



Medicines & Healthcare products Regulatory Agency

Pharmacovigilance Office Based Risk Assessment (OBRA) Form

Section 1: OBRA plan (completed before OBRA is conducted)	
MHRA Inspection Number:	Insp GPvP 14/18891608-0002
Company/MAH name	The Boots Company
Parent inspection number and dates	Insp GPvP 14/18891608-0001, 21, 23 – 24 February 2022
OBRA team	██████████ (Lead), ██████████
Objective of OBRA	To determine whether actions taken to address and prevent the critical deficiency CR.1 a) (identified at Insp GPvP 14/18891608-0001), where updated patient information leaflets (PILs) had not been implemented into product packaging for two products, have been effectively implemented and are robust.
Estimated number of OBRA days required	3
Suggested dates for OBRA	11 – 15 December 2023
MS Team for OBRA	New MS Teams site created
Scope of OBRA	<p>Corrective actions within the inspection report <i>Insp GPvP 14/18891608-0001</i> for CR.1 a).</p> <ul style="list-style-type: none">• Deliverables• Associated deviation report• Any further documents as relevant. <p>Preventative actions, including:</p> <ul style="list-style-type: none">• Updated procedure for supporting implementation of artwork• Updated Contract Service Provider (CSP) slip, sample of CSP slips for updated PILs, and updated associated procedure• Escalation process• Componentry oversight tracker• Training of staff on updated procedures• Wider review of the process functioning in practice. <p>The scope will not just be limited to the above and will be decided upon by the lead inspector as the OBRA is conducted. The above is to provide the MAH with an outline of what to expect for provision of documents and SME availability if necessary.</p>
Section 2: OBRA summary (completed after OBRA is conducted)	

Number of actual inspector days for OBRA	3.0 days
Further critical or major findings identified*	<p>Requirements: The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 5 Marketing Authorisations, Regulation 76.</p> <p>MHRA Guidance: Medicines: packaging, labelling and patient information leaflets, Published 18 December 2014.</p> <p>MA.1 a) Implementation of reference safety information Examples were identified where actions Boots put in place to rectify critical deficiency CR.1 a) identified at Insp GPvP 14/18891608-0001 were ineffective.</p> <ol style="list-style-type: none"> i. Shortly prior to the conduct of the OBRA, Boots identified one batch of one product with implementation of superseded PIL and packaging beyond the 6-month cut-off date. Batch [REDACTED] of Boots [REDACTED] [REDACTED] was certified for release by the Qualified Person (QP) of contract manufacturer [REDACTED] with superseded product information 17 days after the implementation deadline of 14 August 2023. PIL updates included amendments to existing warnings and the addition of adverse reactions. Boots documented this in company deviation [REDACTED] on 25 October 2023. A corrective and preventative action (CAPA) plan was associated with the deviation [REDACTED] [REDACTED] that listed corrective and preventative actions and effectiveness checks. Despite this being a failure to appropriately address a previous critical finding, it is acknowledged that this was self-identified and appropriate actions were initiated and therefore has been given the grading of major. The MAH should document the CAPA plan in response to this deficiency as part of this OBRA form. ii. Deficiencies in the process for managing contract service provider (CSP) slips implemented by Boots in response to the critical finding were identified. CSP slip records for four variations initiated under revision [REDACTED] of procedure [REDACTED] [REDACTED] (effective 17 June 2022) were not completed by service providers as required by the procedure, and no planned or unplanned deviations were recorded for these or other variations that deviated from the process. The MAH indicated that the procedure was not fit-

	<p>for-purpose and a change was required; however, this had not been documented and communicated to staff via a planned deviation.</p> <p>iii. The componentry implementation tracker put in place by Boots to track batch and componentry information of superseded product information for oversight purposes did not match batch and QP certification documentation provided for the OBRA for CSP [REDACTED]. It was noted that the issues identified did not appear to impact on compliance of the relevant variations. Examples included:</p> <p>a. For variation [REDACTED] for [REDACTED] [REDACTED], QP certification documentation for the last batch containing the superseded PIL related to batch [REDACTED] and showed it was certified 17 January 2022. However, the implementation tracker indicated the last batch with the superseded PIL was batch [REDACTED], dated 03 January 2023.</p> <p>b. For variation [REDACTED] for [REDACTED] [REDACTED], QP certification documentation gave the QP certification date for the last batch containing the superseded PIL as 26 June 2023 for batch [REDACTED]. On the tracker, the date was 02 June 2023.</p> <p>c. For variation [REDACTED] for [REDACTED] [REDACTED], the first batch with the new PIL was batch [REDACTED], QP certified on 04 December 2023. On the tracker, this was shown as batch [REDACTED], QP certified on 25 September 2023.</p> <p>For these examples, the MAH confirmed no superseded PILs were released beyond six months of an updated PIL version being approved and an investigation was underway with the CSP.</p>
<p>Further minor findings identified (including comments or recommendations)</p>	<p><u>MI.1 a) Implementation of reference safety information</u></p> <p>i. There was a delay of almost two months in updating the electronic medicines compendium (emc) and company website boots.com after safety variation [REDACTED] for [REDACTED] [REDACTED] was approved by the MHRA on 17 June 2022. The updated product information was uploaded on 08 August 2022. If the product information is available on the emc or company-sponsored websites, the MHRA expects updated PILs and SmPCs containing new or</p>

