CASE AUTH/2987/10/17

ANONYMOUS V SHIRE

Alleged promotion prior to the grant of a marketing authorisation

A contactable complainant who wished to remain anonymous complained about Shire and its communication with payers, key opinion leaders (KOLs) and other stakeholders. It appeared that the complainant was an ex-employee of Shire.

The complainant identified three matters (a market research survey, a review by the National Institute of Health and Care Excellence (NICE) and visits by medical science liaison staff (MSLs)).

The detailed response from Shire is given below.

The complainant alleged that an agency communicated to external KOLs and payers on behalf of Shire regarding a market research study exploring a study linked to managed entry agreement types. The email was not approved and highlighted Shire and the medicine's name teduglutide (Revestive).

According to the complainant, Shire failed to take action when this issue was raised by the agency and the response was not to do anything to avoid escalation of the matter (lack of transparency).

The Panel noted that it appeared that both the UK company and Shire International had a role in the market research in question, although the response was not entirely consistent on this point. The extent of each affiliates' responsibilities were not clear. Nonetheless, the Panel noted that the email in question was sent to UK recipients and that aspect of its use came within the scope of the Code. The UK company was responsible for the acts and omissions of its overseas affiliate that came within the scope of the Code. The Panel also noted that although the communication was sent by a third party agency it was an established principle that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that the email in question sent by the third party UK based agency to ten UK health professionals invited them to participate in market research to test the managed entry agreement (MEA) design for Revestive and stated that the agency was working with Shire Pharmaceuticals to design a complex patient access scheme (PAS) to improve cost effectiveness and facilitate patient access to its new product for short bowel syndrome (SBS) – Revestive (teduglutide). Teduglutide was described as the first approved treatment in Europe for this debilitating disease and that it offered an important new treatment option to patients who were reliant on parenteral nutrition.

The Panel noted the broad definition of promotion and considered that the email in question was promotional and noted Shire's admission that the promotional nature of the email would not have been clear to the recipients. Its promotional nature was

therefore disguised. The Panel therefore ruled a breach of the Code as acknowledged by Shire.

The email was sent without Shire UK's consent or knowledge. The email was described as unauthorised. In an email dated 16 February an international Shire employee stated that the agency was commissioned from his/her budget and that the third party agency was briefed on the CMLR process and he/she was surprised that this had happened. It was unclear whether the CMLR process included examination of materials and thus the Panel was unable to comment on whether the agency was appropriately briefed. An email dated 16 February sent by a UK employee stated that as it was not a UK only project and was 'signed by international' 'we needed to know more about the contracting, briefing of the agency on the SOPs and other procedure'. It thus appeared that there were internal governance concerns about activities taking place in the UK which were commissioned, at least in part internationally. Such activities had to comply with the Code and the company's internal processes should facilitate this. The Panel noted its comments and ruling above and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that Shire had provided evidence to show that the matter was escalated within Shire and actions were taken to investigate the matter. Shire provided material demonstrating the action taken to stop any further communication by the market research agency without full review and approval by UK signatories.

The Panel noted that the complainant bore the burden of proof. The Panel considered that bearing in mind all the evidence before it the complainant had not established that Shire had asked its employees not to address the issue and to avoid escalation or that Shire failed to take action when the issue was raised as alleged. No breach of the Code was ruled in this regard.

Noting its comments and rulings above the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

The complainant further alleged that Shire communicated with the NHS during the process of a review of teduglutide by the National Institute for Health and Care Excellence (NICE). The company sent both medical and market access (commercial team) to discuss pricing and product reimbursement before the product was approved by the Committee for Medicinal Products for Human Use (CHMP) ie off-licence discussion. The complainant alleged that Shire had also tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the clinical reference groups (CRGs) directly and not the National Health Service (England) (NHSE) committee. The complainant noted that the CRGs were mainly clinicians who could prescribe. The complainant subsequently stated that the medicine at issue was Natpar and that he/she had emails on communication with the NHSE to try to influence the clinicians to vote to exclude Natpar (parathyroid hormone) (product for Hypo-parathyroid) out of the NICE process. He/she stated that there were also emails communicating with the NHSE CRG directly as well as commercial discussion with medical on those items.

The complainant alleged that the market access team, with medical, attended meetings to discuss the pricing for a product that was not licensed and access options were made.

Negotiation with NHS directly was very minimal. Shire did not inform NICE of the communication on purpose to pass the process as they knew they would not pass NICE CE (cost effectiveness) limit.

The Panel noted that the complainant's original complaint referred to Teduglutide but he/she later confirmed that Natpar was the product at issue. The Panel therefore considered the complainant's allegation with regard to Natpar.

The Panel noted the broad role of the CRGs as described by Shire, namely to advise NHSE on the best ways that specialised services should be commissioned and paid for. The Panel noted that given the CRG's role and the broad definition of promotion in the Code there was a possibility that interactions with a CRG, especially those initiated by a company, might be considered promotional. The Panel noted that the status of each such interaction should be considered on its individual merits.

Shire had not argued that any of its interactions constituted advance budgetary information but did refer to certain interactions being with health professionals making policy decisions on budgets.

The Panel noted Shire's submission that Natpar was licensed in the UK on 26 April 2017.

In relation to the interactions between a named CRG clinician and Shire in December 2016 and a telephone call in January 2017 these appeared to be in response to the health professional's original unsolicited request and supplementary unsolicited request in December. The Panel did not have the original email communications but based on the company's account there was no evidence that the company's interactions went beyond the information requested by the clinician or was otherwise promotional in nature or went beyond the scope of the original requests. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion in relation to unsolicited requests and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of the Code was ruled. This ruling was not appealed.

In relation to the interaction with another named member of the Specialised Endocrine CRG in January the Panel noted that the original request from the health professional was described by Shire as unsolicited. There was no evidence that the response went beyond the original request. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion in relation to unsolicited enquiries and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of the Code was ruled. This ruling was not appealed.

The Panel considered that the face-to-face meeting in January 2017 with the named CRG clinician above was different to the interactions described above as it had been initiated by Shire. It could thus not take the benefit of the exemption to the definition of promotion in relation to unsolicited enquiries. Part of the meeting appeared to explore the possibility of the named CRG clinician from becoming a key opinion leader and

referred to participation in advisory boards, clinical trials and registries and other global medical activities. In the Panel's view such interactions were legitimate but had to comply with the Code. The Panel noted that the meeting was also attended by a member of the Shire market access team to answer questions about policy as the named CRG clinician had previously wanted to propose a policy about Natpar to the CRG. Whilst noting Shire's submission that the member of the market access team had a non promotional role, the Panel considered that certain aspects of the individual's job description might be considered promotional. Noting the general comments above about the broad definition of promotion and the CRG's role, the Panel considered, on the balance of probabilities, that the meeting was promotional, it had been initiated by Shire in anticipation of, *inter alia*, discussions about Natpar and the CRG policy prior to the grant of Natpar's licence. Shire had apparently arranged for the attendance of the market access team member who, in part, had a promotional role. On balance, a breach of the Code was ruled. Noting the arrangements for the meeting, the Panel considered that, on balance, high standards had not been maintained. A breach of the Code was ruled. These rulings were appealed by Shire.

The Panel noted the complainant's concern that Shire tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the CRGs directly and not the National Health Service (England) (NHSE) committee and that Shire had tried to influence the CRG clinicians to vote to exclude Natpar from the NICE process.

In relation to the discussion with NICE in February 2017 regarding access issues for rare diseases and the proposed Natpar submission, clinical trial data and advice on a phase IV study, the Panel noted that information supplied to national public organisations such as NICE was exempt from the definition of promotion in the Code providing the information was factual, accurate and not misleading. Shire had not sought to take the benefit of this exemption. It was not clear to the Panel on the limited information before it whether the exemption applied to the interaction in question. The Panel did not know who had initiated the discussion. The complainant bore the burden of proof and had not established that the interaction was promotional and the Panel thus ruled no breach of the Code. This ruling was not appealed.

In relation to the subsequent telephone conversation between the two named CRG clinicians above and Shire's market access team member and a medical manager in February, the Panel noted that, according to Shire, NICE had suggested that Shire got agreement from NHSE perhaps through the CRG on certain matters. The Panel noted that the original conversation with NICE had included discussion about the phase IV study. This was reflected in a conversation in early February which was summarised in a subsequent email. It appeared that NICE had agreed with Shire's approach that the NICE assessment be delayed/suspended pending phase IV study results and suggested that agreement be obtained from NHSE perhaps through the CRG, although NICE was unsure about the level of decision making required for this in NHSE. The complainant appeared to object in principle to these discussions. In the Panel's view, such discussions were legitimate so long as they complied with the Code. The interaction with the CRG in February had apparently taken place at the suggestion of NICE and the suggestion had arisen during the course of what, on the evidence before it, the Panel had considered to be a non promotional conversation. In the Panel's view the complainant had not established that this aspect of the discussions (in relation to delaying/suspending the

NICE assessment) with the CRG was promotional as alleged. No breach of the Code was ruled. This ruling was not appealed.

