PHARMACISTS v PROVECA

Letter regarding the supply of unlicensed and off-label glycopyrronium

Two prescribing team pharmacists from a clinical commissioning group (CCG) (Case AUTH/3058/8/18) and a community pharmacist (Case AUTH/3060/8/18) complained about a letter sent in August 2018 by Proveca about the supply of unlicensed and off-label glycopyrronium bromide. Proveca marketed Sialanar (glycopyrronium bromide) for the symptomatic treatment of severe sialorrhoea in children aged 3-17 years. The letter at issue was copied to the Medicines and Healthcare products Regulatory Agency (MHRA).

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The complainants noted that the letter was sent to at least two GP surgeries within the CCG and alleged that Proveca had taken a very aggressive marketing approach since it launched Sialanar and appeared to be communicating with surgeries and provider trusts in a similar intimidating vein. One of the complainants stated that he/she had previously received a similar letter in his/her capacity as a hospital pharmacist approximately three months ago.

The complainants explained that one key distinction between glycopyrronium 'specials' and Sialanar was the concentration of glycopyrronium bromide; the branded product was 2mg/5ml whereas the concentration historically used as a 'special' was 5mg/5ml. Hence, the two products were not of an equivalent strength. A switch from a 'special' to Sialanar might be appropriate in some instances but it meant that the liquid volume to be given to a child with severe drooling would be increased 2.5 – fold. There might be valid reasons why a specials product had to be used. The last sentence of the letter ('It is only failing all of the above, and lack of importation of an approved medicinal product, that a 'special' may be supplied') recognised that there might be exceptions to the general guidance of using a special, although the first sentence of the same paragraph ('Therefore, not only is it not allowed to dispense an unlicensed drug where there is a licensed alternative, but a licensed product should be the preferred option for other indications outside of its authorization, given that it has already been assessed for safety and efficacy') seemed to claim that it was not permissible to dispense an unlicensed medicine.

The complainants alleged that although the letter described the relevant national guidance on the prescribing of 'specials' – from the MHRA and General Medical Council (GMC) – the way the letter was written and some of the wording was in breach of the Code.

The style of the letter was explicitly aggressive and threatening. The second paragraph referred to a 'breach of the law'. The sentence '…. officially putting you on notice for illegitimate dispensing practices …' was clearly designed to scare staff. Likewise, the request that surgeries confirmed that they had ceased these activities back to the company was totally unnecessary and a scare tactic.

Although addressed to the surgery, the letter referred to 'your pharmacy' and implied that there might have been commercial and financial damage to Proveca. Pharmacies, or even dispensaries in surgeries, dispensed what was prescribed on the GP prescription and their actions should not be disparaged for doing so. Further, the letter seemed to suggest that specials were used on cost grounds ('Dispensing off-label on cost grounds where a licensed product is available and will meet the same therapeutic need is not acceptable…'). The complainants stated that the 'special' had been used for many years and any move away from the special to Sialanar needed careful consideration because of the different concentration. If the switch did not happen quickly enough for Proveca then it was likely to be because this was not a simple switch.

The letter referred to the Medicines and Healthcare products Regulatory Agency (MHRA) and a copy had supposedly been sent to the MHRA. The complainants queried whether this was a copy of every single letter or just a copy of the master letter and whether the MHRA had given the permission required to include reference to it in the letter.

The detailed response from Proveca is set out below.

The Panel noted that according to Proveca the letter at issue was sent to around 16,000 pharmacies, primarily consisting of community pharmacists and hospital outpatients. The letter urged pharmacies to refrain from dispensing glycopyrronium bromide 'specials', and off-license preparations for children with chronic drooling and ensure that Sialanar was dispensed.

The Panel noted that the letter in question was promotional and bore prescribing information. It was not necessarily unacceptable to draw the attention of prescribers to the prescribing legal framework, however such material had to comply with the Code. In the Panel's view there was a difference between writing to all pharmacists as opposed to those whose dispensing was the subject of Proveca's concern. The Panel noted the company's submission that it was not possible for

the company to know which pharmacists were dispensing glycopyrronium bromide.

