CASE AUTH/2849/6/16

A CONSULTANT ONCOLOGIST AND A PHARMACIST v LILLY

Oncology handbook

A consultant oncologist, and a pharmacist, complained in June 2016 about an error which appeared in the 8th edition of the Handbook of Systemic Treatments for Cancer and related to the use of Alimta (pemetrexed) marketed by Eli Lilly and Company. The complainants had recently received a letter from Lilly about the medically significant error.

The complainants stated that they had previously received emails from Lilly indicating that copies of the handbook could be ordered through the company's oncology website which promoted its products and such resources. The website currently mentioned the handbook, but access to it had been disabled without any explanation. When queried, the Lilly representative explained that it was because of the error and an updated 9th edition was being developed by Lilly. The complainants had received copies of the two previous editions of the same handbook.

The complainants stated that whilst the error identified raised an important question about the reliability, quality and standard of materials disseminated by Lilly, the purpose of their complaint was to also raise a serious concern regarding the veracity, accuracy and transparency of the disclaimer that appeared on these handbooks which suggested that Lilly had no role whatsoever in the development of the handbooks and that all aspects of the publication, including editorial control, were fully owned and retained by the publisher. However, if this were so, one would have anticipated that an erratum, such as the one received, would have been issued by the publisher. As Lilly issued the erratum, the complainants assumed that Lilly did in fact retain editorial control over the contents of the entire handbook, its distribution and also forwarded the erratum to all UK recipients of the handbook. This would also be consistent with the fact that no other pharmaceutical company had ever provided or sponsored the handbooks despite many of their medicines being referred to in them. It appeared that the commercial arrangement between Lilly and the publisher was dubious and less than transparent and excluded the wider dissemination of the valuable medical educational resource by Lilly's competitors thereby facilitating the promotion of only Lilly and its products. Notably, some contributors to the handbooks appeared to be closely associated with Lilly and had previously supported its other commercial interests.

The complainants stated that it was likely that the handbook contained other medically significant errors and inaccuracies that could jeopardise patient safety.

The detailed response from Lilly appears below.

The Panel noted that a company could sponsor material, produced by a third party, which mentioned its own products, and not be liable under the Code for its contents, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties.

With regard to the disclaimer the Panel noted that the handbook had originally been conceived and published by Lilly with the help of key pharmacy staff at a named hospital. Lilly outsourced production of the 8th edition to a third party as the complexity of the information had increased but it maintained close association with relevant pharmacy staff at the hospital; two of the three authors had contributed to previous editions. A flowchart showing the review and edit process noted that new monographs would be included with the agreement of Lilly and one of the authors based on criteria used for the 7th edition. In the Panel's view, there was no arm's length arrangement between the parties. The handbook was initiated and its production managed by Lilly. Lilly submitted that it took full responsibility for the handbook.

The Panel noted that although the handbook had been updated by a third party, Lilly was responsible under the Code for its contents. Lilly's involvement with the handbook was obvious. The Panel noted that the statement on page 3 of the handbook that 'Lilly's role as sponsor of this handbook, has been limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the [Code]' should have more accurately reflected the extent of the company's involvement. Nonetheless, it was abundantly clear from the references to Lilly on the front and back covers and numerous inside pages that it was a Lilly-sponsored item and on balance, the Panel ruled no breach of the Code which was upheld on appeal by the complainants.

With regard to Lilly's products, the Panel noted that the drug monographs appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the 108 monographs detailed the responsible pharmaceutical company, such detail was given in a list of references. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company. Overall, the Panel did not consider that, given the presentation of the monographs, the handbook was disguised promotion of Lilly's products as alleged and no breaches were ruled including no breach of Clause 2. These rulings were upheld on appeal by the complainants.

The Panel noted Lilly's submission that it had not informed health professionals about the error in the handbook when the complaint was submitted in early June. The Panel also noted that the complainants referred to a 'medically significant error relating to the use of Alimta' which Lilly, in its response, assumed was about the dosing of Vitamin B_{12} which the complainants confirmed in response to a request for further information. According to

Lilly, a letter was sent to health professionals in mid June 2016 after a third party had comprehensively reviewed the 8th edition of the handbook following receipt of this complaint. The Panel noted that that letter to health professionals stated that there were multiple omissions and errors in the handbook but did not specifically refer to the Vitamin B_{12} dosing error. The Panel noted Lilly's submission that it was advised of this particular error in March 2016 and removed the handbook from its website the same day. Lilly staff were briefed by email three days later to destroy copies of the handbook. If customers asked about the error they were to be told that the handbook was being updated and they could have a new version once re-approved. The briefing detailed the Vitamin B_{12} dosing error.

