sufficient, however, a formal risk assessment on visual inspection will be carried out at Wasdell.
	Quality Control		
s47			
		Low	This observation is not expected to have any quality impact.
		Low	Although the complete DP batch number consists of 3 parts (xxxxx-yyyy-zz), the last 2 parts together (-xxxx-zz) uniquely identify the batch, regardless of the strength.
Medicinal Product Wholesaling Activities			
s47		Low	This observation relates to the s47 Wasdell does not provide s47 servides to Takeda.
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
s47 [redacted]		Low	
		Low	
		Low	
		Low	
		Low	
OTHER DEFICIENCIES			
	PERSONNEL		
s47 [redacted]		Low	Minor observation, no impact to the quality of the Takeda product is expected here, no mitigation implemented by Takeda
	DOCUMENTATION		
s47 [redacted]		Low	Minor observation, no impact to the quality of the Takeda product is expected here, no mitigation implemented by Takeda
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	
		Low	

ATTACHMENT 1 - TAKEDA RISK ASSESSMENT, TAKING TAKEDA MITIGATION INTO ACCOUNT			
HPRA Deficiency Number	**HPRA Deficiency Details (applies to ALL Wasdell products)**	**TAKEDA Risk Assessment (applies only to Takeda products)**	**TAKEDA Controls/Mitigation/Comments (applies only to Takeda products)**
Critical			
	QUALITY CONTROL		
s47			
		Low	This observation relates to the analytical QC testing. Wasdell does not provide analytical QC testing services to Takeda
		Low	This observation relates to the analytical QC testing. Wasdell does not provide analytical QC testing services to Takeda
SELF-INSPECTION			
s47		Low	Minor observation, no impact to the quality of the Takeda product is expected here, no mitigation implemented by Takeda
POINTS FOR CLARIFICATION			
s47		Low	Is related to non-Takeda product, no mitigation required by Takeda.
POINTS TO NOTE			
s47		N/A	N/A

Person in Plant (PIP) Oversight - Guidelines for Wasdell

Person in Plant (PIP) will attend site as per shared calendar unless due to unforeseen circumstances this is not possible.

No primary packaging of Takeda products will take place beyond a Critical Checkpoint unless approval has been given by the PIP. The Critical Checkpoints are:

- Line Cleaning
- Completion of Material Loading & Eng Setup.
- Completion of Reconciliation (after Batch has been completed and line emptied)

If the PIP is not on-site at the scheduled time of arrival as per the communicated schedule, this is considered to be an exceptional occurrence, then Wasdell may commence production activities at the scheduled time (plus grace period of 30 minutes). However, upon arrival the PIP should be made aware of the activities which have occurred since the start time. The PIP will then review all of these activities.

Once on site, it should be the PIP's first priority to attend the production area. Once in production, the PIP's priority will be approving lines that have not already commenced and either in reconciliation, clean down, setup or loading statuses.

Wasdell will provide the PIP with the priority of the lines to be checked as per the production schedule and requirements of Takeda.

