ANONYMOUS v SHIRE

Alleged promotion prior to the grant of a marketing authorization

An anonymous, non-contactable complainant who referred to him/herself as a health professional managing ADHD (attention deficit hyperactivity disorder) complained that an experienced MSL [medical science liaison] from Shire discussed with him/her an amphetamine medicine not licensed in the UK which Shire planned to launch next year [Vyvance (lisdexamphetamine mesylate) (LDX)]. The complainant alleged that Shire had instructed the MSLs to create 'noise' in the market about the new medicine and that they were set targets for the number of physicians willing to prescribe LDX or speak about it. The complainant further alleged that Shire also encouraged specialists to try the medicine on a 'named' scheme for patients.

One of the complainant's consultant colleagues often attended a two day monthly advisory panel meeting and recently attended another one. This was the third or fourth such Shire meeting this person had attended in 2012. The complainant had no doubt this busy consultant was likely to write many prescriptions for the new medicine.

The detailed response from Shire is given below.

The Panel noted that the complainant had provided little information and no documentation to support his/her complaint. As with any complaint, the complainant had the burden of proving his/her complaint on the balance of probabilities; the matter would be judged on the evidence provided by the parties.

The Panel noted Shire's submission that the MSL role was non-promotional and provided medical support for unsolicited enquiries about all of Shire's ADHD medicines. A document submitted by Shire entitled 'Clinical Development and Medical Affairs Guidance' described them as field counterparts to office-based medical affairs staff. They were not incentivized based on sales of medicines and targets were not set for interactions with health professionals.

The Panel noted from the job description submitted by Shire that a senior MSL reported to the associate director, international medical science liaison. The first 'essential function' noted on the job description was 'Through unsolicited requests for medical and scientific information, develop and raise Healthcare Professionals' level of understanding of medical and scientific data, using oral discussions, presentations and other appropriate media/techniques'. Other 'essential functions' included participation in cross-functional initiatives, delivery of medical education presentations and information gathering. One of the key skills and competencies listed referred to '…the non-promotional activities of this role'.

The 'Clinical Development and Medical Affairs Guidance' document stated that the medical and scientific activities of MSLs were proactive and reactive. The proactive activities included, *inter alia*, key opinion leader introductions and on-going relationship management, research support, issue management, disease state discussions and collection and input into scientific platforms. The reactive activities included, *inter alia*, responding to unsolicited requests for information and presentation on topics such as formulary/health economic outcomes resource, disease state and/or scientific data. Section VI of this document, 'Interactions with HCPs' [health professionals] noted that MSLs might meet health professionals to, *inter alia*, respond to unsolicited requests for information and to provide 'in-depth on-label information about Shire product, including changes to approved label'. The Panel considered that it was not clear as to whether this latter activity was proactive or reactive.

The Panel noted that a number of briefing documents for medical affairs were provided in relation to Vyvanse. A fact sheet contained a number of questions about the availability of LDX, mechanism of action, key data and side effects. The document was marked 'Reactive Use Only' and noted that the medicine was not yet licensed in the UK.

Two presentations, described by Shire as medical affairs training slides to respond to unsolicited medical information requests from health professionals, detailed results of two LDX studies in children and adolescents. The Panel noted that there appeared to be no briefing documents for Shire employees about the use of these presentations and there was no statement on any of the slides that the presentations were only to be used reactively.

The Panel noted that a further question and answer document entitled 'Availability of Shire ADHD products May 21, 2012' was marked 'For Internal Use Only. Not to be Forwarded or Distributed', but there was no indication that the information was only to be used reactively. In response to a question on which countries, *inter alia*, LDX was approved and marketed, this document stated that Vyvanse was approved and marketed in the US and Canada and was recently launched in Brazil under the name of Venvanse. A further question was 'Is Vyvanse [LDX] available via a 3rd party importer outside of the US?' and the answer stated was 'Shire only markets and promotes its products in accordance with regulatory guidelines in the countries where they are approved'. The document then stated that, if pressed, details could be provided of a specialist company which imported medicines on a named patient basis.

The Panel noted that the parties' accounts differed. A decision had to be made on the evidence before it. The complainant had provided no evidence in relation to his/her allegation that MSLs had been instructed to create 'noise' in the market about LDX, that they were set targets in relation to contacts with health professionals or that they encouraged health professionals to try LDX on a named patient basis. The Panel had some concerns about the material; it was not clear whether the MSL role was entirely reactive when it came to on-label discussion of Shire products and some of the briefing material about LDX could have been clearer that information on the medicine should only be provided in response to an unsolicited request. The Panel was also concerned about the absence of briefing materials indicated above. However, the Panel considered that there was no evidence to suggest that the MSLs had promoted, or had been briefed to promote, LDX before a marketing authorization that permitted its sale or supply was granted, nor was there evidence that the MSLs had promoted the use of LDX via a named patient programme. No breaches of the Code were ruled.