The Panel noted that another letter which the complainant referred to briefly as a similar letter had been sent by Proveca's Medical Director in March 2018. That letter, which was not the subject of complaint, gave the licensed indication of Sialanar and stated that it had come to Proveca's attention that many pharmacists were continuing to supply unlicensed and off-label glycopyrronium bromide products even when the prescription was for a child with chronic drooling. The letter further stated that unless specifically requested by the prescribing physician, the licensed product should be dispensed as per the National Pharmacy Association (NPA) guidance on the supply of unlicensed medicines, and an extract of the guidance was included at the bottom of the letter. The Panel noted that the letter sent in March 2018 was very different to that sent in August 2018.

Turning to the letter at issue, sent in August 2018, the Panel noted the complainant's concern that pharmacies and dispensaries in surgeries were being disparaged for dispensing what was prescribed by GPs. Paragraph 2.2 of the MHRA guidance on 'The supply of unlicensed medicinal products ("specials")' allowed a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or other prescriber to decide whether an unlicensed medicine should be supplied in preference to a licensed medicine where the licensed product could not meet an individual patient's special needs. The Panel noted that the letter at issue highlighted that any pharmacy continuing to dispense unlicensed and off-label preparations for children was in breach of the pharmaceutical legal framework. The Panel noted the complainant's allegation that the letter implied that supplying a special in preference to the use of Sialanar was illegal. The Panel noted the company's response that if there was a *bona fide* reason for the prescription of an unlicensed product then it was the prerogative of the prescriber and Proveca was not suggesting that it was not dispensed. The Panel noted Proveca's submission that it might be suitable to prescribe an unlicensed product instead of Sialanar when the concentration of Sialanar (2mg/5ml) was too low and a much lower volume of product would be required. However, the Panel considered that the letter misleadingly implied that the activity was illegal by stating that if a pharmacy was supplying unlicensed or off-label preparations of glycopyrronium bromide for the indication of chronic drooling in paediatric patients then it should consider the letter as officially putting it on notice for illegitimate dispensing practices which might be a contravention of legally established rights and have caused Proveca significant commercial and financial damage. The Panel noted, as acknowledged by Proveca, that the supply of an unlicensed medicine was legally permissible in certain circumstances where there was a patient with a 'special need'. The Panel considered that the letter in question queried a health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances, which in the Panel's view might potentially put patient safety at risk. The letter stated that such a decision was inconsistent with MHRA Guidance and law and implied that serious consequences could ensue. The Panel further noted the negative responses received from at least six recipients of the letter. It appeared that the recipients considered that the content of the letter was such that it questioned the reader's professional judgement. In the Panel's view, the content and tone of the letter was such that it disparaged the professional opinion of health professionals and a breach was ruled.

The letter stated that Proveca had brought the disparaging practice at issue to the attention of the MHRA which was copied into the letter.

In the Panel's view, the implication was that the MHRA approved or otherwise endorsed the content of the letter. The Panel noted that it appeared that the MHRA had not asked to be copied into the letter. The Panel did not consider that Proveca's account of a conversation with the MHRA meant that the wording in the promotional letter in question was specifically required by the MHRA and thus a breach was ruled.

The Panel noted its comments and rulings above and ruled that Proveca had failed to maintain high standards.

The Panel considered that the letter in question queried a health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances which in the Panel's view might potentially put patient safety at risk. The letter stated that such a decision was inconsistent with MHRA Guidance and law and implied that serious consequences could ensue if the letter was not adhered to. The Panel was very concerned about the content and tone of the letter and noted its comments and rulings above. In the Panel's view, pharmacists who had received the letter would be very concerned by the misleading implication that his/her dispensing practices were potentially illegal and that legal consequences including an implication that a claim for financial damages might ensue. The Panel noted that not all recipients of the letter would have dispensed glycopyrronium bromide. The tone of the promotional letter could be seen as threatening and, in the Panel's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Proveca appealed all the Panel's rulings of breaches of the Code. The Appeal Board upheld all the rulings of breaches of the Code.

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The complainant stated that the crux of his/her complaint was that the tone of the letter was quite threatening; it had been copied to the MHRA and alleged that illegitimate dispensing practices were being followed.

The complainant had had a discussion with colleagues at a local surgery about the issues surrounding the letter to remedy any issues following clinical review from a local GP. The complainant alleged that the letter was unnecessarily threatening towards the pharmacy and making the switch would pose an additional cost burden on the NHS. An additional concern was that the original prescriptions were initiated in secondary care so there might be clinical reasons for prescribing the original unlicensed special. The complainant had sought clarification from a local primary care clinician who would hopefully feedback at the appropriate time.

