CASE AUTH/0304/10/24

VOLUNTARY ADMISSION BY PIERRE FABRE

Uncertified material circulated to UK oncologists

CASE SUMMARY

This case was in relation to a voluntary admission from Pierre Fabre regarding a promotional email sent on behalf of their European parent company by a third party to UK health professionals (HCPs). It was agreed to remove UK HCPs from the distribution list but human error by the third party publisher meant UK HCPs were included in the distribution list.

The outcome under the 2021 Code was:

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1	**Making a misleading claim**
Breach of Clause 6.4	**Making claims that did not reflect the available evidence regarding possible adverse reactions**
Breach of Clause 8.1	**Failing to certify promotional material**
Breach of Clause 12.1	**Failing to include up-to-date prescribing information**
Breach of Clause 12.4	**Failing to include prescribing information within the digital material or via direct, single click link**
Breach of Clause 12.9	**Failing to include the prominent adverse event reporting statement**
Breach of Clause 15.6	**Disguising promotional material**

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

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

FULL CASE REPORT

A voluntary admission was received from Pierre Fabre Ltd.

VOLUNTARY ADMISSION

The voluntary admission wording is reproduced below:

> "We regret to notify you that we have been informed by our Global colleagues that a promotional email for Nerlynx (neratinib) developed by them has been sent in error to a significant number of UK healthcare professionals. The promotional email and its approval did not comply with the requirements of the ABPI 2021 Code. The details of this are provided later in this letter but in summary we consider that the following clauses of the 2021 ABPI Code have been breached:
>
> - Clause 5.1
> - Clause 6.1
> - Clause 6.4
> - Clause 8.1
> - Clause 12.1
> - Clause 12.4
> - Clause 12.9
> - Clause 15.6
>
> Please see the email in question.
>
> ***Background***
>
> In October 2023, Pierre Fabre Medicament (our European parent company) entered into a contract with [named third-party publisher] to develop and distribute an email alert on certain guidelines published by the European Society of Medical Oncology (ESMO).
>
> The standard order agreement relating to this service provides details of the intended target audience for this email alert which initially included, amongst others, physicians in the UK specialising in haematology/oncology (clause 1.A.4). Further communication clarified that this was specifically for a target audience that had previously interacted with breast cancer content. Initially the statement of work was intended as an overarching agreement covering the services with the objective of having several assets for different territories (including the UK).
>
> The relevant ESMO guidelines were published in March 2024 and work began on the email alert in May 2024. The email alert was approved by our Global colleagues on 12th June 2024 to the standard of the EFPIA Code to provide information to European Oncologists.
>
> On 24th June, a Global representative instructed [named third-party publisher] by e-mail to remove UK oncologists/haematologists from the target audience. The removal of the UK healthcare professionals was confirmed by [named third-party publisher] on 24th June by the [representative].
>
> This information was then updated by [named third-party publisher] in the internal portal that they use as the point of reference for targeting information. On 26th June

[named third-party publisher] reiterated (via email) that the target audience would not include healthcare professionals from the UK.

However, the email in question was distributed by [named third-party publisher] on 3rd July by an unnamed member of staff to, amongst others, UK oncologists/haematologists who had previously interacted with breast cancer content on [named third-party publisher].

[Named third-party publisher] stated that the target audience listed in the standard order agreement was used to set up the distribution list and not the information from the internal portal that confirmed the details of the updated target audience.

The error of including UK physicians in the distribution list for the email alert was discovered by [named third-party publisher] only on 29 August when they were asked to share the statistics for the email alert that had been sent 3rd July.

[named third-party publisher] has not provided any explanation for the delay in identifying their error [named third-party publisher], our Global colleagues, and our UK company have not been contacted by UK healthcare professionals via medical information or our MSL team.

Our Global colleagues were notified by [named third-party publisher] of the error on Monday 2 September and the UK affiliate notified by Global on the same day. [named third-party publisher] have acknowledged full responsibility for the error and confirmed that Pierre Fabre had no knowledge that the email was going to be sent to the UK target audience.

Contact with UK healthcare professionals

It appears that of the 3,710 physicians who received the email in Europe, 887 were UK healthcare professionals on the basis of their e-mail address (approximately 24%).

Compliance activities

[A senior employee] is considering the matter, including the investigation thus far. We propose to update the panel in due course.

