PATIENT v PFIZER

Information about Champix

A member of the public alleged that Pfizer had failed to warn of serious side effects of Champix (varenicline). Champix was indicated for smoking cessation.

The complainant stated that Champix came onto the UK market in 2006. The patient leaflet made no mention of convulsions. When the complainant took the medicine in January 2008 there was also no mention of convulsions on the leaflet. The complainant submitted that she stopped smoking within a week of starting Champix. Although the complainant was supposed to take a 12 week course, at week 10 she started to feel depressed and thought of killing herself; this was out of character. The complainant's doctor told her to stop taking Champix, and within 24 days of the last dose she had a grand-mal convulsion in her sleep and then a second less than two weeks later. She had never previously had convulsions and was subsequently diagnosed with epilepsy.

The complainant submitted that in 2010 following a friend's experience with Champix she asked her doctor if her convulsions were connected to the Champix; her doctor thought that they could be and told the complainant to report her epilepsy as a possible withdrawal effect of Champix.

The complainant provided a patient leaflet prepared by Pfizer Australia in February 2007 that stated, *inter alia*, that before taking Champix a patient should tell his/her doctor if he/she suffered from repeated fits or convulsions. The complainant stated that leaflets in Canada also mentioned seizures but there was still no mention of this in UK leaflets. The complainant stated that on 22 May 2008 the Food and Drug Administration (FDA) asked Pfizer about the link between varenicline and seizures. The prescription leaflet noted that pilots, controllers and truckers should not take varenicline from 2008 due to the risk of seizures. The complainant stated that the FDA then issued a further warning to include seizures in 2009.

The complainant alleged that Pfizer had failed to properly warn consumers and was primarily concerned with protecting profits, even at the expense of patients' health. The complainant stated that anti-smoking medicines might adversely affect certain individuals more than others and alleged that the scientific literature, the very place doctors looked for a warning, contained barely a hint of problems in the UK, about withdrawal symptoms seen with varenicline.

The complainant included a detailed discussion on the link between nicotine receptors and various central nervous system disorders. The complainant submitted that genetic mutations in these receptors might make some patients particularly susceptible to developing epilepsy.

The complainant stated that post-marketing clinical trials mentioned grand-mal and peti-mal seizures happening within 30 days of the last dose of varenicline. It also mentioned deaths, but as it was after last dose, Pfizer did not put these forward. This was the only information after 2 years that said anything about last dose of varenicline. Everywhere seemed to state that there were no side effects from Champix after the last dose.

The complainant stated that Pfizer had told her on several occasions that no seizures were seen in any clinical trial involving the correct dose. When the complainant asked her first neurologist, in 2010 if she thought that Champix could have triggered epilepsy, her exact words were 'I am not prepared to put my job on the line by answering that question'. The complainant was very angry by this answer and found that Pfizer funded projects for the local NHS, so was it a case of don't bite the hand that feeds you. The complainant noted other possible conflicts of interest between Pfizer and other organizations.

The complainant alleged that she and others had, and still were, suffering the effects of Champix. They were given no warning of these side effects of this medicine, had reported it through the correct channels, and still nothing had been done. In the US a class action had been brought against Pfizer for $150 million for no warning of side effects. The complainant would like help to prove that Pfizer had breached the Code and that by giving no warning, it had put the public at risk.

The detailed response from Pfizer is given below.

The Panel noted that the complainant had provided much material and comment. Patient safety was extremely important. The Panel's role was to consider the allegations in relation to the requirements of the Code. In this regard, the Panel considered that the key issue raised by the complainant was that patient leaflets for Champix produced by Pfizer were misleading in relation to the risk or otherwise of convulsions associated with the use and/or discontinuation of the medicine.

The Panel noted that the complainant referred to 'leaflets' for Champix but it was unclear whether she had seen the summary of product characteristics (SPC), the leaflet that accompanied the medicine (PIL) or some other patient leaflet produced by Pfizer. No examples of UK materials were provided by the complainant. The Panel further noted that the PIL and SPC were regulatory documents, the content

of which was governed by the relevant EU or UK regulatory authority. The Code was clear that neither SPCs nor the leaflet that accompanied a medicine (PIL) were included in the definition of promotion. The contents of such documents were covered by regulations. However, Pfizer had submitted that it had also produced further leaflets, for both patients and health professionals, based on the PIL and SPC for Champix. The Panel considered that the content of these was within the scope of the Code and had to comply with it. Such material had to accurately reflect the SPC.

The Panel noted the complainant stated that she started a 12 week course of Champix in January 2008 which was discontinued after 10 weeks. The SPC submitted by Pfizer as current at that time (which was approved in April 2007) did not refer to fits or seizures in Section 4.8, Undesirable effects. Section 4.4, Special warnings and precautions for use, stated that there was no clinical experience with Champix in patients with epilepsy.

Pfizer submitted an additional patient leaflet for Champix that was available when the complainant took the medicine (prepared November 2007). One section, entitled 'What side effects might I experience?', referred to side effects associated with giving up smoking, including mood changes, sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain. Common side effects for Champix were also stated, including nausea, headache, difficulty sleeping and abnormal dreams. Reference was also made to dizziness and sleepiness. Similarly to the SPC, there was no mention of fits or seizures.

The Panel noted that the current Champix SPC (13 April 2012) again referred in Section 4.4, Special warnings and precautions for use, to lack of clinical experience with Champix in patients with epilepsy. There was no reference to seizures or fits in Section 4.8, Undesirable effects. A current patient leaflet produced by Pfizer (prepared October 2012) referred to similar side effects as the previous patient leaflet and, in addition, to changes in behaviour and thinking, depression and anxiety, worsening of psychiatric illness and suicidal thoughts and attempts. Again there was no reference to seizure or fits.

The Panel noted that the complainant had submitted a patient leaflet from Australia dated February 2007 which referred to seizures and fits and advised the patient to seek immediate medical help if these were experienced. The Panel further noted Pfizer's submission that this leaflet was common to Australia and New Zealand and that the New Zealand datasheet did not refer to seizures or fits.

The Panel noted that the reference to seizures and fits in the Australian/New Zealand document dated February 2007 had, according to Pfizer, been made in error and had been removed in September 2007. The complainant had stated that her treatment course began in January 2008. The Panel noted that there was no reference in UK regulatory documents (SPC and PIL), either currently or when the complainant took Champix, that Champix treatment, or discontinuation of treatment, was associated with seizures or fits. The Panel further noted Pfizer's submission that there was currently no evidence of a causal relationship between varenicline and seizure. The Panel thus considered that failure to refer to seizures or fits in any Pfizer-produced patient leaflets for the UK was not a failure to reflect the available evidence about these side effects. No breach of the Code was ruled. Not referring to fits and seizures in Champix patient material did not render that material incorrect or unbalanced and no breach of the Code was ruled. The Panel noted its rulings above and subsequently ruled no breach of the Code including Clause 2. The complainant appealed all the Panel's rulings.