	<p>updated safety information to be uploaded by the MAH within 10 working days.</p> <p><u>MI.2 a) Pharmacovigilance System Master File</u> There were inaccuracies or missing information in the Boots PSMF [REDACTED] (revision [REDACTED] December 2023):</p> <ul style="list-style-type: none"> i. Manufacturer [REDACTED] was not listed in the PSMF, including Annex [REDACTED], even though [REDACTED] contact details were located on product packs and PILs and there was a contract in place stating that [REDACTED] will provide quality and safety/adverse events to Boots (Technical Agreement [REDACTED] version [REDACTED], last revised 01 November 2023, section 4.14 Complaints). ii. The PSMF section on completed audits (Annex [REDACTED] listed audits conducted by third party MAHs of Boots where Boots was a distributor. Audits that do not relate to The Boots Company's PV system, or to marketing authorisations held by Boots, should not be listed in the Boots PSMF. iii. A planned audit of manufacturer [REDACTED] described in [REDACTED] as "Onsite audit of [REDACTED] manufacturing site to take place to include an assessment of their processes to enact product changes" with due date 30 April 2024, was not listed in PSMF Annex [REDACTED] Scheduled Audits and Inspections. Although this would be a GMP audit and in general GMP audits should not be listed in the PSMF, if there are significant elements of the PV system being assessed by the audit, e.g. assessment of the last batch release process following safety variation updates, this should be listed in the PSMF. The fact that this CAPA is associated with the deviation described in MA.1 a) suggests this audit will be of relevance to pharmacovigilance. It is recommended that a note can be added to the PSMF to indicate the PV-relevant aspects being assessed. <p><u>MI.3 a) Management of CAPA</u> Preventative actions in response to the critical finding identified in the 2022 MHRA GPvP inspection (Insp GPvP 14/18891608-0001) were completed late. The MAH did not request an extension from the MHRA, and a deviation to the inspection CAPAs was not documented.</p> <ul style="list-style-type: none"> i. The due date for the preventative action "Training on procedures and additional training and effectiveness check on use of Componentry Tracker" was 15 July 2022. Although training was
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	<p>completed by this date, effectiveness checks were not completed until after the due date, between 20 July 2022 and 08 September 2022.</p> <p>ii. The due date for new/updates to procedures [REDACTED] and [REDACTED] was 31 May 2022; however, the effective date of the procedures was 17 June 2022, 17 days after the preventative action due date.</p> <p><u>MI.4 a) Written procedures</u> Examples were identified of deficiencies in written procedures:</p> <p>i. The CSP slip process was updated in procedure [REDACTED] revision [REDACTED] (effective 19 April 2023); however, reference to the old process remained in [REDACTED] and [REDACTED], which had the potential to cause confusion among staff and service providers:</p> <p>a. [REDACTED] [REDACTED] (revision [REDACTED], effective 17 June 2022), Appendix 3, action 1 of the verification actions states "Completed Part 2 of the CSP change implementation slip received from the CSP"; however, the CSP was no longer required to complete and return the slips.</p> <p>b. [REDACTED] (revision [REDACTED], effective 19 April 2023), Appendix 1 instructed Boots staff to include the following in a personal message to CSP staff on Box: "Please ensure you return the signed Change Implementation Slip when the changes have been Implemented." However, returning and signing the slip was no longer required as part of the revised process.</p> <p>ii. MHRA expects safety-related changes to product information to be uploaded to emc and company websites within 10 working days; however, procedure [REDACTED] [REDACTED] (revision [REDACTED], effective date 21 June 2022), Sections 4.1 and 4.2 allowed up to 15 working days.</p> <p><u>Comment: Documentation provided for OBRA</u> Errors were identified in information supplied for inspection during the OBRA.</p> <p>i. Incorrect Bill of Materials (BOM) documents were provided as part of the documentation supporting closure of the critical finding CAPA. Correct information was subsequently provided; however,</p>
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	<p>the MAH must ensure it has retained the correct documentation within its CAPA systems.</p> <p>ii. Incorrect marketing status was entered into a spreadsheet provided as part of the OBRA for product [REDACTED] [REDACTED] [REDACTED]). The company explained that this was due to human error when compiling the spreadsheet.</p>
Final outcome of OBRA	Inspector recommends that MAH is put on routine inspection schedule.
Closing meeting date and attendees	<p>15 December 2023.</p> <p>Attendees from Boots:</p> <ul style="list-style-type: none"> • [REDACTED], Head of Product Delivery Own Brand OTC Health • [REDACTED] Medical Director & UK QPPV • [REDACTED], In-Market Vigilance Manager & dQPPV • [REDACTED] Head of Safety & Regulatory & dQPPV • [REDACTED] Global Head of Quality • [REDACTED] Technical Director, Boots Brands & Exclusives
Signed by lead inspector	<p>Signature: [REDACTED]</p> <p>Date: 8 April 2024</p>
Signed and acknowledged by UK QPPV	<p>Statement of acknowledgement: Signatur [REDACTED]</p> <p>Date: 8 April 2024</p>

