NO BREACH OF THE CODE

CASE AUTH/3759/4/23

COMPLAINANT v BOEHRINGER INGELHEIM

Activity at the British Sarcoma Group (BSG) Conference 2023

CASE SUMMARY

This case related to the allegations about the distribution of flyers concerning a Phase 2/3 clinical trial to delegates at the BSG Conference.

The outcome under the 2021 Code was:

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 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 5.6	**Requirement that material should only be made available to those groups of people whose need for or interest in it can reasonably be assumed**
No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**

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

FULL CASE REPORT

A complaint was received from an anonymous, non-contactable complainant about Boehringer Ingelheim.

COMPLAINT

The complainant stated that they wished to draw attention to an activity carried out by Boehringer Ingelheim at the BSG conference in March 2023. The company was running a phase 2/3 clinical trial in liposarcoma with MDM2 molecule. A leaflet which described the trail*[sic*] to recruit patients was included in conference bags. Hence every registrant attendee received this leaflet. Five categories of professionals were allowed to register, including medical students, Nurses/ANPs, consultants, junior doctors and researchers. Patient groups also attended. The leaflet provided a brief description of the trial, and it implied the licensed indication of this drug (e.g. First line MDM2 amplified dedifferentiated liposarcoma in adult patients). Because this conference was open to a broader audience, not only to doctors who saw/treated sarcoma patients, it was crucial to evaluate how appropriately this leaflet be distributed to all the attendees. As an investigator for similar research, they had not seen pharmaceutical companies would reach clinicians with full details of the study before clinicians showed interest in participating in trials. Any attendee who was not an HCP (such as research

scientists, patient groups or medical students) could be considered a member of the public. In the UK pharmaceutical companies were not allowed to recruit patients directly by reaching out to members of the public. If that was acceptable, companies should be able to promote their clinical studies on social media for speedy recruitment. Furthermore, the company received an innovation passport in October last year for this investigational molecule to treat de-differentiated liposarcoma. An innovation passport was the first step in the innovation Licensing and Access Pathway (ILAP) which accelerated obtaining marketing authorisation. Also, the ILAP process would allow companies to get MA with phase 2 data. In this scenario, this activity could be considered a pre-license promotion. (as stated above, the licenced indication was very much evident on the leaflet). Additionally, the leaflet included a Boehringer Ingelheim email address for contact details for potential inquiries for recruitment. Therefore, this leaflet solicited inquiries for unlicensed medication from HCPs and non-HCPs. Finally, the disclaimer 'This investigational compound is not approved for use in the United Kingdom or globally and its efficacy and safety has not been established' was ambiguous. If this molecule was not approved for use, why was it used in a clinical study? Was it ethical?

When writing to Boehringer Ingelheim, the Authority asked it to consider the requirements of Clauses 3.1, 5.6, 6.1 and 5.1 of the Code.

RESPONSE

Boehringer Ingelheim Limited stated that it took compliance with the Code very seriously. Boehringer Ingelheim had steps in place to ensure robust procedures continued to underpin all its activities and Boehringer Ingelheim embraced a compliance culture that was fully embedded into the business with the support of senior leadership and the Ethics & Compliance Department.

As per the requirements of the Code, Boehringer Ingelheim had a Standing Operating Procedure ('SOP') in place for Materials Approval, which ensured that all materials were reviewed and certified for accuracy and compliance with Code requirements prior to being made available. Boehringer Ingelheim also ensured that all relevant staff completed SOP training, and that training emphasises the requirements for digital materials; in addition, other relevant training such as quarterly Code case review was expected for all staff involved in materials development and approval.

Boehringer Ingelheim stated that the complaint referred to the distribution of a leaflet at the British Sarcoma Group (BSG) Conference 2023 to raise awareness of a clinical trial in a rare disease space managed by the highly specialised attendees.

Overall, Boehringer Ingelheim did not believe that it had breached Clauses 3.1, 5.6, 6.1 and 5.1 of the 2021 Code, and therefore had upheld high standards.

- The leaflet included a clear disclaimer that the Boehringer Ingelheim molecule was an investigational compound.
- Boehringer Ingelheim molecule was referred to as 'investigational agent' and there was no reference to its mode of action; the molecule was not named.
- The flyer was targeted and disseminated to a highly specialised HCP audience whose interest it could reasonably be assumed.
- The content of the leaflet was limited to factual and non-promotional information on the clinical trial only, without specifics on its design.

- The information provided on the leaflet was accurate, balanced, fair, objective, and unambiguous.