The detailed response from Proveca is given below.

The Panel noted that the letter urged pharmacies to refrain from dispensing glycopyrronium bromide 'specials', and off-license preparations for children with chronic drooling and ensure that Sialanar was dispensed.

The Panel noted that the letter in question was promotional and bore prescribing information. The Panel noted that it was not necessarily unacceptable to draw the attention of prescribers to the prescribing legal framework, however such material had to comply with the Code. In the Panel's view there was a difference between writing to all pharmacists as opposed to those whose dispensing was the subject of Proveca's concern. The Panel noted the company's submission that it was not possible for the company to know which pharmacists were dispensing glycopyrronium bromide.

The Panel noted the complainant's submission that the original prescriptions were initiated in secondary care so there might be clinical reasons for prescribing the original unlicensed special.

The Panel noted Proveca's submission that it might be suitable to prescribe an unlicensed product instead of Sialanar when the concentration of Sialanar (2mg/5ml) was too low and a much lower volume of product would be required (provided by a higher concentration of special eg 5mg/5ml). However, the Panel considered that the letter in question misleadingly implied that the activity was illegal by stating that if a pharmacy was supplying unlicensed or off-label preparations of glycopyrronium bromide for the indication of chronic drooling in paediatric patients then it should consider the letter as officially putting it on notice for illegitimate dispensing practices which might be a contravention of legally established rights and have caused Proveca significant commercial and financial damage. The Panel noted, as acknowledged by Proveca, that the supply of an unlicensed medicine was legally permissible in certain circumstances where there was a patient with a 'special need'. The Panel considered that the letter in question queried the health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances, stating that such a decision was inconsistent with MHRA Guidance and law and implying that serious consequences could ensue.

The Panel noted that the letter in question stated that Proveca had brought the dispensing practice at issue to the attention of the MHRA which was copied into the letter. In the Panel's view the implication was that the MHRA approved of or otherwise endorsed the content of the letter which was not so. The Panel further noted the negative responses received from at least six recipients of the letter at issue. It appeared that the recipients considered that the content of the letter was such that it was threatening and questioned the reader's professional judgement. In the Panel's view Proveca had failed to maintain high standards and a breach was ruled.

The Panel considered that the letter in question queried a health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances which in the Panel's view might potentially put patient safety at risk. The letter stated that such a decision was inconsistent with MHRA Guidance and law and implied that serious consequences could ensue if the letter was not adhered to. The Panel was very concerned about the content and tone of the letter and noted its comments and rulings above. In the Panel's view, pharmacists who had received the letter would be very concerned by the misleading implication that his/her dispensing practices were potentially illegal and that legal consequences including an implication that a claim for financial damages might ensue. The Panel noted that not all recipients of the letter would have dispensed glycopyrronium bromide. The tone of the promotional letter could be seen as threatening and, in the Panel's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Proveca appealed all the Panel's rulings of breaches of the Code. The Appeal Board upheld all the rulings of breaches of the Code.

Two prescribing team pharmacists from a clinical commissioning group (CCG) (Case AUTH/3058/8/18) and a community pharmacist (Case AUTH/3060/8/18) complained about a letter (ref Sia/Legal/01) sent in August 2018 by Proveca Ltd about the supply of unlicensed and off-label glycopyrronium bromide. Proveca marketed Sialanar (glycopyrronium bromide) for the symptomatic treatment of severe sialorrhoea in children aged 3-17 years. The letter at issue was copied to the Medicines and Healthcare products Regulatory Agency (MHRA).

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COMPLAINT

The complainants noted that the letter was sent to at least two GP surgeries within the CCG and alleged that Proveca had taken a very aggressive marketing approach since it launched Sialanar and appeared to be communicating with surgeries and provider trusts in a similar intimidating vein. One of the complainants noted that he/she had previously received a similar letter in his/her capacity as a hospital pharmacist approximately three months ago.

