CASE AUTH/2032/11/07 NO BREACH OF THE CODE

BRISTOL-MYERS SQUIBB v NOVARTIS

Alleged disguised promotion of unlicensed medicine

Bristol-Myers Squibb alleged that ENACT (Expanding Nilotinib Access Clinical Trial), represented disguised promotion by Novartis of an unlicensed medicine. By providing inadequate written consent information for patients Novartis had not conducted itself to the high standards expected of the industry. Bristol-Myers Squibb alleged that because Novartis had misused a clinical trial as disguised promotion of an unlicensed medicine and compromised patient safety and integrity it had brought discredit upon and reduced confidence in the industry in breach of Clause 2 of the Code.

Bristol-Myers Squibb explained that the treatment of chronic myeloid leukaemia (CML) was revolutionised by the introduction of Glivec (imatinib) by Novartis over five years ago. Since this major breakthrough the problem of resistance or intolerance to Glivec had, regrettably, increased. Bristol-Myers Squibb received a marketing authorization for Sprycel (dasatinib) in November 2006, specifically for the treatment of adult CML patients who were resistant or intolerant to imatinib. Novartis was now developing nilotinib, for which it had submitted a marketing authorization application seeking a licence for the same patient population, adults who developed resistance or intolerance to imatinib. Nilotinib was a direct competitor to Sprycel.

According to the ENACT website, 'ENACT is a global access program for Nilotinib. It was created to provide early access to the drug's promising effects during the regulatory review. Eligible patients will receive Nilotinib through sites worldwide, at no cost, until it becomes commercially available'. Despite a statement on the website that the trial was intended to allow early access to CML patients 'who are either resistant or intolerant to treatment with Glivec (imatinib) *and who do not have acceptable treatment options*' (emphasis added), the study in the UK did not specify that patients had to be ineligible for Sprycel treatment before being considered for entry into this trial.

Bristol-Myers Squibb was concerned that the website displayed a promotional intent in respect of nilotinib, which was inappropriate as it was unlicensed. The title of ENACT (Expanding Nilotinib Access Clinical Trial) and the comment on the website that ENACT 'was created to provide early access to the drug's *promising effects* during the regulatory review' (emphasis added), when considered in the context of the glowing testimony to nilotinib as being 'Built on the vast knowledge and experience Novartis acquired during the development of imatinib…' created a promotional impression.

Despite the website stating that ENACT was intended for imatinib-resistant or intolerant CML patients who had no other treatment options, the fact that the selection criteria for the study ignored direct or indirect reference to Sprycel as a licensed option was further evidence that by sponsoring this trial Novartis intended to promote nilotinib.

The Panel noted that ENACT was a worldwide, multicentre, expanded access programme for Novartis' product, nilotinib. Four UK medical centres were listed on the ENACT website as actively recruiting patients. The Panel considered that the arrangements for the expanded access programme were subject to the Code.

The Panel noted that companies often provided medicines to those who had participated in clinical trials and/or other patients who might benefit from treatment before the medicine was licensed and commercially available. It was a question of whether the arrangements were reasonable. It could be argued that the expanded access programme met the definition of promotion given in the Code in that it promoted the administration of nilotinib.

It was explained on the website that the expanded access programme provided access to nilotinib to eligible patients who had no other treatment options until it was commercially available in individual countries. Individual eligibility was determined by investigators. The Panel noted Novartis' explanation that as the programme only applied to patients considered to be inappropriate for other therapeutic options, reference to resistance or intolerance to other therapies within the programme's inclusion/exclusion criteria was superfluous. The Panel noted that the programme had ethical committee approval. The Panel did not consider that Bristol-Myers Squibb had established that the ENACT programme was disguised promotion as alleged. The failure to state that UK patients had to be resistant or intolerant to Sprycel did not suffice in this regard. No breach of the Code was ruled including of Clause 2.