The Panel considered that the inclusion of the error which listed the intramuscular dose of Vitamin B_{12} at 1g instead of 1mg when used before and during treatment with Alimta meant that the information in the handbook was inaccurate, misleading and not capable of substantiation. Breaches of the Code were ruled as acknowledged by Lilly including that high standards had not been maintained.

The Panel noted that a ruling of a breach of Clause 2 was used as a sign of particular censure. An example of an activity likely to be in breach of Clause 2 and listed in the supplementary information, was prejudicing patient safety. Whilst the Panel was concerned to note the Vitamin B_{12} dosing error within the handbook, it also noted that the presentation of Vitamin B_{12} (hydroxocobalamin) injection was such that in order to administer 1g, as incorrectly stated in the handbook, health professionals would have to open 1000 ampoules. In the Panel's view it was thus unlikely that such a dosing error leading to an overdose would occur. The Panel considered that Lilly had taken reasonable steps when it was notified of the error in March; it removed the handbook from its website and briefed all customer-facing teams. In mid June, however, following receipt of an interim report revealing additional errors and omissions in the handbook, Lilly wrote to all oncology health professionals requesting the immediate withdrawal and destruction of the handbook. The Panel noted its comments above and did not consider that the circumstances warranted a ruling of a breach of Clause 2. Following an appeal by the complainants the Appeal Board considered that any dosing error, regardless of its magnitude and no matter how unlikely it was to occur, was a serious matter. In addition, the error was in association with one of Lilly's medicines which the company should have identified. In the Appeal Board's view that the dosage error existed at all was such as to reduce confidence in the industry being able to produce complex material to the required quality standards. A breach of Clause 2 was ruled.

A consultant oncologist, and a pharmacist, complained about an error which appeared in the 8th edition of the Handbook of Systemic Treatments for Cancer (ref UKONC00326, February 2014) and related to the use of Alimta (pemetrexed) marketed by Eli Lilly and Company Limited; the handbook was provided to the complainants' team by a Lilly representative. The complainants had recently received a letter from Lilly about the medically significant error.

'Lilly Oncology' appeared in the bottom right hand corner of the front and back covers of the handbook and the back cover also referred to 'A Medical Education Goods and Services item by Lilly Oncology UK'. Page 3 included a note from the publisher which stated that Lilly's role as sponsor was limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the Code.

COMPLAINT

The complainants stated that they had previously also received email newsletters from Lilly indicating that copies of the handbook could be ordered through the company's oncology website which promoted its products and such resources. This website currently mentioned the handbook, however, access to the handbook seemed to have been disabled without any explanation or any reference to the Alimta related error. On enquiry from the complainants the Lilly representative explained that it was because of the error and an updated 9th edition was being developed by Lilly. The complainants had also previously received copies of the 6th and 7th editions of the same handbook.

The complainants stated that whilst the error identified raised an important question about the reliability, quality and standard of materials disseminated by Lilly, the purpose of their complaint was to also raise a serious concern regarding the veracity, accuracy and transparency of the disclaimer that appeared on these handbooks which suggested that Lilly had no role or involvement whatsoever in the development of the handbooks and that all aspects of the publication, including editorial control, were fully owned and retained by the publisher.

The complainants questioned the latter arrangement because if this were so, one would have anticipated that any erratum, such as the one received, would have been issued by the responsible party, ie the publisher, to all recipients of the publication, as was usual practice. As Lilly, not the publisher, issued the erratum, the complainants assumed that Lilly did in fact retain editorial control over the contents of the entire handbook, its distribution and also forwarded the erratum to all UK recipients of the handbook. This would also be consistent with the observation that no other pharmaceutical company had ever provided or sponsored the handbooks despite many of their medicines being referred to in them. It appeared that the commercial arrangement between Lilly and the publisher excluded the wider dissemination of the valuable medical educational resource by Lilly's competitors thereby facilitating the promotion of only Lilly and its products. Notably, it also appeared that various contributors to the handbooks were closely associated with Lilly and had previously supported its other commercial interests.

The complainants stated that they would be grateful if this matter could be addressed to Lilly as it was likely that the handbook also contained other medically significant errors and inaccuracies that

could jeopardise patient safety and because of the dubious and less than transparent nature of the historical and current collaboration between the publisher and Lilly.