The Appeal Board considered that patient safety was extremely important. The Appeal Board noted that this was a highly personal and important issue for the complainant and it did not doubt her sincerity on the matter. The complainant had submitted a large volume of information and had referred to the conduct of other organisations. The Appeal Board noted that the complainant stated in response to a question at the appeal that she had sent all of her documents in this case to the MHRA. The Appeal Board noted that its only role was to consider matters in relation to the requirements of the Code and specifically the Panel's rulings of no breach of the Code. As stated in the introduction to the PMCPA Constitution and Procedure, the complainant had the burden of proving their complaint on the balance of probabilities.

The Appeal Board examined two documents which were current when the complainant was prescribed Champix. The Champix SPC (reviewed 26 April 2007) stated in Section 4.4, Special warnings and precautions for use, that there was no clinical experience with Champix in patients with epilepsy. Section 4.8 of the same SPC, Undesirable effects, did not refer to seizures, epilepsy or fits. The Appeal Board noted that the SPC and the PIL were regulatory documents and their contents were agreed with the regulators, the MHRA and the EMA. The PIL was based on the agreed SPC. The Pfizer leaflet entitled 'Information for patients who have been prescribed Champix (varenicline tartrate)' (prepared in November 2007) had to reflect the SPC and PIL and not be inconsistent with those regulatory documents. The Appeal Board noted that the Pfizer leaflet similarly did not refer to seizures, epilepsy or fits in the section headed 'What side effects might I experience'. The Pfizer leaflet did not state that there was no clinical experience with Champix in patients with epilepsy; the Appeal Board, however, did not consider that the Pfizer leaflet was inconsistent with the SPC in that regard.

The Appeal Board noted that the current Champix SPC did not refer to seizures, epilepsy or fits as possible adverse effects and so similarly neither did the current PIL.

The Appeal Board noted that the complainant had provided the Drug Analysis Print (DAP) for Champix which listed spontaneously reported adverse events

reported in the UK from 1 July 1963 to 18 December 2012. The report run date was 19 December 2012. The earliest reaction date was 26 December 2006. The document provided by the complainant stated that the report recorded where at least one suspected adverse drug reaction (ADR) report had been received that specified the product as a 'suspected drug' (ie suspected causal association with the reaction). It further stated that suspected ADR reports sent to the Yellow Card scheme were called spontaneous reports.

In this regard the Appeal Board noted the section 'seizures and seizure disorders NEC [not elsewhere classified]' gave a combined total of 74 for convulsions, epilepsy, partial seizures and status epilepticus. Other sections of the DAP recorded 3 reports of petit mal epilepsy and 15 of grand mal convulsions. The Appeal Board noted that no evidence had been provided to show that this was more than might normally have occurred in the general population who had not taken Champix. The Appeal Board noted that the DAP did not break down the data and there was no record of the situation in January 2008 when the complainant took Champix. The Appeal Board noted that the listing of an adverse event in the DAP did not prove that it had been caused by Champix. It was a record that the adverse event had happened in a patient who at the same time was taking Champix and that it *might* be causally related.

The Appeal Board noted that it was the role of the relevant EU or UK regulatory authority to decide the wording of SPCs and PILs. The wording of an SPC was likely to change over time as experience with a medicine grew. In that regard the Appeal Board noted correspondence between the complainant and the MHRA and in particular an email from the MHRA dated 1 October 2012 which stated that cases of seizures and epilepsy reported for varenicline (Champix) would be reviewed within the European regulatory framework in the next couple of months. It was important that the MHRA was provided with all relevant information and the complainant stated to the Appeal Board that she had provided all of her documents to the MHRA. At the appeal hearing the Appeal Board queried the accuracy of some aspects of the material submitted by the complainant and the conclusions drawn.

The Appeal Board noted that the complainant had provided a copy of a leaflet prepared by Pfizer Canada Inc (last revised 14 December 2011). Under a heading 'Warnings and precautions' patients were advised not to engage in potentially hazardous tasks such as driving or operating machinery as some people had reported, among other things, blackouts and seizures. Such events, however, were not included in the section of the leaflet headed 'Side effects and what to do about them'. The US full prescribing information (revised December 2012) listed convulsion as a rare side effect. Neither the Canadian nor the US document specifically included the word 'epilepsy'. The Appeal Board also noted that the patient leaflet from Australia (dated February 2007) referred to seizures and fits. Pfizer had submitted that this leaflet was used in both Australia and New Zealand and that the New Zealand data sheet did not refer to seizures or fits. Pfizer had submitted that the reference to seizures and fits in the Australian/New Zealand document had been an error and had been removed in September 2007.

The Appeal Board noted that the information provided by Pfizer in the UK reflected the information in the SPC and PIL which had been agreed with the UK regulatory authorities. The Appeal Board considered that it had not been provided with any evidence to show that the information Pfizer had provided to patients taking Champix in January 2008 when the complainant took Champix, was inconsistent with the evidence available at that time with regard to the possibility of developing epilepsy as a consequence of taking or stopping treatment with Champix. Therefore the failure to refer to seizures or fits in Pfizer produced patient leaflets for the UK available in January 2008 was not a failure to reflect the available evidence. Thus the Appeal Board upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.

Similarly the Appeal Board considered that it had not been provided with any evidence to show that information provided to the public by Pfizer in January 2008 was not factual or balanced with regard to the side-effect profile of Champix. Not referring to fits and seizures in Pfizer produced patient leaflets did not mean that this material was incorrect or unbalanced. Thus the Appeal Board upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and consequently upheld the Panel's ruling of no breach of the Code was ruled including Clause 2. The appeal on this point was unsuccessful.

A member of the public alleged that Pfizer had failed to warn of serious side effects of Champix (varenicline). Champix was indicated for smoking cessation.

COMPLAINT

The complainant stated that Champix came onto the UK market in 2006. The patient leaflet made no mention of convulsions. The complainant took the medicine in January 2008, at which time there was also no mention of convulsions on the leaflet. The complainant submitted that she stopped smoking within a week of starting Champix. The complainant stated that she was supposed to take a 12 week course but at week 10 she started to feel depressed and thought of killing herself; this was out of character. The complainant was told by her doctor to stop taking Champix, and within 24 days of the last dose she had a grand-mal convulsion in her sleep. She had never had a convulsion. The complainant stated that she then had a second one in her sleep within two weeks of the first one and was subsequently diagnosed with epilepsy.

The complainant submitted that in 2010 a friend was told that he was not suitable for Champix as he had a history of head injury and that it might cause a seizure. The complainant then contacted her doctor to see if her convulsions were connected to the Champix, her doctor thought that they could be and told the complainant to report her epilepsy as a possible withdrawal effect of Champix.