Bristol-Myers Squibb Pharmaceuticals Limited complained about a number of activities undertaken by Novartis Pharmaceuticals UK Ltd. A number of queries and issues were raised including whether the requirements of Paragraph 5.2 of the Constitution and Procedure had been met and whether a prima facie case had been established.

The only allegation to be considered by the Panel related to ENACT (Expanding Nilotinib Access Clinical Trial) constituting disguised promotion.

COMPLAINT

Bristol-Myers Squibb alleged that ENACT represented disguised promotion of an unlicensed medicine in breach of Clauses 10.1 and 3.1 of the Code. By providing inadequate written consent information for patients Novartis had not conducted itself to the high standards expected of the industry in breach of Clause 9.1. The misuse of a clinical trial as disguised promotion of an unlicensed medicine and the compromising of patient safety and integrity led Bristol-Myers Squibb to conclude that Novartis had brought discredit upon and reduced confidence in the industry in breach of Clause 2.

Background to the therapy area and its treatment

The treatment of chronic myeloid leukaemia (CML) was revolutionised by the introduction of Glivec (imatinib) by Novartis over five years ago. One of the noticeable elements associated with the introduction of imatinib was the great increase in the cost of treating CML, with consequent severe pressure on budgets within NHS oncology services.

Since this major breakthrough in the management of CML, the problem of resistance or intolerance to imatinib had, regrettably, increased. Bristol-Myers Squibb received a marketing authorization for its product Sprycel (dasatinib) in November 2006. Sprycel was specifically licensed for the treatment of adult CML patients who were resistant or intolerant to imatinib.

Novartis was developing nilotinib, for which it sought a marketing authorization for the same patient population, adults who developed resistance or intolerance to imatinib. Nilotinib was a direct competitor to Sprycel.

Background to ENACT

The ENACT website stated, 'ENACT is a global access program for Nilotinib. It was created to provide early access to the drug's promising effects during the regulatory review. Eligible patients will receive Nilotinib through sites worldwide, at no cost, until it becomes commercially available'. Despite the statement on the website that the trial was intended to allow early access to CML patients 'who are either resistant or intolerant to treatment with Glivec (imatinib) **and who do not have acceptable treatment options**' (emphasis added), the study in the UK did not specify that patients had to be ineligible for Sprycel treatment before being considered for entry into this trial.

Disguised promotion of an unlicensed medicine

Bristol-Myers Squibb was concerned that the website displayed a promotional intent in respect of nilotinib, which was inappropriate given its unlicensed status. The very title of ENACT (Expanding Nilotinib Access Clinical Trial) and the comment on the website, that ENACT 'was created to provide early access to the drug's **promising effects** during the regulatory review' (emphasis added), when considered in the context of the glowing testimony to nilotinib as being 'Built on the vast knowledge and experience Novartis acquired during the development of imatinib…' created a promotional impression.

Despite the website statement that ENACT was intended for imatinib-resistant or intolerant CML patients who had no other treatment options, the fact that the selection criteria for the study ignored direct or indirect reference to Sprycel as a licensed option was further evidence that by sponsoring this trial Novartis intended to promote nilotinib. If this clinical trial was truly for patients 'who do not have (an) acceptable treatment option', then one would have expected the selection criteria to include an entry criterion such as 'has the patient failed treatment on licensed treatments for patients with imatinib resistance or intolerance'. This would then have meant that patients with imatinib resistance or intolerance would have had to have had failed on Sprycel before being considered for ENACT since Sprycel was the only licensed option for such patients.

Accordingly, Bristol-Myers Squibb alleged ENACT represented disguised promotion of an unlicensed medicine and in breach of Clauses 10.1 and 3.1.

The misuse of a clinical trial as disguised promotion of an unlicensed medicine led Bristol-Myers Squibb to conclude that Novartis had brought discredit upon and reduced confidence in the industry, in breach of Clause 2.