For your ease of reference, Boehringer Ingelheim had addressed each question below.

Response to questions raised by the PMCPA:

1. An original or a good quality colour copy of the material at issue and a copy of the certificate approving the material in question.

Response: Boehringer Ingelheim stated that a copy of the material in question was provided together with the metadata. The material was certified on the 20/01/2023 by a PMCPA registered signatory.

The material in question was certified as a non-promotional material suitable for UK healthcare professionals (HCPs), healthcare organisations (HCOs) and patient organisation representatives, however the flyer itself had a statement that the material was for UK HCPs only. As per the metadata related to the job bag, the material was categorised as Information Sheet and intended to be distributed as a standalone A5 printout to be included in the delegate conference bags and as an A5 insert into the print and digital conference programme on the BSG Conference website.

2. Please provide details as to how the material was distributed and to whom the material was directed

Response: Boehringer Ingelheim stated that the material was distributed to all attendees at the 2023 BSG Conference, the association of the specialist clinicians, nurses and supporting professionals who treated patients with sarcoma, a rare disease, in England, Wales, Scotland and Northern Ireland, with agenda topics covering advances in sarcoma research and patient management. An email received from the conference organisers confirmed that all BSG attendees were HCPs. Given the highly specialised audience, which was a multi professional sarcoma treating community, and the rarity of the disease for which clinical trial recruitment could be particularly challenging, to include a material aimed at encouraging recruitment of eligible patients to the ongoing Boehringer Ingelheim trial was deemed appropriate.

The flyer was submitted for information to the HRA (Health Research Authority) as the distribution of the flyer to HCPs to encourage patient recruitment constituted a non-substantial amendment to the existing ethics approval. The IRAS reference number was also included at the bottom page of the flyer.

The flyer was distributed to all delegates as a one-page A5 size flyer within their conference bags and was also included as a one-page A5 size insert in the Conference Programme, which was available as print and as digital content on the BSG conference website. The flyer had a clear statement at the top that the material was for UK HCPs only.

The flyer contained factual and non-promotional information about the clinical trial, in compliance with the supplementary information to Clause 4.6, which aimed to raise awareness of recruitment of eligible dedifferentiated liposarcoma (DDLPS) patients to the ongoing Boehringer Ingelheim sponsored Brightline-1 clinical trial.

Given the highly specialised audience, which was a multi-professional sarcoma community of HCPs it was reasonable to include a flyer aimed at recruitment of interested HCPs and eligible DDLPS patients to the ongoing BI UK sponsored clinical trial Brightline-1; a Phase II/III, randomised, open-label, multi-centre study. DDLPS was a rare disease for which trial recruitment could be particularly challenging where many patients travel long distances to receive treatment given the rarity of the disease.

The flyer did not mention any specific medicine name or mode of action and was non-promotional in nature in compliance with the supplementary information to Clause 4.6. It also provided an email address allowing interested UK HCPs involved in the management of sarcoma, who might have eligible patients that wished to be enrolled, to contact Boehringer Ingelheim for further information on the study.

3. Please provide details of Boehringer Ingelheim's presence at the conference and information about the conference, including location and the make-up of the delegates/attendees.

Response: Boehringer Ingelheim stated that the BSG Conference was an Annual Conference multi-pharma sponsored sarcoma event which was held at the International Conference Centre Wales. The meeting was attended by 270 specialist clinicians, nurses and supporting professionals who treated patients with sarcoma in the UK. The conference organisers confirmed that all BSG attendees were HCPs.

As a platinum sponsor, Boehringer Ingelheim offered BSG financial contribution towards the meeting costs. As part of the sponsorship package, Boehringer Ingelheim was acknowledged as a platinum sponsor on the BSG Conference website pages. The package also included a 50-word company information on the Conference website with a link to the Boehringer Ingelheim company home page. The Boehringer Ingelheim logo and company description was included in the Abstract Book and Conference Programme. An A6 pocket notebook with a single pen was handed to delegates from the registration desk on arrival.

Boehringer Ingelheim stated that it was also given a 30 minute 'Sponsor Symposium' which was fully organised and funded by Boehringer Ingelheim. This was an educational non-promotional symposium entitled 'Surgical Advances in Soft Tissue Sarcoma' that was delivered by a leading surgeon. Additionally, a full-page advertisement in the Programme and Abstract Book was also offered to Boehringer Ingelheim. The material in question was distributed to delegates as a one-page A5 size flyer within their conference bags and was also included as a one-page A5 size insert in the Conference Programme, which was available as print and as digital content on the BSG conference website.