In the meantime, [named third-party publisher] has revised its process to include an additional target audience check at the point of email distribution and training has been provided to relevant [named third-party publisher] staff in that regard.

Analysis of Code breaches

The breaches are analysed on a scenario where the material was intended for a UK specialist oncology audience, although this was not the intent.

Given that the email alert was sent to UK healthcare professionals in error and the UK affiliate was not provided the opportunity to approve the email in that regard, we consider that there has been a failure to certify promotional material, in breach of

Clause 8.1 Further, certain obligatory information was missing from the email, specifically:

- Prescribing information was not included in the email nor was there a link to this, in breach of Clauses 12.1 and 12.4 and
- There was no adverse event reporting statement in the email, contrary to the requirements of Clause 12.9.

In addition, we have reviewed the content of the email alert, noting the following issues:

- The email address from which the alert was sent could give the impression that the email was a clinical update rather than a promotional email. On this basis this could be considered disguised promotion so in breach of Clause 15.6
- The content header should have been clearer that it was a promotional email on specific aspects of the ESMO guidelines and included absolute risk information. We consider this would amount to breaches of Clause 6.1.
- The intent should have been highlighted in the subject header of the email.
- Although mentioned in the email, we consider that it should have been more prominently stated that neratinib was subject to additional risk minimisation measures. We also do not consider it appropriate to refer to the safety profile of the product as 'predictable'. We would consider that this is therefore in breach of Clause 6.4

For ease of analysis, we have enclosed version of the e-mail with these comments to show what we would have adapted taking into consideration the requirements of the Code and readability for a busy healthcare professional.

Conclusion

We and our Global colleagues as well as [named third-party publisher] understand and appreciate that certification is the foundation of self-regulation.

Though our Global colleagues acted swiftly to notify us and were able to address the error, we consider that we and our Global colleagues have been badly let down by [named third-party publisher].

We accept that locally we are responsible for acts or omissions of Global colleagues which fall within the scope of the Code. We and our Global colleagues consider that there has been a failure to maintain high standards and we acknowledge a breach of Clause 5.1 in that regard.

We understand that the Panel may wish to consider the requirements of Clause 2. To our knowledge, no HCPs reported unforeseen events and [named third-party publisher] have taken prompt steps to inform us and to remedy the breaches.

We trust that the above and enclosed provides sufficient information for the Panel to consider this matter and rule on the breaches.

It is acknowledged that we will be asked to respond to this voluntary admission and to provide any additional information considered necessary in that regard."

When writing to Pierre Fabre, the PMCPA asked it to consider the requirements of Clauses 2, 5.1, 6.1, 6.4, 8.1, 12.1, 12.4, 12.9 and 15.6 of the 2021 Code.

PIERRE FABRE'S RESPONSE

The response from Pierre Fabre is reproduced below:

"Thank you for your letter of 2 October regarding the above cited voluntary admission by Pierre Fabre.

Our investigation into this matter has identified two key root causes, as detailed below:

- The standard order provided by Pierre Fabre Medicament (our European parent company) to [named third-party publisher] which included the intended target audience for the email alert was not updated following the decision and subsequent email instruction to [named third-party publisher] to remove the UK from the distribution list.
- The internal portal that [named third-party publisher] used as the point of reference for targeting information was not checked before the email alert was distributed by [named third-party publisher].

To address these causes specifically the following steps have been taken:

- An email was sent by our Global Regulatory & Compliance [employee] to all Global material owners reminding them of their responsibilities for third parties. These responsibilities included a need to update written instructions (including any statement of work) should requirements change.
    - This email required a read receipt from recipients; please find enclosed confirmation of that
- [named third-party publisher] have introduced an additional step in their process when sending such emails to ensure that the target audience is re-checked to confirm that any amendments have been implemented and training on this was provided to relevant [named third-party publisher] staff on 9 September 2024.

