**CASE/0349/11/24 and CASE/0350/11/24**

# COMPLAINANT v LEO

## Dosage inaccuracies within a patient app

### CASE SUMMARY

**This case was in relation to two complaints about the inclusion of inaccurate and misleading information in the 'Tinzahelp administration' app for patients prescribed tinzaparin sodium, and a failure to withdraw such information immediately.**

**The outcome under the 2024 Code was:**

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|---|---|
| **Breach of Clause 2** | **Bringing discredit upon, and reducing confidence in, the pharmaceutical industry** |
| **Breach of Clause 5.1(x2)** | **Failing to maintain high standards** |
| **Breach of Clause 6.1(x2)** | **Providing misleading information** |
| **Breach of Clause 26.2** | **Providing inaccurate information about a prescription only medicine to the public** |

| | |
|---|---|
| **No Breach of Clause 3.1** | **Requirement that a medicine must not be promoted prior to the grant of its marketing authorisation** |
| **No Breach of Clause 3.6** | **Requirement that materials and activities must not be disguised promotion** |
| **No Breach of Clause 26.3** | **Requirement that items for patient support made available to patients must meet the requirements of the Code** |

**The Appeal Board was concerned that the patient app remained available to download for approximately three months after LEO Pharma had become aware of significant errors, including dosage volume inaccuracies. The Appeal Board gave consideration to the use of additional sanctions but decided that none were required.**

**This summary is not intended to be read in isolation.**
**For full details, please see the full case report below.**

## FULL CASE REPORT

Two complaints were received from anonymous, non-contactable complainants, who described themselves as health professionals, about LEO Pharma. The case preparation manager decided to amalgamate the two cases as they were based on essentially similar evidence, in accordance with Paragraph 5.2 of the Constitution and Procedure. As the complainants were non-contactable, they were unable to appeal this decision.

## COMPLAINT

### Case/0349/11/24

The complaint wording is reproduced below:

> "I am a Healthcare professional that works with various patients, I decided to make some training modules on thrombosis treatments/prophylaxis. I was aware of the tinzahelp app and decided to use this for the training slides. Upon opening the app and going into the how to inject section I can see the volume for 2,500IU, 3,500IU and 4,500IU was incorrect. This is a major patient safety risk as the volumes provided will result in a suboptimal dose for the patients and this is a breach of clause 2. Furthermore the information about excipients within the app under the FAQ [frequently asked questions] has excipients for the vial further causing confusion and it is not clear if there is information just for patients on the treatment indication or the prophylactic indication which is again confusing for both patients and HCPs alike. This is a breach of clause 5.1 as high standards are not maintained and breach of clause 26.2/26.3 as the information provided to the patients via the app is not factual and is inaccurate. I would appreciate if this is to be investigated as I can see there are already downloads via the app stores on Apple devices and Android devices so I am worried there is a risk patients have been injecting the incorrect doses, thus worsening their conditions."

When writing to LEO Pharma, the PMCPA asked it to consider the requirements of Clauses 2, 5.1, 6.1, 26.2 and 26.3 of the 2024 Code.

### COMPLAINT Case/0350/11/24

The complaint wording is reproduced below:

> "Complaint Regarding Inaccurate Information on the Tinzahelp Patient App. I am writing to formally raise a concern regarding the Tinzahelp patient app, which I recently explored to aid in my patient counselling part of my role as a clinical pharmacist. A colleague in the healthcare profession recommended this app, prompting its use. Upon examination, I identified significant inaccuracies in the dosing information provided for the LMWH [low molecular weight heparin], specifically for the dosages of 2,500 IU, 3,500 IU, and 4,500 IU. The app does not present the correct volumes required for these dosages, which could lead to suboptimal dosing for patients. I am deeply concerned about the potential implications for patient safety. Inaccurate dosing information could significantly increase the risk of thrombosis and other related complications, thereby posing a serious risk to patient health. I believe that this situation may violate several clauses of the ABPI Code of Practice 2021, specifically: Clause 2: "The health of patients must be the primary consideration." The inaccuracies

> in this app directly jeopardise patient safety and care. Clause 3.1: “There should be a distinction between promotional and non-promotional material.” The app appears to present itself as a reliable source of information, yet it provides potentially harmful inaccuracies. Clause 7.2: “Promotional material must be accurate and not misleading.” While this clause speaks specifically to promotional content, the inaccuracies present could mislead users regardless of the app’s intended purpose. Clause 9.1: “Information must be presented in a balanced and truthful manner.” The misleading information in the app fails to meet this requirement, risking patient safety. Clause 10.1: “Any information must be accurate and not misleading, and must be based on the most up-to-date clinical evidence.” The failure to provide accurate dosing information contradicts this principle and can lead to serious health risks. Clause 13.1: “Companies must take all reasonable steps to ensure that their activities do not compromise patient safety.” The inaccuracies present in this app raise significant safety concerns for patients who rely on it for guidance. I urge the PMCPA to investigate this matter thoroughly to protect patient safety and uphold the high standards expected in our profession. Thank you for your attention to critical issue.”