The complainant stated that this was when she started her research and submitted a patient leaflet that was prepared by Pfizer Australia in February 2007. This leaflet stated, *inter alia*, that before taking Champix a patient should tell his/her doctor if he/she suffered from repeated fits or convulsions. The complainant stated that leaflets in Canada also mentioned seizures but there was still no mention of this in UK leaflets. The complainant stated that on 22 May 2008 the Food and Drug Administration (FDA) asked Pfizer about the link between varenicline and seizures. The prescription leaflet noted that pilots, controllers and truckers should not take varenicline from 2008 due to the risk of seizures. The complainant stated that the FDA then issued a further warning to include seizures in 2009.

The complainant alleged that Pfizer had failed to properly warn consumers and was primarily concerned with protecting profits, even at the expense of the health of those trying to quit smoking to prolong their lives. The complainant submitted that genetic engineering altered DNA in ways which would never occur in nature. These mutations could easily cause unforeseen complications, such as formation of toxins or allergens. The effects of these problems might not be easy to detect. The complainant stated that medicines of this nature might adversely affect certain individuals more than others and alleged that the scientific literature, the very place doctors looked for a warning, contained barely a hint of problems in the UK and almost stated that no withdrawal symptoms were seen with varenicline.

The complainant stated that varenicline was developed by Pfizer Inc in 1997; it was based on the naturally-occurring alkaloid cytisine which was extracted from the seeds of the Laburnum, (Golden Rain), a shrub or small tree. It was one of the Laburnum anagyroides, or Latin name *Leguminosae/Fabaceae*. The seeds also contained proteins, tannins, glycosides and choline. Cytisine was isolated and used in pharmaceutical preparations to treat, for example, hypotension. The complainant stated that in homeopathy a tincture prepared from the fresh leaves and flowers was sometimes used to treat various neurological and digestive disorders. Laburnum was classed as a dangerous plant; it should never be collected and used for self-medication as the seeds were highly toxic due to cytisine content. Symptoms of cytisine poisoning included dilation of the pupils, stomach cramps, vomiting, giddiness, muscular weakness, convulsions, respiratory failure and death. These were all signs of a neurotoxin, most being the reactions one would have to snake venom.

The complainant stated that a clinical trial, Bonn *et al*, sponsored by Pfizer and GlaxoSmith [sic] resulted in the creation of cytisine 27, generic name for Tabex, (which was patented and marketed and produced by GlaxoSmith [sic]) and the creation of the cytisine analogue varenicline, a DNA copy of cytisine (this was not a naturally occurring alkaloid). This was then patented by Pfizer and marketed and produced as Chantix in Canada and the US and as Champix in the UK.

The complainant alleged that nicotinic acetylcholine receptors (nAChRs) had been implicated in a number of disorders affecting the nervous system (eg Tourette's syndrome, schizophrenia, epilepsy, depression, anxiety) as well as pathologies in non-neuronal tissues and cells (eg small-cell lung carcinoma or inflammatory bowel disease). However, the main focus in the field of these ligand-gated ion channels was on their involvement in neurodegenerative diseases such as Alzheimer's or Parkinson's and in antinociception. The complainant stated that the etiology of this neuropsychiatric disorder and the mechanism of the beneficial effect of nicotine remained unclear. It was observed that the density of alpha-7 receptors had been reduced in the CA3 region of hippocampus in the brain of schizophrenics.

All this information was from a paper published by the Pfizer group in 2000. There was knowledge of a link. Dinucleotide polymorphism at chromosome 15q13-14, a site of the alpha-7 subunit gene CHRNA7, had been found. Epilepsy, in particular, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), epileptic seizures occurring mainly during the sleep, was associated with mutation in the gene coding for either the alpha-4 or beta-2 nAChR subunit. These mutations had been reported to be responsible only for some factors leading to the clinical manifestation of the disease, however, not for all the symptoms of ADNFLE. There were experimental indications that also alpha-7 subunits were involved in seizure control.

The complainant stated that depression/anxiety were also believed to be related to nAChR dysfunction. Direct evidence of altered nAChR function in individuals suffering from these disorders was missing, but genetic studies showed a positive correlation between tobacco dependence and major depression. In addition, smoking was more prevalent in patients suffering from depression than in the general population.

Alzheimer's disease was a neurodegenerative disease characterised by a progressive loss of short-term memory and higher cognitive functions. The most marked changes in the neurotransmitter system of patients were the degeneration of the cholinergic innervation and the reduction of the choline acetyl transferase activity in the hippocampus and cerebral cortex. There was accumulating evidence that the function and density of neuronal nAChRs (especially alpha-4-beta-2 subtype) was reduced in the brains of Alzheimer's patients. In addition beta-amyloid peptides, which were part of the neuritic plaques found in the brains of Alzheimer's patients, had been shown to bind to alpha-7 nAChRs and were neurotoxic. Thus, medicines targeted for treatment of Alzheimer's

disease, through modulation of nAChRs, should either targ*et al*pha-4-beta-2 subtype and cause receptor activation or activate alpha-7 and improve cell survival.

The complainant noted that patients with Parkinson's disease suffered from motor dysfunction which resulted in muscular rigidity, tremor and uncoordinated movement. Parkinson's disease was a neurodegenerative disease manifested by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta accompanied by parallel loss of high affinity nicotine binding in these regions. Nicotine improved the symptoms of Parkinson's disease and the beneficial effects of the tobacco alkaloid were consequences of increased dopamine levels in the substantia nigra and mesolimbic system, as well as of possible inhibition of monoamine oxidase B. The complainant stated that the risk of developing Parkinson's disease was inversely correlated with the number of cigarettes smoked.

The complainant submitted that pain and nAChRs were linked since the discovery of antinociceptive properties of the nicotine agonist epibatidine, which possessed a 200-fold higher analgesic effect than morphine in the hot-plate test. The complainant stated that the initial euphoria of this discovery disappeared because of the highly toxic effects of epibatidine mediated by peripheral nAChRs. Conversely, ABT-594, a selective nicotinic agonist for neuronal subtypes had been reported to be in clinical trials for the treatment of neuropathic pain, even if the side effect profile of this compound was not improved compared with epibatidine. The complainant stated that tobacco smoking, despite its positive effect in etiology of diseases such as Alzheimer's or Parkinson's, was the leading cause of preventable death worldwide. Nicotine mediated its action through nAChRs in the central nervous system especially via dopamine release in the nucleus accumbens or prefrontal cortex. These brain regions were connected to the ventral tegmental area that was a part of the reward system in the human brain. Nicotine administration in a form of gum, transdermal patch, nasal spray and inhaler or the non-nicotine based antidepressant bupropion was used for the treatment of nicotine addiction. Administration of nicotine by any form was statistically more effective than placebo, but the long-term relapse rates were as high as 80%. Thus, improving the long-term efficacy was a key component of novel pharmacotherapies for smoking cessation.

The complainant stated that human post-marketing clinical trials mentioned grand-mal and peti-mal seizures happening within 30 days of the last dose of varenicline. It also mentioned deaths, but as it was after last dose, Pfizer did not put these forward. This was the only information after 2 years that said anything about last dose of varenicline. Everywhere seemed to state that there were no side effects from Champix after the last dose.