Turning to Shire's advisory boards, the Panel noted that advisory boards were a legitimate activity; all of the arrangements had to comply with the Code. The company must be able to demonstrate that it had a bona fide need for the advice being sought. The choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to meaningfully contribute to the purpose and expected outcomes of the meeting. The number of participants should be limited so as to allow active participation by all. The agenda should allow adequate time for discussion. The overall number of meetings should be limited and both the number of meetings and the number of participants at each should be driven by need and not the invitees' willingness to attend. Invitations to participate in an advisory board meeting should state the purpose of the meeting, the expected advisory role and the amount of work to be undertaken.

The Panel noted that Shire's global policy on advisory boards stated that advisory boards must be solely intended and necessary to fulfill a legitimate, unmet business need for information, advice and feedback from participants regarding Shire products or other topics relevant to Shire business and must be designed to elicit bona fide information from advisors. The advisory board should address questions in order to provide advice or feedback that had not previously been provided by either the advisors or through market research or otherwise.

The Panel noted that the complainant had not identified the individual who he/she alleged had attended a number of Shire's advisory boards. The Panel noted that it was not necessarily unacceptable for an individual to attend more than one such advisory board so long as the meetings themselves and the associated arrangements, including the selection of candidates, complied with the Code. In addition the complainant had referred to the subsequent likelihood of this individual writing many prescriptions for the new product. The Panel's view was that it thus had to consider whether the overall arrangements for the advisory boards were promotional. The Panel further noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. Given that the complainant was non-contactable, the Panel could not ask further questions in relation to the identity of his/her colleague, establish that that person had attended a number of advisory boards or consider the legitimacy of that colleague attending those advisory boards in relation to LDX.

The Panel noted that since January 2011 Shire had run ten advisory boards in the UK related to ADHD: an inaugural market access advisory board in January 2011; three clinical advisory boards (October 2011 Clinicians advisory board, January 2012 ADHD clinicians adolescent advisory board, June 2012 LDX advisory board on safety data and post-marketing surveillance data); two on economic/budget modelling (January 2011 and June 2012); a pharmacy advisory board (March 2012 which looked at *inter alia* information to budget holders) and three miscellaneous advisory boards (April 2012 Working group meeting, LDX UK market access advisory board, June 2012 Treatment individualization advisory board and February 2012 2nd International ADHD advisory board).

The Panel further noted Shire's submission that the marketing authorization approval for LDX was expected in the first quarter of 2013 and the application was currently under review by the Medicines and Healthcare products Regulatory Agency (MHRA).

The Panel noted the agendas and presentations provided by Shire. When determining whether there was a legitimate unmet question which Shire needed to address the Panel noted Shire's long standing commercial interest in the therapy area and thus considered that it would be reasonably familiar with the ADHD market. Nonetheless, LDX would be the first long-acting pro-drug of d-amphetamine and changes to the NHS meant that ADHD service provision might change. The Panel thus considered that there would be legitimate questions which the company needed to address before the launch of LDX.

The Panel noted the agenda items presented and/or discussed at each advisory board and was concerned about the number of meetings and the overlap between the agendas. Some topics or closely similar topics were discussed at more than one advisory board.

The Panel noted some of its concerns outlined above in relation to the number of advisory boards held on very similar topics over a relatively short period of time. It also noted that the complainant was anonymous and non-contactable and that the Panel could not ask him/her for further details about the health professional in question. The Panel considered that the complainant had not established

that the selection and attendance of the unidentified health professional at several advisory board meetings was contrary to the requirements of the Code. The complainant had not established that the advisory boards had promoted LDX before the grant of a marketing authorization that permitted its sale or supply. On the very narrow grounds of the allegation, no breaches of the Code were ruled.

An anonymous, non-contactable complainant who referred to him/herself as a health professional managing ADHD (attention deficit hyperactivity disorder) complained about the activities of Shire Pharmaceuticals Limited. Shire marketed Equasym XL (methylphenidate extended release) for the management of ADHD and planned to launch Vyvance (lisdexamphetamine mesylate (LDX)) in 2013.