The case preparation manager noted that the complainant had cited the 2021 Code and appeared to have cited clauses from a different Code. As the complainant was non-contactable, they could not be asked to confirm the clauses raised. The case preparation manager reviewed the allegations from the complainant and, when writing to LEO Pharma, asked it to consider the requirements of Clauses 2, 3.1, 3.6, 5.1, 6.1 and 26.2 of the 2024 Code.

## LEO PHARMA’S RESPONSE

The response from LEO Pharma is reproduced below:

> “Further to your letter regarding the above case dated 11 November 2024, please find below LEO Pharma’s response to the complaints. Patient safety is of paramount importance to LEO Pharma; we take any complaint seriously and seek to resolve the concerns raised.
>
> Both complaints are about the same item (tinzaparin sodium patient app) and are very similar in nature. We note that both complaints were made at a similar time on 07 November 2024 by health professionals who have chosen to be non-contactable. Therefore, we have provided one response and addressed the different concerns raised by the two complainants where applicable below. If you prefer that we separate our responses to each complaint, please let us know.
>
> **Background**
>
> LEO Pharma UK and Ireland produces a non-promotional app for patients who are treated with tinzaparin sodium (innohep®). Tinzaparin sodium is a low molecular weight heparin and is licensed for the following indications:
>
> - Prophylaxis of venous thromboembolism in adult patients undergoing surgery, particularly orthopaedic, general or oncological surgery.
>
> - Prophylaxis of venous thromboembolism in non-surgical adult patients immobilised due to acute medical illness including: acute heart failure, acute

respiratory failure, severe infections, active cancer, as well as exacerbation of rheumatic diseases.

- Prevention of clotting in extracorporeal circuits during haemodialysis and haemofiltration in adults.

- Treatment of venous thrombosis and thromboembolic disease including deep vein thrombosis and pulmonary embolus in adults.

- Extended treatment of venous thromboembolism and prevention of recurrences in adult patients with active cancer.

The app is available for download on app stores by members of the public. The app clearly states that it is intended for use by tinzaparin sodium patients only in the UK and Ireland. It is for those patients who have been prescribed tinzaparin sodium for treatment or prevention of deep vein thrombosis or pulmonary embolism by prefilled syringe i.e. self-injection. Users are prompted to confirm if they have been prescribed tinzaparin sodium before the app launches.

The intention of the app is to present information from the Patient Information Leaflet in a digital medium to support the use of tinzaparin sodium in pre-filled syringe by patients. Users of the app are prompted to select their prescribed dosage on the app and are then presented with injection technique information (including videos), as well as frequently asked questions and information on potential side effects.

The app which was in use at the time of the complaints was certified for use on 08 Jul 2024. It was then made available in the app stores. It was available on 23 July 2024 on the Apple store and 31 July 2024 on the Google Play store. There have been 23 downloads across both stores from these dates to 25 November 2024.

The app covers information for prophylaxis of venous thromboembolism, available in pre-filled syringes (2,500 IU, 3,500 IU and 4,500 IU) and also information on the treatment of venous thromboembolism available in pre-filled syringe presentations (8,000 IU/0.4 ml, 10,000 IU/0.5 ml, 12,000 IU/0.6 ml, 14,000 IU/0.7 ml, 16,000 IU/0.8 ml, 18,000 IU/0.9 ml).

The LEO Pharma Medical Affairs team became aware of inaccuracies within the app including with the dosing volume information on 22 August 2024. As highlighted by both the complainants, there was inaccurate information with the dosing volumes for the doses used in prophylaxis. The incorrect volume information is in the list of dosages to select in the app for the following:

- 2,500 IU/0.15 ml
- 3,500 IU/0.2 ml
- 4,500 IU/0.2 ml

Also 4,500 IU/0.25 ml in the information section.

The information should read:

- 2,500 IU/0.25 ml
- 3,500 IU/0.35 ml
- 4,500 IU/0.45 ml

The remaining dosages in the list are given with the correct volumes.

The incorrect information with the dosing volumes was assessed as not having an impact on patient safety by two senior Medical Affairs employees for LEO Pharma. This assessment was made because patients prescribed a prophylaxis dose of tinzaparin sodium are required to inject the entire volume of the syringe, they are not required to calculate a volume to inject. In addition, the pre-filled syringes are non-graduated for the prophylaxis range, therefore it is not possible and is not recommended to administer an alternative dosage/volume from these syringes with any degree of accuracy given the lack of graduation and the low volume of solution in the syringes. The syringes are colour-coded by dose, and therefore easily identifiable. It was also considered that the use of tinzaparin sodium for prophylaxis use is very well established in clinical practice (for over twenty-five years) and is usually prescribed by dosage, e.g. 4,500 IU rather than by volume. Healthcare professionals working in this specialty are usually very experienced and familiar with administering the full volume from a prophylaxis syringe and counselling patients to do so. We have included photographs of the 4,500 IU pre-filled syringe to show what it looks like for a patient and the lack of graduation on the syringe and a photograph of the 10,000 IU pre-filled syringe which clearly shows graduations on the syringe.