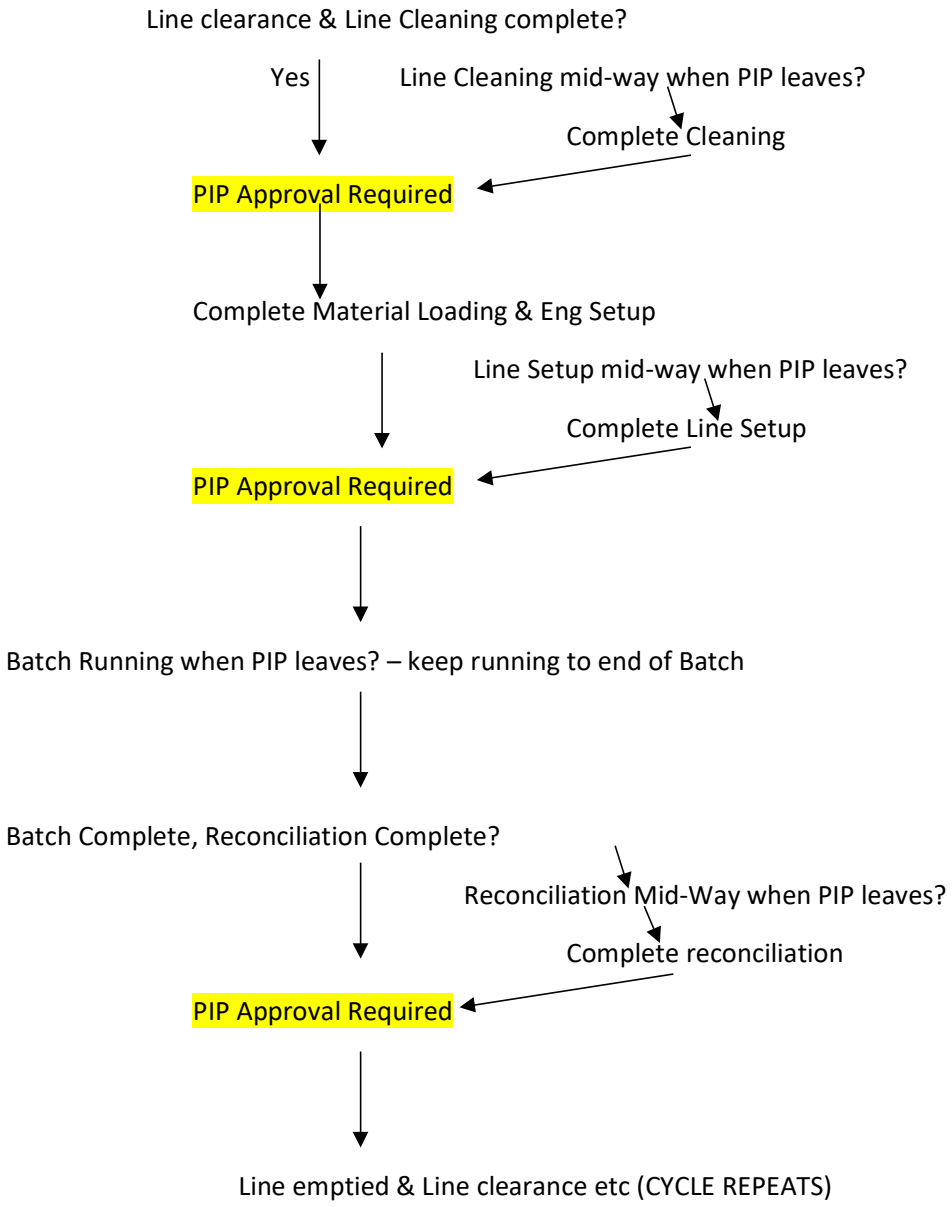
Wasdell brings any deviation, intervention or unexpected issue to the PIP's attention immediately during production. This includes if the PIP is not present on the production line, e.g. if they are on a break. Exceptions to this will be limited to routine engineering interventions such as the changing of consumable packaging material such as label rolls, TE sticker rolls, PVC and foil rolls.

If an unexpected event is not brought to the attention of the PIP at the time of occurrence, then upon the PIP becoming aware of the issue, the PIP may request the line be stopped until they are satisfied that there is no potential compliance or quality issue.

Takeda PIPs have approval to stop production lines without prior Takeda approval and they will provide notification of the stoppage to Takeda.

Takeda Risk Assessment – Attachment 2

PIP Oversight Model



NOTE 1: Wasdell can continue on to end of batch once PIP Leaves if batch already approved to start by PIP.

NOTE 2: Wasdell must wait at the 3 checkpoints highlighted above for PIP approval.

From: s22
To: Medicine Shortages; s22
Subject: RE: VYVANSE medicine shortage meeting minutes of 9-Jan-2024 [SEC=OFFICIAL]
Date: Tuesday, 16 January 2024 2:19:19 PM
Attachments: image001.png
image002.jpg
20240109 Takeda-TGA VYVANSE Shortage Meeting Minutes.pdf
Takeda TGA Meeting Vyvanse Supply_240109 V2.pdf

Thanks s22 just copying in s22 too I think we could probably ask for s22 help updating the web statements in line with publication tomorrow – what do u all think?

From: Medicine Shortages <medicine.shortages@health.gov.au>
Sent: Tuesday, 16 January 2024 2:17 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>
Subject: FW: VYVANSE medicine shortage meeting minutes of 9-Jan-2024 [SEC=OFFICIAL]

Hi team,

I'm just forwarding this to everyone in the minutes, hope this is OK.

Kind regards

s22

From: s22 @takeda.com>
Sent: Tuesday, 16 January 2024 2:13 PM
To: Medicine Shortages <medicine.shortages@health.gov.au>
Cc: s22 @takeda.com>
Subject: VYVANSE medicine shortage meeting minutes of 9-Jan-2024

Dear s22

Thank you so much for the discussion on VYVANSE medicine shortages. Please find attached here meeting minutes and copy of Takeda's presentation.

Further to this, Takeda wish to request your feedback on the following please:

- Given the shortage notification has now been lodged for VYVANSE 40mg, what is the timeframe for TGA to update information regarding this strength on the TGA's VYVANSE medicine shortage website page https://www.tga.gov.au/safety/shortages/information-about-major-medicine-shortages/about-shortages-vyvanse-lisdexamfetamine-dimesilate-capsules
- As proposed in the meeting, Takeda wish to provide updates to TGA's VYVANSE medicine shortage website page to help maintain latest information. Could you please let me know what the process is to meet this end.