In response to a request for further information the complainants stated that unfortunately they had not retained the letter at issue as they had stopped using the handbook in question. The complainants stated that the letter was widely disseminated to oncologists and related to an error in that a significant overdose of Vitamin B_{12} was recommended when using Alimta.

The complainants stated that they stopped using the handbook because of the above and concern that there were other potential errors therein. The complainants were also concerned that the contents of the handbook were not up-to-date in relation to newly licensed products available for the treatment of the cancers referred to in it. For example the omission of medicines such as nivolumab (lung cancer) and ramucirumab (gastric cancer) was misleading and did not reflect the purpose of the handbook which was to be an authoritative reference text which provided relevant, accurate and up-to-date information on medicine for various cancers.

The complainants presumed that Lilly's medical or medical information department would have the necessary information regarding what was communicated.

When writing to Lilly, the Authority asked it to consider the requirements of Clauses 2, 9.1, 7.2, and 7.4 in relation to the error and Clauses 2, 9.10, 9.1 and 12.1 in relation to the disclaimer.

RESPONSE

Lilly submitted that the 8th edition was a non-promotional, medical educational item as stated on the back cover and was not an independent textbook. Lilly accepted full responsibility for the 8th edition and all previous editions of the handbook.

Lilly noted that the complainants referred to a recently received letter from Lilly which highlighted an error with respect to dosing Vitamin B_{12} and pemetrexed. Following a thorough internal investigation Lilly could not explain how the complainants received such a letter, as no correspondence had been sent to any health professional or other person when the complaint was submitted. However, Lilly took this issue very seriously and was grateful to the complainants for drawing this matter to the PMCPA's and Lilly's further attention.

Lilly stated that the 8th edition was published in February 2014, two years after the publication of the 7th edition. The first edition was published by Lilly in collaboration with the named hospital around 20 years earlier and each subsequent edition had always been produced in consultation with key pharmacy staff at that hospital. The handbook was conceived and published by Lilly to assist health professionals in their day-to-day patient management by providing concise information as guidelines for the administration of medicines commonly used for the treatment of cancer. Subsequent editions included new anticancer agents as these came to market. The 7th edition included additional information to support the care of cancer patients such as the 'Oncology/Haematology Helpline Triage Tool' developed by the UK Oncology Nursing Society and endorsed by MacMillan Cancer Support. This information was also included in the 8th edition.

The handbook was widely distributed by Lilly to cancer treating institutions in the NHS. Chemotherapy nurses and cancer nurse specialists were the primary users and feedback consistently confirmed that the handbook, in its various editions, was a well-regarded and valued resource among health professionals.

Given the enduring heritage of the handbook since its first edition, many health professionals routinely referred to it as the 'Lilly Chemo Handbook' or even the 'Lilly Handbook' such had been the recognition of its value and long-term production by Lilly. As the complexity of information included increased, Lilly Oncology decided in 2013 to outsource the production of the 8th edition to a third party, while maintaining the close association with key pharmacy staff at the named hospital. Two of the three authors (as acknowledged on page 2 of the handbook) were from that hospital. The third author was a lead chemotherapy nurse from a Cancer Network.

A copy of the letter notifying health professionals about the errors was provided as were the instructions to representatives about the distribution, content and withdrawal of the handbook. The withdrawal letter was dated 16 June 2016. It advised that there were multiple errors and omissions in the handbook and that all copies (whichever edition) should be destroyed.

Lilly stated that the 8th edition was reviewed and approved through the certification process and subsequently certified by two signatories. Various comments were made during this review, however, regrettably nothing was noted in relation to the error noted by the complainants. On the draft version of the 8th edition there were Lilly comments made with regard to ensuring clarity that this was a Lilly publication. In addition, questions were raised about the inclusion of 'Very Rare' and 'Unknown' side-effects in light of the handbook being a summary of the summary of product characteristics (SPC). Comments were also made regarding the online version of the 8th edition and links to the electronic medicines compendium (eMC) in the list of SPC references. Further comments were made about inclusion of dates of first authorisation in the SPC references.

Lilly provided copies of relevant documents which described the extent of its influence over the handbook and a detailed account of Lilly's role in relation to the creation of the handbook.

The contract with the third party was by way of a master services agreement and associated work order. As set out in the work order, the information contained in the 8th edition was to consist of the chemotherapy pathway, nursing guidelines, summaries of more than 80 oncology agents and

an educational/practical appendix section. As prior editions of the handbook had proven to be a valuable resource for health professionals, there was a recognised need to continue to produce an updated copy to reflect changes in SPCs and guidelines.