In addition to the incorrect information regarding dosing volume, there was also incorrect information regarding timing of having a spinal/epidural anaesthetic following the last injection of tinzaparin sodium in the FAQ section. The answer states that spinal/epidural anaesthetic should not be given within 24 hours of the last injection of tinzaparin sodium. This is correct for the treatment range, but for the prophylaxis range it can be given within 12 hours. This information would lead to a more conservative approach and again would not impact patient safety.

Based on this assessment and lack of impact on patient safety there was a decision not to withdraw the app immediately but to certify a corrected version as soon as possible and to make the update available on the app stores when the new version was certified and ready for use.

An internal investigation was undertaken to understand how the app had been certified with inaccurate information and a deviation was raised on 03 September 2024. The app was certified by a third-party agency. They were informed and conducted their own investigation into the issue. We have enclosed a copy of the LEO Pharma deviation and Corrective and Preventative Actions plan (CAPA), and a redacted copy of the third party CAPA document.

The app has been updated and certified and was pushed to the app stores on 19 November 2024. There was a technical issue with it being made available on the Google Play store therefore it was decided to deactivate the current version (the version with the inaccurate information) in both the Apple store and the Google Play store on 19 November until the updated version was made available. The updated app was available to download on 22 November 2024.

**Allegations made by both complainants**

LEO Pharma was asked to respond to clauses 6.1 and 26.2 in both complaints sent by the PMCPA. As the information regarding the dosing volumes in the tinzaparin sodium app were not accurate or factual, LEO Pharma accepts a breach of clauses 6.1 and 26.2. As the incorrect information was not picked up during certification of the app, high standards were not maintained and therefore LEO Pharma accepts a breach of clause 5.1.

Both complainants alleged that the incorrect dosing volumes given were a patient safety concern as they believed this would result in suboptimal dosing. As explained above, the dosages with the incorrect volumes listed in the app come in pre-filled, non-graduated syringes which are injected in their entirety and therefore the volume information is not relevant to administration of the pre-filled syringe. In turn this does not result suboptimal dosing. Therefore, LEO Pharma is confident that patient safety has not been impacted and refutes a breach of Clause 2.

**Additional allegations made in Case/0349/11/24**

The complainant has alleged a breach of clause 26.3 however it is in relation to information being inaccurate; "…a breach of clause 26.2/26.3 as the information provided to the patients via the app is not factual and is inaccurate." It is unclear whether clause 26.3 is the intended clause to be alleged as this does not relate to the allegation made. Please provide further context so that we can address this fully.

The complainant has commented about the excipients listed. LEO Pharma has taken a conservative approach and listed all excipients which carry allergy warnings from each formulation (20,000 IU/ml vial, 20,000 IU/ml treatment range, 10,000 IU/ml vial and 10,000 IU/ml prophylaxis range) in the app. From a safety perspective it was deemed more appropriate to include all potential allergens. The app is not intended to replace the counselling or information provided by a healthcare professional to a patient, and a healthcare professional could clarify this for the patient if the patient raised concerns about allergens. In addition, the patient could also consult their Patient Information Leaflet to check the particulars of their formulation. Therefore, LEO Pharma refutes the allegation of not maintaining high standard which was made in relation to this point (Clause 5.1).

**Additional allegations made in Case/0350/11/24**

The complainant has alleged a breach of clause 3.1 however this appeared to be in the context of distinguishing between promotional and non-promotional materials. In addition, LEO Pharma was asked to respond to clause 3.6. The app contains information from the patient information leaflet and does not contain promotional claims. It is clearly labelled for use by patients who have been prescribed tinzaparin sodium and it is advertised on the app store by name only, no indications are mentioned until the app is downloaded. This can be seen in the certified material provided. Users are asked to confirm if they have been prescribed tinzaparin sodium before the app launches. Tinzaparin sodium is licenced for use in the indications in the

app, therefore there was no promotion before the granting of a marketing authorisation. LEO Pharma refutes a breach of clauses 3.1 and 3.6.

We are unclear why the complainant attached a screenshot highlighting the 13,000/0.65 ml dose. The information in this screenshot is accurate.

**Actions taken since receiving the complaints**

As outlined above, a deviation had been raised and an investigation had been carried out with regard to the inaccuracies in the app before the complaints were received. The app has been updated and has been available on the Apple app store since 19 November 2024 and the Google Play store since 22 November 2024.