I will be grateful if you could provide your feedback as soon as possible.

Thank you again.

Kind regards
s22 [redacted]

s22 [redacted]
s22 [redacted] – Oceania Cluster
Takeda Pharmaceuticals Australia Pty Ltd
Grosvenor Place, Level 39
225 George Street
Sydney NSW 2000 Australia
Mobile: s22 [redacted]
s22 [redacted]@takeda.com

TGA meeting with Takeda Pharmaceuticals re: Vyvanse Medicine Shortages
Date: 09-Jan-2024
Time: 2.00-3.00pm

Attendees:
TGA – Medicine Shortages Section: s22 [redacted]

Takeda: s22 [redacted]

Meeting started at 2.02pm with the introduction of both teams.

s22 started by giving the TGA an introduction setting the scene to how shortages started and developed leading up to the current situation. Vyvanse 30mg shortage started in August-2023 at which time it was anticipated to last to end December 2023. Takeda had a meeting with the TGA in Aug-2023 and following that, communication letters were dispatched to all stakeholders.

s22 presented the Vyvanse 40mg stock situation and the anticipated shortage. The reason for the 40mg shortage is due to the significant increase in demand following the current shortages in the 20mg, 30mg, and 50mg presentations. As with any medicine shortage, demand increases for the available presentations because i) buy-up situations vs. standard demand, and ii) patients' redistribution across remaining presentations.

s22 then presented an overview of stock levels (all presentations) at Takeda and wholesalers levels, and the expected shipments from Ireland and Germany until Jun-2024. s22 also presented the following points:

- An initial 10,000 units from every impacted SKU are preserved as 'emergency supply' from the time of confirmed shortage
- There have been no changes to the supply plan for 40mg
- From Apr to Jun 2024 there will be dual supply from both Ireland and Germany
- Jul-2024 onwards, supply from Germany only
- The 40mg stock is expected to exhaust in Jan 2024
- To mitigate delays in receipt of S8 documentation, Takeda is providing an Express Pre-Paid envelope with every order for return of those documents. Takeda also explored whether emailed and/or scanned copies of receipts would be acceptable as an interim measure, but that was not accepted
- All wholesalers currently have stock of Vyvanse 20mg

s22 discussed the communication plan noting that the standard (conventional) one is becoming less efficient with each shortage notification as it's heavily impacted by the accuracy of the email and mailing lists, notifications might not be received or opened on time, etc. Therefore, there is a need to communicate in a more timely manner and to ensure consistency with the content of TGA

communications. Takeda proposed to partner with the TGA to use the Medicines Shortage page (Vyvanse-specific) on the TGA website as a single source of information and to direct stakeholders here for the most up-to-date information; for that purpose, Takeda's subsequent communication letters will include direction to the TGA website. Takeda will also provide a list of FAQs (including responses) for TGA to review before aligning on agreed content to reflect on the TGA page.

s22 then talked about the DEA quota explaining that the DEA have confirmed that the 2024 quota remain flat to 2023 despite more than 4500 submissions supporting an appropriate increase.

TGA Questions

- s22 Shortage reason - concerns that we didn't forecast/model for the increased demand in the available strengths. What is the current reason for the shortage (previously the cause of the shortage was GMP issues at Ireland site; have those been resolved?)
  Response: GMP situation at Wasdell site has improved but it is not the cause for the 40mg shortage as we are experiencing more than anticipated increase in demand for the 40mg strength. Takeda has been expecting redistribution to 40mg given current shortages for 30mg, 50mg and 60 mg strengths (due to manufacturing delays), and proactively communicated with KOLs to see how patients can be managed, and then used this information to model demand forecast. However, the shortages of the strengths complicated the situation and demand outstripped modelling.

- s22 Surge in uptake of 20mg strength will now be expected after Takeda notifies 40mg shortage.
  Response: Yes, that possibility is anticipated. With the current level of supplies coming through and modelling, Takeda does not anticipate shortage situation for 20mg and 70mg however we will continue to monitor this.

- s22 Has Takeda considered supply under S19A.
  Response: Yes, we have considered it but, unfortunately, we have no global surplus stock for Vyvanse. Takeda was also not successful in obtaining US-labeled stock.

- s22 is Takeda aware of any signs of stockpiling at pharmacies?
  Response: Takeda has no visibility at that level, only at wholesalers, but is currently exploring ways to see if this data can be obtained noting that DoH can assist with constraining wholesalers.