The complainants explained that one key distinction between glycopyrronium 'specials' and Sialanar was the concentration of glycopyrronium bromide; the branded product was 2mg/5ml whereas the concentration historically used as a 'special' was 5mg/5ml. Hence, the two products were not of an equivalent strength. A switch from a 'special' to Sialanar might be appropriate in some instances but it meant that the liquid volume to be given to a child with severe drooling would be increased 2.5 – fold. There might be valid reasons why a specials product had to be used. The last sentence in paragraph 3 on page 2 of the letter ('It is only failing all of the above, and lack of importation of an approved medicinal product, that a 'special' may be supplied') recognised that there might be exceptions to the general guidance of using a special, although the first sentence of the same paragraph ('Therefore, not only is it not allowed to dispense an unlicensed drug where there is a licensed alternative, but a licensed product should be the preferred option for other indications outside of its authorization, given that it has already been assessed for safety and efficacy') seemed to claim that it was not permissible to dispense an unlicensed medicine.

The complainants submitted that although the letter described the relevant national guidance on the prescribing of 'specials' – from the MHRA and General Medical Council (GMC) - they considered that the way the letter was written and some of the wording was in breach of the Code. In particular:

Clause 2 – Discredit to, and reduction of confidence in, the industry. The style of the letter was explicitly aggressive and threatening. The second paragraph referred to a 'breach of the law'. The final sentence commencing at the bottom of page 2, '…. officially putting you on notice for illegitimate dispensing practices…' was clearly designed to scare staff at the surgery. Likewise, the request that surgeries confirmed that they had ceased these activities back to the company was totally unnecessary and a scare tactic.

Clause 8.2 The health professions and the clinical and scientific opinions of health professionals must not be disparaged. Although addressed to the surgery, the letter referred to 'your pharmacy' and implied that there might have been commercial and financial damage to Proveca. Pharmacies, or even dispensaries in surgeries, dispensed what was prescribed on the GP prescription and their actions should not be disparaged for doing so. Further, the letter seemed to suggest that specials were used on cost grounds ('Dispensing off-label on cost grounds where a licensed product is available and will meet the same therapeutic need is not acceptable…'). The complainants submitted that the 'special' had been used for many, many years and any move away from the special to Sialanar needed careful consideration because of the different concentration. If the switch did not happen quickly enough for Proveca then it was likely to be because this was not a simple switch.

Clause 9.5 Promotional material must not include any reference to the Commission on Human Medicines, the Medicines and Healthcare products Regulatory Agency or the licensing authority, unless this is specifically required by the licensing authority. The letter referred to the MHRA and a copy had supposedly been sent to the Agency. The complainants queried whether this was a copy of every single letter that had gone to each and every surgery or just a copy of the master letter and whether the MHRA had given the permission required to include reference to it in the letter.

When writing to Proveca, the Authority asked it to consider the requirements of Clause 9.1 in addition to Clauses 8.2, 9.5 and 2 as cited by the complainant.

RESPONSE

Proveca submitted that it was a small pharmaceutical company which specialised in the development and licensing of off-patent medicines through the paediatric – use marketing authorization (PUMA) regulatory route. The law and guidelines from the MHRA were very clear as to when an off-licence medicine could be dispensed to patients. It was not the prerogative of the pharmacists (with the exception of pharmacist independent prescribers) to choose an unlicensed medicine where a licensed alternative existed. It was the prerogative of the health practitioner in accordance with the law. Proveca stated that it had noted this in an earlier letter of March 2018 which resulted in very little change in practice. Rather than considering legal action, the company thus sent the letter in question to reiterate the position as a courtesy to the pharmacists.

The letter was sent to 16,154 pharmacies across the UK, primarily consisting of community pharmacists and hospital outpatients.

The letter at issue was intended to inform all pharmacists of the licensed status of Sialanar and the legal requirement for the dispensing and supply of unlicensed products. Proveca stated that it consulted with the MHRA which agreed with its proposal to write to pharmacists to remind them of their legal obligations with a 'cease and desist' letter. If this was not successful, the MHRA suggested that the company get back in touch to see how the Agency might be further involved. Despite the March 2018 letter informing pharmacists that there was now a licensed product available, significant off-label and unlicensed dispensing of glycopyrronium bromide continued to be widespread for children with chronic drooling. Proveca took legal advice to ensure its communications were aligned with UK law and sent the letter at issue to remind pharmacists of their obligations around supply of unlicensed medicines.