**Conclusion**

To conclude, LEO Pharma take patient safety very seriously. A swift assessment of the impact of the errors in the app on patients using the app was made as soon as we became aware of them. We have put in place a corrective and preventative action plan to ensure this does not happen again and to learn from the issue.

LEO Pharma accepts the allegations of a breach of clauses 6.1, 26.2 and 5.1. We refute the allegations of a breach of clauses 3.1 and 3.6. As discussed throughout the response, due to the lack of impact on patient safety we refute a breach of clause 2.

We have enclosed photographs of two of the pre-filled syringes, a copy of the LEO Pharma deviation, the third party CAPA, the certified copy of the app and a document showing the user experience as requested (navigation flow) along with a copies of the summary of product characteristics for tinzaparin sodium and copies of the patient information leaflet for the pre-filled syringes."

**PANEL RULING**

This case related to two complaints regarding the inclusion of inaccurate information in the 'Tinzahelp administration' app for patients prescribed tinzaparin sodium.

LEO Pharma submitted the app was available for download by members of the public and that the app clearly stated it was intended for use by patients prescribed tinzaparin sodium pre-filled syringes in the UK and Ireland; users were prompted to confirm if they had been prescribed tinzaparin sodium before the app launched.

The Panel noted the app appeared to have five key sections: Home; Injection technique video; How to inject; Daily injection reminder; and FAQs. The homepage described the app as a "guide to treating or preventing blood clots with innohep® or tinzaparin sodium" for patients in the UK or Ireland and which "does not replace the guidance found in your package leaflet".

LEO Pharma submitted the intention of the app was to present information from the Patient Information Leaflet (PIL) in a digital medium to support the use of tinzaparin sodium in pre-filled syringe by patients. Users of the app were prompted to select their prescribed dosage on the app and were then presented with injection technique information (including videos), as well as frequently asked questions and information on potential side effects. The app covered

information for prophylaxis of venous thromboembolism, (2,500 IU, 3,500 IU and 4,500 IU) and the treatment of venous thromboembolism (8,000 IU, 10,000 IU, 12,000 IU, 14,000 IU, 16,000 IU and18,000 IU) available in pre-filled syringes.

Both complainants alleged the volumes provided for the 2,500 IU, 3,500 IU and 4,500 IU doses were incorrect. LEO Pharma accepted there were inaccuracies regarding the dosage volume for prophylaxis: the app listed 2,500 IU in 0.15 ml instead of 0.25 ml, 3,500 IU in 0.2 ml instead of 0.35 ml, and, in two different parts of the app, 4,500 IU in 0.2 ml and 4,500 IU in 0.25 ml instead of 0.45 ml.

Clause 6.1 required that information must be accurate and not mislead. Clause 26.2 included that information about prescription only medicines made available to the public must be factual.

The Panel noted the discrepancies in dose volumes appeared in the list of doses to select, as well as the headings in the dose specific administration guidance within the "How to inject" section. Information provided in relation to the dosing of tinzaparin sodium was therefore inaccurate and misleading and the Panel ruled **a breach of Clauses 6.1 and 26.2**, as acknowledged by LEO Pharma.

The Panel noted that one complainant had cited Clause 26.3 alongside Clause 26.2 in this regard. The Panel considered, however, that the complainant made no allegation relating to items for patient support. The Panel therefore ruled **no breach of Clause 26.3**.

One complainant alleged that "the app appears to present itself as a reliable source of information, yet it provides potentially harmful inaccuracies"; the complainant incorrectly cited Clause 3.1 as stating "there should be a distinction between promotional and non-promotional material". The Panel noted that LEO Pharma had been asked by the case preparation manager to respond to Clause 3.6, which required that materials and activities must not be disguised.

The Panel considered that the complainant's allegation was unclear. The Panel noted that the burden of proof was on complainants to establish their case on the balance of probabilities, and it was not for the Panel to infer reasons on behalf of the complainant. It appeared to the Panel that there was an allegation that the app represented disguised promotion; however, the complainant had not provided clear reasons for this allegation. The Panel noted LEO Pharma's submission that the app contained information from the patient information leaflet and did not contain product claims, and that it was clearly labelled for use by patients who had been prescribed tinzaparin sodium. The Panel took account of the requirement that users of the app had to self-certify they were patients who had been prescribed tinzaparin and noted its comments above that the homepage stated at the outset that the app was "your guide to treating or preventing blood clots with innohep® or tinzaparin." The Panel considered that there was no evidence before it that the app was disguised promotion and ruled **no breach of Clause 3.6** accordingly.

Clause 3.1 required that a medicine must not be promoted prior to the grant of its marketing authorisation. The Panel noted tinzaparin sodium had a marketing authorisation and that there was no relevant allegation by the complainant in this regard. The Panel therefore ruled **no breach of Clause 3.1**.