COMPLAINT

The complainant stated that he/she was approached by an experienced MSL [medical science liaison] from Shire to discuss an amphetamine medicine not licensed in the UK which Shire planned to launch next year. The MSLs were allegedly under clear instructions from the company to create 'noise' in the market about the new amphetamine based medicine. The MSLs were set targets to achieve every quarter and these included the number of physicians who were willing and ready to write prescriptions for the new medicine which was not licensed and the number of specialists happy to speak about the new medicine and these figures were monitored every couple of months or so. The complainant further alleged that Shire also encouraged specialists to try the medicine on a 'named' scheme for patients where patients had to pay high costs privately. This intense campaign had created a perception of inadequacy and dissatisfaction with the current widely prescribed and very effective products available in the NHS such as long-acting methylphenidate which risked an unfair drain on already squeezed resources in favour of an unlicensed medicine in the UK.

The complainant noted that sales representatives always declined to discuss unlicensed medicines and cited ABPI rules. The complainant queried whether MSLs were bound by the ABPI. This was confusing.

One of the complainant's consultant colleagues often attended a two day monthly advisory panel meeting and recently attended another one. This was the third or fourth such Shire meeting this person had attended in 2012. The complainant had no doubt this busy consultant was likely to write many prescriptions for the new medicine. The complainant stated that the Medicines and Healthcare products Regulatory Agency (MHRA) and the media stated that companies could not promote unlicensed medicines and that such activities were unlawful and sometimes harmed patients.

When writing to Shire, the Authority asked it to respond in relation to the requirements of Clauses 3.1, 9.1 and 2 of the 2012 Code.

RESPONSE

Shire refuted the alleged breaches of Clauses 3.1, 9.1 and 2 of the Code and stated that the complainant's allegations were vague and no proof was provided, and as the complainant was anonymous further specific details could not be confirmed. Following an investigation into the conduct of all of Shire MSLs working in the therapeutic area, Shire was satisfied that they worked within its policies and the Code.

In their contact with health professionals Shire's MSLs must act only in accordance with their defined roles and responsibilities. Furthermore, the MSLs had not been instructed to create 'noise' in the market about any product, they did not have targets based on physician visits and they did not encourage physicians to try any products on a named patient scheme. The complainant had also referred to advisory boards held in relation to the therapeutic area and to Vyvanse. As set out below, all of Shire's advisory boards had been held in accordance with Shire's relevant standard operating procedures (SOPs) which were consistent with the Code.

Shire submitted that it had not found any evidence to support the allegations. Shire had not conducted pre-licence promotion and would never allow such promotion by any of its staff. It was confident that there had been no breach of the Code.

Shire submitted that it had two MSLs who supported the UK ADHD therapy area. Shire's MSLs carried out non-promotional functions and reported to the medical affairs department. They provided medical support for unsolicited medical enquiries in relation to all of Shire's ADHD products. MSLs were not incentivized on product sales and no targets were set for the number of MSL interactions with health professionals. Shire submitted that its MSLs performed a strictly non-promotional role and therefore they did not promote the prescription, supply, sale or administration of any medicine.

The MSL teams had been clearly briefed and trained in this role with clear and defined responsibilities. A copy of the MSL job description was provided.

The role and objectives of Shire's MSLs was set out in the Clinical Development and Medical Affairs document: Medical Science Liaison activities, which stated that:

> 'MSLs act as field counterparts to office-based Shire Medical Affairs staff. The primary role of the MSL is to address the scientific needs of HCPs [healthcare professionals] by fostering fair and balanced scientific communications that are not misleading. To further ensure that Shire MSLs conduct appropriate medical and scientific communications, the activities of the Shire MSLs are divided into two categories: proactive and reactive.'

The document went on to list various proactive activities which included, *inter alia*, interactions with key opinion leaders (KOLs); research support; issue

management and disease state discussions. The reactive activities listed included responding to unsolicited requests for information from HCPs and others; research support; delivery of presentations; attendance at advisory boards; publication support and issues follow-up.

The document went on to detail the appropriate interactions of MSLs with sales and marketing. It was clearly stated that MSLs and sales representatives had different roles and should work independently of each other and that joint sales calls and/or in-person meetings involving sales representatives and MSLs were not permitted except where a sales representative was introducing the MSL to a health professional at an initial meeting following that health professional's unsolicited request for detailed scientific or medical information. In this circumstance, the different roles of the MSL and sales representative should be explained to the health professional, and the sales representative should not participate during the scientific discussions between the MSL and health professional.

Shire provided copies of materials used by its MSLs in relation to responding to unsolicited medical information requests.

The MSLs did not meet the definition of 'representative' as defined in Clause 1.6 of the Code:

> 'The term "representative" means a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.'

Shire submitted that its MSLs did not initiate 'calls'. In the UK, since January 2012, the two MSLs working in ADHD had 131 scientific exchange interactions with health professionals (primarily responding to unsolicited medical enquiries on any Shire products especially Equasym XL, key opinion leader introductions, disease state discussions and research support), which included MSL attendance at Shire advisory boards.