The complainant stated that she had contacted Pfizer UK on several occasions and the company had told her that no seizures were seen in any clinical trial involving the correct dose. The complainant then found, with help from her MP, that many members of Parliament and of the House of Lords had shares, private interests or other links with pharmaceutical companies including Pfizer. Also Pfizer sponsored a lot of projects within the NHS. When the complainant asked her first neurologist in 2010 if she thought that Champix could have triggered epilepsy, her exact words were 'I am not prepared to put my job on the line by answering that question'. The complainant was very angry by this answer and found that Pfizer funded projects in the local NHS, so was it a case of don't bite the hand that feeds you. The complainant noted other possible conflicts of interest between Pfizer and other organisations. The complainant stated that she had set up a petition on the subject of conflict of interest and needed 100,000 signatures for it to be listened to in the House of Lords.

The complainant alleged that she and others had, and still were, suffering the effects of Champix. They were given no warning of these side effects of this medicine, had reported it through the correct channels, and still nothing had been done. In the US a class action had been brought against Pfizer for $150 million for no warning of side effects. The complainant alleged that Pfizer had breached the Code and that by giving no warning, it had put the public at risk. The complainant wanted to sue and the money to be put back into the NHS.

When writing to Pfizer the Authority asked it to respond in relation to the requirements of Clauses 2, 7.9, 9.1 and 22.2.

RESPONSE

In reviewing the complaint, Pfizer submitted that it was important first to separate out from its content which aspects fell within the scope of the Code. Pfizer proposed that the following information was out of scope of the Code.

Cytisine

- Information on genetic engineering and the plant *Laburnum*, the seeds of which contain cytisine; cytisine had a molecular structure similar to that of nicotine and varenicline – as the complainant has noted, the concept for varenicline in early drug discovery was based partly on cytisine.
- Details provided regarding the 'creation' of cytisine 27 (Tabex) – this medicine was not produced by Pfizer; the complainant noted that Tabex was patented, marketed and produced by GlaxoSmith [sic]. Pfizer could find no information to confirm this, desk research indicated it was produced by Sopharma AD in Bulgaria, and leading key opinion leaders had published a paper on Tabex as an aid to smoking cessation for the past 40 years, having been licensed in Eastern Europe (Zaatonski *et al* 2006). There was insufficient information on its effectiveness to warrant licensing by modern standards.

Role of nAChRs in human pathology

- The information provided was about the role of nAChRs in human pathology and the perceived link with varenicline. No causal link had been

established to demonstrate that varenicline caused schizophrenia, Tourette's syndrome, epilepsy, depression and anxiety, or the neurodegenerative Alzheimer's and Parkinson's diseases. It was unclear as to which paper the complainant had referred in the statement 'This information was from a paper published by the Pfizer group in 2000. There was knowledge of link'. Pfizer took the safety of all its medicines seriously and conducted ongoing programmes of clinical research and global surveillance of spontaneous reports to monitor and assess the safety of its medicines. All of this information was shared with worldwide medicine regulators, including the European Medicines Agency (EMA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

Patient information

- Pfizer could not comment on the individual patient's clinical history or why the complainant's friend was/was not prescribed varenicline by his doctor.

Notes and comments

- Potentially disparaging comments were indicated about the patient's neurologist and others – these were outside the scope of the Code and it would not be appropriate for Pfizer to comment, for example, on a private conversation between the complainant and her neurologist (ref: 'I am not prepared to put my job on the line by answering that question.').

General allegations

Pfizer submitted that the patient's general allegation was that Pfizer had failed to provide comprehensive information about the safety profile of varenicline. The main safety issue the complainant appeared to focus on was that of seizure. Pfizer worked closely with worldwide regulators to monitor and review all sources of data for varenicline, including post-marketing reports of adverse events on an ongoing basis. Currently there was no scientific evidence to demonstrate a causal relationship between varenicline and seizure.

The complainant included a leaflet from Australia that appeared to be patient information, prepared in February 2007. 'Seizures or fits' were included in the 'Side effects' section, as follows:

> 'If any of the following happen, tell your doctor immediately or go to A&E at your nearest hospital: wheezing, difficulty in breathing or shortness of breath; severe chest pain; seizures or fits; fainting; swelling of the face, lips, mouth, tongue or throat; severe sudden onset of itchy swellings on the skin; and severe skin reaction with painful red blisters with chills, fever, aching muscles and generally feeling unwell.'

The current consumer medicine information (CMI) for varenicline in Australia, updated in December 2010, did not contain the same information, and was therefore not different to the UK patient information leaflet (PIL) in that regard. It mentioned areas in which varenicline had not been studied, including repeated fits or convulsions (epilepsy), in line with that of the UK varenicline summary of product characteristics (SPC). With regard to adverse effects, there was no listing for epilepsy, convulsion or seizures. An analysis of post-marketing adverse effects reports received by the US FDA, conducted by the Institute for Safe Medication Practices (ISMP), was also included in the complainant's letter. As the authors themselves concluded, whilst reports of side effects of varenicline, including skin reactions and seizures, were received, these did not establish causality and only identified potential causes.

Pfizer stated that the basis of its response to this complaint was in relation to the safety and tolerability materials which had been developed for varenicline. These were materials that could be provided to health professionals together with information provided to smokers by their health professional in the form of a patient tear-off information sheet. In addition, the PIL provided essential information which included special warnings and precautions, side effects and dosing. This enabled smokers to use the medicine appropriately and gain the most benefit whilst maximising patient safety. Pfizer had a responsibility to ensure that in all information provided either to health professionals or patients was consistent with the SPC, was accurate, balanced, up-to-date, not misleading or exaggerated, and was capable of substantiation.

Patient information leaflet

Pfizer noted that as for centrally approved products, the PIL was approved by the European Medicines Agency (EMA) in line with Title V (Labelling and Package Leaflet) of the Council Directive 2001/83/EC. Pfizer submitted that the Champix PIL provided a clear overview of the medicine's safety and tolerability profile (a copy was provided). It clearly stated from the outset that the patient should read the information before starting the medicine. Additionally, it referred the patient to their health professional for any further clarification or the onset of any serious side-effects, or side effects not reported within the document.

Pfizer submitted that the PIL provided a clear overview of the indication for varenicline under the heading 'What is Champix and what is it used for'. The section entitled 'Before you take Champix' provided the patient with an overview of the contra-indications together with the special warnings and precautions for varenicline. The special warnings and precautions section provided an overview of the neuropsychiatric and cardiovascular events reported in patients taking varenicline with clear guidance to seek immediate support from their doctor in the event of any changes in symptoms. This section also made the patient aware of the potential effects of stopping smoking, discontinuing varenicline and interactions with other medicinal products. The safety profile of varenicline in pregnancy and breast feeding together with its use while driving and operating machinery were all clearly documented within the PIL. The dosage, including dose, frequency, and duration of treatment together with guidance on what action to take if the patient missed

a dose or accidentally overdosed was captured within this document.