One complainant raised concerns that it was unclear whether information related to treatment or prophylaxis. In particular, the complainant referred to an FAQ (frequently asked question)

asking, “What should I be aware of before using innohep® or tinzaparin sodium?”, which stated, among other things in a bullet-pointed list, not to use the medicine if there was an allergy to “innohep® or tinzaparin sodium or any of the other ingredients (sodium metabisulfite, sodium hydroxide, benzyl alcohol and water for injections)”. The complainant alleged that this was the list of excipients for injection vials (rather than the pre-filled syringes).

The Panel noted the 20,000 IU/ml pre-filled syringes for treatment contained sodium metabisulfite, sodium hydroxide and water for injections. The 10,000 IU/ml pre-filled syringes for prophylaxis contained sodium acetate trihydrate, sodium hydroxide and water for injections. The Panel was not provided with the summary of product characteristics for injection vials.

Noting that sodium acetate trihydrate was not listed in the answer to the FAQ, the Panel queried LEO Pharma’s submission that it had listed all excipients which carry allergy warnings from each formulation. In the Panel’s view, the bullet point referring to allergens misleadingly implied that the list given was a complete list, for both prophylaxis and treatment, which was not so; it was not clear the excipients did not relate to the pre-filled syringes used in prophylaxis. The Panel therefore ruled **a breach of Clause 6.1**.

Companies needed to take the utmost care when producing materials for patients to ensure that patients were provided with accurate information and could not be misled. High standards had not been maintained and the Panel ruled **a breach of Clause 5.1** in relation to the incorrect dosing volumes, as acknowledged by LEO Pharma, and **a breach of Clause 5.1** in relation to the list of excipients in the FAQ section.

The Panel noted the following timeline of events, constructed from LEO Pharma’s submission:

- **21 August 2024** – Errors identified by LEO Pharma employee when showing the app to a customer

- **22 August 2024** – The LEO Pharma medical affairs team became aware of inaccuracies within the app; internal review undertaken of the approved app

- **3 September 2024** – LEO Pharma initiated its corrective and preventative actions (CAPA) plan, as documented in a deviation form

- **8 October 2024** – LEO Pharma informed its third-party approval agency

- **10 October 2024** – LEO Pharma’s third-party approval agency issued its CAPA plan, which identified similar issues and recommended that the app be updated as soon as possible

- **11 November 2024** – The PMCPA wrote to LEO Pharma, advising it of Case/0349/11/24 and Case/0350/11/24

- **19 November 2024** – The app (the version with the errors) was deactivated in the Apple store and the Google Play store

- **22 November 2024** – An updated version of the app was available to download

The Panel noted the issues identified in LEO Pharma's deviation form included the following, some of which were in addition to the allegations made in this complaint:

1. "Incorrect volume of syringe listed – 2,500 IU is in 0.25 ml, 3,500 IU is in 0.35 ml and 4,500 IU is in 0.45 ml. At one stage it is said that 4,500 IU is in 0.2 ml, on another page it says 4,500 IU is in 0.25 ml.
2. Spelling of active name incorrect in some places – tinzaprin rather than tinzaparin
3. Link to patient information leaflet on medicines.ie for prophylaxis syringes links to a patient information leaflet for multidose vials which does not contain the same excipients nor does this patient information leaflet carry information on how to self-inject
4. In the section 'What should I be aware of before using innohep® or tinzaparin sodium?' there is advice on not having a spinal/epidural anaesthetic within 24 hours of the last injection of innohep®. This is correct for the treatment range, but not the prophylaxis range, where the gap is 12 hours.
5. In Step 6 of the guide, on the prophylaxis syringes it states, 'There is no need to remove the air bubble if you need the total quantity in the syringe before your dose'. These are not graduated syringes and a partial dose would not be recommended. It doesn't seem that the information has been taken from the patient information leaflet for the prophylaxis range. It may have been taken from the treatment range PIL."

The Panel took account of LEO Pharma's submission that the incorrect dosage volumes in the app would not have led to suboptimal dosing as volume information was not relevant to administration of the pre-filled syringe which came in non-graduated, color-coded pre-filled syringes that were injected in their entirety for prophylaxis. In relation to point 4 of its deviation form above, LEO Pharma submitted the 24-hour gap would lead to a more conservative approach than 12 hours and again would not impact patient safety. LEO Pharma submitted based on this assessment, and lack of impact on patient safety, there was a decision not to withdraw the app immediately but to certify a corrected version as soon as possible.

Company produced material for patients had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in the patient information leaflet, videos in the app or the health professional counselling.

The Panel considered the inaccuracies and misleading information in the app regarding dosage volumes and excipients, along with the other issues identified as part of LEO Pharma's deviation form, raised significant concerns about the quality and clarity of patient materials provided by the company.