- s22 Does Takeda consider that we will be resolving the supply issues in March/April 2024?
  Response: yes, but also noted that returning patients to their original prescriptions could take a few weeks/months, which could elongate the shortages.

- s22 S8 Receipt Documentation - Did this just start? Is it related to a single order?
  Response: this is ongoing, and we'll continue to provide pre-paid (express post) envelopes with each order.

- s22 when does Takeda Australia patent for Vyvanse expire?
  Response: this information is commercial in confidence however not for several years.

Takeda Questions

- s22 Takeda proposes partnering with TGA for updating TGA's Vyvanse shortage page, for e.g. Takeda would like to share commonly asked questions and responses which could be helpful to HCPs. The aim is to have aligned messaging.

Response: TGA sees the value of this proposal and it supports and welcomes the partnership with Takeda to keep the Vyvanse shortage page, including FAQs, up-to-date. There are restrictions by TGA regarding wording of responses to FAQs so will need to collaborate with Takeda before uploading.

- s22 raised obstacles and challenges that have been shared with Takeda through our Medical Information team to date throughout the shortage, including: complexity of S8 prescription requirements, substitution of alternative strengths of Vyvanse at pharmacies, prescription hard copies being held at individual pharmacies.

Next Steps:

- Submit 40mg Notification and provide communication letters once available.
- Submit all information and FAQs to the Medicines Shortage Inbox for TGA review and upload.
- Continue to update modelling for 20mg and 70mg to anticipate impact of demand increase vs supply

Meeting ended at 3.10pm.

Takeda & TGA Meeting

VYVANSE (lisdexamphetamine) supply

9th January 2024

Better Health, Brighter Future

Vyvanse Supply - Agenda

#	Title	Lead
1	Welcome and introduction	s22 [redacted] Medicine Shortages Section, TGA s22 [redacted] Regulatory Affairs, Takeda Pharmaceuticals
2	VYVANSE Supply & Demand overview	s22 [redacted] Takeda Pharmaceuticals s22 [redacted] Takeda Pharmaceuticals
3	Communication plan	s22 [redacted] Takeda Pharmaceuticals
4	Customer Feedback, Challenges and Bottlenecks	s22 [redacted] Takeda Pharmaceuticals
5	DEA Aggregate Production Quota 2024	s22 [redacted] Takeda Pharmaceuticals
6	Q & A & Next Steps	All participants

s47

Document 9

s47

Document 9

VYVANSE Stock Levels

Document 9

Stock on Hand at Takeda @ 8th January

	Takeda	Emergency stock to be held at all times	Takeda / TGA notifications
Vyvanse 20mg	53,235	10,000	
Vyvanse 30mg	9,129	10,000	TGA notification Aug-23 (Disruption from Aug-23 - Dec-23) Extension to notification from Dec-23 - Apr-24
Vyvanse 40mg	29,942	10,000	Discussion on potential supply disruption
Vyvanse 50mg	24,863	10,000	TGA notification Oct-23 (Disruption from Nov-23 - Dec-23) Extension to notification from Dec-23 - Apr-24
Vyvanse 60mg	19,911	10,000	TGA notification Nov-23 (Disruption from Dec-23 - Apr-24)
Vyvanse 70mg	45,695	10,000	

Stock on Hand at Wholesalers @ 8th January

WHOLESALERS	SYMBION				API				SIGMA			
	SOH (08.12)	Ave Weekly Normal Demand	Ave Week Cover based on Normal Demand	Pending Dispatch from Takeda (S8 document pending)	SOH (08.12)	Ave Weekly Normal Demand	Ave Week Cover based on Normal Demand	Pending Dispatch from Takeda (S8 document pending)	SOH (08.12)	Ave Weekly Normal Demand	Ave Week Cover based on Normal Demand	Pending Dispatch from Takeda (S8 document pending)
Vyvanse 20mg	s47											
Vyvanse 30mg												
Vyvanse 40mg												
Vyvanse 50mg												
Vyvanse 60mg												
Vyvanse 70mg												

Replenishment from Ireland

* ADDITIONAL SUPPLY FROM GERMANY TO BE ADDED*

Source : Wasdell	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24
Vyvanse 20mg	24,567	25,330		50,000			
Vyvanse 30mg		46,824		40,000	67,500	135,000	
Vyvanse 40mg	75,531			52,115	50,000	35,000	14,000
Vyvanse 50mg	36,874			85,000	151,000		55,000
Vyvanse 60mg	13,713	14,904			82,200		
Vyvanse 70mg	46,727			95,000	25,000		