*For critical or major findings identified from OBRA, the company must provide a written response which includes:

<p>Root Cause Analysis</p> <p>Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.</p>
<p>Further Assessment</p> <p>Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.</p>
<p>Corrective Action(s)</p> <p>Detail the action(s) taken / proposed to correct the identified deficiency.</p>

Preventative Action(s) Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
Deliverable(s) Detail the specific <u>outputs</u> from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due Date(s) Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Please include the company CAPA in the below boxes (overwriting the red text) within 25 days of receipt of this form.

Finding	MA.1 a)
	<p>Examples were identified where actions Boots put in place to rectify critical deficiency CR.1 a) identified at Insp GPvP 14/18891608-0001 were ineffective.</p> <ol style="list-style-type: none"> Shortly prior to the conduct of the OBRA, Boots identified one batch of one product with implementation of superseded PIL and packaging beyond the 6-month cut-off date. Batch [REDACTED] of [REDACTED] [REDACTED] was certified for release by the Qualified Person (QP) of contract manufacturer [REDACTED] with superseded product information 17 days after the implementation deadline of 14 August 2023. PIL updates included amendments to existing warnings and the addition of adverse reactions. Boots documented this in company deviation [REDACTED] on 25 October 2023. A corrective and preventative action (CAPA) plan was associated with the deviation [REDACTED] that listed corrective and preventative actions and effectiveness checks. Despite this being a failure to appropriately address a previous critical finding, it is acknowledged that this was self-identified and appropriate actions were initiated and therefore has been given the grading of major. The MAH should document the CAPA plan in response to this deficiency as part of this OBRA form. Deficiencies in the process for managing contract service provider (CSP) slips implemented by Boots in response to the critical finding were identified. CSP slip records for four variations initiated under revision [REDACTED] of procedure [REDACTED] [REDACTED] (effective 17 June 2022) were not completed by service providers as required by the procedure, and no planned or unplanned deviations were recorded for these or other variations that deviated from the process. The MAH indicated that the procedure was not fit-for-purpose and a change was required; however, this had not been documented and communicated to staff via a planned deviation. The componentry implementation tracker put in place by Boots to track batch and componentry information of superseded product information for oversight purposes did not match batch and QP certification documentation provided for the OBRA for CSP [REDACTED]. It was noted that the issues identified did not appear to impact on compliance of the relevant variations. Examples included: <ol style="list-style-type: none"> For variation [REDACTED] for [REDACTED] [REDACTED], QP certification documentation for the last batch containing the superseded PIL related to batch [REDACTED] and showed it was certified 17 January 2022. However, the implementation tracker indicated the last batch with the superseded PIL was batch [REDACTED], dated 03 January 2023. For variation [REDACTED] for [REDACTED] [REDACTED], QP certification documentation gave the QP [REDACTED]

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[REDACTED] ([REDACTED]), the first batch with the new PIL was batch [REDACTED] QP certified on 04 December 2023. On the tracker, this was shown as batch [REDACTED] QP certified on 25 September 2023.

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