Shire stated that all MSL interactions with health professionals related to any Shire product must be unsolicited and in response to specific requests. These 131 interactions included four LDX-related one-to-one medical information interactions with health professionals, each of which was in response to an unsolicited request for information.

MSLs only attended advisory boards as ADHD experts when requested to do so by the medical affairs department. An MSL was present at seven of the advisory boards.

Shire submitted that MSLs' performance was measured against the core responsibilities contained within the Clinical Development and Medical Affairs document: Medical Science Liaison activities. Specific objectives for MSLs were to provide accurate and timely responses to medical enquiries, facilitate scientific exchange, provide research support on request from Shire R&D and to comply with Shire's policies and the Code.

Marketing authorization approval for LDX was anticipated in the first quarter of 2013. The application was currently under review by the MHRA which was the reference member state under the decentralized procedure.

Shire stated that all MSL product-related interactions or scientific discussions with health professionals were unsolicited, reactive and in response to specific requests. This applied to any approved Shire products, including Equasym XL and pre-approval or pipeline products. The guidelines for MSLs in relation to discussion of products was set out in the MSL activities documents. Whenever information was provided to health professionals, MSLs ensured that the information was medical and/or scientific in nature, and that it was not provided in a promotional manner. Sales force promotional materials were never used or distributed by MSLs.

In response to specific questions posed by a health professional, the MSL, depending upon the question, might provide information about a Shire product that was: 'on-label' (ie consistent with the product's approved label); 'off-label' (only if in response to an unsolicited request); or related to a pre-approval or 'pipeline' product.

- If the health professional requested 'off-label' information, the MSL must communicate that the information provided might not be consistent with the approved product labeling.
- Responses to unsolicited requests for information must be narrowly tailored to the question and not be seen as an opportunity to discuss other topics.
- Where pipeline products were concerned, responses must not represent that an investigational new medicine was safe or effective for the purposes for which it was under investigation. MSLs would use caution to avoid the perception of promotional activity by providing all available information regarding the pipeline product, with full disclosure of both positive and negative information.

MSLs might provide specific scientific information about competitor products which was in the public domain, if requested by the health professional. Also:

- MSLs must not discuss any off-label use of a non-Shire product; and
- MSLs must direct the health professional to the relevant pharmaceutical manufacturer.

Shire did not actively encourage nor did it promote named patient supply of LDX. However, the medicine was available through a third party importer in all countries where it did not have a marketing authorization, and where permitted under local laws.
MSLs could not proactively discuss LDX. The Medical Q&A on ADHD Product Availability set out how MSLs should answer specific questions about product availability:

> 'Q. Is Vyvanse available via a 3rd party importer outside the US?

Shire only markets and promotes its products in accordance with regulatory guidelines in the countries where they are approved.

If pressed: [Name of importer], a specialist company based in the UK, imports medicines on a 'named-patient' basis'* For specific information regarding this program or product availability, please contact [importer] directly. Contact details for [importer] are: [contact details were provided]

*Named-Patient refers to the supply of Products which do not have a product licence in the country of destination and/or which are not commercially available and are supplied to meet the special needs of a specific patient or patients under the order of a medical practitioner and in compliance with exceptions to the product licensing requirements in such countries.'

The further information on the import company could only be provided if the enquiring health professional insisted on information, which was the meaning of the instruction 'if pressed'.

Shire did not know how many patients received named patient supply or whether those patients had participated in an LDX clinical trial. The named patient supply scheme was entirely managed by the import company.

ADHD was a serious medical condition which presented as a complex and difficult to manage set of behaviours, often associated with poor provision of services and significant delay in care. Diagnosis most commonly occurred in primary school. As such the need to understand the NHS perspective, and the perspective of academic and practising clinicians, was key to the introduction of a new chemical entity in ADHD treatment.

Shire took responsibility within ADHD very seriously and had the challenge of gaining information about the care of children in the UK from several different constituents, some of whom had a wider range of healthcare responsibilities.

In order to meet the demands of this complex area Shire UK had held advisory boards to gather advice from or about: NHS management; academic clinicians; hospital clinicians and ADHD treatment (non LDX). Two international advisory boards had also been held in the UK. The agendas, invitations and attendance lists for all the meetings were provided.

The Shire advisory boards were conducted in accordance with the SOP which specifically applied ABPI standards to advisory boards held in the UK.

In summary, Shire submitted that one of its key priorities was to act with integrity and maintain the highest ethical standards. Its compliance procedures were central to this effort. A dedicated international team of specialists at Shire supported the UK team, including signatories, in maintaining compliance. Furthermore, Shire's MSLs were managed by a dedicated R&D management team and subjected to training and oversight by Shire's R&D compliance function.