Summary of Supply Update

Likelihood of Shortage Impact extending to other strengths

- **Addition of 40mg to shortage notification**
  - **Stock exhausted worst case January, potentially February**
- **Anticipated redistribution to remaining strengths 20mg and 70mg - shortage impact considered low risk but is difficult to predict**
- **On schedule to provide continuity of supply for 30mg, 50mg and 60mg as planned in March / April 2024**

S8 Receipt Documentation Issue

- Based on the wholesalers SOH report (8/01/24), wholesalers now have stock of Vyvanse 20mg in their DC.
- There are still stock pending dispatch due to S8 documents not yet received by DHL

Wholesalers	Wholesalers SOH (units)	Pending Dispatch at Takeda due to S8 document
Symbion	s47	
Sigma		
API		

- Express pre-paid envelopes are sent with every order for prompt document return
- DHL are emailing and calling wholesalers & pharmacies to chase for pending documentation
- Explored the opportunity to accept emailed versions of these S8 documents as an interim measure

Communication Plan

Key Principles

- Alignment and speed
- Most up to date information as quickly as possible
- One single source of truth
    - Propose TGA Medicines Shortage Vyvanse page
- Letter of notification of 40mg shortage and providing direction for future comms

Customer Feedback, Challenges and Bottlenecks

Takeda Improvement Focus

- More efficient communication method
- More efficient and sustainable approach to emergency supply management
- S8 paperwork – following up, EXPRESS paid envelopes
- Future impact modelling; prescriber and patient dynamics during and post supply impacts

Key Areas outside of Takeda Control for consideration

- MoH requirements for receipt of S8 docs
- Section 19A
- Pharmacy substitution for alternative strengths
- Hard copy script limitations

US FDA/DEA Aggregate Production Quota for Vyvanse active pharmaceutical ingredient (API)

- The current interruption to supply is NOT related to any DEA production quotas or restrictions on API.

- The DEA indicated in November 2023 that the 2024 Aggregate Production Quota for lisdexamfetamine base API would be held flat to 2023.
- In December, Takeda made a submission to the FDA/DEA on behalf of all Takeda marketing companies affected.
- Submissions were also made by certain Australian professional and patient ADHD interest groups.
- Despite more than 4,500 submissions being received, the DEA have not changed their position regarding the 2024 production quota.

From: s22
To: Medicine Issues
Cc: s22
Subject: RE: Vyvanse (lisdexamfetamine dimesilate) 20mg capsule - AUST R 284019 - Issue 819062 [SEC=OFFICIAL]
Date: Friday, 18 October 2024 10:18:30 AM
Attachments: image003.png
Vyvanse (lisdexamfetamine dimesilate) 20mg capsule - AUST R 284019 - Issue 819062_18 Oct 2024 Final for Submission.pdf

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Dear s22

Please find enclosed Takeda's response to your request for information dated 23 Sep 2024, advising Takeda of a potential quality problem relating to Vyvanse (lisdexamfetamine dimesilate) 20mg capsule.

As concluded in the response, after thorough investigation of the complaints reported, evaluation of relevant manufacturing records for the Vyvanse 20mg, batch 12677000 Exp. Oct 2026 and Vyvanse 20mg, batch 12782459 Exp. Sep 2026, Takeda has found no quality issue with the afore-mentioned Vyvanse products.

Should you require further information, please do not hesitate to contact us again.

Kind regards
s22

s22
Takeda Pharmaceuticals Australia Pty Ltd
Level 39, 255 George Street
Sydney, NSW 2000 Australia
Mobile +s22
s22 @takeda.com
www.takeda.com/en-au

From: s22 @health.gov.au>
Sent: Monday, September 23, 2024 3:58 PM
To: s22 @takeda.com>; s22 @takeda.com>; s22 @takeda.com>
Subject: Vyvanse (lisdexamfetamine dimesilate) 20mg capsule - AUST R 284019 - Issue 819062 [SEC=OFFICIAL]

Dear Sir/Madam

The TGA has received a report from a consumer regarding a potential quality problem involving Vyvanse (lisdexamfetamine dimesilate) 20mg capsule. The product batch details are B: 12677000 (Exp. 10/26) and B:12782459 (Exp. 09/26)

Issue

The report described that there has been some inconsistency in the amount of medication inside each capsule. They also had noticed a decrease in effect.

Information required

To determine the cause and extent of the reported quality problem, please investigate and provide the following:

1. The number of reports and/or complaints of the similar problem for this product in the last 12 months reported directly to your company.
2. The quantity of the product supplied for the same period.
3. Your assessment if this quality problem is widespread within this product range.
4. The details of the investigation undertaken by your company to date in relation to this matter.
5. The details of the investigation undertaken to identify the root cause of the quality problem and any corrective and preventative action proposed to prevent reoccurrence of this problem.
6. Confirm if there have been any recent variations in manufacturing the 20mg strength capsules
7. Confirmation of capsule weigh checks and processes (including for these batches).