Further, the following broader preventive actions are planned:

- Annual external EFPIA and ABPI Code training for [named third-party publisher] staff is scheduled for 30 October 2024
- External bespoke mandatory training for impacted Global colleagues on when activities fall in scope of the Code and their responsibilities in relation to third parties (date TBC)

To inform our decision as to whether we should contact the health professional recipients of the email alert, we analysed enquiries to Medical Information to assess whether there was any indication of an increase in questions as a result of the email. From 3 July to date, enquiries relating to Nerlynx in the following areas were received:

Date received	Topic	Number of enquiries
17 July 2024	Ordering information and price details	1
24 July 2024	Stability of Nerlynx once bottle has been opened. Stability if decanting into amber bottle.	1
23 August 2024	Dose administration, swallowing difficulties	1
10 September 2024	IRELAND - Request for neratinib HCP materials and SmPC to be posted	1
13 September 2024	Request for Risk Minimisation Measure – Educational Materials to Nerlyfe study site	1
4 October 2024	Request for Risk Minimisation Measure – Educational Materials (+ adverse event report for Diarrhoea)	1

Based on this analysis, we did not consider there was any indication that the email had caused confusion in the relevant medical community and therefore decided that there was no need to contact recipients of the email alert.

We have no further comment on the clauses referred to in our letter of 30 September. We note that we have been asked to respond to the requirements of Clause 2; as previously stated we understand that the Panel may want to consider this clause in relation to this matter.

Finally, please find enclosed the following requested information:

- Summary of Product Characteristics (SPC) for Nerlynx
- European Society of Medical Oncology (ESMO) guidelines

In relation to the qualification of the signatory that certified the email at issue, as it was not intended for a UK audience nor was it originated by the UK, it was not certified by a signatory as defined in Clause 8.1.

I trust that the above and enclosed provides sufficient information for the Panel to consider this matter. I am of course aware that we will be asked to respond to this voluntary admission and to provide any additional information considered necessary in that regard."

PANEL RULING

The voluntary admission related to a promotional email sent in error to a significant number of UK health professionals by a third-party publisher on behalf of Pierre Fabre's European parent company.

The Panel noted the mailing appeared to form part of a global initiative by Pierre Fabre's parent company. Pierre Fabre submitted that the intended target audience initially included, amongst others, physicians in the UK specialising in haematology/oncology that had previously interacted with breast cancer content. In June 2024, a global representative instructed the third-party to remove UK health professionals from the mailing list, and this was confirmed. However, in

September 2024, the UK affiliate was notified by its global counterpart that, due to an error, the email had been sent to UK health professionals in July 2024.

The Panel noted 887 of the 3,710 physicians who received the email in Europe were UK health professionals. It was a well-established principle that UK companies were responsible for the acts or omissions of overseas parents or affiliates that came within the scope of the Code. The email at issue had been targeted at and distributed to UK health professionals and therefore came within the scope of the UK Code.

The email at issue was titled "New ESMO Guidelines for HER2+ eBC" and came from the "Clinical Update" email address of the third-party publisher. The promotional email included Nerlynx's indication followed by a visual illustration of the ESMO guidelines and a number of claims. Pierre Fabre's logo was included at the bottom of the email beneath the references.

The Panel noted the email promoted Nerlynx but that there was no prescribing information. A **breach of Clauses 12.1 and 12.4** was ruled, as acknowledged by Pierre Fabre. The email also did not include a prominent adverse event reporting statement as required by the Code for promotional materials and a **breach of Clause 12.9** was ruled, as acknowledged by Pierre Fabre.

The promotional email had not been certified for use in the UK prior to its issue and a **breach of Clause 8.1** was ruled, as acknowledged by Pierre Fabre.

The Panel noted that the Code did not require promotional material to be labelled as such, however, it must not be disguised. The supplementary information to Clause 15.6 included that promotional material must not imply that the contents are non-promotional.

The Panel considered the email titled "New ESMO Guidelines for HER2+ eBC" that came from the clinical update email address from a third-party publisher, gave the impression of a non-promotional clinical update email, which was not so. Only on opening the email was it obvious that the email was not a clinical update but promotional. In this regard, Pierre Fabre submitted the intent should have been highlighted in the header of the email. The Panel considered that, on balance, the nature of the email had been disguised by the title and sender and a **breach of Clause 15.6** was ruled**,** as acknowledged by Pierre Fabre.

With regards to the contents of the email, Pierre Fabre admitted concerns with invasive disease-free survival (iDFS) data presented in the email which was presented in large font in a visual graphic and stated "51% reduction in the risk of recurrence at 2 years with Nerlynx vs. placebo". The Panel noted Pierre Fabre's comments that the prominent claim "highlights the relative risk but not the absolute risk. Both should be included and highlighted evenly and clearly to allow an accurate representation of the data".