As part of the sponsorship package, Boehringer Ingelheim was also provided with complimentary full conference registrations and four Boehringer Ingelheim employees as well as an employee from Boehringer Ingelheim Global attended the conference.

4. Copies of all references cited in your response and a copy of any relevant summary of product characteristics (SPC).

Response: Boehringer Ingelheim referred to the references section. No SPC was available because the flyer related to an investigational molecule.

Response to the Clauses asked to be considered

Boehringer Ingelheim addressed the specific concerns that were raised by the complainant to the PMCPA.

Clause 3.1 A medicine must not be promoted prior to the grant of the marketing authorisation

Special care was taken to ensure the material did not constitute promotion of the investigational compound, in compliance with Clause 3.1 and its supplementary information. Given that the Phase III trial had not yet commenced, Boehringer Ingelheim believed this conference took place at least 18 months away from any potential license submission.

The complainant alleged the flyer implied the licensed indication of the drug; however, the flyer did not name the molecule being investigated, in fact the molecule did not yet have a drug name as its efficacy and safety was not yet established and so could not yet be considered a medicine. Additionally, there was no claim related to efficacy or safety which would then be deemed promotion of a medicine. The content of the flyer was limited to factual and non-promotional information about the clinical trial, as per the supplementary information to Clause 4.6, and included the clinical trial's key eligibility criteria, primary and secondary endpoints but no specifics on study design.

The investigational molecule did not yet have a drug name and could not be considered a viable pharmaceutical medicine as it was still in early clinical development. As stated in Case AUTH/3478/2/21 it was clear that if a molecule was in early development and had not yet been named, it could not be considered a viable pharmaceutical medicine. In addition, the investigational compound was not available outside of the strict regulations of an approved clinical trial and associated trial sites.

The disclaimer at the bottom end of the flyer clearly stated that it was an investigational molecule which was not approved for use in the UK or anywhere else and that its efficacy and safety had not been established yet due to the ongoing nature of the trial.

The link to clinicaltrials.gov was deliberately omitted from the flyer to prevent HCPs from being able to access the molecule name/number and instead the Boehringer Ingelheim email address was included with the sole purpose of providing a contact point to Boehringer Ingelheim for further information about the trial.

Boehringer Ingelheim stated therefore that it did not feel that an unnamed investigational molecule, which was being evaluated in an early phase clinical trial setting and therefore not currently available to both patients and HCPs in the UK outside the context of the trial, with no mention of mode of action or claims around safety or efficacy could constitute pre-licence promotion and thus refuted the allegation of a breach to Clause 3.1.

The complainant referred to the Innovation Licensing and Access Pathway (ILAP), which was a regulatory framework to obtain feedback on the clinical development of a molecule and guidance on what was required for an accelerated license submission. It provided opportunities for enhanced regulatory and other stakeholder input during the clinical development stages of the molecule which could be entered from pre-clinical development up until Phase 3. The gateway to entry into the ILAP pathway was via the 'Innovation Passport' (IP) which

incorporated broad and inclusive concepts of innovation and patient need. The Boehringer Ingelheim investigational compound was awarded an IP in October 2022. Boehringer Ingelheim was currently considering the choice to undertake further steps to obtain formal feedback via the ILAP framework and if so, would then have to consider how this feedback was incorporated into any future clinical development plans and license submission. As no commitment was made during the ILAP process to undertake any license submission Boehringer Ingelheim did not feel the ILAP process equated to a marketing authorisation submission and therefore refuted the claim that this flyer constituted pre-license promotion. Given that the Phase III trial had not yet commenced Boehringer Ingelheim believed this conference took place at least 18 months away from any potential license submission.

Clause 5.6 *Material should only be provided to those groups of people whose need for or interest in it can reasonably be assumed, and it should be tailored to the targeted audience*

Boehringer Ingelheim stated that the material in question aimed to raise awareness of recruitment of eligible DDLPS patients to the ongoing Boehringer Ingelheim-sponsored Brightline-1 clinical trial and contained factual and non-promotional information about the trial, in compliance with the supplementary information to Clause 4.6.

Given the highly specialised audience of the BSG 2023 Annual Conference, which was a multi-professional sarcoma-treating HCP community, it was appropriate to distribute a one-page flyer aimed at encouraging recruitment of eligible DDLPS patients to the ongoing Boehringer Ingelheim trial. The highly specialised targeted audience was appropriate given BSG's aim to support research and the development of more effective treatment and care pathways, and the rarity of DDLPS for which clinical trial recruitment could be particularly challenging. The flyer was certified as non-promotional material for this intended audience.