Lilly oncology decided to partner with the third party to ensure an efficient and sustainable delivery. The third party took over the editorial management including ongoing content updates.

The third party subcontracted relevant and key health professionals to clinically validate the updated content and new content developed by the third party, and to further improve the features of the 8th edition. The intended work on the 8th edition was set out in a flowchart, which showed that the 8th edition was to include 24 new medicine monographs, and 86 existing monographs (2 were removed).

For the 8th edition, the third party was to use its editorial teams which included oncology pharmacists.

The authors of the 8th edition were paid by the third party.

The handbook was distributed by Lilly to healthcare organisations and health professionals in oncology in response to direct requests to Lilly switchboard, by post or email to Lilly; or requested via the Lilly oncology website or via requests made to Lilly's salesforce. In addition, health professionals could download the handbook from the Lilly oncology website. When the handbook was provided by sales representatives the Lilly procedure for a medical educational good or service would be followed ensuring that it was provided during a non-promotional call.

The 8th edition was first distributed after an oncology sales force meeting (March 2014). Lilly's oncology medical liaison ran a session for representatives and marketing on introducing the 8th edition of the handbook, outlining recall of the 7th edition and availability of the 8th edition.

Lilly was notified of the error with respect to the dosing of Vitamin B_{12} for pemetrexed by a nurse on Friday, 18 March 2016. The error listed the dose of Vitamin B_{12} as 1g instead of 1000mcg (1mg). Medical information reported the error to the oncology medical team. That same day the handbook was removed from the Lilly oncology website. The oncology team also prepared a briefing on the withdrawal of the handbook for all customer-facing teams, this was sent by email on Monday, 21 March. Following review of previous editions, Lilly established that the error in the dosing of Vitamin B_{12} for pemetrexed was unique to the 8th edition.

Following receipt of the complaint, Lilly commissioned a third party, to assist in a complete and comprehensive review of the 8th edition for any further errors. In light of an interim report showing there were other errors and omissions on 16 June, Lilly sent a letter from the business unit director, Lilly Oncology to all oncology health professionals in its customer database instructing the immediate withdrawal and destruction of all copies of the handbook.

Lilly submitted that in order to prevent future errors in clinical summaries, Lilly oncology would not publish further editions of the handbook.

The letter explaining the nature of the error dated 16 June 2016, was sent to over 3000 oncology health professionals. Emails were sent on 18 June to all oncology health professionals for whom Lilly held a current permission to email. Following approval and certification on 27 June, the letter was made available at all relevant locations on the Lilly oncology website.

Lilly accepted that the highlighted error identified in the 8th edition with respect to dosing Vitamin B_{12} and pemetrexed meant it had breached Clauses 7.2, in that the information was not accurate; 7.4, as the information in the handbook could not be substantiated; and 9.1, as Lilly had not maintained high standards in relation to the Code. Lilly took these breaches very seriously and would now unreservedly accept the Panel's ruling on Clause 2 should it so rule in this regard.

Lilly referred to the disclaimer in the 8th edition (page 3) that:

> 'Welcome to the 8th edition of the Lilly Handbook of Systemic Treatments for Cancer (2014).
>
> The intent of this handbook is to assist healthcare professionals in their day-to-day patient management by providing concise information and guidelines for the administration of commonly used pharmacological agents for the treatment of cancer.
>
> The contents of this handbook have been developed collaboratively by nurse and pharmacist teams at the [named hospital, named authors] on behalf of Eli Lilly and Company Ltd ("Lilly") and the publisher.
>
> Lilly's role, as the sponsor of this handbook, has been limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the PMCPA Code of Practice for the Pharmaceutical Industry.
>
> Save for the above, and the compilation of the "Appendices" section, the updated contents of the handbook have been developed independently by the authors in collaboration with the publisher.
>
> The monographs in this handbook were compiled from manufacturers' summaries of product characteristics (SPCs) and other established resources. Some of the information presented may reflect local practice and the clinical expertise of the healthcare professionals involved. The monographs of the products contained herein are not intended to be a substitute for the manufacturers' SPCs. Only adverse events deemed to be of particular relevance are included. The publisher has tried to ensure that the information contained in this handbook is accurate and up-to-date at the time of publication. **It is the user's responsibility to check for any variation in the product SPC subsequently**. These

can be found at www.medicines.org.uk/emc. It is important not to use copies of the handbook that are out of date or pass on old editions.