Proveca explained that it was only by a narrowly drawn exemption expressed in Article 5(1) of Directive 2001/83/EC, implemented in Regulation 167 of the Human Medicines Regulations 2012 (SI/2012/1916), that the supply of an unlicensed drug was legally permissible. This was where a patient had a 'special need' namely where there was no other available licensed medicine and a company received a *bona fide* unsolicited request from a

prescriber for a specific individual patient. Proveca noted that where there was a prescription for an unlicensed product it had not suggested that it was not dispensed; if there was a *bona fide* reason for the prescription this was the prescriber's prerogative.

Proveca submitted that several pharmacists had emailed the company following receipt of the letter. In total 65 emails had been received; 59 confirmed receipt of the letter, advising the company of actions taken and/or thanking it for the information; 6 expressed some level of concern at the letter but acknowledged its content. Proveca had met with or called everyone who contacted it. The overwhelming response to the calls was that, now they were aware of their obligations, the pharmacist was keen to comply with the law and move away from dispensing specials in situations where their use was not warranted, justified or prescribed by a health professional. Some pharmacists stated that the communication had been helpful in allowing them to ensure good governance.

Proveca denied a breach of Clause 2.

Proveca stated that it had not been its intention to disparage the clinical and scientific opinions of health professionals and it did not consider that the letter at issue did so. The letter was sent to all pharmacists as it was not possible for the company to know which pharmacists were dispensing glycopyrronium bromide and, in any event, it was never suggested that any 'Specials' dispensing was intentionally contravening legal requirements.

Proveca noted that it had communicated the licensed status and the requirement for licensed dispensing in its letter in March. Despite that, off-label and unlicensed dispensing continued to be widespread for children. The company consulted with the MHRA and took legal advice and as a result had sent the letter at issue which intended to clarify the legal position with respect to the continued dispensing of off-label and unlicensed glycopyrronium bromide where a licensed product existed. The letter was sent on the assumption that pharmacists were not deliberately breaching the law but simply did not know about the law applicable to 'Specials' and/or the fact that Sialanar had been authorised for use in paediatrics. This was also indicated in the company's recommendation to 'Specials' manufacturers that they contact any unaware prescribers placing the order accordingly, to ensure proper observance of the rules that health professionals were bound to follow. Proveca referred to the narrow exemption in the regulations stated above.

Proveca submitted that health professionals remained free to prescribe whatever they considered was suitable for their patients. However, if they prescribed a product off-label then they bore the product liability. Pharmacists were obliged to supply the product prescribed by the health professional and 'specials' could only be prescribed and supplied in accordance with the law as explained in the letter. Proveca further submitted that unlicensed product should only be prescribed and supplied in instances where there was an unmet patient need which could not be met by the licensed product. Only under these circumstances could an unlicensed medicine be dispensed. Sialanar was the only glycopyrronium bromide licensed for children and had been designed specifically for the paediatric population. Examples of when it would be unsuitable would include allergy to one of the ingredients or the child being unable to take a liquid. Proveca had not suggested that, in such circumstances, an unlicensed product might not be the appropriate choice, and as such had not questioned any professional knowledge and decision making.

With regard to high standards, Proveca submitted that the letter at issue was professionally written and courteous. It provided in a clear and comprehensive manner, the legal position which it appreciated pharmacists might not be familiar with. The company denied a breach of Clause 9.1.

With regard to Clause 9.5, Proveca stated that it referred to the MHRA as it was copied into the letter and it had sought advice from the Agency previously. The company submitted that to this end, omission of such a reference would have been misleading and it denied a breach of Clause 9.5.

FURTHER INFORMATION FROM PROVECA

In response to a request for further information Proveca provided details of a telephone call with the MHRA on 11 September 2017 which consisted of a short discussion around the extent of the MHRA's involvement in cease and desist letters sent by companies. The MHRA explained that whilst the MHRA was not involved in the issue or drafting of cease and desist letters (and therefore had no templates or examples to share), it was aware of this practice by companies sending such letters referring to MHRA Guidance Note 14. Proveca suggested drafting a letter along these lines and the MHRA agreed. Proveca considered reference to the relevant guidance crucial for informing the recipients of the applicable rules and their obligations by reference to national guidance, instead of risking being perceived as suggesting its own rules and interpretation of the applicable framework. Proveca considered this an objective and factual reference to the applicable national rules and in line with the informative tone that it sought to adopt.