Shire had not conducted pre-licence promotion and would never allow such promotion by any of its staff. LDX was widely prescribed in the US and was also marketed in Brazil and Canada. Child and adolescent psychiatrists were likely to know about this medicine from international colleagues, publications and the Internet.

Following a request for further information, Shire submitted that meeting reports for all advisory boards demonstrated that the intended objectives for each were achieved. Shire noted that the meeting reports for the international advisory boards had been reviewed, UK reports were not for dissemination and therefore did not require approval.

Shire submitted that ADHD was a complex disease area and there were many scientific and clinical topics upon which it needed to obtain expert advice. The advisory board meetings referred to were built around different topics in the management of ADHD that Shire must better understand in order to focus its planning and investment. These objectives had informed the selection of advisers for each meeting. Advisers were individually selected for each meeting based on their speciality, expertise and areas of special interest where those were directly relevant to the specific advice to be sought at the meeting.

Shire submitted that its medical affairs department selected advisers at the following advisory boards:

- October 2011, LDX Child Advisory Board (n=12)
- January 2012, LDX Adolescent Advisory Board (n=16)
- April 2012, LDX Working Group (product profile) (n=9)
- June 2012, LDX Advisory board - Safety data & post-marketing surveillance data (n=14)
- June 2012, Treatment Individualisation Advisory Board (n=12)

Shire's UK market access group selected advisers for the following advisory boards:

- January 2011, LDX UK Market Access Advisory Board (n=14)
- June 2012, Budget Impact Model advisory board (n=10)
- March 2012, Advanced Budget Notification Advisory Board (n=8)

Shire's health economics and outcomes research group selected the 6 advisers who attended the LDX economic modelling advisory board held in January 2011.

Twelve delegates attended each of the international advisory boards held in December 2011 and June 2012.

Shire's international medical affairs team selected advisers at the LDX abuse liability advisory board held in February 2012.

Shire submitted that more specific criteria for adviser selection included:

1 Speciality/areas of academic and/or clinical special interest;
2 Advisers' job roles and responsibilities, including patient sub-groups managed (such as children, adolescents, patients with ADHD and co-morbidities, patients within the criminal justice system). This was important information to Shire because ADHD patient sub-groups were managed and treated differently, for example children were often managed differently to adolescents or adults;
3 Prescribers and non-prescribers because ADHD was not always treated with pharmacological products. Non-pharmacological interventions were also an integral part of ADHD management pathways, as per the National Institute for Health and Clinical Excellence (NICE) guidelines/EU guidelines; and
4 Budget holders across all therapy areas and also those with specific ADHD responsibility to understand the interaction between the two and how the priorities are assessed.

Shire provided a breakdown of the subsistence, accommodation and other costs incurred at each meeting and slides sets for all presentations. Materials were not provided to delegates before, during or after the meetings. The meeting reports were prepared for 'Shire internal use only' and were not sent to the delegates. These reports were then referred to by relevant Shire colleagues as they planned their strategies and approaches in all areas of Shire's business going forward.

Shire submitted that, in relation to the January 2011 advisory board, it telephoned proposed advisers to seek their agreement in principal to participate and to ask them to save the date. Confirmation invitations were sent as a follow up (copies provided). The advisers were selected on the basis of their knowledge of ADHD services and policies in the UK and to satisfy the main objectives of the advisory board which were to understand the current service provision in the UK with respect to adolescent ADHD service users including the transition from child to adolescent and into adulthood.

The meeting in January 2011 was a market access advisory board and therefore the attendees were different from the advisory boards focused on the needs of prescribers. The introductions section of the meeting report (copy provided) described the main objectives of the meeting. As well as having commissioners, payers and health professionals present to answer Shire's questions about changes to the NHS, there was a representative from an ADHD patients group, a teacher, nurses, a special educational needs co-ordinator (SENCO) and also a consultant with expertise in substance misuse. These participants could provide valuable information on service provision. Attitudes to ADHD were very challenging in the UK so this meeting helped Shire to 'set the scene' and understand what the current issue were. ADHD care was multidisciplinary and teachers, SENCOs and nurses were often key members of community and mental health services (CAMHS) teams. This was very different from the treatment pathways for many other medical conditions when assessment, treatment and monitoring was restricted to a much more narrowly defined group of health professions. Shire hoped that it was apparent from the meeting report how useful this meeting was and how much was learnt from it.

Shire submitted that honoraria levels for all of its advisory boards were determined with reference to the adviser's specialty and level of expertise (including academic and clinical expertise) in order to provide fair market value compensation. Honoraria levels for each advisor were provided.

Shire noted that it engaged an independent healthcare consultant to provide certain services in relation to this meeting including preparation of slides, support on agenda development, attendance at the review meeting in January as well as facilitating and chairing the advisory board.