Response due date

Please provide your response on or by COB 18 October 2024. Thank you for your attention to this matter.

If you have any questions in relation to this matter, please do not hesitate to contact me.

Regards,

Dr s22 *[Her/She]*
Medical Officer – Medicines Surveillance and Signal Investigation
Pharmacovigilance Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
Location: Level 12, 130 George St. Parramatta NSW 2150

The Department of Health and Aged Care ak owledges First Nations peoples as the Traditional Owners of Country throughout Aus ralia, and their o ntinuing o nnec ion to land, s a and o mmunity We pay our respec s to them and their cultures and to all Elders both pas and pres nt.

Vyvanse (lisdexamfetamine dimesilate) 20mg capsule - AUST R 284019 - Issue 819062

Potential quality problem with VYVANSE 20 mg, Batch 12677000 Exp. Oct 2026 and VYVANSE 20 mg, Batch 12782459 Exp Sep 2026.

Responses to TGA Request for Information dated 23 Sep 2024

Date of Response: 18 Oct 2024

Issues 819062- Responses to TGA Request for Information dated 23 Sep 2024

1.0 TGA'S LIST OF QUESTIONS AND COMPANY'S RESPONSE

Further to your email dated 23 Sep 2024 advising Takeda of potential quality problem relating to the afore-mentioned products and requesting company to provide further information.

Below please find company's response to the requests for information.

As concluded in the response, after thorough investigation of the complaints reported, evaluation of relevant manufacturing records for the Vyvanse 20mg, batch 12677000 Exp. Oct 2026 and Vyvanse 20mg, batch 12782459 Exp. Sep 2026, Takeda has found no quality issue with the afore-mentioned Vyvanse products.

1. ***The number of reports and/or complaints of the similar problem for this product in the last 12 months reported directly to your company.***

Company response:

Takeda currently distributes six (6) different product strengths of Vyvanse across the Australian market.

- **AUST R 199227** Vyvanse 30mg x 30 Caps AUS
- **AUST R 199226** Vyvanse 50mg x 30 Caps AUS
- **AUST R 284019** Vyvanse 20mg x 30 Caps AUS
- **AUST R 284020** Vyvanse 40mg x 30 Caps AUS
- **AUST R 284021** Vyvanse 60mg x 30 Caps AUS
- **AUST R 199228** Vyvanse 70mg x 30 Caps AUS

A review of similar complaints to those reported to the TGA for the Vyvanse product range, received from the Australian market was completed for the period 01 Sep 2023 to 23 Sep 2024.

A total of sixty-five (65) similar complaints have been received (excludes complaints raised for the current TGA query).

Complaint Subcategory	Total
Lack of Effect	44
Volume – Varied	10
Volume – Empty	5
Volume – Underfilled	6
Volume – Overfilled	0

Issues 819062- Responses to TGA Request for Information dated 23 Sep 2024

2. The quantity of the product supplied for the same period.

Company response:

As requested the distribution data for the Vyvanse Products for the time frame 01 Sep 2023 – 23 Sep 2024 is recorded below.

In total s47 [redacted] units of Vyvanse product across all strengths have been distributed within the Australian market.

AUST R 199227 Vyvanse 30mg x 30 Caps AUS	s47 [redacted]	units*
AUST R 199226 Vyvanse 50mg x 30 Caps AUS		units*
AUST R 284019 Vyvanse 20mg x 30 Caps AUS		units*
AUST R 284020 Vyvanse 40mg x 30 Caps AUS		units*
AUST R 284021 Vyvanse 60mg x 30 Caps AUS		units*
AUST R 199228 Vyvanse 70mg x 30 Caps AUS		units*

**One unit is described as a single bottle of 30 capsules*

A breakdown of the batch numbers distributed in Australia for the specific strengths mentioned in the complaints received, and quantities for each batch distributed over the time frame is included in the table below:-