According to Proveca, the MHRA suggested that once Proveca had taken a number of steps, including a cease and desist letter, to remedy the situation it considered wrong, it could then contact the MHRA explaining the position and the steps that Proveca had taken, so that the MHRA could then take a view on whether there was scope for the Agency's involvement.

Proveca submitted that, it was therefore clear that Proveca could not have consulted the MHRA more specifically about the letter, seeking any pre-approval, and Proveca did not consider it appropriate to take up the Agency's time considering that they did not issue such letters. Proveca submitted, however, that it did promptly send copies of the

finalised letter to the MHRA. No comments or correspondence were received from the MHRA in response to the letter.
The MHRA responded to a pharmacist who complained about the letter that this was not an enforcement matter and it would be handled by either the regulatory affairs or customer services teams, if appropriate.

Whilst the MHRA suggested that Proveca contact the Agency if its approach was unsuccessful, Proveca wished to exhaust all possible avenues of informing the concerned parties of the illegitimacy of the specials dispensing practice without justification, before involving the Agency. Given the recency of the letters sent by Proveca, it wanted to wait for an appropriate time to elapse in order to assess the success of its effort to inform pharmacists.

Proveca provided anonymised copies of the 6 emails from health professionals setting out concerns following receipt of the letter at issue. Proveca also provided a copy of the letter that it sent to pharmacists in March 2018 informing them of the existence of a licensed product. No responses to this letter were provided.

Proveca considered that it might be suitable to prescribe an unlicensed product instead of Sialanar when:

- the concentration of Sialanar was too low and a much lower volume of product would be required (provided by a higher concentration of special eg 5mg/5ml). This would be unusual but there could be the rare occasion.

- the child had an allergy to one of the excipients of Sialanar, where a special might exclude the excipient. Again, this would be highly unlikely since Sialanar contained very few ingredients. The lack of such ingredient would need to be assured in the special formulation.

PANEL RULING

The Panel noted that according to Proveca the letter at issue was sent to 16,154 pharmacies across the UK, primarily consisting of community pharmacists and hospital outpatients. The letter urged pharmacies to refrain from dispensing glycopyrronium bromide 'specials', and off-license preparations for children with chronic drooling and ensure that Sialanar was dispensed. The letter in question stated Sialanar's licensed indication in the second paragraph on the first page, namely that it was the only product licensed in the UK for the symptomatic treatment of severe drooling in the paediatric population (children aged 3-17 years).

The Panel noted that the letter in question was promotional and bore prescribing information. The Panel noted that it was not necessarily unacceptable to draw the attention of prescribers to the prescribing legal framework, however such material had to comply with the Code. In the Panel's view there was a difference between writing to all pharmacists as opposed to those whose dispensing was the subject of Proveca's concern. The Panel noted the company's submission that it was not possible for the company to know which pharmacists were dispensing glycopyrronium bromide.
The Panel noted that another letter which the complainant referred to briefly as a similar letter had been sent by Proveca's Medical Director in March 2018. That letter, which was not the subject of complaint, gave the licensed indication of Sialanar and stated that it had come to Proveca's attention that many pharmacists were continuing to supply unlicensed and off-label glycopyrronium bromide products even when the prescription was for a child with chronic drooling. The letter further stated that unless specifically requested by the prescribing physician, the licensed product should be dispensed as per the National Pharmacy Association (NPA) guidance on the supply of unlicensed medicines, and an extract of the guidance was included at the bottom of the letter. The Panel noted that the letter sent in March 2018 was very different to that sent in August 2018.