Shire confirmed that during the two day October 2011 meeting, dinner was provided at a restaurant close to the Royal College of Physicians and the hotel. The hotel was modest and not deluxe or lavish. A private dining room (set house menu) was used because it was anticipated that the participants might discuss proceeding of the advisory board over dinner. The subsistence offered was appropriate and not out of proportion to the occasion. In accordance with the Code, the costs involved did not exceed the level which the recipients would normally apply when paying for themselves.

No participant attended on the first day only. One participant attended on the second day of the meeting only and so was paid a reduced fee to reflect the level of her participation.

Shire confirmed that one of the attendees at the meeting in April and June 2012 was an independent and supplementary nurse who was an expert on the management of ADHD in the prison environment and a leading UK authority on misuse, abuse and diversion of abusable substances in youth offending. That delegate also had a specialist interest in addictions, prison work and forensic psychiatry and managed ADHD patients in this setting.

Shire submitted that it only provided overnight accommodation for advisory boards where necessary based on the length of the meeting or the adviser's individual circumstances. Relevant factors included the distance the adviser needed to travel and whether he/she was required for a pre-meeting briefing the night before. Hospitality was strictly limited to the purpose of the event. The level of subsistence offered was appropriate and not out of proportion to the occasion. In accordance with the Code, the costs involved did not exceed the level which the recipients would normally apply when paying for themselves.

Shire submitted details of participants who were provided with dinner and accommodation for the two day advisory board meeting in January 2012. The dinner provided an opportunity for the majority of the group to continue to discuss some of the key topics during the evening. No participant attended on the first day only, but one participant attended on the second day only. A reduced honorarium for one day's participation was paid.

Shire provided a copy of the final agenda for the advisory board in April and noted that one participant did not arrive until the second day and thus only received a reduced honorarium.

Shire provided a copy of the objectives statement referred to in the invitation for the budget impact advisory board in June 2012 and confirmed that only one participant received overnight accommodation.

Shire submitted that for another two advisory boards in June 2012, verbal invitations were extended by the MSLs and followed by a formal letter of engagement (copy provided). Accommodation was only offered to those with long and difficult journeys as the two meetings started at 8.30am and 9.30 am, respectively. No dinner was provided, only accommodation. Some delegates with long distance journeys declined the invitation for accommodation. Details of those who had overnight accommodation the nights before the meetings were provided.

Shire confirmed that the international advisory board in February 2012 was the second in a series of three meetings. The first was held in December 2011 in Zurich and the third was held in June 2012 in Paris. Copies of meeting agendas, invitations, delegate information and meeting reports were provided.

Shire confirmed that there were currently no other advisory boards planned.

Shire provided details of all Shire staff attendance at each advisory board. There were no specific briefing documents for these employees. However Shire staff who were involved with the advisory boards attended an initial planning meeting and subsequent meetings and/or teleconferences to ensure all staff were informed and updated on the objectives and content of the meeting, including their roles and responsibilities at the meetings. All Shire and agency participants were fully trained and aware of their ABPI responsibilities and the requirements of the Code.

Shire confirmed that there was a UK SOP for advisory boards (copy provided) and that it was currently finalising a new international SOP for which a new UK document would be in place.

Shire submitted that the advice it gathered from external experts in advisory boards was crucial to assist it in planning its investment and activities. Shire's advisers were selected individually based on their relevant knowledge and expertise.

Shire hoped that it had demonstrated that its UK ADHD advisory boards complied with the Code, did not constitute pre-market promotion and that it had maintained high standards and was therefore not in breach of Clauses 3.1, 9.1 or 2.

Shire hoped that LDX would be granted a licence in the UK because current ADHD therapy options were limited and a new therapy choice would help many patients and their families and provide value for the NHS.

Shire stated that ADHD care presented special challenges, especially in the UK where belief in ADHD as a medical condition was often disputed and access to services was delayed. At the heart of this issue were children of six years of age being considered for treatment with amphetamine. Shire therefore took this situation very seriously. Shire's efforts to understand those challenges and plan its activities accordingly was part of its philosophy which was 'to be as brave as the people we help' and 'to enable people with life altering conditions to lead better lives'.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable and had provided little information and no documentation to support his/her complaint. As with any complaint, the complainant had the burden of proving his/her complaint on the balance of probabilities; the matter would be judged on the evidence provided by the parties.

The Panel noted Shire's submission that the MSL role was non-promotional and provided medical support for unsolicited enquiries in relation to all of Shire's ADHD medicines. A document submitted by Shire entitled 'Clinical Development and Medical Affairs Guidance' described them as field counterparts to office-based medical affairs staff. They were not incentivized based on sales of medicines and targets were not set for interactions with health professionals.