It was crucial that patients, and health professionals alike, could rely upon the pharmaceutical industry for accurate and up-to-date information about their medicines. Failure to withdraw inaccurate information for patients, particularly in relation to dosing, was a serious matter, no matter how unlikely the company considered it was that a patient safety issue would occur. In this regard, the Panel was extremely concerned about LEO Pharma's lack of urgency in addressing any issues as set out above and its conscious decision to keep the app live with the inaccuracies for approximately 3 months.

In the Panel's view, that the dosage volume inaccuracies existed at all, amongst other errors, and that the app was not withdrawn immediately, was such as to reduce confidence in the industry being able to produce patient material to the required quality standards. The Panel ruled **a breach of Clause 2**.

## APPEAL BOARD CONSIDERATION OF THE CASE REPORT

LEO Pharma provided the requisite undertaking and assurance and, as the case completed at Panel level, the Appeal Board received the case report as set out in Paragraphs 13.1 and 15.4 of the 2024 Constitution and Procedure.

The Appeal Board was very concerned that the patient app remained available to download for approximately three months after LEO Pharma had become aware of significant errors, including dosage volume inaccuracies.

The Appeal Board was of the view that consideration should be given to the imposition of additional sanctions under Paragraph 13.2 (iv) of the 2024 Constitution and Procedure.

The Appeal Board sought an explanation from LEO Pharma about its processes for checking the accuracy of material which is put on apps and other patient resources, its processes for withdrawal of material which is found to be incorrect, and its rationale for not withdrawing the app immediately when it became aware of the dosage errors.

LEO Pharma was required to respond to these concerns in writing and was invited to attend a meeting of the Appeal Board when this matter would be considered. LEO Pharma was provided with a copy of the papers for this matter.

## COMMENTS FROM LEO PHARMA

LEO Pharma's written response is reproduced below.

> "Further to your letter regarding the above case dated 1 May 2025, please find LEO Pharma's response below.
>
> LEO Pharma is committed to working in a compliant way to ensure patient safety and confidence in the company and industry. We have robust processes in place which support our governance. We regret this situation and recognise that it was not managed appropriately within our compliance framework and has impacted the trust which patients and health professionals have in pharmaceutical companies to produce accurate information about their medicines.
>
> We address the questions raised by the Appeal Board in turn below.
>
> **1 Processes for checking the accuracy of material which is put on apps and other patient resources**
>
> The enclosed document (SOP_022408) outlines the Standard Operating Procedure (SOP) for the electronic review, approval, and certification of materials and activities at LEO Pharma UK/IE. Below is a concise summary highlighting **the key principles** to ensure the accuracy of promotional and non-promotional materials, including materials created for patients.
>
> The SOP applies to all LEO Pharma UK/IE employees and contractors involved in creating, reviewing, and certifying materials and events, ensuring full oversight and compliance. It is applicable to all materials, including digital materials such as apps.

**Material Standards and Certifications**

- Materials must be accurate, balanced, and compliant with ABPI and IPHA codes. Claims must be substantiated, safety data must accompany efficacy data, and materials must reflect the product's risk-benefit profile. All references must be appropriate, fully substantiated, and correctly cited.

- Quality control (QC) is the responsibility of all reviewers at every stage of the review cycle, including originators, material coordinators, medical reviewers, and final signatories.

- Certificates confirm that materials are accurate, truthful, and compliant with regulations. Final Signatories or Appropriately Qualified Persons (AQPs) are responsible for ensuring accuracy and certification at the final stage.

- Materials must be certified in their final, unalterable form. Hard copies require additional checks to ensure they match the certified electronic version.

- Online materials must be checked within 24 hours of publication to ensure they appear exactly as certified and that all links to other documents (e.g., prescribing information, patient leaflets) work correctly.

**Accuracy Checks in the Review Process**

- **Preparation**: Materials are assigned unique identifiers, references, and metadata. Supporting documents, including highlighted references, are uploaded to Veeva PromoMats.

- **Quality Check:** Job bag coordinators initiate the QC process, ensuring materials are accurate, fair, balanced, and scientifically valid. They verify that claims are substantiated, prescribing information is correct, and adverse event reporting statements are included before initiating the review cycle. A "two pairs of eyes" principle is applied to the review of complex, high-risk materials.

- **Review Cycles:** All reviewers assess every element of the material for compliance with SOPs, codes, and legislation. Medical reviewers ensure that claims and information are supported by the latest evidence, references are accurate, and materials are suitable for the intended audience.

- **Annotations:** Reviewers tag annotations as mandatory or optional, with mandatory changes required for approval.

This SOP emphasises rigorous accuracy checks at every stage of the review and certification process to ensure compliance with regulatory and ethical standards.