The practice guidance presented in this handbook is offered as recommendations, and does not diminish the requirement for clinical judgment. Readers are strongly advised to check these recommendations against their local protocols and guidelines and to make their own further enquiries of manufacturers or specialists in relation to particular drugs, treatments or advice. Lilly, the publisher and the authors cannot accept liability for errors or omissions, and disclaim any liability arising out of the use of this handbook in practice.'

In relation to Clause 12.1, Lilly submitted that the handbook was a Lilly medical educational good or service which could be requested, downloaded or provided to healthcare organisations and health professionals in the field of oncology as described above.

In relation to Clause 9.10, Lilly submitted its sponsorship of the handbook was clear and transparent, (paragraph 3 of the disclaimer quoted above and on both the front and back cover of the handbook). Furthermore, the 8th edition was Lilly's copyright and the footer on each odd numbered page read 'Lilly Handbook of Systemic treatments for Cancer 8th Edition'. Therefore, Lilly respectfully submitted that it did not breach Clauses 9.10 or 12.1 with respect the disclaimer and that it maintained high standards in accordance with Clause 9.1 and therefore had not breached Clause 2.

In response to a request for further information, Lilly submitted that it had previously set out the corrective steps that it took immediately following the original notification on 18 March 2016 of an error in the 8th edition of the handbook. The corrective steps included commissioning a comprehensive review of the handbook by an independent third party. Lilly provided confidential copies of both the interim report and the final report prepared by the third party.

Lilly reassured the PMCPA that it recognised the seriousness of the obligations that the Code placed upon pharmaceutical companies in relation to the accuracy of industry sponsored publications. Lilly wished to engage with the PMCPA with full transparency in its consideration of this matter.

Lilly noted the history of the handbook as set out above. Lilly now recognised that, by the 8th edition, the objectives and content of the handbook had grown in scope and ambition to such an extent that it was beyond the sponsoring capabilities of a pharmaceutical company. The number of products included and the differences in interpretation between the hospital editorial team, health professionals and indeed the third party review team meant that the handbook was not an appropriate industry sponsored medical educational good or service. It should not have been commissioned, it should not have been certified, and it should not have been distributed. Lilly submitted that it would not produce further editions of the handbook.

On 16 June 2016 Lilly received an interim report from the third party revealing additional errors and omissions in the handbook to that identified in the complaint. In light of that report, Lilly sent a letter on the same day to all oncology health professionals on its database requesting the immediate withdrawal and destruction of all copies of the handbook. That was followed by an email to all oncology health professionals, for whom Lilly had email permission, including to members of the UK Oncology Nursing Society who subsequently disseminated it to its wider membership.

Following the interim report, Lilly requested that the third party proceed immediately with its comprehensive review of the entire handbook.

Lilly immediately put in place a communications plan to address any external enquiries received by medical information regarding the withdrawal of the handbook. To date Lilly had not received any enquiries related to individual patient safety. If enquiries about individual patient safety were received, Lilly had an action plan in place to ensure they would be reported in the appropriate way to the Medicines and Healthcare products Regulatory Agency (MHRA).

In addition to the actions taken above, Lilly reassured the PMCPA that it was committed to ensuring that incidents of this type did not occur again.

PANEL RULING

The Panel noted that it was possible for a company to sponsor material, produced by a third party, which mentioned its own products, and not be liable under the Code for its contents, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties. In practical terms the arrangements must be such that there could be no possibility that the pharmaceutical company had been able to exert any influence or control over the final content of the material. Factors which might mean there had not been a strictly arm's length arrangement would include, but not be restricted to:

- Initiation of the material, or the concept for it, by the pharmaceutical company
- Influence from the pharmaceutical company on the content/balance/scope of the material
- Choice/or direct payment of the authors by the pharmaceutical company
- Influence from the pharmaceutical company on the list of persons to whom the material was sent.

With regard to the disclaimer the Panel noted Lilly's submission regarding the history of the handbook, it was originally conceived and published by Lilly with the help of key pharmacy staff at the hospital. Lilly outsourced production of the 8th edition to a third party as the complexity of the information had increased but it maintained close association with relevant pharmacy staff at the hospital; two of the three authors had contributed to previous editions. A flowchart showing the review and edit process noted that the list of new monographs to be included would be agreed with Lilly and one of the authors based on criteria used for the 7th edition. In the

Panel's view, there was no arm's length arrangement between the parties. The handbook was initiated and its production managed by Lilly. Lilly submitted that it took full responsibility for the 8th Edition and all previous editions of the handbook.