The Panel noted from the job description submitted by Shire that a senior MSL reported to the associate director, international medical science liaison. The first 'essential function' noted on the job description was 'Through unsolicited requests for medical and scientific information, develop and raise Healthcare Professionals' level of understanding of medical and scientific data, using oral discussions, presentations and other appropriate media/techniques'. This accounted for 45% of the role's function. Other 'essential functions' were to participate in the company's cross-functional initiatives; deliver quality medical education presentations and gather information. One of the key skills and competencies listed was 'Deep understanding and knowledge of local regulations and codes of practice for the pharmaceutical industry, in particular as they apply to the non-promotional activities of this role'.

The 'Clinical Development and Medical Affairs Guidance' document stated in Section II, Overview of Roles and Responsibilities of Shire MSLs, that the medical and scientific activities of MSLs were divided into two categories; proactive and reactive. The reactive activities included, *inter alia*, key opinion leader introductions and on-going relationship management, research support, issue management, disease state discussions and collection and input into scientific platforms. The reactive activities included, *inter alia*, responding to unsolicited requests for information and presentation on topics such as formulary/health economic outcomes resource, disease state and/or scientific data. Section VI of this document, Interactions with HCPs [health professionals] noted that MSLs might meet health professionals to, *inter alia*, respond to unsolicited requests for information and to provide 'in-depth on-label information about Shire product, including changes to approved label'. The Panel considered that the latter was not clear as to whether this activity was proactive or reactive, but the impression created by separating this activity from responding to unsolicited requests was that discussion of on-label information was proactive. This appeared to be inconsistent with the statements in Section II of the document and with the MSL job description. Such proactive activity might also satisfy the definition of a representative in Clause 1.6.

The Panel noted that a number of briefing documents for medical affairs were provided in relation to LDX. A fact sheet (UK/LO/COPR/11/0172) contained a number of questions about the availability of LDX, mechanism of action, key data and side effects. The document was marked 'Reactive Use Only' and noted that the medicine was not yet licensed in the UK. However, the document also stated that it was for UK health media and the Panel questioned whether this was in fact a document intended to be used by Shire communications personnel rather than MSLs.

A presentation, described by Shire as a medical affairs training slide deck to respond to unsolicited medical information requests from health professionals detailed results of a European safety and efficacy study of LDX in children and adolescents (SPD489-325). The Panel noted that there appeared to be no briefing document for Shire employees about the use of this presentation and there was no statement on any of the slides that the presentation was only to be used reactively. A further presentation, SPD489-326 Summary of Results, was similarly described by Shire and detailed the results of a Phase III safety and efficacy trial of LDX in children and adolescents aged 6-17 with ADHD. Again, there did not appear to be any briefing document for this presentation or indication on the slides that they should only be used reactively. A statement on the title slide read 'Confidential Material Not For Distribution'. Two separate question and answer documents for these trials (SPD486-325 and SPD489-326) were provided and both were entitled 'Medical Q&A for reactive statements'.

The Panel noted that a further question and answer document entitled 'Availability of Shire ADHD products May 21, 2012' was marked 'For Internal Use Only. Not to be Forwarded or Distributed', but there was no indication that the information was only to be used reactively. In response to a question on which countries, *inter alia*, LDX was approved and marketed, this document stated that Vyvanse [LDX] was approved and marketed in the US and Canada and was recently launched in Brazil under the name of Venvanse. A further question was 'Is Vyvanse [LDX] available via a 3rd party importer outside of the US?' and the answer stated was 'Shire only markets and promotes its products in accordance with regulatory guidelines in the countries where they are approved'. The document then stated that, if pressed, details could be provided of a specialist company which imported medicines on a named patient basis.

The Panel noted that the parties' accounts differed. A decision had to be made on the evidence before it. The complainant had provided no evidence in relation to his/her allegation that MSLs were under clear instruction to create 'noise' in the market about LDX, that they were set targets in relation to contacts with health professionals or that they encouraged health professionals to try LDX on a named patient basis. The Panel had some concerns about the material; it was not clear whether the MSL role was entirely reactive when it came to on-label discussion of Shire products and some of the briefing material about LDX could have been clearer that information on the medicine should only be provided in response to an unsolicited request. The Panel was also concerned about the absence of briefing materials indicated above. However, the Panel considered that there was no evidence to suggest that the MSLs had promoted, or had been briefed to promote, LDX before the granting of a marketing authorization that permitted its sale or supply, nor was there evidence that the MSLs had promoted the use of LDX via a named patient programme. No breach of Clause 3.1 was ruled. Subsequently no breaches of Clauses 9.1 and 2 were ruled.