Pfizer submitted that a detailed account of the possible side effects of varenicline including: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) were all documented within the PIL. Importantly, this section highlighted the importance for the patient to stop treatment and contact their doctor immediately if they experienced neuropsychiatric symptoms, swelling of the face, mouth or throat or if their skin started to peel or blister. In summary, Pfizer stated that the Champix PIL provided a clear overview of the safety and tolerability profile with guidance to seek support from a doctor/pharmacist in certain circumstances. The PIL was consistent with the SPC and was legible, clear, easy to use and enabled the user to act appropriately.

Patient tear-off information sheet

Pfizer submitted that a patient tear-off information sheet, which health professionals could provide to patients, was also consistent with the SPC. The indication for varenicline, together with its contra-indications, were clearly stated under the heading 'Am I suitable for Champix?'. Furthermore, a section entitled 'What side effects might I experience?' provided an overview of some of the common side effects of varenicline and some of the common withdrawal symptoms associated with smoking cessation. The effects of varenicline on the ability to drive and use machinery were described. Within this section, the special warnings and precautions in relation to neuropsychiatric and cardiovascular disease were addressed. The importance of stopping medication and seeking support from a doctor should such symptoms arise was also highlighted.

Pfizer stated that in addition, patients were advised to seek their health professional's support should they be concerned about any side effects, if the side effects became serious, or if the patient noticed side effects not in the package leaflet. The list of side effects reported in the tear-off sheet was not exhaustive and there was clear guidance that the patient should refer to the PIL for other side effects that had been reported. Regarding potential interactions with other medicines, there was also a section entitled 'Can I take Champix with my other medication?'. This was consistent with the SPC for varenicline and in addition provided the patient with information regarding the effects of stopping smoking on other medicines which might require dose adjustment.

Pfizer submitted that another important area for consideration was the dosage of varenicline and this was addressed in the material providing the patient with information on the dose, frequency, duration of treatment and also guidance on what to do should the patient miss a dose. In summary, this patient information sheet provided a clear overview of the key features of the SPC to ensure that the patient was aware of the safety and tolerability profile of varenicline.

Pfizer noted that the item was a pad to be distributed to health professionals and therefore included varenicline prescribing information. The tear-off sheets were only provided to patients already prescribed varenicline, and the information sheets, once torn from the pad, did not include prescribing information.

Safety and tolerability folder

Pfizer stated that for further education for health professionals around the safety and tolerability of varenicline, Pfizer had also generated a specific folder to raise awareness of its safety profile (a copy was provided). Pfizer noted the use of the black triangle to denote that special reporting was required in relation to adverse reactions. The folder provided an overview of the very common side effects reported with an incidence of ≥10% for varenicline, together with the common symptoms of nicotine withdrawal. There was clear guidance for the health professionals as to the frequency of these adverse events together with the severity and discontinuation rates due to adverse events compared with placebo. Further information regarding interactions with other medicines was also documented.

Pfizer submitted that the special warnings and precautions for varenicline in relation to neuropsychiatric and cardiovascular issues and clarification for health professionals to stop treatment immediately if such symptoms arose had been effectively communicated, and was consistent with the SPC. As the folder did not cover all aspects from the SPC there was an additional clear statement referring health professionals to the SPC for further information on the safety profile of varenicline. This document was consistent with the SPC, accurate, balanced, up-to-date, not misleading or exaggerated and capable of substantiation.

Pfizer stated that the material which had been generated by Pfizer for health professionals and patients was at all times consistent with the SPC, accurate, balanced, up-to-date, not misleading or exaggerated and capable of substantiation. The material had been generated to maintain patient safety by ensuring accurate communication of the safety and tolerability profile of varenicline for health professionals and for patients. The patient-specific material provided key information as to what the patient could expect from taking varenicline. In addition, it clearly stated what action needed to be taken regarding any neuropsychiatric or cardiovascular symptoms or any side effects that were of a concern to the patient which might arise while taking the medicine.

Pfizer considered that the materials communicating the safety of varenicline both to health professionals and to patients had not brought discredit upon, or reduced confidence in, the pharmaceutical industry and therefore that Clause 2 had not been breached. Pfizer submitted that as evident from the material provided, it had at all times provided a consistent, accurate and balanced reflection of the information from the varenicline SPC regarding the safety and tolerability profile. Pfizer had never implied that

varenicline was safe and had provided a clear overview of the indication, contra-indications, special warnings and precautions in relation to neuropsychiatric and cardiovascular events, dosing regimen, potential side effects and interactions for varenicline. Pfizer denied a breach of Clause 7.9.

Pfizer considered that high standards had been maintained at all times in the generation of the material for health professionals and patients to ensure that it was consistent with the SPC in relation to the safety and tolerability profile of varenicline. Pfizer denied a breach of Clause 9.1.

Pfizer stated that the material generated about the current safety and tolerability of varenicline had always been factual and presented in a balanced way. It did not raise unfounded hopes of successful treatment and was not misleading with respect to the safety of the product. It had been generated to ensure that health professionals and patients were aware of the safety and tolerability profile of varenicline to support patient safety and appropriate prescribing. Pfizer denied a breach of Clause 22.2.

Pfizer stated that in summary, the safety and tolerability material generated for varenicline provided an overview as to what a patient could expect from taking varenicline including common adverse events, special warnings and precautions and was fully consistent with the SPC. Pfizer had always provided comprehensive information about the side effect profile of varenicline and therefore strongly denied any breach of Clauses 2, 7.9, 9.1 or 22.2.

Following a request for further information, Pfizer submitted that the previously supplied PIL was approved in April 2007. Two earlier versions of the PIL were provided. The first was approved in September 2006 and was in varenicline packs December 2006 - July 2007. The second was approved in February 2007 and was in varenicline packs July 2007 - May 2008.

Pfizer stated that varenicline received marketing authorization in the EU on 26 September 2006 via a centralised procedure. Varenicline labelling, including the SPC and package leaflet was therefore consistent across the EU.

Pfizer submitted that during 2006 and 2007 there were both type I and type II variations, as well as notifications that led to changes in the varenicline SPC and package leaflet. During 2008 there were substantive updates to the varenicline labelling, including the SPC and package leaflet. These occurred subsequent to January 2008 and related primarily to neuropsychiatric events and hypersensitivity reactions. Between 2006 and 2008 there were no changes to the UK SPC or PIL with regard to seizures or epilepsy. Throughout this time the SPC stated in Section 4.4 'There is no clinical experience with CHAMPIX in patients with epilepsy'. Seizures or fits were not listed in Section 4 'Undesirable effects' in either the UK PIL already submitted (April 2007) or in the PILs provided subsequently.