The Panel noted Lilly's submission about the number of medicines/treatments included in the handbook and that it was designed to be comprehensive. Each even page of the book was dated February 2014.

The Panel noted that the handbook, although updated by a third party, had been initiated and managed by Lilly which was responsible under the Code for its contents. The preface on page 4 stated that the handbook was a Lilly initiative and through the use of bright red font on pages 3 and 4 and tear out cards on the following page, Lilly's involvement with the handbook was obvious. The Panel noted the requirements of Clause 9.10 and considered that the statement on page 3 of the handbook that 'Lilly's role as sponsor of this handbook, has been limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the PMCPA Code of Practice for the Pharmaceutical Industry' should have more accurately reflected the extent of the company's involvement. Nonetheless, it was abundantly clear from the various references to Lilly on the front and back covers, pages 3 and 4 and all odd numbered pages that it was a Lilly-sponsored item and on balance, the Panel ruled no breach of Clause 9.10.

With regard to Lilly's products, the Panel noted that the medicine monographs appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the 108 monographs detailed the responsible pharmaceutical company, such detail was given in a list of references. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company. Overall, the Panel did not consider that, given the presentation of the monographs, the handbook was disguised promotion of Lilly's products as alleged and no breach of Clause 12.1 was ruled. This ruling was appealed by the complainants.

The Panel noted its rulings above and ruled no breach of Clauses 9.1 and 2. These rulings were appealed by the complainants.

The Panel noted that the complaint dated 28 May was received on 3 June 2016. The Panel noted Lilly's submission that it had not informed health professionals about the error in the handbook when the complaint was submitted. The Panel also noted that the complainants referred to a 'medically significant error relating to the use of Alimta' which Lilly, in its response, assumed was about the dosing of Vitamin B_{12} which the complainants confirmed in response to a request for further information. According to Lilly, a letter was sent to health professionals on 16 June 2016 after it had commissioned a third party to conduct a comprehensive review of the 8th edition of the handbook following receipt of this complaint. The Panel noted that that letter to health professionals stated that there were multiple omissions and errors in the handbook but did not specifically refer to the Vitamin B_{12} dosing error. The Panel noted Lilly's submission that it was advised of this particular error on 18 March 2016 and it removed the handbook from the Lilly oncology website the same day. Lilly staff were briefed by email on 21 March to destroy copies of the handbook. If customers asked about the error they were to be informed that the handbook was being updated and they could have a new version once re-approved. The briefing gave details about the Vitamin B_{12} dosing error.

The Panel considered that the inclusion of the error which listed the intramuscular dose of Vitamin B_{12} at 1g instead of 1mg when used before and during treatment with Alimta meant that the information in the handbook was inaccurate, misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled as acknowledged by Lilly. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was used as a sign of particular censure. An example of an activity likely to be in breach of Clause 2 and listed in the supplementary information, was prejudicing patient safety. Whilst the Panel was concerned to note the Vitamin B_{12} dosing error within the handbook, it considered that such an overdose was unlikely to occur as Vitamin B_{12} (hydroxocobalamin) was supplied in 1ml ampoules each containing 1mg. In order to administer 1g, as incorrectly stated in the handbook, health professionals would have to open 1000 ampoules. In the Panel's view it was thus unlikely that such a dosing error leading to an overdose would occur. The Panel considered that Lilly had taken reasonable steps when it was notified of the error in March; it removed the handbook from the Lilly oncology website and briefed all customer-facing teams. On 16 June, however, following receipt that day of an interim report revealing additional errors and omissions in the handbook to that identified in this complaint, Lilly sent a letter to all oncology health professionals on its database requesting the immediate withdrawal and destruction of all copies of the handbook. That was followed by an email to all oncology health professionals, for whom Lilly had email permission, including to members of the UK Oncology Nursing Society who, Lilly submitted, subsequently disseminated it to its wider membership. The Panel noted its comments above and did not consider that the circumstances warranted a ruling of a breach of Clause 2. This ruling was appealed by the complainants.

During consideration of this case the Panel noted that the supplementary information to Clause 18.1, Textbooks, stated that in appropriate circumstances independently produced medical/educational publications such as textbooks could be given for health professionals to use in accordance with Clause 19.1 – Medical and Educational Goods and Services – but they must not be given to individuals. The Panel noted that the handbook in question was not independently produced, it was clearly initiated and sponsored by Lilly and included information about its medicines. The Panel thus queried whether the handbook could be given as

a medical or educational good or service. Further, it appeared that, contrary to Code requirements regarding provision of medical and educational goods or services, the handbook had been given to individuals. Tear out cards stated 'Do you know someone who would like a copy of the handbook? Hand them this card to order one free of charge'.