The Panel noted that the discussion in February had also occurred in relation to Shire's proposal of a managed entry agreement, and according to the email this matter had also been referred to earlier. No details of the managed entry scheme were provided. The Panel considered that managed access schemes were acceptable in principle under the Code but that they should be carried out in conformity with its requirements. The Panel noted the broad definition of promotion in the Code and the advisory role of the CRG in relation to commissioning and funding as set out above. The Panel considered that it was difficult to see this aspect of the discussion as anything other than promotional. As Natpar did not have the benefit of its licence at the relevant time a breach of the Code was ruled. The Panel considered that high standards had not been maintained and ruled a breach of the Code. These rulings were appealed by Shire.

In relation to the meeting that occurred with the Department of Health in March there was insufficient information before the Panel in relation to the status of the discussions. The complainant bore the burden of proof and the Panel considered that it had not been established that these meetings were promotional or otherwise in breach of the Code. No breach of the Code was ruled. This ruling was not appealed.

The Panel noted that independently of the interactions above Shire had updated four members of the CRG about Natpar's price. An email referred to their request to be updated with information about rhPTH (1-84) which was described as unlicensed and referred to their role on the CRG in making policy decisions on budgets. Shire submitted that two of these individuals had made a verbal request to be updated on pricing at an advisory board. The Panel noted that the other two members of the CRG had previously been involved in the discussions at issue above. The Panel noted that the complainant bore the burden of proof and had not established that any of the interactions were promotional as alleged. No breach of the Code was ruled. This ruling was not appealed.

The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled. This ruling was not appealed.

The Appeal Board noted that Natpar was indicated in the treatment of a rare disease (adults with chronic hypoparathyroidism) and so the number of accessible clinicians in the therapy area would be small. In the rare disease arena it was likely that many of the health professionals involved would be prescribers as well as policy makers and so, with regard to activities related to Natpar, it would be difficult for Shire to avoid having to interact with those who, of necessity, wore 'two hats'. In discussions and the like with such people, the Appeal Board considered that companies should be extremely careful to correctly characterise their activities as either promotional or non-promotional; it was otherwise too easy for the boundaries to become blurred. The Appeal Board noted the broad definition of promotion. Participants in a meeting should be given clear sign posts as to its promotional status. Companies should be careful not to compromise the independence of prescribers who were also policy makers. The Appeal Board accepted that rare diseases presented some difficulties and it was often hard for companies to ensure they had the right conversations with the right people. Nonetheless, compliance must be achieved. The Appeal noted that although the number of patients affected by rare diseases was small, the cost of their treatment was significant to the NHS. The

Appeal Board noted that Natpar's licence was granted in April 2017 ie shortly after the activities subject to the complaint.

The Appeal Board noted that it had the benefit of more information than that which had been submitted to the Panel. The Appeal Board noted the context for the meeting in January 2017. The Appeal Board noted that the attending clinician was both a prescriber and policy maker, it nonetheless did not consider that, on the balance of probabilities, Natpar had been promoted at the meeting prior to the grant of its marketing authorisation. No breach of the Code was ruled. In that regard the appeal on this point was successful.

The Appeal Board was concerned, however, about the lack of a detailed record of the meeting. The Appeal Board considered that given the difficulties discussed above about working in the area of rare diseases, the rigour with which Shire had documented the meeting was poor and in that regard it considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

With regard to the telephone call which took place in February 2017, and subsequent email, the Appeal Board noted that there appeared to be no precise definition of what a managed entry agreement was. Shire submitted that although the email, the record of the call, referred to a managed entry agreement it also referred to such as being 'in line with the criteria for in year service developments'. The Appeal Board noted the company's definition of managed entry agreement and in year service development and considered that the difference between the two activities was not sufficiently clear; at the very least there appeared to be a degree of overlap and both might potentially involve data collection. The Appeal Board noted that the call record referred to a previous conversation with NICE in which in year service developments were discussed and which implied that an in-year service development for a small cohort of patients was already supported by the CRG. The need for an in-year service development arose because it was thought unlikely that the current Natpar data set would be sufficient for a positive recommendation from NICE. Shire thus wanted to delay the NICE submission and so the CRG would need to prepare for an alternative mechanism of access post licence. Shire's representatives explained that this would involve collecting data in a high risk population and that this activity was initially proposed by the CRG. The Appeal Board considered that, given the circumstances and the context in which the call had occurred, Natpar had not been promoted prior to the grant of its marketing authorisation. No breach of the Code was ruled. The call had been well documented and in that regard the Appeal Board considered that high standards had been maintained. No breach of the Code was ruled. The appeal on both points was successful.

The complainant further alleged that Shire's internal strategy had MSLs target numbers of visits to physicians and linked this to their key performance indicators (KPIs) despite the fact that an MSL role should be reactive and not proactive, particularly when it came to many products not yet licensed. The complainant stated that this might have changed after the internal team complained however, it was a strategy that showed a lack of respect for ethics and code of conduct.

The complainant alleged that the MSL issue was linked to targets for medical team to meet with KOLs, it was linked to their evaluation and possible bonuses, which was against the ethics of the industry and the role of MSLs to be reactive and not proactive.

The Panel noted that the complainant bore the burden of proof and that the complainant had provided no evidence to establish, on the balance of probabilities, that proactive promotional discussions about unlicensed medicines had occurred. No breach of the Code was ruled.

The Panel noted the MSL Performance Goals and Objectives. The Panel noted that the MSL role varied across the industry but the relevant part of the Authority's guidance applied to those that had a non promotional role. The Panel noted the MSL key performance indicators and Shire's submission that the quantative measure for health professional interactions was an aspirational measure. The Panel considered that applying an aspirational KPI in relation to the number of visits to KOLs (rather than the percentage of visit requests completed or similar), which was linked to an MSL's remuneration, was inappropriate and might encourage behaviour that was inconsistent with the Code. High standards had not been maintained in this regard and a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. No breach of Clause 2 was ruled.

A contactable complainant who wished to remain anonymous complained about Shire Pharmaceuticals Limited and its communication with payers, key opinion leaders (KOLs) and other stakeholders. It appeared that the complainant was an ex-employee of Shire.

The complainant identified three matters (a market research survey, a review by the National Institute of Health and Care Excellence (NICE) and visits by medical science liaison staff (MSLs)). The complainant added three further emails to his/her initial complaint in further correspondence.

In writing to Shire, attention was drawn to the requirements of Clauses 2, 3, 9.1, 12.2 and 18.1 of the Code as well as the supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes which May Significantly Affect Expenditure.

Shire stated that it was unclear whether the complainant was a Shire employee, ex-employee or another type of complainant.

1 Market Research Survey

COMPLAINT

The complainant alleged that Shire communicated through an agency to external KOLs and payers around doing a market research study exploring a study linked to managed entry agreement types. However, the agency communicated with the external stakeholders without approving the email internally, the email highlighted the company and the medicine's generic name.

In a second email to the Authority, the complainant stated that the email to the KOLs/payers could be investigated as part of the communication. The complainant did not have any emails but stated that the agency could be questioned as part of the investigation. The complainant stated he/she was then asked not to do anything, to let it go instead of addressing it.

In a third email, the complainant stated he/she did not have emails, but if the PMCPA investigated the agency, and the emails on the possible break of the Code, the PMCPA would have the trail if it asked for it, and would see how Shire asked the team not to do anything about it and not to address it to avoid the escalation.

In a fourth email, the complainant stated that the market research agency used for Revestive (teduglutide), a product for short bowel syndrome, communicated the brand name and the company to the participants, an email was sent to external participants without being approved internally through Zinc process. Shire failed to take action when this issue was raised by the agency and the response was not to do anything to avoid escalation of the matter (lack of transparency).