The flyer also provided an email address, allowing interested UK HCPs involved in the management of sarcoma who might have eligible patients that wished to take part to contact Boehringer Ingelheim for further information on the study.

Given the PMCPA had issued guidance on raising clinical trial awareness via social media, (PMCPA Social Media Guidance, 2023) Boehringer Ingelheim believed this flyer followed the principles and spirit of this guidance and the Code and was appropriate for the highly specialised audience at the conference, and so refuted a breach of Clause 5.6.

Clause 6.1 Information, claims and comparisons

As stated above, the content of the flyer was limited to factual and nonpromotional information about the clinical trial, in compliance with the supplementary information to Clause 4.6, and included the clinical trial's key eligibility criteria, primary and secondary endpoints as per the clinical trial protocol. MDM2 overexpression/amplification was a key element of the patient inclusion criteria as patients that did not have this genotype would not be able to enrol in the trial.

The flyer included a clear disclaimer that the material itself was for HCPs only, that the investigational compound being evaluated in the clinical trial was not approved for use in the UK or anywhere else globally and that its efficacy and safety had not been established as the molecule was still in early clinical development. The flyer informed the reader about the nature

of the trial and the way to find out more information from Boehringer Ingelheim if the HCP were interested in participating.

Based on the above, Boehringer Ingelheim did not believe that Clause 6.1 was breached as the information about the clinical trial provided on the leaflet itself was accurate, balanced, fair, objective, and unambiguous.

Clause 5.1 High standards must be maintained at all times

The development of this flyer took into account careful consideration of all the required Code requirements at every stage of development, review and approval. The method of dissemination and the content of the leaflet, which was limited to factual and non-promotional information on the trial, did not constitute pre-licence promotion to HCPs. Further to this, Boehringer Ingelheim also believed that the language used, including its layout, intended audience and overall impression, was appropriate to the targeted audience. Given the PMCPA had issued guidance on raising clinical trial awareness via social media (PMCPA Social Media Guidance, 2023) Boehringer Ingelheim believed this flyer fully followed the principles and spirit of this guidance and was appropriate for the audience at the conference.

Moreover, the intention to distribute the one-page flyer at the BSG conference was processed appropriately through MHRA Ethics Approval and an IRAS number was included at the bottom end of the material.

As such Boehringer Ingelheim refuted that it had breached Clause 5.1 and failed to maintain high standards.

Summary

For the reasons stated above, Boehringer Ingelheim did not believe that it had breached Clauses 3.1, 5.6, 6.1 or 5.1 of the 2021 Code, and therefore had upheld high standards.

- The content of the leaflet was limited to factual and non-promotional information on the clinical trial only, without specifics on design.
- The information provided on the leaflet was accurate, balanced, fair, objective, and unambiguous.
- The leaflet included a clear disclaimer that the Boehringer Ingelheim molecule was an investigational compound; because the name of the compound was not included on the flyer, it could not be considered a pharmaceutical medicine as its safety and efficacy were not yet defined as the compound was still in early clinical development.
- The flyer was targeted and disseminated to a highly specialised HCP audience whose interest in the trial could reasonably be assumed. Furthermore, the ILAP framework provided the opportunity for enhanced regulatory and other stakeholder input during the clinical development of a molecule and equated neither to a decision to progress to seek marketing authorisation, nor to a marketing authorisation submission.

PANEL RULING

The Panel noted the complaint related to multiple allegations about the proactive dissemination of a flyer about a Phase 2/3 clinical trial included in the conference delegate bags at the British Sarcoma Group (BSG) Conference 2023.

The Panel noted that the flyer had 'For UK healthcare professionals only' at the top followed by the names of the trial and the sponsoring company and its logo. The main body of the flyer had a bright blue flash stating the purpose of the trial 'A phase 2/3 randomised controlled study of an investigational agent compared with doxorubicin in first line dedifferentiated liposarcoma (DDLPS)'. This was followed by an orange flash informing readers that the trial was currently recruiting and further information could be obtained from Boehringer Ingelheim via the contact email or QR code provided. A smaller orange flash containing the word 'Eligibility' highlighted a bulleted list of the key eligibility criteria and below which were two blue flashes the first stating the primary endpoint of the trial and the second, which was paler in colour and in a smaller font, listed the secondary endpoints. A reminder that the information related to an investigational molecule which was not approved for use and its safety and efficacy had not been established appeared at the bottom of the main body of flyer above a list of the full terms for the acronyms used. The footer, a blue band, included the job code, date of preparation, IRAS (research registration) code and the tagline 'Let's collaborate' 'Oncology from Boehringer Ingelheim'.