The Panel further noted that the 8th edition handbook was certified on 14 March 2014; it was still in use in June 2016. In that regard, the Panel noted that the Code stated that material still in use must be certified at intervals of no more than two years to ensure continued compliance with the Code. The Panel noted that all material had to be up-to-date and current and in that regard it noted the complainant's additional comments that some cancer medicines were not included in the handbook. These comments appeared to be a fresh allegation that the handbook was not up-to-date. If the complainants wanted this allegation considered they would have to submit a new complaint (Case AUTH/2872/9/16).

Although noting that the handbook had been withdrawn, the Panel requested that its concerns be drawn to Lilly's attention.

APPEAL FROM THE COMPLAINANTS

The complainants noted that Lilly had stated, unsurprisingly, that it had accepted 'unreservedly' that it had brought the industry into disrepute and breached Clause 2 of the Code. It was therefore unclear why the Panel had not accepted this admission and ruled accordingly. The complainants alleged that it appeared that this pre-emptive self-censure had led the Panel to completely absolve Lilly from any sanction or responsibility or liability to uphold the Code. The latter was particularly surprising given the unequivocal and unforced admission from Lilly that '… the handbook was not an appropriate industry sponsored medical educational good or service. It should not have been commissioned, it should not have been certified, and it should not have been distributed'. The complainants were genuinely unclear as to what more the Code deemed necessary to invite a breach of Clause 2 of the Code. Given the latter and the seriousness of the issues, the complainants respectfully requested that the Appeal Board consider a breach of Clause 2, in respect of their entire complaint.

The complainants further did not accept Lilly's contention that the handbook was non-promotional and provided as a medical education good or service. In this regard the complainants noted that the handbook was available for download on the Lilly oncology website which was a promotional platform for Lilly's products. On various pages of the website the handbook was directly associated with hyperlinks which promoted the availability of 'ALIMTA Literature' and 'Alimta Abbreviated Prescribing Information'. This was exemplified by the screenshots which were accessed on 17 June 2016 (provided) and appeared to contravene the requirements of the Code in respect of the need to dissociate the provision of a medical education good or service and product promotion.

The complainants alleged that it was therefore evident that Lilly was covertly using the handbook as a tool to help promote products such as Alimta which was, as such, disguised promotion in breach of Clauses 2, 9.10 and 12.1.

In response to a request to confirm if they were appealing Clause 9.1 or 9.10 or both, the complainants stated that they wanted to include Clauses 9.1 and 9.10 in their appeal. Although Lilly had disclosed its sponsorship of the handbook, the complainants alleged that it was evident from the Panel's ruling that the disclaimer was not sufficiently clearly worded so as to inform the reader that the handbook was not developed independently by the publishers as suggested. Lilly's involvement was not at 'arms-length'.

COMMENTS FROM LILLY

Lilly noted that in its ruling, the Panel was clear that the circumstances of the complaint, the nature of Lilly's remedial action, and the unlikely impact on patient safety meant that a ruling of a breach of Clause 2 was not warranted. Lilly submitted that this was the correct decision, and respectfully requested that the Appeal Board uphold the ruling of the Panel.

Lilly noted that the complainants' appeal alleged specifically that the Panel's ruling on Clause 2 was inappropriately influenced by Lilly's original admissions and the Chemotherapy Handbook was a promotional item being used covertly to promote Lilly's medicines.

Lilly submitted that its interactions with the Panel had been full, transparent and had enabled the Panel to consider this matter thoroughly and without any undue influence. This had been Lilly's intention throughout, and Lilly remained committed to the integrity of the complaints process.

Lilly noted that in its original response, it did not accept unreservedly that it had brought the industry into disrepute and breached Clause 2. The letter stated that Lilly would unreservedly accept the Panel's ruling on Clause 2. The Panel ruled no breach of Clause 2 which Lilly unreservedly accepted.

Lilly submitted that the handbook was conceived and published by it with the help of pharmacy staff at a named hospital to assist health professionals in their day-to-day patient management by providing concise information and guidelines for the administration of commonly used pharmaceutical agents for the treatment of cancer. The 8th Edition included all approved cancer medicines available in the UK at the end of November 2013.

Lilly submitted that as the Panel noted in its ruling, '…the medicine monographs appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the 108 monographs detailed the responsible pharmaceutical company, such detail was given in a list of references. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company'.