RESPONSE

Shire stated that it did not understand the details and wording of the original complaint above. Shire was not aware of any market research carried out exploring a study and managed entry agreements. It was difficult at first to know where to start looking and investigate due to the unspecific nature and lack of details in the allegation, however with the further information provided in the complainant's fourth email Shire looked to see if it had conducted any market research using a market research agency, with regard to Revestive and managed entry agreements. There were a number of challenges encountered, namely:

- Shire was still not entirely certain as to which market research activity the complainant referred to as the details in the allegation were not specific.
- Shire considered that the market research which might be at issue was initiated at the beginning of 2016 by Baxalta International. Baxalta was acquired by Shire from Baxter Healthcare in June 2016 and many of the systems and records either no longer existed or were difficult to access particularly as Shire was not certain exactly where to look or know what it was looking for
- Many of those who worked at Baxalta/Shire when this market research was conducted were no longer with the organisation (Shire UK had had more than 85% staff turnover due to company acquisition, restructuring and office relocation).

Shire provided an email trail from a market research agency; it understood that this market research was commissioned by Shire International based in Switzerland and assumed that this was the activity to which the complainant referred. It appeared that the market research agency sent a communication to ten UK health professionals without the knowledge or consent of Shire UK (copy provided).

Shire submitted that contrary to the complainant's allegations, this matter was escalated to European compliance. As evidenced in the email trail provided, actions were taken to investigate this matter and identify what had happened and how. There was no evidence that Shire's response was not to do anything to avoid escalation as alleged. The precise nature of the actions and outcome of what happened with this issue, however, were uncertain as neither of the UK employees involved still worked for Shire and so it was not possible to follow up with them. Further, this was the only email trail Shire had been able to find relating to this matter.

Also, contrary to the allegation that Shire failed to take any action when this matter was raised, Shire provided copies of a discussion guide and associated slides that went through UK review

and approval after the unauthorised communication by the agency to UK health professionals had initially been flagged. This demonstrated that Shire stopped any further communication by the market research agency without full review and approval by UK signatories.

Shire noted that Revestive was licensed in the UK in August 2012 whereas the Revestive market research was conducted in the UK, and the market research agency communicated with the ten UK health professionals, in February 2016. Shire UK recognised that although the communication was sent to UK health professionals by a third party market research agency instructed by Shire International, this came within the scope of the UK Code and Shire UK was responsible for the actions of that third party. Shire also recognised that the initial communication sent to the ten UK health professionals by the market research agency promoted Revestive although this would not have been clear to the recipients, therefore Shire acknowledged that there had been a breach of Clause 12.2 of the Code.

Despite there being a breach of Clause 12.2 in relation to this specific part of the allegations, Shire did not accept that high standards had not been maintained and/or that Shire had bought discredit to or reduced confidence in the industry because:

- The communication (copy provided) was sent to a limited number of UK health professionals by a third party market research agency without the knowledge and/or authority of Shire UK – Shire UK had been badly let down by the third party
- On discovering that this had happened, contrary to the complainant's allegations, Shire UK took immediate action, escalated the matter to the European head of compliance and reviewed and approved a subsequent non-promotional communication (copy provided) to be sent to UK health professionals as part of this market research activity
- Clause 12.2 stated that market research activities must not be disguised promotion and must be conducted with a primarily scientific or educational purpose. Shire UK submitted that the market research activity itself met the criteria of Clause 12.2 – it was just the initial communication sent to the limited number of UK health professionals without the knowledge and/or authority of Shire UK that did not.

Shire therefore submitted that high standards had been maintained; it had not brought discredit upon and/or reduced confidence in the industry and therefore there was no breach of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The Panel also noted that the complainant was responsible for describing those matters which he/she considered were potentially in breach of the Code. In this regard the Panel noted Shire's submission that it did not understand the wording and details of certain parts of the complaint.

The Panel noted that it appeared that both the UK company and Shire International had a role in the market research in question, although the response was not entirely consistent on this point. According to the response the agency which produced and disseminated the email in question was instructed by Shire International. An internal email dated February 2016 described the activity as 'not a UK only project', noting that the contracts with the agency were completed

through Shire International. A further email also dated February 2016 described the market research as a market access project with 'a UK pilot managed by UK NST'. The extent of each affiliates' responsibilities were not clear. Nonetheless, the Panel noted that the email in question was sent to UK recipients and that aspect of its use came within the scope of the Code. The UK company was responsible for the acts and omissions of its overseas affiliate that came within the scope of the Code. The Panel also noted that although the communication was sent by a third party agency it was an established principle that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that the email in question sent by the third party UK based agency to ten UK health professionals invited them to participate in market research to test the managed entry agreement (MEA) design for Revestive and stated that the agency was working with Shire Pharmaceuticals to design a complex patient access scheme (PAS) to improve cost effectiveness and facilitate patient access to its new product for short bowel syndrome (SBS) – Revestive (teduglutide). Teduglutide was described as the first approved treatment in Europe for this debilitating disease and that it offered an important new treatment option to patients who were reliant on parenteral nutrition.

The Panel noted the broad definition of promotion and considered that the email in question was promotional and noted Shire's admission that the promotional nature of the email would not have been clear to the recipients. Its promotional nature was therefore disguised. The Panel therefore ruled a breach of Clause 12.2 as acknowledged by Shire.

The email was sent without Shire UK's consent or knowledge. The email was described as unauthorised. The supplementary information to Clause 12.2 stated that market research should be examined to ensure that it did not contravene the Code. In an email dated 16 February an international Shire employee stated that the agency was commissioned from his/her budget and that the third party agency was briefed on the CMLR process and he/she was surprised that this had happened. It was unclear whether the CMLR process included examination of materials and thus the Panel was unable to comment on whether the agency was appropriately briefed. An email dated 16 February sent by a UK employee stated that as it was not a UK only project and was 'signed by international' 'we needed to know more about the contracting, briefing of the agency on the SOPs and other procedure'. It thus appeared that there were internal governance concerns about activities taking place in the UK which were commissioned, at least in part internationally. Such activities had to comply with the Code and the company's internal processes should facilitate this. The Panel noted its comments and ruling above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Shire had been asked to respond to Clause 18.1 of the Code. The Panel did not consider that the complaint raised a Clause 18.1 matter and thus ruled no breach of Clause 18.1 on this point.

The Panel noted that Shire had provided evidence to show that the matter was escalated within Shire and actions were taken to investigate the matter. Shire provided a discussion guide and associated slides that were approved in the UK demonstrating the action taken to stop any further communication by the market research agency without full review and approval by UK signatories.

The Panel noted that the complainant bore the burden of proof. The Panel considered that bearing in mind all the evidence before it the complainant had not established that Shire had

asked its employees not to address the issue and to avoid escalation or that Shire failed to take action when the issue was raised as alleged. No breach of Clause 9.1 was ruled in this regard.

Noting its comments and rulings above the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

2 NICE Review

COMPLAINT

The complainant alleged that Shire communicated with the NHS during the process of a review of teduglutide by the National Institute for Health and Care Excellence (NICE). The company sent both medical and market access (commercial team) to discuss pricing and product reimbursement before the product was approved by the Committee for Medicinal Products for Human Use (CHMP) ie off-licence discussion. The complainant alleged that Shire had also tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the clinical reference groups (CRGs) directly and not the National Health Service (England) (NHSE) committee. The complainant noted that the CRGs were mainly clinicians who could prescribe.

In a second email, the complainant stated that he/she had emails on communication with the NHSE to try to influence the clinicians to vote to exclude Natpar (parathyroid hormone) (product for Hypo-parathyroid) out of the NICE process. He/she stated that there were also emails communicating with the NHSE CRG directly as well as commercial discussion with medical on those items.

In a third email, the complainant stated that the medicine at issue was Natpar, not teduglutide and provided some of the emails from market access and medical in Shire trying to influence prescribers in the CRG to overturn the NICE process discussion to take the product out of the process as Shire did not think it would be successful. The complainant confirmed that the email attachments provided were only for the Panel and not to be sent to Shire. The Panel decided not to take these email attachments into account as Shire had not had an opportunity to respond to the matters raised therein.

The complainant alleged that the market access team, with medical, attended meetings to discuss the pricing for a product that was not licensed.

In a fourth email, the complainant stated that Natpar was the product Shire communicated with CRGs and NHSE around, using a dual contact (market access and medical together). The product was off-licence when communication around pricing, as well as access options were made. Negotiation with NHS directly was very minimal. Shire did not inform NICE of the communication on purpose to pass the process as they knew they would not pass NICE CE limit.

RESPONSE

Shire explained that, at the time of the alleged activity, teduglutide had a marketing authorisation – it was granted in August 2012. Shire was not aware of any pre-licence activity for teduglutide in the UK and therefore could not comment on any activities prior to licence.