The Panel noted the complainant had raised several concerns that the flyer constituted pre-licence promotion. They stated that the investigational molecule had been granted an innovation passport which accelerated the grant of a marketing authorisation. Boehringer Ingelheim submitted that while the grant of an innovation passport could result in an accelerated assessment of a future submission for a marketing authorisation application this was not inevitable and according to Boehringer Ingelheim no commitment had been made to during the Innovation Licensing and Access Pathway (ILAP) process to undertake submission of an application for a marketing authorisation. The compound was at Phase 2/3 clinical trial stage, Boehringer Ingelheim had submitted that it was at a relatively early stage of development, in fact the molecule did not yet have a drug name as its efficacy and safety was not yet established and so could not yet be considered a medicine. In the Panel's view, regardless of the grant of the Innovation Passport, no application for a license had been submitted and was some way off. Accordingly, the Panel did not consider that the investigational molecule could be considered a medicine at the time of the BSG conference.

In this regard the Panel further noted that the complainant had alleged that that the future licensed indication was implied in the description of the purpose of the trial and that the inclusion of the Boehringer Ingelheim email address solicited inquiries about an unlicensed medicine. Noting the above the Panel ruled that no medicine had been promoted prior to the grant of a marketing authorisation as alleged. **No breach of Clause 3.1** was ruled by the Panel.

The Panel noted that the complainant had alleged that some conference attendees were medical students, research scientists and individuals from patient groups and thus were members of the public. The conference organiser had confirmed to Boehringer Ingelheim that all attendees were health professionals working in sarcoma, despite the conference having registration categories for medical students and research scientists who, for the purposes of the Code, were not health professionals. Boehringer Ingelheim provided the metadata and certificate to demonstrate that the flyer had been certified for distribution to delegates (mostly health professionals but also healthcare organisations and patient organisation representatives) attending the BSG annual conference. The Panel noted the flyer was marked 'For UK Healthcare Professionals Only' but considered that despite the statement it was likely the flyer would have been provided to attendees who while not health professionals were working in or had a particular interest in the therapeutic area. In the Panel's view it was not entirely clear who

had received the flyer, which was included in the conference delegate bags and as an insert in the conference programme.

In this regard the Panel noted that recruiting participants for clinical trials could be complex and challenging and would be particularly so in rare diseases. It would be to patients' benefit to advertise that a trial was recruiting including via social media. The PMCPA social media guidance provided information in this regard. Further, the Code did not prohibit companies from notifying health professionals, patient organisations or patients about clinical trials provided the information met the requirements of the Code including Clause 5.6 which required material to be provided or made available only to those groups of people whose need for or interest in it could reasonably be assumed and that the material was tailored to the audience to whom it was directed. The appropriateness of distributing the flyer to all categories of potential conference delegates would depend on the layout, content and overall impression created by the A5 size flyer.

In considering the layout, contents and overall impression of the flyer the Panel was mindful of the requirements of Clause 6.1 and its supplementary information which made it clear that application of the Clause was not limited to information or claims of a medical or scientific nature but could be more broadly applied.

In the Panel's view the information provided was factual, objective and unambiguous, did not go beyond what was essential to raise awareness of the clinical trial and did not create a misleading impression, raise unfounded hopes of entry into the trial or successful treatment outcomes. Notwithstanding the statement on the flyer that it was intended for UK health professionals only the Panel considered the flyer was appropriate for use with all potential attendees at the conference, health professionals, research scientists and patient organisations working in sarcoma. As such the Panel considered that the flyer was not in breach of the Code and therefore it ruled **no breach of Clauses 6.1 and 5.6**.

The Panel noted Boehringer Ingelheim's submission that it had taken careful consideration of all the required Code requirements at every stage of development, review and approval of the flyer, including that the intention to distribute the one-page flyer at the BSG conference had been processed through MHRA Ethics Approval and an IRAS number included at the bottom end of the material. Noting its findings above the Panel did not consider that Boehringer Ingelheim's action in developing and distributing the flyer indicated a failure to maintain high standards and **no breach of Clause 5.1** was ruled.

Complaint received **4 April 2023**

Case completed **28 May 2024**