Finished Goods Batch Number	Bulk Batch Number/ Manufacturer	Vyvanse 20mg x 30 Caps AUS Units* Distributed			
		Batch Release for Distribution Date	First Distribution Date	Last Distribution Date	Total Qty Distributed
12372559/ 3210232D	3210232 (s47 [redacted])	05-Jun-23	07-Aug-23	28-Sep-23	s47 [redacted]
12450216/ 3211056B	3211056 (s47 [redacted])	26-Jun-23	02-Sep-23	28-Sep-23	
12486112/ 3211056D	3211056 (s47 [redacted])	01-Sep-23	21-Sep-23	17-Nov-23	
12434504/ 3211053A	3211053 (s47 [redacted])	24-Jul-23	17-Nov-23	19-Dec-23	
12558466/ 3215417A	3215417 (s47 [redacted])	16-Oct-23	19-Dec-23	19-Feb-24	
12665453/ 3216204C	3216204 (s47 [redacted])	02-Jan-24	18-Feb-24	15-Mar-24	
12670846/ 3216204A	3216204 (s47 [redacted])	04-Mar-24	10-Mar-24	29-Apr-24	
12677000	12649784 (s47 [redacted])	10-Apr-24	16-Apr-24	20-Jun-24	
12686724	12649785 (s47 [redacted])	10-Apr-24	18-Jun-24	13-Aug-24	
12782459	3223310 (s47 [redacted])	09-Aug-24	13-Aug-24	23-Sep-24	

Issues 819062- Responses to TGA Request for Information dated 23 Sep 2024

3. ***Your assessment if this quality problem is widespread within this product range.***

Company response:

From the Vyvanse distribution data provided from 01 Sep 2023 – 23 Sep 2024 (ref. company response 2), a total of s47 units have been distributed within the Australian market. A total of sixty-five (65) complaints similar to the defects reported to TGA have been initiated within this same period. This is equivalent to a complaint rate of s47 **%** for this 12 month period. The reported complaints are split across the different strengths of Vyvanse and are not specific for one product strength. Investigations have been performed as appropriate for these complaints.

None of the complaints received in this period for Lack of Effect or Capsule Volume - Over/Under/Varied/Empty have been confirmed. A review of the analytical testing is performed within the investigations and there were no atypical results for ID, Assay, Content Uniformity or Dissolution testing.

- Capsule fill weight is monitored throughout the process and all capsules are 100% weight checked to remove any outside of the specified weight range.
- Stability history and the on-going stability programme continues to support the product on the market to shelf life.

Takeda considers this complaint rate of s47 % to be low. No quality problems with the Vyvanse product have been identified therefore, Takeda do not consider a widespread problem within the product range.

4. ***The details of the investigation undertaken by your company to date in relation to this matter.***

Company response

Assessment of the complaint types are provided as follows:

- Lack of Effect (LoE) reports are classified as Adverse Events and are communicated to Pharmacovigilance (PhV) within Takeda. PhV have primary responsibility for all medical related complaints.
- A Product Quality Complaint (PQC) is raised by Market Surveillance and a link is created between the PQC and PhV systems by means of an ARGUS reference. This allows for reconciliation between the two departments.

If a safety signal is detected via the PhV system, Market Surveillance are notified, and an investigation performed as per Takeda procedures. To date, no LoE signals have been received from PhV for lack of effect for this product.

Investigations performed in relation to the manufacturing, testing and trending of the batches has found no evidence of a quality issue or atypical process behaviour that would lead to lack of effect

complaint cases. Stability history and the on-going stability programme continues to support the product on the market to shelf life. The stability program has not identified any atypical results for ID, Assay (s47 %) or Dissolution. No deviations have been initiated on the release trends for these attributes. Vyvanse 40mg batch 3207029C was distributed to the Australian market in 2022. This bulk batch was placed on the stability programme in 2022 and has met all requirements of stability testing to date.

This is the second report of LoE received for batch 12782459 and also for batch 12677000.

A review of the complaints received from the Australian market for the last 12 months was performed. A total of 44 other LoE complaints were received. None of these LoE complaints were confirmed to be caused by product quality issues.

s47 s47 ; capsule fill weight is monitored throughout the process and all capsules are 100% weight checked to remove any outside of the specified weight range. s47 s47 . This is due to the different blend formulation requirements of each strength.

s47 s47 s47 However, patients may have the perception that the capsule is under or variably filled since their assessment is most likely made by what they see in the volume of the capsule that is filled, rather than the net weight of what is filled into each capsule.

This is the second report of "Volume Varied" for batch 12782459 and the first report of "Volume Varied" for batch 12677000.

Based on this evaluation of the reported defects, Takeda is satisfied that no quality problem with Vyvanse product has been identified.

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5. ***The details of the investigation undertaken to identify the root cause of the quality problem and any corrective and preventative action proposed to prevent reoccurrence of this problem.***

Company response:

In response to the report from TGA, four complaints were initiated within Takeda's complaints handling system Trackwise:

Complaint number	Reported defect	Finished Goods Batch number	Bulk Batch	Bulk manufacturer	API batch number	API Manufacturer
PR 4595119	Volume Varied	12677000	12649784	s47 [redacted]	R0103346	s47 [redacted]
PR 4595131	Lack of Effect	12677000	12649784		R0103346	
PR 4595124	Volume Varied	12782459	3223310		0000145093	
PR 4595139	Lack of Effect	12782459	3223310		0000145093	

An investigation into the manufacturing of bulk batch 3223310 (20mg) was performed by the manufacturing CMO s47 [redacted]. This bulk batch was manufactured on 17 Oct 2023.

s47 [redacted] Capsules that do not meet the specified range are rejected at the checkweigher. The weight of s47 [redacted] is checked at defined intervals throughout encapsulation. Target = s47 [redacted] Specification limit range is s47 [redacted] All weight checks passed and were within the alert limits.