Shire noted the subsequent correspondence and information provided by the complainant and submitted that again, due to the wording and unspecific nature of the allegations, it struggled to know exactly how to investigate this matter. It considered that it might be helpful if it summarised Shire's activities in the UK relating to Natpar, CRGs, NHSE, NICE and the communication with these groups around pricing for Natpar which was licensed in the UK on 26 April 2017.

Background – about Clinical Reference Groups (CRGs) role in commissioning

Shire noted that National Health Service England (NHSE) had six programmes of care boards (NPoC). Each NPoC has several CRGs to provide clinical advice and leadership. These groups of clinicians, commissioners, public health experts, patients and carers used their specific knowledge and expertise to advise NHSE on the best ways that specialized services should be provided ie commissioned and payed for.

CRGs led on the development of clinical commissioning policies, service specifications and quality standards. They also provided advice on innovation, horizon scanning, service reviews and guide work to reduce variation and deliver increased value. CRGs, through their Patient and Public Voice (PPV) members, also helped ensure that any changes to the commissioning of specialised services involved patients and the public.

Natpar (recombinant human parathyroid hormone, rhPTH – the product mentioned by the complainant in the second and third correspondence) was a hormone replacement therapy for adults with underactive parathyroid glands, a condition known as 'hypoparathyroidism' and therefore would be within scope of the Specialised Endocrinology CRG to review, assess and advise the NHSE accordingly and as mentioned above.

Shire interactions with of the Specialised Endocrinology CRG related to Natpar

Shire provided a list of the membership of the Specialised Endocrinology CRG – four names which were marked in bold were with whom Shire interacted before the grant of the Natpar marketing authorisation (26 April 2017).

In December 2016, Shire Medical Information received an unsolicited request from a named CRG clinician (and member of the CRG), who was preparing a briefing for the NHS and the Specialised Endocrinology CRG. He/she wanted a point of contact from the Medical Department at Shire who could provide him with guidance on the development of Natpar. This was routed to the UK medical team. A Shire medical manager emailed the named CRG clinician to ask what specific information was required. Following a telephone call, the named CRG clinician confirmed he/she wanted information to help complete sections of the NHSE Provisional Policy Proposal (PPP) form, specifically with reference to information about Natpar. Upon discussion, there was no urgent timeline for response and the named clinician was happy to wait for a response until after the Christmas break.

There was a further unsolicited request from the named CRG clinician later in December requesting, from Shire's perspective, the likely population size for Natpar for the proposed indication so that he/she could update the CRG with respect to the development of the application of a commissioning policy. This process was started by the CRG completing a PPP form. On 4 January 2017, the Shire medical manager telephoned the named CRG clinician and referred him to Section 17 of the PPP form which stated that if 'there is a planned or published Technology Appraisal, then NHSE cannot proceed to form a policy'. The Shire medical

manager also told the clinician that as Natpar was on the work plan for NICE, there was no longer a requirement for the CRG to complete the form with the intent of the CRG developing a commissioning policy.

The clinician emailed on the same day (4 January) and referred to the conversation with the Shire medical manager and noted that at the forthcoming CRG meeting when updating the group about the product he/she would ensure that the current consideration of Natpar by NICE was discussed. Shire would be advised of the outcome of these discussions including whether further information was required'.

On 9 January, there was an unsolicited request from another named member of the CRG to a Shire employee. This request for specific information was passed for response to the Shire medical manager. The named CRG clinician appeared frustrated as Shire's non-promotional market access team member had requested that the CRG Chair send a formal request in writing specifically outlining exactly and specifically what information was required. This was done to remain compliant with the Code as at that point Natpar did not have a marketing authorisation. The clinician responded expressing frustration at the process, noting that material was normally circulated to the CRG a week beforehand and asked whether Shire had contacted a named CRG clinician and requested copies of any correspondence.

The Shire employee sent the following response and a one-page document on 9 January (copy provided):

'I understand you have verbally requested the following information:

1) Proposed indication and expected timeline for licence
2) Literature source for pivotal study
3) Estimated eligible population in England
4) Potential positioning of the product
5) NICE review update
6) Cost of the product.'

Face-to-face meeting with the initial named CRG clinician (joint meeting with the Shire medical manager and market access)

The Shire employee requested a face-to-face meeting with the named CRG clinician to discuss participation in Shire activities around hypoparathyroidism ie fact finding, participation in advisory boards, clinical trials, registries, symposiums, and being involved in global medical activities. The meeting was also to better understand how hypoparathyroidism was managed in a specific leading centre; the non-promotional meeting took place on 19 January. The meeting was also attended by Shire's market access team member. Shire's market access team member was asked to attend with the Shire medical manager to answer any questions about policy as the named CRG clinician had previously wanted to propose a policy for Natpar to the CRG.

On 2 February, there was a debrief call set up by a senior Shire market access executive about a discussion that Shire had had with NICE on 1 February about access issues for rare diseases. During their discussions, the possibility of delaying the Natpar submission to NICE was discussed given the nature of the clinical trial data and seeking advice from NICE about the proposed phase IV study (further information was provided in the email below).

On 6 February, a call took place between the two named CRG clinicians, referred to above, the Shire market access team member and the Shire medical manager. The purpose of this call was to provide the clinicians with an update on the discussion with NICE, who suggested Shire contact the Specialised Endocrine CRG, which was followed by the following email from the Shire medical manager to the named CRG clinician and the Chair from the CRG on 8 February:

> 'Many thanks for joining the call today following a request to be updated on the progress with NICE. This is the brief synopsis of our discussion, which you have requested I put in writing prior to your discussion. The information below is confidential.
>
> - rhPTH (1-84) - recombinant parathyroid hormone (currently unlicensed) - has recently been included on the NICE work plan for a single technology appraisal (STA).
>
> - Based on the clinical trial and economic evidence currently available, it is very unlikely that NICE will make a positive recommendation through the STA process. Furthermore, Shire engaged with the NICE Scientific Advice Committee in November 2016, to seek advice on the proposed Phase IV study which was being designed to enrich the current dataset in the indicated population. However, changes were suggested by NICE to the inclusion criteria and endpoints within the proposed trial, which Shire are now incorporating into the study, in order to address NICE's requirements.
>
> - Due to challenges with the limited dataset, and with the support from the Endocrine CRG, we would like to propose delaying/suspending the NICE STA until the Phase IV study has been completed, giving a full data package in the indicated population. The results for the study are expected in 2019/20.
>
> - In the interim, we would like to get the support of the CRG with regards to proposing an in-year service development, for the small cohort of patients (approx. 60-80 patients in the UK) who are difficult to control and have high resource utilisation due to recurrent hospitalisations, monitoring and specialist visits.
>
> - As discussed previously, Shire would be willing to discuss a suitable Managed Entry Agreement in line with the criteria for in year service developments, to allow for a predictable budget impact and the collection of data to provide evidence of efficacy and safety in this severe population.
>
> - Last week, Shire met with [NICE] to discuss access issues for rare diseases as well as the approach suggested above, outlining the challenges with the current data package, the scientific advice from NICE on the proposed Phase IV study, the CRG support for an in year service development for a small cohort of patients, and the possibility of delaying/suspending NICE until Shire has Phase IV results. NICE could see the sense in this approach and suggested to get agreement from NHSE, perhaps through the Endocrine CRG setting out the case and sending to NICE However, [NICE] couldn't confirm the level of decision making in NHSE that would be needed but suggested that the CRG approach may be an appropriate one.

- Based on the information above, would the Endocrine CRG be supportive of this approach for delaying the NICE STA? If in agreement, we will need your help to identify who (if anyone) in NHSE would need to endorse this above the CRG. Furthermore, the case will need to be submitted to NICE before 18 February 2017 asking to delay I suspend their review.'

On 13 February, the Shire market access team member followed up with the Specialised Endocrine CRG with the following:

> 'Would it be possible for you to update me on your progress regarding a potential CRG communication/ letter to NICE as discussed last week. The deadline is the 18th Feb, which is the end of this week. If you are happy to share your progress and decision that would be really helpful.
>
> As the CRG members had wanted to be kept updated with regards to NICE and Natpar, and on the advice of [NICE], Shire provided information to the CRG members to ask if this was an appropriate approach to delay NICE until the data package for Natpar was complete, and to consider a commissioning policy in the interim.'

Department of Health (DoH) meeting (9 March 2017) and pricing discussions with CRG

Shire met with the DoH on 9 March 2017 to discuss the higher price for Natpar compared with the originally marketed Preotact. For the rare disease of hypoparathyrodism Natpar was to be priced much higher than the price of Preotact (the same chemical entity) when licensed and marketed some years earlier and in a different therapy area.