The supplementary information to Clause 6.1 included that referring only to relative risk, especially with regard to risk reduction, can make a medicine appear more effective than it actually is. In order to assess the clinical impact of an outcome, the reader also needs to know the absolute risk involved. In that regard, relative risk should never be referred to without also referring to the absolute risk.

In the Panel's view, if relative risk reduction is stated, the absolute risk should be prominent and presented in such a way as to allow the reader to make an immediate assessment of the clinical impact of an outcome.

The Panel noted the claim at issue was followed by a footnote, in smaller font and of similar prominence to the references and disclaimers, that read "iDFS: 95.3% with Nerlynx (n=670) vs 90.8% with placebo (n=664). HR: 0.49 (95% CI: 0.30-0.78) p=0.002". The Panel had not been provided with the cited reference but considered the footnote appeared to refer to absolute risk.

In the Panel's view, the email highlighted and placed disproportionate emphasis on the relative risk reduction of 51% and, in that regard, the immediate impression given by the data in the email was a misleading comparison between Nerlynx and placebo. A breach of **Clause 6.1** was ruled, as acknowledged by Pierre Fabre.

Pierre Fabre also accepted a breach of Clause 6.4 in relation to the safety section in the email which appeared in a blue box and began with the statement "Nerlynx has a predictable tolerability profile" in bold and a list of common adverse events followed by the recommendation to initiate anti-diarrhoeal prophylaxis with the first dose of Nerlynx.

The Panel noted Pierre Fabre's comments that it would have removed the statement regarding the predictable tolerability profile and would have highlighted the grade of adverse event along with making it clear and prominent. Pierre Fabre further submitted it should have been more prominently stated that Nerlynx was subject to additional risk minimisation measures.

The Panel did not have any risk minimisation materials before it but noted they related to diarrhoea. Section 4.4, Special warnings and precautions for use, of the Nerlynx SPC included:

> "Diarrhoea has been reported during treatment with Nerlynx (see sections 4.2 and 4.8). The diarrhoea may be severe and associated with dehydration.
>
> Diarrhoea generally occurs early during the first or second week of treatment with Nerlynx and may be recurrent.
>
> Patients should be instructed to initiate prophylactic treatment with an anti-diarrhoeal medicinal product with the first dose of Nerlynx, and maintain regular dosing of the anti-diarrhoeal medicinal product during the first 1-2 months of Nerlynx treatment, titrating to 1-2 bowel movements per day."

The Panel took account of how the safety information was presented in the email. The Panel noted the email included the statements "primary anti-diarrhoeal prophylaxis was not protocol specified in the ExteNET trial" and "it is recommended to initiate anti-diarrhoeal prophylaxis with the first dose of Nerlynx", the latter of which was provided in a different text colour in bold.

While information regarding anti-diarrhoeal prophylaxis had been included, the Panel considered it was unclear that this formed part of Nerlynx's risk minimisation measures. Reference to "this medicinal product is subject to risk minimisation measures" appeared further down, at the bottom of the email, in small bold font beneath the references section. In the Panel's view, this was insufficient.

Clause 6.4 included that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It was an established principle under the Code that material had to be capable of standing alone.

The Panel considered the misleading impression of the safety information provided was such that it did not reflect the available evidence or was capable of substantiation. A **breach of Clause 6.4** was ruled, as acknowledged by Pierre Fabre.

The Panel noted its rulings of breaches of the Code above including that the promotional email, distributed to UK health professionals, was misleading and did not have the prescribing information or adverse event reporting statement; such obligatory information was an important contributor to patient safety. In the Panel's view, the circumstances of the case were such that high standards had not been maintained and a **breach of Clause 5.1** was ruled, as acknowledged by Pierre Fabre.

The Panel considered Pierre Fabre had been let down by the third-party publisher. In the Panel's view, its concerns were adequately covered by its breach rulings above and the particular circumstances of this case did not warrant a breach of Clause 2, which was a sign of particular censure. The Panel therefore ruled **no breach of Clause 2**.

Complaint received **30 September 2024**

Case completed **18 March 2025**