Pfizer stated that it had contacted Pfizer Australia/New Zealand about the reference to seizures on the CMI leaflet from Australia/New Zealand dated February 2007. The varenicline CMI was a common document used in both Australia and New Zealand. Varenicline was launched in New Zealand in April 2007 with the CMI dated February 2007. The CMI was revised in September 2007, in which 'seizures or fits' was deleted to ensure consistency with the data sheet in New Zealand. The data sheet was the New Zealand equivalent of the SPC, and 'seizures or fits were not listed in the SPC. Varenicline was not launched in Australia until December 2007 and used the CMI dated September 2007 (ie not the February 2007 CMI).

Following a request for further information, Pfizer submitted that, regarding product labelling in Australia and New Zealand, there were separate health authorities. In Australia it was the Therapeutic Goods Administration (TGA) and in New Zealand the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE). The core labelling documents ('PI' in Australia; 'datasheet' in New Zealand) were different for each country. The CMIs, however, were common to both countries, hence the joint Australia/New Zealand addresses on the documents. CMIs were released through an organisation called Heathlinks in Australia. In New Zealand CMIs were made available through MEDSAFE.

Varenicline was launched in Australia in December 2007, with the September 2007 CMI. The February 2007 CMI was never released via Healthlinks in Australia, but might have been provided to those who participated in an Australian patient familiarisation program which ran in the second half of 2007. Varenicline was launched in New Zealand in April 2007, with the February 2007 CMI (made available on the MEDSAFE website). The CMIs did not go into packs in Australia or New Zealand but would have been available electronically in New Zealand at launch. It was therefore possible that the complainant obtained the CMI electronically when it was live in New Zealand but not issued in Australia.

The New Zealand datasheet did not refer to seizures or fits. Pfizer submitted that unfortunately its records did not show why these terms were included in the CMI, but the most likely explanation was that this was an oversight. This was rectified as soon as the discrepancy between the CMI and the datasheet was discovered. The CMI must reflect what was in the product datasheet so reference to 'seizures and fits' in the CMI was removed when the discrepancy between the CMI and product datasheet was noted.

PANEL RULING

The Panel noted that the complainant had provided much material and comment. Patient safety was extremely important. The Panel noted that the complainant stated that she had provided information to her doctor who advised her to report her epilepsy as a possible withdrawal effect of Champix. It was not clear whether the complainant had done so although she had contacted Pfizer about the matter. The pharmacovigilance procedures at

Pfizer should have ensured that the relevant data was added to its possible adverse event database. Pfizer had not stated whether this was so but in that regard the Panel noted that the company did not know the complainant's identity. The complainant's doctor also had a role in reporting the matter following any discussion with the complainant about the possibility of the complainant's seizures being linked to Champix. The Panel's role was to consider the allegations in relation to the requirements of the Code. In this regard, the Panel considered that the key issue raised by the complainant was that patient leaflets for Champix produced by Pfizer were misleading in relation to the risk or otherwise of convulsions associated with the use and/or discontinuation of the medicine.

The Panel noted that the complainant referred to 'leaflets' for Champix but it was unclear whether she had seen the PIL or SPC, or some other patient leaflet produced by Pfizer. No examples of UK materials were provided by the complainant. The Panel further noted that the PIL and SPC were regulatory documents, the content of which was governed by the relevant EU or UK regulatory authority. Clause 1.2 of the Code was clear that neither SPCs nor the leaflet that accompanied a medicine (PIL) were included in the definition of promotion. The contents of such documents were covered by regulations. However, Pfizer had submitted that it had also produced further leaflets, for both patients and health professionals, based on the PIL and SPC for Champix. The Panel considered that the content of these was within the scope of the Code and had to comply with it including, in particular, Clauses 7 and 22. Such material had to accurately reflect the SPC.

The Panel noted the complainant stated that she started a 12 week course of Champix in January 2008 which was discontinued after 10 weeks. The SPC submitted by Pfizer as current at that time (which was approved in April 2007) did not refer to fits or seizures in Section 4.8, Undesirable effects. Section 4.4, Special warnings and precautions for use, stated that there was no clinical experience with Champix in patients with epilepsy.

Pfizer submitted an additional patient leaflet for Champix that was available when the complainant took the medicine (ref SCE055, prepared November 2007). One section, entitled 'What side effects might I experience?', referred to side effects associated with giving up smoking, including mood changes, sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain. Common side effects for Champix were also stated, including nausea, headache, difficulty sleeping and abnormal dreams. Reference was also made to dizziness and sleepiness. Similarly to the SPC, there was no mention of fits or seizures.

The Panel noted that the SPC submitted by Pfizer as the current Champix SPC (13 April 2012) again referred in Section 4.4, Special warnings and precautions for use, to lack of clinical experience with Champix in patients with epilepsy. There was no reference to seizures or fits in Section 4.8, Undesirable effects. A current patient leaflet produced by Pfizer (ref CHA1413, prepared October 2012) referred to similar side effects as the previous patient leaflet and, in addition, to changes in behaviour and thinking, depression and anxiety, worsening of psychiatric illness and suicidal thoughts and attempts. Again there was no reference to seizure or fits.

The Panel noted that the complainant had submitted a patient leaflet from Australia dated February 2007 which referred to seizures and fits and advised the patient to seek immediate medical help if these were experienced. The Panel further noted Pfizer's submission that this leaflet was common to Australia and New Zealand and that the New Zealand datasheet did not refer to seizures or fits.

The Panel noted that the reference to seizures and fits in the Australian/New Zealand document dated February 2007 had, according to Pfizer, been made in error and had been removed in September 2007. The complainant had stated that her treatment course began in January 2008. The Panel noted that there was no reference in UK regulatory documents (SPC and PIL), either currently or when the complainant took Champix, that Champix treatment, or discontinuation of treatment, was associated with seizures or fits. The Panel further noted Pfizer's submission that there was currently no evidence of a causal relationship between varenicline and seizure. The Panel thus considered that failure to refer to seizures or fits in any Pfizer-produced patient leaflets for the UK was not a failure to reflect the available evidence about these side effects. No breach of Clause 7.9 was ruled. Not referring to fits and seizures in Champix patient material did not render that material incorrect or unbalanced and no breach of Clause 22.2 was ruled.

The Panel noted its rulings above and subsequently ruled no breach of Clauses 9.1 and 2.

APPEAL BY THE COMPLAINANT

The complainant submitted a number of detailed comments, attachments and enclosures from a variety of sources including the National Institute for Health and Clinical Excellence (NICE) and the MHRA in support of her appeal. The complainant provided a copy of the Drug Analysis Print (DAP) for Champix which listed spontaneously reported adverse events. The complainant later stated that these submissions were only sent as they supported her final report provided as her final comments (see below).

RESPONSE FROM PFIZER

Pfizer submitted that whilst it had sympathy for the complainant's concerns it did not believe that it had breached the Code and therefore it agreed with the Panel's ruling.

Pfizer submitted that its materials for health professionals and patients responsibly described the safety profile of Champix, including any specific special warnings and precautions. The safety information was accurate and balanced and was

consistent with the SPC. Pfizer assured the Appeal Board that any safety changes to the SPC were always reflected rapidly in its materials for health professionals and patients. It was clearly important that the most up-to-date information was provided, and that it was based on the SPC.