**Enhancements Since November 2024**

To further strengthen the review and signatory process, LEO Pharma has implemented the following measures:

- Enhanced governance for the creation, review, approval, and withdrawal of materials, as well as the CAPA process, ensuring the process is more robust.
- Employed a dedicated contracted resource to provide technical review services and accuracy checks which is integrated into LEO processes.
- Hired additional signatories to support the certification together with planned investment to enable further training for the current signatory teams.
- Conducting weekly signatory and compliance meetings.
- Holding weekly cross-functional meetings between signatories and cross functional teams to ensure robust communication and efficient decision-making.
- Created decision logs to document signatory and compliance-related decisions, with oversight by the Medical Director and Compliance Lead; thereby giving greater visibility and accountability.

**2 Processes for withdrawal of material which is found to be incorrect**

The enclosed SOP (SOP_004781) outlines the controlled withdrawal process for promotional, non-promotional, and educational materials in the UK and Ireland. It ensures compliance with ABPI, IPHA, MHRA, and HPRA regulations, as well as internal guidelines. Below is a summary emphasising when and how materials should be withdrawn and the roles involved.

**Key Principles**: Withdrawals must be completed promptly, especially in cases of safety concerns or regulatory rulings. The process involves clear communication, thorough documentation, and strict reconciliation to ensure compliance. Roles are clearly defined, with the **Withdrawal Coordinator** playing a central role in managing the process.

**When Materials Should Be Withdrawn**

**Specific Triggers:**

- Following a ruling or complaint from regulatory bodies (e.g., ABPI, PMCPA, HPRA, IPHA).
- In response to promotional complaints from other pharmaceutical companies, healthcare professionals, or the public.
- Errors in materials, such as incorrect claims or safety concerns, requiring immediate action.

**Routine Withdrawals:**

- Updates to the Summary of Product Characteristics (SmPC) or Prescribing Information (PI).
- Periodic reviews, changes in marketing strategy, or product withdrawal.
- Replacement of outdated materials with updated versions.

**Safety Concerns:**

- Receipt of significant clinical information or safety updates necessitating immediate withdrawal.

**How Materials Should Be Withdrawn**

**Initiation:** Withdrawals for specific triggers are initiated by the **Medical Director** or **Compliance Department**.

- Routine withdrawals or those due to strategic reasons are initiated by the **Withdrawal Coordinator** (usually the Marketing Manager or Originator).

**Creation of Withdrawal Folder:** A dedicated folder is created on SharePoint, containing all relevant documentation, including the decision to withdraw, checklists, and correspondence.

**Notification: Internal Personnel:** Withdrawal instructions are sent via Microsoft Forms or email to relevant staff (e.g. Field Force, Medical, Regulatory Affairs). Urgent withdrawals require immediate follow-up until 100% compliance is achieved.

- **Third Parties:** Media agencies, Patient Support Programme (PSP) providers, and other vendors are instructed to destroy materials and confirm actions via email.
- **Customers/Patients**: If necessary, a letter is drafted and approved internally, detailing the reasons for withdrawal and required actions.

**Material Handling:**

- **Hard Copies:**

    1. For specific triggers (e.g., complaints or safety concerns), materials must be returned to the Marketing Materials Warehouse for destruction.

2. For routine withdrawals, materials can be shredded and disposed of in household waste or returned to the warehouse.

- **Digital Materials:**

1. IT ensures removal from platforms (e.g., Veeva, shared drives, websites, app stores, etc.).

2. Field Force personnel must sync devices to delete materials.

3. Third-party websites are notified, and written confirmation of removal is required.

**Reconciliation and Documentation:**

- The **Withdrawal Coordinator** reconciles returned materials against distributed quantities.

- The Marketing Materials Warehouse confirms destruction, and a reconciliation email is sent to the Medical Director/Compliance Department.

- The status of withdrawn materials is updated to "withdrawn/obsolete" in PromoMats, and the Active Material List is revised.

- All documentation, including withdrawal instructions, responses, and reconciliation records, is stored in the Withdrawal Folder. Approved copies of withdrawn materials are archived for future inspections or internal queries.

**Roles in the Withdrawal Process**

**Withdrawal Coordinator:**

- Oversees the entire withdrawal process, including communication, reconciliation, destruction, and filing.

- Ensures all relevant personnel and third parties are informed, and actions are completed.

**Medical Director/Compliance Department:**

- Initiates withdrawals for specific triggers.

- Reviews reconciliation data and confirms completion of the withdrawal process.

**Line Managers/Process Owners:**

- Communicate withdrawal instructions to their teams and ensure compliance.
- Update staff returning from extended leave on withdrawn materials.

**Field Force and Other Personnel:**

- Respond to withdrawal instructions, return or destroy materials, and confirm actions.

**Third Parties (e.g., Media Agencies, PSP Providers):**

- Destroy materials and confirm actions in writing.