RESPONSE

Novartis was profoundly disappointed that Bristol-Myers Squibb should have made these formal allegations after assuring Novartis through inter-company dialogue that its response was satisfactory and that Bristol-Myers Squibb considered the matter closed. To proceed in this manner displayed a disregard for the value of inter-company dialogue and directly contradicted assurances that Bristol-Myers Squibb wished to foster a cordial and candid relationship between the companies where concerns such as these could be discussed and resolved. It appeared that Bristol-Myers Squibb's actions in this matter, together with those associated with a second complaint which Novartis had considered resolved through inter-company dialogue were motivated by a complaint made to the Authority about the promotion of Sprycel. However unlike Bristol-Myers Squibb, Novartis had brought to the attention of the Authority only those matters for which no inter-company agreement could be reached. Such behaviour and the inflammatory language used by Bristol-Myers Squibb was contrary to the spirit of cooperation and self-regulation which underlayed the Code and seriously compromised any future possibility of inter-company dialogue.

Novartis did not accept that it had breached the Code.

Novartis provided print outs of the whole site and noted that there was a clear disclaimer on entering the site which confirmed that:

> *'This is a global website for ENACT (Expanding Nilotinib Access in Clinical Trials) information. The information you requested is intended for healthcare professionals only. Information on this site is not country-specific and may contain information that is different from the regulatory requirements, legal requirements or medical practices in the country in which you are located.'*

In addition, every page also carried a statement that:

> *'The compound Nilotinib described in this Website is an investigational drug. Efficacy and safety have not been established.'*

> *'There is no guarantee that Nilotinib will become commercially available.'*

Therefore this website was quite clearly both non-promotional and also not specifically targeted to a UK audience. Following inter-company dialogue Novartis asked its global teams (who managed the website) to remove reference to any UK sites from the listing, in the spirit of inter-company cooperation. Once again, Novartis was assured that this action would allay any remaining concerns that Bristol-Myers Squibb might have.

In response to the specific allegation regarding the study entry criteria listed on the web page, as explained above, the study was an expanded access programme and so only applied to patients considered by their doctor to be inappropriate for other therapeutic options. Therefore, there was no need to refer to resistance or intolerance to other therapies (including dasatanib) within the inclusion/exclusion criteria.

In summary Novartis did not consider that the allegations were supported by the evidence cited, nor did it accept that its activities had compromised patient safety or brought discredit upon or reduced confidence in the industry. It therefore strongly rejected the allegation of a breach of Clause 2.

Novartis submitted that ENACT followed the required regulations and was reviewed and approved by an ethics committee. Similar expanded access programmes had been run by other companies including Bristol-Myers Squibb.

PANEL RULING

The Panel noted that ENACT was a worldwide, multicentre, expanded access programme for Novartis' product, nilotinib. Four UK medical centres were listed on the ENACT website as actively recruiting patients. The Panel considered that the arrangements for the expanded access programme were subject to the Code.

The Panel noted that companies often provided medicines to those who had participated in clinical trials and/or other patients who might benefit from treatment before the medicine was licensed and commercially available. It was a question of whether the arrangements were reasonable. It could be argued that the expanded access programme met the definition of promotion given in Clause 1.2 in that it promoted the administration of nilotinib.

It was explained on the website that the expanded access programme provided access to nilotinib to eligible patients who had no other treatment options until it was commercially available in individual countries. Individual eligibility was determined by investigators at participating cancer care centres based on established medical criteria. The Panel noted Novartis' explanation that as the programme only applied to patients considered by their doctors to be inappropriate for other therapeutic options there was no need to refer to resistance or intolerance to other therapies within the programme's inclusion/exclusion criteria. The Panel noted that the programme had ethical committee approval. The Panel did not consider that Bristol-Myers Squibb had established that the ENACT programme was disguised promotion as alleged. The failure to state that UK patients had to be resistant or intolerant to Sprycel did not suffice in this regard. No breach of Clause 10.1 was ruled. It thus followed there was no breach of either Clause 9.1 or 2.

Complaint received	**8 August 2007**
Case completed	**15 January 2008**