The following email was sent as selected CRG members had requested to be kept updated on pricing of Natpar:

> 'Dear XX
>
> I hope you are very well.
>
> As you have requested to be kept up to date with information relating to rhPTH(1-84)- which is currently unlicensed, and you have a role in the Endocrinology CRG in making policy decisions on budgets, I would like to make an appointment to see you to discuss pricing.
>
> Apologies there is a tight timeline for me to provide this information which will be available from the middle of next week 1st of March to the 9th March.
>
> If you could let me have some slots within that timescale that you are available I will do my best to accommodate.'

A briefing document entitled 'Additional information to provide to [health professionals] who have requested further information about pricing' – was certified on 8 March 2017 to provide a discussion guide for the Shire market access team leader when discussing pricing with health professionals – a copy of the certified briefing document was provided.

In relation to this, meetings were held by the Shire market access team member either as a teleconference (TC) or face-to-face (F2F) with the selected CRG members in March 2017.

Two of the Specialised Endocrinology CRG members that attended meetings, as well as the two named CRG clinicians had previously attended Shire advisory boards on hypoparathyroidism, and had verbally requested to be kept updated on pricing of Natpar.

The marketing authorisation for Natpar was granted on 26 April 2017.

Shire submitted that none of the activities in the UK relating to Natpar, the Specialised Endocrinology CRG NHSE, NICE and its communication with these groups around pricing for Natpar constituted pre-licence promotion because:

- Communication was limited to a small number of individuals who had leadership roles either within NHSE, the Specialised Endocrinology CRG or NICE
- Communication was reactive and/or when these key individuals had requested to be kept updated
- Communication content was limited to pricing and specific details these individuals needed to know in order to plan their budgets in relation to their commissioning roles
- Activity involved medical and other non-promotional employees - the number of Shire employees involved in these activities was also limited.

As a result, Shire submitted that there was no pre-licence promotion of Natpar with the Specialised Endocrinology CRG, NHSE or NICE as alleged and therefore no breaches of Clauses 3, 3.1, 9.1 or 2.

PANEL RULING

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant had made detailed allegations but provided little evidence in support. The Panel noted Shire's submission about the wording used by the complainant and the unspecific nature of the allegations.

The Panel noted that the complainant's original complaint referred to Teduglutide but he/she later confirmed that Natpar was the product at issue. The Panel therefore considered the complainant's allegation with regard to Natpar.

The Panel noted the broad definition of promotion at Clause 1.2 of the Code. The Panel noted the broad role of the CRGs as described by Shire, namely to advise NHSE on the best ways that specialised services should be commissioned and paid for. The Panel noted that given the CRG's role and the broad definition of promotion in the Code there was a possibility that interactions with a CRG, especially those initiated by a company, might be considered promotional. The Panel noted that the status of each such interaction should be considered on its individual merits.

The Panel noted that Clause 1.2 provided an exemption to the definition of promotion stating that replies made in response to individual enquiries from members of the health professions or other relevant decision makers or in response to specific communications from them whether of enquiry or comment, were excluded from the definition of promotion, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature.

The Panel noted that Clause 3.1 stated that a medicine must not be promoted prior to the grant of the marketing authorization that permitted its sale or supply. The supplementary information to Clause 3.1, in recognition of the fact that NHS organisations and others had to plan estimated budgets in advance, allowed a narrow exemption for advance notification of new products or product changes. The supplementary information provided a list of requirements which must be met to ensure that companies provided *bona fide* advance notification. Shire had not argued that any of its interactions constituted advance budgetary information but did refer to certain interactions being with health professionals making policy decisions on budgets.

The Panel noted Shire's submission that Natpar was licensed in the UK on 26 April 2017.

In relation to the interactions between the named CRG clinician and Shire in December 2016 and a telephone call in January 2017 these appeared to be in response to the health professional's original unsolicited request and his supplementary unsolicited request. The Panel did not have the original email communications but based on the company's account there was no evidence that the company's interactions listed above went beyond the information requested by the named CRG clinician or was otherwise promotional in nature or went beyond the scope of the original requests. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion at Clause 1.2 in relation to unsolicited requests and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of Clause 3.1 was ruled. This ruling was not appealed.

In relation to the interaction with a second named member of the CRG in January 2017, the Panel noted that the original request from the health professional was described by Shire as unsolicited. There was no evidence that the response went beyond the original request. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion at Clause 1.2 in relation to unsolicited enquiries and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel considered that the face-to-face meeting on 19 January 2017 with the first named CRG clinician above was different to the interactions described above as it had been initiated by Shire. It could thus not take the benefit of the exemption to the definition of promotion set out at Clause 1.2 in relation to unsolicited enquiries. Part of the meeting appeared to explore the possibility of the named CRG clinician becoming a key opinion leader and referred to participation in advisory boards, clinical trials and registries and other global medical activities. In the Panel's view such interactions were legitimate but had to comply with the Code. The Panel noted that the meeting was also attended by a member of the market access team to answer questions about policy as the named CRG clinician had previously wanted to propose a policy about Natpar to the CRG. Whilst noting Shire's submission that the member of the market access team had a non promotional role, the Panel considered that certain aspects of the individual's job description might be considered promotional. Noting the general comments above about the broad definition of promotion and the CRG's role, the Panel considered, on the balance of probabilities, that the meeting was promotional, it had been initiated by Shire in anticipation of, *inter alia*, discussions about Natpar and the CRG policy prior to the grant of Natpar's licence. Shire had apparently arranged for the attendance of the market access team

who, in part, had a promotional role. On balance, a breach of Clause 3.1 was ruled. Noting the arrangements for the meeting, the Panel considered that, on balance, high standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed by Shire.

The Panel noted the complainant's concern that Shire tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the clinical reference groups (CRGs) directly and not the National Health Service (England) (NHSE) committee and that Shire had tried to influence the CRG clinicians to vote to exclude Natpar from the NICE process.

In relation to the discussion with NICE on 1 February to discuss access issues for rare diseases and the proposed Natpar submission, clinical trial data and advice on a phase IV study, the Panel noted that an exemption to the definition of promotion stated that information supplied to national public organisations such as NICE was exempt from the Code providing the information was factual, accurate and not misleading. Shire had not sought to take the benefit of this exemption. It was not clear to the Panel on the limited information before it whether the exemption applied to the interaction in question. The Panel did not know who had initiated the discussion. The complainant bore the burden of proof and had not established that the interaction was promotional and the Panel thus ruled no breach of Clause 3.1 of the Code. This ruling was not appealed.

In relation to the subsequent telephone conversation between the two named CRG clinicians, Shire's market access team member and its medical manager on 6 February, the Panel noted that, according to Shire, NICE had suggested that Shire get agreement from NHSE perhaps through the Endocrine CRG on certain matters. The Panel noted that the original conversation with NICE had included discussion about the phase IV study. This was reflected in the conversation on 6 February which was summarised in a subsequent email dated 8 February. It appeared that NICE had agreed with Shire's approach that the NICE assessment be delayed/suspended pending phase IV study results and suggested that agreement be obtained from NHSE perhaps through the Endocrine CRG, although NICE was unsure about the level of decision making required for this in NHSE. In the Panel's view, the complainant appeared to object in principle to these discussions. In the Panel's view, such discussions were legitimate so long as they complied with the Code. The interaction with the CRG on 6 February had apparently taken place at the suggestion of NICE and the suggestion had arisen during the course of what, on the evidence before it, the Panel had considered to be a non promotional conversation. In the Panel's view the complainant had not established that this aspect of the discussions (in relation to delaying/suspending the NICE assessment) with the CRG was promotional as alleged. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel noted that on 6 February discussion had also occurred in relation to Shire's proposal of a managed entry agreement, and according to the email dated 8 February this matter had also been referred to prior to 6 February. No details of the managed entry scheme were provided. The Panel considered that managed access schemes were acceptable in principle under the Code but that they should be carried out in conformity with its requirements. The Panel noted the broad definition of promotion in the Code and the advisory role of the CRG in relation to commissioning and funding as set out above. The Panel considered that it was difficult to see this aspect of the discussion as anything other than promotional. As Natpar did not have the benefit of its licence at the relevant time a breach of Clause 3.1 was ruled. Noting the content of the discussion and its ruling of a breach of Clause 3.1, the Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. These rulings were appealed by Shire.