Pfizer considered that in its response to the complaint and to the appeal, it had addressed any matters related to the Code.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant stated that patients with neuropsychiatric disorders had a typically two to four-fold higher chance of being a smoker. Studies conducted in a variety of neuropsychiatric populations (eg attention-deficit hyperactivity disorder (ADHD), epilepsy, Alzheimer's, schizophrenia, Parkinson's) had collectively suggested that nicotine, was efficacious in remediating selected cognitive deficits associated with these disorders, thus providing a framework for understanding the specific vulnerability of these patients to smoking initiation and maintenance. However, the specific gain in cognitive performance produced by nicotine administration in healthy subjects with normal cognitive function was less clear. This submission reviewed the current understanding of central nicotinic acetylcholine receptors (nAChRs) systems in normal and neuropsychiatric disease states and, specifically, their role with respect to cognitive dysfunction and clinical symptoms in several specific neuropsychiatric populations, including ADHD, Alzheimer's, Parkinson's disease, Tourette's disorder, schizophrenia and affective disorders.

The complainant stated that mice which lacked the dopamine (DA) transporter (DAT) gene exhibited a phenotype reminiscent of schizophrenia and ADHD, which were alleviated by antipsychotic agents.

The complainant stated that alteration of nicotinic neurotransmission in DAT knockout (KO) mice showed that constitutively hyper dopaminergic (DAergic) DAT KO mice exhibited modifications in nicotinic receptor density in an area and subtype-dependent manner. In some DAergic areas, the small decrease in the Beta2* nicotinic subunit (nAChR) density contrasted with higher decrease and increase in the Alpha6* and Alpha7* nAChR densities, respectively.

Mutant mice were hypersensitive to the stimulant locomotor effects of nicotine at low doses, probably due to enhanced nicotine-induced extracellular DA level. They also showed hypersensitivity to the hypolocomotion induced by nicotine. In contrast, no hypersensitivity was observed for other nicotine-induced behavioral effects, such as anxiety or motor activity. Co-administration of nicotinic agonists at sub-active doses elicited opposite locomotor effects in wild-type and DAT KO mice.
These findings showed that a targeted increase of DA tone could be responsible for significant adaptations of the cholinergic/nicotinic neurotransmission. This study provided potential leads for the use of nicotine or combined nicotinic agonists to treat psychiatric disorders.

The complainant noted an article titled 'Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders' by Sacco *et al* (2004). The complainant further noted that Pfizer had stated that Champix had not been tested in these people. In the complainant's view it clearly had, as the papers looked at mentioned Champix, and all the papers' dates were before recommendations for Champix to be used as first-line treatment by NICE, for use on UK NHS. Also, one of Pfizer's scientists had the patent for the nicotinic receptors as he created the genetically altered mutated mice. He bred them and supplied them to Pfizer for medicine development looking at treatments for ADHD, Alzheimer's, epilepsy and other diseases that were triggered by mutations of nAChRs on withdrawal of Champix. His special mice had been purposely bred to have the Alpha4 mutation.

The complainant stated that the Alpha4 mutation was the one linked to epilepsy and Alpha7 and was linked to Alzheimer's and heart problems. Beta4 was linked to Parkinson's. The complainant stated that she could see the rational of design of potent medicines with selective binding properties but there were still many unanswered questions about these synthetic compounds.

The complainant stated that in her opinion too many were given out by the NHS just for stopping smoking in the general population. If it was used as second-line treatment for example in people who were showing symptoms of early COPD due to years of smoking or even lung cancer, with proper medical supervision, and a weaning off programme, then for these areas of the population it might be worth the risk as it could up their survival as it did stop you smoking while on the medicine.

The complainant stated that Pfizer must have known that withdrawal of Champix could trigger seizures and any of the above mentioned in 10% or more of the general population, as all nAChRs, dual inhibitors had very similar application.

5-HTa4+a7 association with Epilepsy. (Epilepsia, 2006 and Heterocyles, 2006).

The complainant stated that the 5-HTa4+a7 haplotype was associated with epilepsy type disorders, of which there were over 50 different types. Extracellular concentrations of norepinephrine and dopamine in the prefrontal cortex could triggered ADNFLE. Antagonist Champix made norepinephrine efflux greater than other compounds alone. Norepinephrine reuptake inhibitors were used for depression, ADHD and epilepsy.

Dopaminergic polymorphisms and regulatory problems in infancy. (Zeitschrift fur Kinder-und Jugendpsychiatrie and Psychotherpie, 2007).

The complainant stated that the presence of certain alleles in polymorphisms of the dopamine receptor gene (DRD4) and the dopamine transporter gene

(DAT1) increased a child's risk of developing ADHD or another mental disorder and effected girls slightly more than boys.

The complainant stated that this showed that smoking whilst pregnant could cause the polymorphisms before you were born, but until triggered by medicines that artificially stimulated DAT1 like Champix did. Withdrawal could trigger diseases as previously mentioned. And also as stated before, these papers showed, nicotine was therapeutic and vital in some people with any history of mental illness or seizures, who carried mutations of this nature. NRT would not have triggered epilepsy in the complainant, or others on withdrawal. This only happened from artificial stimulation of nAChRs, from Champix. There was no warning of any of this in any Pfizer prescribing monograph or SPC for GPs, NICE or the MHRA. It had been estimated that at least 20% of patients with epilepsy might present with features of ADHD (Tan and Appleton, 2005).

The incidence of first provoked and unprovoked seizure in patients with and without psychiatric diagnoses (Epilepsia, 2007 and Indian Pediatrics, 2005).

The complainant noted that the authors concluded that the results of this study were consistent with previous reports showing that patients with psychiatric disorders had a higher incidence rate of seizures than the general population.

Linkage disequilibrium which might point towards co-segregation of two polymorphisms was showing in population more often than expected.

DAT1 gene effects

The complainant stated that DAT1 gene effects in the striatum were involved in translating the genetic risk of ADHD. DAT1 genotype would affect brain activation patterns in a manner similar to that of stimulant medication, eg nicotine.

Management of access to branded psychotropic medications in private health plans (Clinical Therapeutics, 2007).

The complainant noted private plans were managing psychotropic costs using co-payment incentives rather than administrating controls. This approach was less intrusive for clinicians, but resulting higher co-payments could worsen already high rates of nonadherence.

Statement by NICE (August 2012).

The complainant stated that NICE had told patients they should sue health authorities if they denied them medicines deemed cost-effective for NHS. The complainant stated that cost-effective did not mean a medicine was safe to use, it was down to doctors to decide if a medicine was safe for most of their patients who they had available to them their medical history, to help make that prognosis not the head of NICE who did not have medical training to do so. This was proof that the government put profit before peoples' health; the price of medication should not come into it, full stop.