Turning to the letter at issue, sent in August 2018, the Panel noted the complainant's concern that pharmacies and dispensaries in surgeries were being disparaged for dispensing what was prescribed by GPs. The Panel noted that Clause 8.2 stated that health professions and the clinical and scientific opinions of health professionals must not be disparaged. Paragraph 2.2 of the MHRA guidance on 'The supply of unlicensed medicinal products ("specials")' allowed a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or other prescriber to decide whether an unlicensed medicine should be supplied in preference to a licensed medicine where the licensed product could not meet an individual patient's special needs. The Panel noted that the letter at issue highlighted that any pharmacy continuing to dispense unlicensed and off-label preparations for children was in breach of the pharmaceutical legal framework. The Panel noted the complainant's allegation that the letter implied that supplying a special in preference to the use of Sialanar was illegal. The Panel noted the company's response that if there was a *bona fide* reason for the prescription of an unlicensed product then it was the prerogative of the prescriber and Proveca was not suggesting that it was not dispensed. The Panel noted Proveca's submission that it might be suitable to prescribe an unlicensed product instead of Sialanar when the concentration of Sialanar (2mg/5ml) was too low and a much lower volume of product would be required. However, the Panel considered that the letter misleadingly implied that the activity was illegal by stating that if a pharmacy was supplying unlicensed or off-label preparations of glycopyrronium bromide for the indication of chronic drooling in paediatric patients then it should consider the letter as officially putting it on notice for illegitimate dispensing practices which might be a contravention of legally established rights and have caused Proveca significant commercial and financial damage. The Panel noted, as acknowledged by Proveca, that the supply of an unlicensed medicine was legally permissible in certain circumstances where there was a patient with a 'special need'.
The Panel considered that the letter in question queried a health professional's decision to prescribe

a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances, which in the Panel's view might potentially put patient safety at risk. The letter stated that such a decision was inconsistent with MHRA Guidance and law and implied that serious consequences could ensue. The Panel further noted the negative responses received from at least six recipients of the letter at issue. It appeared that the recipients considered that the content of the letter at issue was such that it questioned the reader's professional judgement. In the Panel's view, the content and tone of the letter was such that it disparaged the professional opinion of health professionals and a breach of Clause 8.2 was ruled.

The Panel noted that Clause 9.5 stated that promotional material must not include any reference to, *inter alia*, the Medicines and Healthcare products Regulatory Agency, unless this was specifically required by the licensing authority. The exception in the relevant supplementary information in relation to factual safety information and the MHRA Drug Safety Update did not apply to the letter at issue. The Panel noted that the letter in question referred to the MHRA's Guidance Note 14 on the supply of unlicensed medicinal products (specials) and the hierarchy for the use of unlicensed medicines, an appendix to this guidance note. The letter in question stated that Proveca had brought the dispensing practice at issue to the attention of the MHRA which was copied into the letter. In the Panel's view, the implication was that the MHRA approved or otherwise endorsed the content of the letter. The Panel noted that it appeared that the MHRA had not asked to be copied into the letter. The Panel noted that the impression was supported by Proveca's initial submission that it had consulted with the MHRA which agreed with its proposal to write to pharmacists to remind them of their legal obligations with a 'cease and desist letter' and suggested that Proveca get back in touch with the MHRA to see how it might be further involved should the letter be unsuccessful. The Panel noted Proveca's further submission, following a request from the Panel for further information, regarding the telephone conversation the MHRA in September 2017 around the extent of the MHRA's involvement in cease and desist letters sent by companies. According to Proveca the MHRA explained that whilst it was not involved in the issue or drafting of cease and desist letters (and therefore had no templates or examples to share), it was aware of the practice by companies sending such letters referring to MHRA Guidance Note 14. According to Proveca, the MHRA apparently agreed with Proveca's suggestion of drafting such a letter and suggested that Proveca contact the MHRA explaining Proveca's position and the steps it had taken, including a cease and desist letter, to remedy the situation it considered wrong, so that the MHRA could then take a view on whether there was scope for its involvement. There was no written follow up of this conversation. The Panel did not consider that Proveca's account of the conversation meant that the wording in the promotional letter in question was specifically required by the MHRA as stated in Clause 9.5 and thus a breach of Clause 9.5 was ruled.