In relation to the meeting that occurred with the Department of Health on 9 March there was insufficient information before the Panel in relation to the status of the discussions. The complainant bore the burden of proof and the Panel considered that it had not been established that these meetings were promotional or otherwise in breach of the Code. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel noted that independently of the interactions above Shire had updated four members of the CRG about Natpar's price in March 2017. An email to all 4 CRG members referred to their request to be updated with information about rhPTH (1-84) which was described as unlicensed and referred to their role on the CRG in making policy decisions on budgets. Shire submitted that two of these individuals had made a verbal request to be updated on pricing at an advisory board. The Panel noted that the other two members of the CRG had previously been involved in the discussions at issue above. The Panel noted that the complainant bore the burden of proof and had not established that any of these interactions in March were promotional as alleged. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled. This ruling was not appealed.

During the consideration of this matter the Panel noted the job description of the market access role and noting the broad definition of promotion queried where all aspects of this role were truly non-promotional in nature. The Panel asked that Shire be advised of its concerns.

APPEAL BY SHIRE

Shire noted that the complainant was anonymous and contactable and appeared to be an ex-employee (although this latter point had not been confirmed). The complaint provided little detail and/or evidence and appeared confusing and contradictory in places. The PMCPA contacted the complainant on several occasions to gain more information and clarifications.

Shire, however, appealed the Panel rulings in respect of the NICE Review (two points) a face-to-face meeting which took place on 19 January and allegations relating to managed entry agreements. Shire addressed each part separately.

Face-to-Face meeting on 19 January 2017

Shire noted that the Panel ruled a breach of Clause 3.1 and 9.1 in relation to a face-to-face meeting that took place on 19 January 2017 with the named CRG clinician.

Shire noted that NHSE had six programmes of care boards (NPoC) and each NPoC had several clinical reference groups (CRGs) to provide clinical advice and leadership. The CRGs were made up of clinicians, commissioners, public health experts, patients and carers, used their expertise to advise NHSE on the most appropriate provision of specialised services. They also led on the development of clinical commissioning policies, service specifications and quality standards.

The Specialised Endocrinology CRG was reviewing and advising the NHSE in relation to Natpar (recombinant human parathyroid hormone, rhPTH).

Shire had been in contact with some members of the Specialised Endocrinology CRG prior to the grant of the marketing authorisation for Natpar. This had been set out in detail in the original response to the complaint and the Panel found that there had been no breach of the Code in respect of those communications. In order to understand the context of the meeting with the named CRG clinician on 19 January 2017 Shire submitted that it was necessary to look at the timeline of some of those communications:

13 December 2016 Shire medical information received an unsolicited request from the named CRG clinician who was preparing a briefing for the NHS and the Specialised Endocrinology CRG. He wanted a point of contact within Shire to provide him with guidance on the development of Natpar. This request was routed to the named CRG clinician.

14 December 2016 The request was routed to the UK medical team.

15 December 2016 The named CRG clinician was contacted by Shire's medical manager asking what specific information was sought. The clinician wanted help and support completing the NHSE Provisional Policy Form (PPP), specifically with reference to information about Natpar. Further clarity was sought about the PPP form, and level of detail required.

Additionally, in the same call, Shire's medical manager checked whether the named CRG clinician would be willing to meet face-to-face to discuss medical activities that he/she could take part in. The intention of the meeting was not to talk about Natpar at all and was a non-promotional medical affairs meeting. There was to be no product discussions at this meeting. The purpose of this meeting was to ascertain the clinician's willingness to take part in Shire medical activities around hypoparathyroidism, for example, advisory boards, phase 4 studies and registries, and also to learn about how hypoparathyroidism was managed at a UK leading centre the clinician suggested late January. The Shire medical manager had previously contacted the clinician to seek his willingness to take part in a Shire Delphi Panel, but the clinician had not responded to this email.

16 December 2016 Email from the Shire medical manager to the named CRG clinician thanking him/her for call on 15 December and seeking additional clarity about the literature search required for the PPP form.

The Shire medical manager sent a text message to the named CRG clinician to ask if the F2F meeting could take place on 19 January. There was no response to this text message.

19 December 2016 The Shire medical manager sent a text message to the named CRG clinician the CRG to ask if they could speak to confirm the F2F meeting. A call was arranged, and on that telephone call, the clinician wanted additional information about Natpar to brief the CRG on 10 January. The clinician was asked to document this in an email so the medical team member could respond specifically to that enquiry.

	The named CRG clinician by email set out the subject matter of his/her enquiry, namely the likely population size for the indication so that the CRG could be updated about the development of an application to NHSE for consideration of development of a commissioning policy. The Shire medical manager sent a text message to pencil in the date for the F2F meeting on 19 January.
4 January 2017	The Shire medical manager telephoned the named CRG clinician and referred him/her to section 17 of the PPP which stated that if 'there is a planned or published Technology Appraisal, the NHSE cannot proceed to form a policy'. The Shire medical manager told the named CRG clinician that as Natpar was on the work plan for NICE, there was no longer a requirement for the Specialised Endocrinology CRG to complete the form with the intent of the CRG developing a commissioning policy.
4 January 2017	The named clinician responded by email and referred to the conversation with the Shire medical manager and noted that at the forthcoming CRG meeting when updating the group about the product he/she would ensure that the current consideration of Natpar by NICE was discussed. Shire would be advised of the outcome of these discussions including whether further information was required.
9 January 2017	An unsolicited request from another named CRG clinician to a Shire market access team member by email. The request was passed to the Shire medical manager and not responded to by Shire's market access team member as all the non-promotional activities were being led on and managed by the Shire medical team and the person with the medical/scientific expertise to be able to address the questions and requests. The CRG clinician appeared frustrated that Shire market access team member had requested a formal written request. This was in order to understand the specific nature of the request.
9 January 2017	The clinician responded by email expressing frustration at the process noting that material was normally circulated to the CRG a week beforehand and asked whether Shire had contacted a named CRG clinician and requested copies of any correspondence.
9 January 2017	The Shire medical manager responded to the CRG clinician by listing what he/she understood to be the 6 items which were the subject of the verbal request. A one page document setting out the information the CRG clinician requested headed 'Please note that rhPTH (1-84) is currently unlicensed in Europe, including the UK' was provided.
10 January 2017	Specialised Endocrinology CRG meeting took place at which Natpar was discussed.

Shire submitted that initially, the meeting on 19 January was only to be attended by the Shire medical manager, as the remit of the meeting had been to understand the named CRG clinician's willingness to take part in Shire medical activities. However, after internal team discussions and the fact that the CRG meeting had taken place, it was decided that Shire market access team member should attend this meeting with the Shire medical manager in a non-promotional capacity. The team had also discussed the level of frustration with the second named CRG clinician with how it appeared that Shire were being bureaucratic, slow and apparently unwilling to share information about Natpar. Given that the CRG meeting had taken place nine days earlier, and that there might be questions and requests at that meeting specifically in relation to specialised commissioning, the internal decision was made for Shire market access team member to attend, as he/she would have the specific expertise to answer/address any questions that might be raised. It would be likely that these questions would be raised at the 19 January meeting, and therefore in a non-promotional capacity and there only to reactively respond to any such specialist questions, Shire's market access team member attended with the Shire medical manager.

The Shire medical manager recorded this meeting on Shire's CRM system and referred to the meeting as an introductory meeting (it was the first time the Shire medical manager met the named CRG clinician face-to-face). The objective of the meeting was recorded as 'Burden of Illness'. There was no mention of product (Natpar) which was an option to be selected in the CRM system, highlighting that discussions were merely about fact finding and not about Natpar.

The non-promotional element of the meeting was further evidenced in the Shire medical manager's follow up email to members of Shire's global medical team which referred to the clinician's willingness to take part in Shire medical activities.

Following this face-to-face meeting, the named CRG clinician had engaged with Shire to participate in the ongoing Phase IV study and registry.

The non-promotional roles of the medical lead and the market access lead were explained to the named CRG clinician at the beginning of the meeting. Most of the meeting was taken up by the Shire medical manager on the medical side and a short period of time at the end of the meeting was spent by the Shire medical access team member responding to queries from the named CRG clinician about a potential in-year service policy as a result of the Specialised Endocrinology CRG on 10 January 2017.

Shire noted that the Panel found that all interactions between 13 December 2016 and 19 January 2017 were in compliance with the Code.

Shire noted that the Panel ruled that the 'on the balance of probabilities, that the meeting was promotional, it had been initiated by Shire in anticipation of, *inter alia*, discussions about Natpar and the CRG policy prior to the grant of Natpar's licence'.