This SOP ensures a structured and compliant approach to withdrawing materials, safe-guarding regulatory and ethical standards.

**3 Rationale for not withdrawing the app immediately**

As per our response dated 29 November 2024, following the identification of the errors in the app an immediate assessment was made regarding the impact on patient safety by two senior Medical Affairs employees for LEO Pharma:

- An immediate assessment was undertaken to check whether patients may have been provided with incorrect information which would lead to underdosing or overdosing.
- It was confirmed that the information in the app did not contain such errors, and it was therefore assessed as not having an impact on patient safety.

The rationale for this assessment was as follows:

- The app listed an incorrect volume of liquid for a syringe presentation in which the full volume of the syringe is always administered; these are ungraduated prophylaxis syringes and irrespective of what volume was listed on the app, the dose is always administered as one volume.
- The volume had been listed next to the prophylaxis doses to maintain regulatory consistency with the Patient Information Leaflet, however, in practice, when prophylaxis doses are administered for tinzaparin, information on volume is immaterial.
- Therefore, there was a recommendation at that time to update the app and replace the current version based on this assessment of patient safety.

The direction to update the app was then given to the Brand Lead in Thrombosis. In addition, a deviation was raised by the Compliance Lead. The reapproval and deviation

were considered in isolation, and the decision not to withdraw the app was not revisited. This was clearly an error; the Withdrawal SOP (SOP_004781) was not followed. A timeframe for updating the app was not discussed.

Mitigating Factors:

- At the time of this issue occurring (July 2024 to October 2024) there was a reorganisation of the thrombosis business impacting resource and head count; many colleagues' roles were placed at risk of redundancy. There was no dedicated medical support for the UK thrombosis business at this time. Whilst this does not negate the seriousness of the issue and decisions made, we believe this to be a contributing factor.

- Since such time, there has been a change in the approval process in the Thrombosis team to include a technical review by a LEO employee in addition to the review by the material owner and the full review and certification.

  There will also be a change to signatory resource, moving to a dedicated LEO approver and signatory.

  The Withdrawal SOP was updated in November 2024 as part of the routine review cycle. One key update now includes the ability for the Compliance Lead to instigate a withdrawal alongside the Medical Director. We believe these improvements make the approval and withdrawal processes and overall governance more robust.

**4 Conclusion**

LEO Pharma deeply regrets that it produced an inaccurate patient material on this occasion, and that appropriate actions were not taken to rectify the issue immediately.

We have learned from the error and will continue to strengthen our processes to ensure this cannot happen again.

**5 Appeal Board**

We welcome the opportunity to meet with the Appeal Board and discuss the matter further."

**APPEAL BOARD CONSIDERATION**

The Appeal Board remained concerned about the case which had been ruled in breach of the Code.

The Appeal Board heard from the representatives from LEO Pharma at the Appeal Board meeting that LEO Pharma was not experienced with creating and managing apps and had relied on external expertise in that regard.

The Appeal Board took account of LEO Pharma's explanation that, upon discovery of the errors within the app, an assessment had been made about the likely impact on patient safety. The

representatives at the meeting explained that if a dosage/volume error had related to graduated treatment syringes, that would have been assessed as a safety issue that could have resulted in patients receiving an incorrect dose or an incorrect volume, and that the app would have been withdrawn. In this case, because the error was confined to the prophylactic syringes, which had no graduation markings, and where a full dose was administered, LEO Pharma did not consider it a risk to patient safety and did not withdraw the app. The Appeal Board noted LEO Pharma's position that if the same thing happened today they would withdraw the app immediately.

The Appeal Board took account of LEO Pharma's submission that, following the patient safety assessment, the app was incorrectly moved to an "amend and renew" process, rather than following the withdrawal process. While LEO Pharma had a withdrawal process, it was not followed in this case. The Appeal Board expressed concern about gaps in LEO Pharma's processes and whether LEO Pharma had an appropriate process to enable the rapid withdrawal of a digital app. The Appeal Board was concerned about the processes for producing, maintaining and withdrawing an app.

The Appeal Board took account of the submissions from the representatives from LEO Pharma that the company had fully accepted the Panel's rulings of breaches of the Code, and that resources and governance had been enhanced, further training had been done, and processes had been reviewed and amended to add in further checks and scrutiny of such decisions. The Appeal Board recognised that LEO Pharma was committed to further improvements in this regard.

The Appeal Board observed that there had been an apparent lack of urgency in resolving the issues around this case. The Appeal Board welcomed the improvements LEO Pharma was making as a result of this case but stressed the need for urgency in this regard.

The Appeal Board gave consideration to the use of additional sanctions but decided, on balance, that none were required.

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| **Complaints received** | **7 November 2024** |
| **Case completed** | **18 March 2025** |
| **Appeal Board consideration** | **10 April 2025 and 22 May 2025** |