Lilly submitted that its oncology portal provided a resource for health professionals to access promotional and non-promotional items. All links on the portal to the handbook were deactivated on Friday, 18 March 2016. As the Panel agreed, the Chemotherapy Handbook was not a promotional item, and Lilly was not acting 'covertly' in its sponsorship and dissemination of it. Lilly submitted that no disguised promotion had taken place.

Lilly had accepted throughout this case that it should not have sponsored the 8th Edition in the form in which it was published. Lilly submitted that the Panel's ruling in this case was thorough, correct, and unsparing in its assessment of Lilly's shortcomings. Lilly requested that the Panel's decision be upheld.

FINAL COMMENTS FROM THE COMPLAINANTS

The complainants submitted that by stating its willingness to unreservedly accept the Panel's rulings, Lilly had effectively attempted to pre-empt the likelihood of an adverse ruling; indeed, if this were not its intention then there was no obvious reason to state its position in advance of any decision by the Panel. Lilly could simply have accepted, 'unreservedly', the Panel's rulings after the fact. Lilly also clearly indicated that the handbook was not really fit for purpose and so clearly recognised its failings and the gravity of the situation and the likelihood of a breach of Clause 2 being ruled and to this end has attempted to mitigate against this particular sanction.

The complainants alleged that a handbook being used promotionally and produced to such a dangerously low standard that even its sponsor noted in retrospect that it should not have been commissioned, certified or distributed must surely bring disrepute.

The complainants invited the Appeal Board to review the findings of the third party's report which was not provided to them by the Panel but whose comments suggested that the handbook contained many other significant errors.

The complainants alleged that the handbook was associated with promotion of Alimta as evidenced by the direct and close association of Alimta related materials and the handbook. Lilly seemed to rely on counter arguments based on the semantics of the terms disguised and covert. However, there was no getting away from the fact that use of the handbook, classified as a medical education good and service, was not completely disassociated with the promotion of Alimta on the Lilly oncology portal. This association was a form of disguised promotion of Alimta given that the nuances of the Code requirements related to the provision of a MEGS were unlikely to be immediately appreciated or obvious to those health professionals who might not be aware of the Code's requirements in this particular regard. There was also no statement to the contrary on the screenshots to explain this distinction to the viewer.

Finally the complainants alleged that whilst the links to the handbook might have been deactivated on 18 March the fact remained that the screen shots provided clearly evidenced that Lilly referred to the handbook and Alimta on this website prior to and well after this date.

APPEAL BOARD RULING

The Appeal Board noted the Panel's ruling above and agreed that it was abundantly clear in the handbook from the various references to Lilly on the front and back covers, pages 3 and 4 (all in red) and all odd numbered pages that it was a Lilly-sponsored item and the Appeal Board therefore upheld the Panel's ruling of no breach of the Clause 9.10. The appeal on this point was unsuccessful.

The Appeal Board noted that the 108 monographs included in the handbook appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the monographs detailed pharmaceutical companies, such detail was given in a list of references at the back of the handbook. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company.

The Appeal Board did not consider that, given the presentation of the monographs, the handbook was disguised promotion of Lilly's products as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 12.1. The appeal on this point was unsuccessful.

Given its rulings above the Appeal Board upheld the Panel's rulings of no breach of Clauses 9.1 and 2. The appeal on this point was unsuccessful.

The Appeal Board noted Lilly's submission at the appeal that the handbook would be used in conjunction with other data sources, notably SPCs. However, screen shots of the Lilly website provided by the complainants showed that the handbook was described as a '…definitive guide to assist you and your colleagues in your day-to-day management of patients with cancer…'. In that regard the Appeal Board considered that the handbook would be regarded by at least some users, as a one-stop document.

The Appeal Board noted that the complainants had only referred to one specific error in the handbook ie that the intramuscular dose of Vitamin B_{12} to be given in assocation with Alimta therapy was 1g instead of 1mg. The Appeal Board noted the magnitude of the error and that such an excessive dose of Vitamin B_{12} was unlikely to be administered given the number of ampoules that would have to be opened. Nonetheless, the Appeal Board considered that any dosing error, regardless of its magnitude and no matter how unlikely it was to occur, was a serious matter. In addition, the error was in association with one of Lilly's medicines and the company should have picked it up. In the Appeal Board's view, that the dosage error existed at all was such as to reduce confidence in the industry being able to produce complex material to the required quality standards. A breach of Clause 2 was ruled. The appeal on this point was successful.

Complaint received **3 June 2016**

Case completed **7 November 2016**