Turning to Shire's advisory boards, the Panel noted that advisory boards were a legitimate activity; all of the arrangements had to comply with the Code. The company must be able to demonstrate that it had a bona fide need for the advice being sought. The choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to meaningfully contribute to the purpose and expected outcomes of the meeting. The number of participants should be limited so as to allow active participation by all. The agenda should allow adequate time for discussion. The overall number of meetings should be limited and both the number of meetings and the number of participants at each should be driven by need and not the invitees' willingness to attend. Invitations to participate in an advisory board meeting should state the purpose of the meeting, the expected advisory role and the amount of work to be undertaken.

The Panel noted that Shire's global policy on advisory boards (06-227Global HGT/ExUSROWSP) stated that advisory boards must be solely intended and necessary to fulfill a legitimate, unmet business need for information, advice and feedback from participants regarding Shire products or other topics relevant to Shire business and must be designed to elicit bona fide information from advisors. The advisory board should address questions in order to provide advice or feedback that had not previously been provided by either the advisors or through market research or otherwise, unless there was a valid, fact-based reason to conclude that i) the advice or feedback would not duplicate the answers, and/or ii) circumstances had changed such that additional advice or feedback was needed, or it was reasonable and necessary to determine if the previous advice was still valid.

The Panel noted that the complainant had not identified the individual who he/she alleged had attended a number of Shire's advisory boards. The Panel noted that it was not necessarily unacceptable for an individual to attend more than one such advisory board so long as the meetings themselves and the associated arrangements including the selection of candidates complied with the Code. In addition the complainant had referred to the subsequent likelihood of this individual writing many prescriptions for the new product. The Panel's view was that it thus had to consider whether the overall arrangements for the advisory boards were promotional. The Panel further noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. Given that the complainant was non-contactable, the Panel could not ask further questions in relation to the identity of his/her colleague, establish that that person had attended a number of advisory boards or consider the legitimacy of that colleague attending those advisory boards in relation to LDX.

The Panel noted that since January 2011 Shire had run ten advisory boards in the UK related to ADHD: an inaugural market access advisory board in January 2011; three clinical advisory boards (October 2011 Clinicians advisory board, January 2012 ADHD clinicians adolescent advisory board, June 2012 LDX advisory board on safety data and post-marketing surveillance data); two on economic/budget modelling (January 2011 and June 2012); a pharmacy advisory board (March 2012 which looked at *inter alia* information to budget holders) and three miscellaneous advisory boards (April 2012 Working group meeting, LDX UK market access advisory board, June 2012 Treatment individualization advisory board and February 2012 2nd International ADHD advisory board).

The Panel further noted Shire's submission that the marketing authorization approval for LDX was expected in the first quarter of 2013 and the application was currently under review by the MHRA which was the reference member state under the decentralized procedure.

The Panel noted the agenda and presentations provided by Shire. When determining whether there was a legitimate unmet question which Shire needed to address the Panel noted Shire's long standing commercial interest in this therapeutic market and thus considered that it would be reasonably familiar with the ADHD market. Nonetheless, LDX would be the first long-acting pro-drug of d-amphetamine and changes to the NHS meant that ADHD service provision might change. The Panel thus considered that there would be legitimate questions which the company needed to address before the launch of LDX.

The Panel noted the agenda items presented and/or discussed at each advisory board. The Panel had some concerns about the number of meetings and the overlap between the agendas. Some topics or closely similar topics were discussed at more than one advisory board, eg current treatments for ADHD appeared to have been discussed at the meetings with clinicians in October 2011, January 2012 and April; service provision in ADHD was discussed at the meetings in January 2011, October 2011 and January 2012; the ADHD landscape (October, April and whilst not on the agenda it was listed as the first objective in the meeting report for the meeting held in January); current prescribing environment in primary and secondary care (March and June). The slides presented by Shire on these topics demonstrated an in-depth knowledge of the subject matter. One slide included the claim 'Shire's expertise and leadership in ADHD established'.

The Panel noted some of its concerns outlined above in relation to the number of advisory boards held on very similar topics over a relatively short period of time. It also noted its comments above that, as the complainant was non-contactable, the Panel could not ask him/her for further details about the health professional in question. The Panel considered that the complainant had not established that the selection and attendance of the unidentified health professional at several advisory board meetings was contrary to the requirements of the Code. The complainant had not established that the advisory boards had promoted LDX before the grant of a marketing authorization that permitted its sale or supply. On the very narrow grounds of the allegation, no breach of Clause 3.1 was ruled. The Panel subsequently ruled no breach of Clauses 9.1 and 2.

Complaint received **6 August 2012**

Case completed **15 October 2012**