Shire submitted that from the information provided above it was clear that there were no product discussions at this meeting nor was it intended that there would be such discussions. Accordingly, it was not a promotional meeting.

Shire noted that even though the market access lead had some promotional aspects to his/her role there were also non-promotional aspects to this role and on this occasion, he/she was acting in a non-promotional capacity. Accordingly, Shire submitted that the meeting was non-promotional and therefore not in breach of Clause 3.1 of the Code. In consequence Shire

refuted a breach of Clause 9.1 and requested that the Appeal Board did not uphold the Panel's rulings.

Discussion on 6 February 2017 re Managed Entry Agreement

Shire noted that the Panel found that there was a breach of Clauses 3.1 and 9.1 in relation to the discussion on 6 February 2017 and Shire's proposal of a managed entry agreement. Shire submitted that a managed entry agreement was usually a risk share agreement between NHS and the company.

In addition to the timeframe set out above, the Appeal Board needed to be aware of the lead up to the discussion/email correspondence on 6/8 February 2017.

1 February 2017 Shire met with NICE to discuss issues for rare diseases. The Panel had ruled no breach of the Code with regard to this interaction. In addition, Shire submitted that these interactions were exempt under Clause 1.2 as long as they were factual accurate and not misleading which they were. At this meeting there was discussion about the challenges with the Natpar data package and the Phase IV study which resulted in the discussion leading to the possibility of delaying the submission to NICE given the nature of the clinical trial data available. There was also discussion around obtaining CRG support for an in-year service development for a small cohort of patients. NICE agreed with this approach and suggested that Shire obtain the agreement of NHSE perhaps through the Specialised Endocrinology CRG. Shire noted that an in year service development ("IYSD") was a term used by NHSE to refer to policies which were cost saving or cost neutral to the NHS. Where a product might lend itself to such an approach often required companies to be proactive to NHSE in highlighting this potential. An accepted entry route into the assessment process that decided whether the product does qualified for IYSD was via the CRG.

6 February 2017 Shire's medical access team member and the Shire medical manager updated the two named CRG clinicians referred to above as representatives of the Specialised Endocrinology CRG of the above discussions with NICE.

8 February 2017 The Shire medical manager emailed the two named CRG clinicians summarising the call on 6 February 2017. The email stated:

> 'Many thanks for joining the call today following a request to be updated on the progress with NICE. This is the brief synopsis of our discussion, which you have requested I put in writing prior to your discussion. The information below is confidential.
>
> - rhPTH (1-84) - recombinant parathyroid hormone (currently unlicensed) - has recently been included on the NICE work plan for a single technology appraisal (STA).
>
> - Based on the clinical trial and economic evidence currently available, it is very unlikely that NICE will make a positive

recommendation through the STA process. Furthermore, Shire engaged with the NICE Scientific Advice Committee in November 2016, to seek advice on the proposed Phase IV study which was being designed to enrich the current dataset in the indicated population. However, changes were suggested by NICE to the inclusion criteria and endpoints within the proposed trial, which Shire are now incorporating into the study, in order to address NICE's requirements.

- Due to challenges with the limited dataset, and with the support from the Endocrine CRG, we would like to propose delaying/suspending the NICE STA until the Phase IV study has been completed, giving a full data package in the indicated population. The results for the study are expected in 2019/20.

- In the interim, we would like to get the support of the CRG with regards to proposing an in-year service development, for the small cohort of patients (approx. 60-80 patients in the UK) who are difficult to control and have high resource utilisation due to recurrent hospitalisations, monitoring and specialist visits.

- As discussed previously, Shire would be willing to discuss a suitable Managed Entry Agreement in line with the criteria for in year service developments, to allow for a predictable budget impact and the collection of data to provide evidence of efficacy and safety in this severe population

- Last week, Shire met with [NICE] to discuss access issues for rare diseases as well as the approach suggested above, outlining the challenges with the current data package, the scientific advice from NICE on the proposed Phase IV study, the CRG support for an in year service development for a small cohort of patients, and the possibility of delaying/suspending NICE until Shire has Phase IV results. NICE could see the sense in this approach and suggested to get agreement from NHSE, perhaps through the Endocrine CRG setting out the case and sending to NICE. However, [NICE] couldn't confirm the level of decision making in NHSE that would be needed but suggested that the CRG approach may be an appropriate one.

- Based on the information above, would the Endocrine CRG be supportive of this approach for delaying the NICE STA? If in agreement, we will need your help to identify who (if anyone) in NHSE would need to endorse this above the CRG. Furthermore, the case will need to be submitted to NICE before 18th February 2017 asking to delay / suspend their review.'

Shire stated that the reference to a 'Managed Entry Agreement' was incorrect in the email of 8 February. The correct reference was made in the subsequent paragraph to 'an in-year service development for a small cohort of patients'. This was what was meant in these communications

on 6/8 February. The idea was that if the NICE route was suspended then the relevant clinicians could make an application to NHSE on a cost neutral basis and NICE had suggested that this was best done through the Specialised Endocrinology CRG at the meeting on 1 February 2017.

There never was a managed entry scheme put in place nor were there any discussions in relation to a managed entry scheme. The discussions with the two named CRG clinicians took place as a result of the suggestion of NICE and the request by the named CRG clinicians to be kept up-to-date on any discussions with NICE and NHSE. The discussion related to in-year service policy only and the issues that had arisen with NICE. There was no promotional aspect to these discussions at any stage.

Shire submitted that although the incorrect use of the term 'Managed Entry Agreement' was used in one part of the email dated 8 February 2017, the intention was set out in the subsequent paragraph whereby Shire was seeking 'CRG support for an in-year service development for a small cohort of patients' and NICE had agreed with this approach and suggested that Shire contact the Specialised Endocrinology CRG.

No details of a managed entry agreement were ever discussed by any of the parties. Shire was merely seeking to understand the correct process by which a potential in year service policy could be developed.

The discussion on 6 February 2017 and subsequent email of 8 February 2017 all related back to the previous CRG commissioning policy discussions in January and the request of the named CRG clinicians to be kept up-to-date. Shire submitted that there was no promotional element to any of these discussions and the Panel was incorrect in finding that 'it was difficult to see this aspect of the discussions as anything other than promotional'.

Accordingly, Shire submitted that the communication was non-promotional and therefore not in breach of Clause 3.1 of the Code. In consequence it also refuted a breach of Clause 9.1 and requested that the Appeal Board did not uphold the Panel's rulings in this regard.

In summary, for all the reasons stated above Shire strongly believed that the two activities were not promotional and therefore no beach of Clause 3.1 had occurred. As a consequence, there was no breach of Clause 9.1. Shire respectfully requested that the Appeal Board did not uphold the Panel's rulings of breaches.

APPEAL BOARD RULING

The Appeal Board noted that Natpar was indicated in the treatment of a rare disease (adults with chronic hypoparathyroidism) and so the number of accessible clinicians in the therapy area would be small. In the rare disease arena it was likely that many of the health professionals involved would be prescribers as well as policy makers and so, with regard to activities related to Natpar, it would be difficult for Shire to avoid having to interact with those who, of necessity, wore 'two hats'. In discussions and the like with such people, the Appeal Board considered that companies should be extremely careful to correctly characterise their activities as either promotional or non-promotional; it was otherwise too easy for the boundaries to become blurred. The Appeal Board noted the broad definition of promotion. Participants in a meeting should be given clear sign posts as to its promotional status. Companies should be careful not to compromise the independence of prescribers who were also policy makers. The Appeal

Board accepted that rare diseases presented some difficulties and it was often hard for companies to ensure they had the right conversations with the right people. Nonetheless compliance must be achieved. The Appeal noted that although the number of patients affected by rare diseases was small, the cost of their treatment was significant to the NHS. The Appeal Board noted that Natpar's licence was granted in April 2017 ie shortly after the activities subject to the complaint.

The Appeal Board noted that it had the benefit of more information than that which had been submitted to the Panel. The Appeal Board noted the context in which the meeting of 19 January had occurred and Shire's submission that it had originally been set up by Shire medical to discuss the attending clinician's participation in Shire activities around hypothyroidism to include, *inter alia*, advisory boards, clinical trials and registries. The company representatives explained that it was decided nearer the time to include a colleague from market access in order that he/she might be able to answer any questions regarding access that had arisen from a CRG meeting that had taken place some days previously. According to Shire there were no specific discussions about the product and although the market access colleague had some promotional elements to his/her role, he/she was bonussed only on qualitative aspects of his/her role, not on sales. In addition, the second named CRG clinician had, ten days before the meeting, emailed the market access colleague and criticised Shire for being 'unbelievably bureaucratic' when he/she had stated, *inter alia*, that he/she could only send information in response to a written request. It was hoped that the attendance of the market access colleague would avoid any further frustration on the part of the CRG. The Appeal Board noted the role of the named CRG clinician and although it had some reservations about the clinician's potential conflicts of interest given he/she was both a prescriber and policy maker, it nonetheless did not consider that, on the balance of probabilities, Natpar had been promoted at the meeting prior to the grant of its marketing authorisation. No breach of Clause 3.1 was ruled. In that regard the appeal on this point was successful.