APPEAL BOARD RULING

The Appeal Board considered that patient safety was extremely important. The Appeal Board noted that this was a highly personal and important issue for the complainant and it did not doubt her sincerity on the matter. The complainant had submitted a large volume of information and had referred to the conduct of other organisations. The Appeal Board noted that the complainant stated in response to a question at the appeal that she had sent all of her documents in this case to the MHRA. The Appeal Board noted that its only role was to consider matters in relation to the requirements of the Code and specifically the Panel's rulings of no breach of Clauses 2, 7.9, 9.1, and 22.2. As stated in the introduction to the PMCPA Constitution and Procedure, the complainant had the burden of proving their complaint on the balance of probabilities.

The Appeal Board examined two documents which were current when the complainant was prescribed Champix. The Champix SPC (reviewed 26 April 2007) stated in Section 4.4, Special warnings and precautions for use, that there was no clinical experience with Champix in patients with epilepsy. Section 4.8 of the same SPC, Undesirable effects, did not refer to seizures, epilepsy or fits. The Appeal Board noted that the SPC and the PIL were regulatory documents and their contents were agreed with the regulators, the MHRA and the EMA. The PIL was based on the agreed SPC. The Pfizer leaflet entitled 'Information for patients who have been prescribed Champix (varenicline tartrate)' (ref SCE055, prepared November 2007) had to reflect the SPC and PIL and not be inconsistent with those regulatory documents. The Appeal Board noted that the Pfizer leaflet similarly did not refer to seizures, epilepsy or fits in the section headed 'What side effects might I experience'. The Pfizer leaflet did not state that there was no clinical experience with Champix in patients with epilepsy; the Appeal Board, however, did not consider that the Pfizer leaflet was inconsistent with the SPC in that regard.

The Appeal Board noted that the current Champix SPC did not refer to seizures, epilepsy or fits as possible adverse effects and so similarly neither did the current PIL.

The Appeal Board noted that the complainant had provided the Drug Analysis Print (DAP) for Champix which listed spontaneously reported adverse events reported in the UK from 1 July 1963 to 18 December 2012. The report run date was 19 December 2012. The earliest reaction date was 26 December 2006. The document provided by the complainant stated that the report recorded where at least one suspected adverse drug reaction (ADR) report had been received that specified the product as a 'suspected drug' (ie suspected causal association with the reaction). It further stated that suspected ADR reports sent to the Yellow Card Scheme were called spontaneous reports.

In this regard the Appeal Board noted the section 'seizures and seizure disorders NEC [not elsewhere classified]' gave a combined total of 74 for convulsions, epilepsy, partial seizures and status epilepticus. Other sections of the DAP recorded 3 reports of petit mal epilepsy and 15 of grand mal convulsions. The Appeal Board noted that no evidence had been provided to show that this was more than might normally have occurred in the general population who had not taken Champix. The Appeal Board noted that the DAP did not breakdown the data and there was no record of the situation in January 2008 when the complainant took Champix. The Appeal Board noted that the listing of an adverse event in the DAP did not prove that it had been caused by Champix. It was a record that the adverse event had happened in a patient who at the same time was taking Champix and that it might be causally related.

The Appeal Board noted that it was the role of the relevant EU or UK regulatory authority to decide the wording of SPCs and PILs. The wording of an SPC was likely to change over time as experience with a medicine grew. In that regard the Appeal Board noted correspondence between the complainant and the MHRA and in particular an email from the MHRA dated 1 October 2012 which stated that cases of seizures and epilepsy reported for varenicline (Champix) would be reviewed within the European regulatory framework in the next couple of months. It was important that the MHRA was provided with all relevant information and the complainant stated to the Appeal Board that she had provided all of her documents to the MHRA. At the appeal hearing the Appeal Board queried the accuracy of some aspects of the material submitted by the complainant and the conclusions drawn.

The Appeal Board noted that the complainant had provided a copy of a leaflet prepared by Pfizer Canada Inc (last revised 14 December 2011). Under a heading 'Warnings and precautions' patients were advised not to engage in potentially hazardous tasks such as driving or operating machinery as some people had reported, among other things, blackouts and seizures. Such events, however, were not included in the section of the leaflet headed 'Side effects and what to do about them'. The US full prescribing information (revised December 2012) listed convulsion as a rare side effect. Neither the Canadian nor the US document specifically included the word 'epilepsy'. The Appeal Board also noted that the patient leaflet from Australia (dated February 2007) referred to seizures and fits. Pfizer had submitted that this leaflet was used in both Australia and New Zealand and that the New Zealand data sheet did not refer to seizures or fits. Pfizer had submitted that the reference to seizures and fits in the Australian/New Zealand document had been an error and had been removed in September 2007. The Appeal Board noted that the information provided by Pfizer in the UK reflected the information in the SPC and PIL which had been agreed with the UK regulatory authorities. The Appeal Board considered that it had not been provided with any evidence to show that the information Pfizer had provided to patients taking Champix in January 2008 when the complainant took Champix, was inconsistent with the evidence available at that time with regard to the possibility of developing epilepsy as a consequence of taking or stopping treatment with Champix. Therefore the failure to refer to seizures or fits in Pfizer produced patient leaflets for the UK available in January 2008 was not a failure to reflect the available evidence. Thus the Appeal Board upheld the Panel's ruling of no breach of Clause 7.9. The appeal on this point was unsuccessful.

Similarly the Appeal Board considered that it had not been provided with any evidence to show that information provided to the public by Pfizer in January 2008 was not factual or balanced with regard to the side-effect profile of Champix. Not referring to fits and seizures in Pfizer produced patient leaflets did not mean that this material was incorrect or unbalanced. Thus the Appeal Board upheld the Panel's ruling of no breach of Clause 22.2. The appeal on this point was unsuccessful.

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

Complaint received **5 October 2012**

Case completed **6 March 2013**

Post Appeal Board Meeting

As this case involved an issue of patient safety, the Appeal Board requested that the following details be provided for information only. Please note that none of the information below was known when the case was considered and it would not have changed the Appeal Board's decision which was based on information available in 2008.

Following the appeal, the complainant provided an email from the MHRA dated 13 March 2013 which included:

> 'A review of seizures was conducted as part of the last Periodic Safety Update Report (PSUR) for Champix. The PSUR assessment was considered by the EU Pharmacovigilance Risk Assessment Committee (PRAC) at its meeting 26-29 November 2012. The minutes of this meeting, which included the outcome of the assessment of seizure-related events, are published on the EMA website …. PRAC recommended that the product information (SPC and PIL) be updated to include seizure-related events.'

The minutes from PRAC stated:

> 'Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Champix, a centrally authorised medicine containing varenicline, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Champix (varenicline) in the approved indication(s) remains favourable.

- The PRAC recommended updating the product information with regard to seizure-related events. Therefore the current terms of the marketing authorisation should be varied …'

The updated SPC dated 11 March 2013 included in Section 4.4 special warnings and precautions for use, the following:

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Section 4.8 Undesirable effects listed seizures as an uncommon nervous system disorder.

The PIL had also been updated. The version on the eMC stated that the leaflet was last approved in 03/2013.