After the encapsulation process, the capsules are processed through the check weigher where 100% of capsules go through for weight check. Capsules that do not meet the specified weight range are rejected at the check weigher. The mean value recorded for bulk batch 3223310 was s47 [redacted] mg (includes capsule shell tare weight s47 [redacted]).

Additionally, a visual "slug" appearance evaluation is performed at defined intervals. The target value of this evaluation is a s47 [redacted] which is s47 [redacted] All slug evaluations were assigned a ranking of s47 [redacted] which is the target.

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The batch yield was within the required range. All in-process controls were within the required specifications.

An investigation into the manufacturing of bulk batch 12649784 (20mg) was performed by the s47 manufacturing site in s47. This bulk batch was manufactured on 13 Nov 2023.

Vyvanse 20mg is a s47 in a capsule. s47 is performed during encapsulation s47. After encapsulation, each individually filled capsule is weighed. The target weight for a 20mg Vyvanse capsule is s47 s47. Any filled capsules weighing less than s47 or more than s47 would have been rejected by the system.

No deviations were reported during the manufacturing process. All in-process controls were within the required specifications.

This is the second report of "Volume Varied" for batch 12782459 and the first report of "Volume Varied" for batch 12677000.

A summary of the analytical results for bulk batch 3223310 and bulk batch 12649784 are as follows:

Analytical Test	Specification	Results bulk batch 3223310	Results bulk batch 12649784
ID	s47	Positive	Positive
Description	#3 ivory opaque body/ivory opaque cap (hard) gelatin capsule containing white to light tan powder. Capsule is axially printed 'S489 20mg' in black ink (orientation of the capsule during printing is random.)	Conforms	Complies
Assay	s47		
Uniformity of Dosage Units s47 s47	s47	Conforms s47	Complies s47

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s47	s47	Conforms s47	Complies s47
Water (s47)	s47		

All analytical results were within the required specifications for release. Batch 3223310 was released by Quality Assurance on 11 Dec 2023. Batch 12649784 was released by Quality on 10 Jan 2024. The Vyvanse 20mg finished goods batches were released for supply against the Australian Marketing Authorisation by the Takeda Authorised Person / Qualified Person on 10 Jan 2024 (Batch 12677000) and 03 Jul 2024 (Batch 12782459).

No quality issue related to capsule filling and weighing has been identified during this investigation therefore, no CAPAs have been identified.

All 20mg Vyvanse batches released for the Australian market are manufactured and tested in accordance with cGMPs. Analytical testing is confirmed to meet required release specifications before release by Quality Assurance. The stability history and the on-going stability program continues to support the safety and efficacy of the Vyvanse product on the market to shelf life.

No root cause for lack of effect was identified.

6. Confirm if there have been any recent variations in manufacturing the 20mg strength capsules

Company response:

In the last 5 years the only change related to the manufacturers of API, DP and FDP has been the addition of s47 as a new site for DP/ FDP manufacture (TGA approval date 07 Sep 2022).

7. Confirmation of capsule weigh checks and processes (including for these batches).

Company response:

s47 bulk batch 3223310

Individual net fill weight checks were performed on s47 at start-up and periodic time points during the encapsulation process prior to check weighing.

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The weight of s47 is checked at batch startup and at every s47. The target weight for the ten capsules is s47. The alert limit range is s47 The specification limit range is s47

After encapsulation, the capsules are processed through the check weigher. A 100% weight check is performed for every capsule. Capsules that do not meet the specified weight range are rejected at the check weigher.

Mean Value: s47 empty capsule shell tare weight).

Reject limits: Any capsules weighing less than s47 or more than s47 would have been rejected

All weight checks passed and were within the required ranges.

s47 bulk batch 12649784

At the capsule filling station, every capsule is opened using partial vacuum, filled, and closed again. Filling of the capsules s47. Every individual capsule is check weighed after encapsulation. Underfilled or empty capsules will automatically be rejected.

The target weight for a Vyvanse 20mg capsule (empty capsule + product fill) = s47

Any capsules weighing less than s47 or more than s47 would have been rejected.

Response prepared on behalf of Takeda Pharmaceuticals Australia Pty Ltd by:

Market Surveillance Team
s47