The Appeal Board was concerned, however, about the lack of a detailed record of the meeting. The meeting was recorded on a medical CRM log form which originated from Shire Global and was designed to record top line data only. It did not appear to have a section to record the fact that a colleague had also attended the meeting. It was not recorded on the form logging the 19 January meeting, and completed by medical, that a market access colleague had also attended. The Shire representatives submitted at the appeal that market access personnel did not have access to the CRM system and so the market access colleague who had attended could not create his/her own record of the meeting. The core communication objectives were recorded as 'Burden of Illness' because, according to the Shire representatives, this was the 'best fit' choice from a short drop-down menu. In the Appeal Board's view this did not adequately reflect the discussions which had taken place. There were no minutes recorded of the meeting; a short email giving very brief detail of the meeting only referred to the clinician wanting to be part of the registry and the Phase 4 study. The Appeal Board considered that given the difficulties discussed above about working in the area of rare diseases, the rigour with which Shire had documented the meeting was poor and in that regard it considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

With regard to the telephone call which took place on 6 February 2017, and subsequent email of 8 February, the Appeal Board noted that there appeared to be no precise definition of what a managed entry agreement was. Shire submitted that although the email of 8 February, the record of the call, referred to a managed entry agreement it also referred to such as being 'in line with the criteria for in year service developments'. The Appeal Board noted the company's

definition of managed entry agreement and in year service development and considered that the difference between the two activities was not sufficiently clear; at the very least there appeared to be a degree of overlap and both might potentially involve data collection. The Appeal Board noted that the call record referred to a previous conversation with NICE in which in year service developments were discussed and which implied that an in-year service development for a small cohort of patients was already supported by the CRG. The need for an in-year service development arose because it was thought unlikely that the current Natpar data set would be sufficient for a positive recommendation from NICE. Shire thus wanted to delay the NICE submission and so the CRG would need to prepare for an alternative mechanism of access post licence. Shire's representatives explained that this would involve collecting data in a high risk population and that this activity was initially proposed by the CRG. The Appeal Board considered that, given the circumstances and the context in which the call had occurred, Natpar had not been promoted prior to the grant of its marketing authorisation. No breach of Clause 3.1 of the Code was ruled. The call had been well documented and in that regard the Appeal Board considered that high standards had been maintained. No breach of Clause 9.1 was ruled. The appeal on both points was successful.

3 Medical Science Liaison (MSL) visits

COMPLAINT

The complainant alleged that Shire's internal strategy had MSLs target numbers of visits to physicians and linked this to their key performance indicators (KPIs) despite the fact that an MSL role should be reactive and not proactive, particularly when it came to many products not yet licensed, ie no CHMP approvals. The complainant stated that this might have changed after the internal team complained however, it was a strategy that showed a lack of respect for ethics and code of conduct.

In a second email, the complainant stated that for the MSL targets, he/she did not have any specific documents as this was conveyed to him/her through the medical team which was not happy with the commercial implications.

In a third email, the complainant stated that he/she did not have emails for the MSL targets but, if the PMCPA investigated, those documents would be available (if Shire had not disposed of them).

In a fourth email, the complainant alleged that the MSL issue was linked to targets for medical team to meet with KOLs, it was linked to their evaluation and possible bonuses, which was against the ethics of the industry and the role of MSLs to be reactive and not proactive.

RESPONSE

Shire strongly refuted the allegations that it had a lack of respect for ethics and code of conduct and that it performed any activity against the pharmaceutical industry's high standards. Shire took the Code and the company's ethical standards very seriously – it was disappointed that the complainant alleged differently – Shire stood by the position that this was simply not correct.

The MSL job description clearly outlined the primary duties for the MSL including the 'compliant communication and education of Shire's marketed and emerging product portfolio to meet the educational and professional needs of Shire's key customers'. In 2016 through to early 2017, there were internal discussions on the most appropriate measures (ie KPIs) for the job

performance for MSLs within Shire. The complainant referred to internal discussions with the Shire International medical affairs team before the agreed performance goals and objectives (KPIs) for MSLs in the UK were approved.

Shire submitted that the division of KPIs for the MSL role was broken down into 4 focus areas where the MSL working time was spent: MSL Plan development and implementation; Leadership and self-management; Cross-functional contribution and Process management and implementation. In the focus area MSL time was spent working on the MSL plan development and implementation: specifically in 'develop and continue execution of MSL plan' bullet of the MSL performance goals and objectives (KPIs) it clearly provided guidance that the quantitative measure for health professional interactions was an aspirational measure. Additionally, the qualitative aspects of interactions with KOLs ('analyse medical insights') were also used as key performance measures for the MSL. Shire strongly believed that the performance measures for MSLs were balanced, ethical and appropriate for a non-promotional role.

The complainant also alleged that the MSLs had undertaken pro-active unlicensed discussions despite not providing any evidence. Shire strongly refuted this allegation and from the MSL job description it could be clearly seen in the 'KOL engagement' responsibility section – 'KOL engagement: through compliant scientific exchange ...' implying that the MSL would only respond to any unlicensed discussion reactively to a request for further information from a health professional. Shire ensured that all MSLs operated in this manner.

Clause 1.7 of the Code stated 'the term "representative" means a representative calling on members for the health professions and other relevant decision makers in relation to the promotion of medicines'. Whilst it was clear that Shire's MSLs called upon on members of the health profession (as per industry standards) it was also clear that, from the MSL job description in terms of primary duties, responsibilities (% of time) and the MSL Key performance measured (as outlined above), the MSL role was neither based upon nor measured through promotion of Shire medicines thereby clearly distinguishing the MSL role from the representative role as per the definition given in Clause 1.7.

In conclusion, Shire strongly refuted the allegations that it had done anything inappropriate, unethical or contrary to the Code in relation to the MSL role within Shire UK. It did not consider that any aspect of the MSL job description and/or KPIs gave any basis for concern nor was in breach of the Code. Shire therefore refuted any allegation of breaches of the Code.

PANEL RULING

As with Points 1 and 2 above, the Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties.

The Panel noted the complainant's allegation that the number of visits to physicians was linked to the MSLs key performance indicators which in turn were linked to bonus payments and inferred that this encouraged proactive discussions of medicines prior to the grant of their licence.

The Panel noted the MSL Performance Goals and Objectives included, *inter alia*, 'HCP interactions: Aspiration for KOL face to face interactions'. They also instructed the MSL of their time to spend on the percentage in the field, aiming to spend less time in internal meetings.

The Panel noted that the complainant bore the burden of proof and that the complainant had provided no evidence to establish, on the balance of probabilities, that proactive promotional discussions about unlicensed medicines had occurred. No breach of Clause 3.1 was ruled.

The Panel noted that guidance about Clause 3 published by the Authority stated that the remuneration of those employed as medical and scientific liaison executives and the like must not be linked to the number of enquiries answered or the number of visits, meetings etc but a bonus scheme linked to the percentage of enquiries or visit requests completed may be acceptable. Remuneration should not be linked to sales in any particular territory or place or to sales of a specific product or products and, in particular, may not include a bonus scheme linked to such sales. Bonus schemes linked to a company's overall national performance, for example sales in the UK, may be acceptable. The Panel noted that the guidance was not part of the Code or its supplementary information but was, nonetheless, relevant.

The Panel noted the MSL Performance Goals and Objectives. The Panel noted that the MSL role varied across the industry but the relevant part of the Authority's guidance applied to those that had a non promotional role. The Panel noted the MSL key performance indicators and Shire's submission that the quantative measure for health professional interactions was an aspirational measure. The Panel considered that applying an aspirational KPI in relation to the number of visits to KOLs (rather than the percentage of visit requests completed or similar), which was linked to an MSL's remuneration, was inappropriate and might encourage behaviour that was inconsistent with the Code. High standards had not been maintained in this regard and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. No breach of Clause 2 was ruled.

Complaint received **25 October 2017**

Case completed **31 July 2018**