The Panel noted its comments and rulings above and considered that Proveca had failed to maintain high standards and a breach of Clause 9.1 was ruled. The Panel considered that the letter in question queried a health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances which in the Panel's view might potentially put patient safety at risk. The letter stated that such a decision was inconsistent with MHRA Guidance and law and implied that serious consequences could ensue if the letter was not adhered to. The Panel was very concerned about the content and tone of the letter and noted its comments and rulings above. In the Panel's view, pharmacists who had received the letter would be very concerned by the misleading implication that his/her dispensing practices were potentially illegal and that legal consequences including an implication that a claim for financial damages might ensue. The Panel noted that not all recipients of the letter would have dispensed glycopyrronium bromide. The tone of the promotional letter could be seen as threatening and, in the Panel's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its ruling of a breach of Clause 2 which would mean that brief details of the case would be the subject of an advertisement. The Panel therefore decided on balance taking all the circumstances into account not to report Proveca to the Appeal Board for it to consider in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY PROVECA

Proveca submitted that the Panel misunderstood and mischaracterised what the letter in question was saying, to whom it was addressed and why; in doing so it had erroneously ruled that Proveca was in breach of Clauses 2, 8.2, 9.1 and 9.5.

Proveca submitted that firstly, the letter in question concerned the application and operation of the applicable legal framework concerning Specials as well as off-label products. It was informative in nature and aimed to enable the pharmacists and manufacturers of Specials to assess whether they were in compliance, and at no point did it discuss or challenge the clinical assessment or scientific opinion conducted by a health professional about the treatment of a patient. Secondly, the letter in question was addressed to dispensers and not prescribers. The clinical judgement of the recipient was never at stake, as the Panel opined; on the contrary, the letter clearly stated that prescribers could decide to prescribe a Special or off-label product to a particular patient if the health professional considered that there was a special need. Thirdly, the parallel drawn with Case AUTH/2971/8/17 was inappropriate, as the present case differed on a number of significant grounds, such as that (a) the MHRA was not the competent authority and its involvement was entirely mischaracterised in Case AUTH/2971/8/17,

as opposed to the present case in which the MHRA were consulted by Proveca about the general situation and (b) in Case AUTH/2971/8/17 the letter at issue misled the recipient about the licensed indication.

Proveca submitted that it had micro SME status, and was engaged in the development and licensing of medicinal products for the paediatric population with chronic and life-limiting conditions. Sialanar was the only oral glycopyrronium product licensed for children on the UK market and the only one licensed for severe chronic drooling. Sialanar was first launched in the UK in February 2017, and prior to its approval, the needs of the market were fulfilled by off-label and unlicensed glycopyrronium bromide products within the 'Special' legal framework. By December 2017, Sialanar's market penetration was very limited and accounted less than 5% of the paediatric market compared to unlicensed and off-label oral glycopyrronium bromide.

Proveca noted that it had become aware of a disproportionately high supply of off-label and unlicensed products compared to its own licensed product, due to its limited market share. This discrepancy could neither be justified nor explained on medical or clinical grounds for preferring unlicensed products in the vast majority of cases. This would only be the case where Sialanar was contraindicated as a result of its excipients or where a significantly different concentration leading to a much lower volume was required. Currently there was no evidence of a gap on the market in respect of glycopyrronium bromide for the licensed indication in children. Considering that there was no shortage of supply of Sialanar, it was obvious that at least some of the off-label and unlicensed product was dispensed outside of the strict conditions established by the legal framework applicable to the supply of Specials.

Upon becoming aware of the extent of the widespread supply of off-label and unlicensed glycopyrronium bromide products, Proveca submitted in the first instance it had sought to discuss this with the MHRA on a general basis. The MHRA agreed with Proveca approaching the potentially infringing parties to explain the rules around off-label and unlicensed supply and to inform them that there was now a licensed glycopyrronium bromide product available to treat severe sialorrhoea in the paediatric population. Proveca was told by the MHRA that if the approach was unsuccessful, it should contact the MHRA again and it would assess whether it should take action.

The issue that Proveca wanted to raise was in the event where the prescription did not specify the product from and/or strength, in which case it was up to the pharmacist to determine what to dispense in order to fulfil the prescription. The legal framework imposed on the pharmacist the obligation to dispense the licensed product, unless there were evidenced medical grounds to dispense a Special or off-label product. With variability in the preparation of unlicensed products and the specific warning in the off-label products that they should not be used in children, there were potential serious public health concerns. Such concerns were what had led to the established legal framework. This was precisely what Proveca wanted to ensure was brought to the pharmacists' and specials manufacturers' attention.

Therefore, Proveca wrote to pharmacists and manufacturers alike to inform them that a licensed product was now available and reminding them about the legal framework applicable to Specials, in a balanced and proportionate manner.

Proveca now addressed the breaches in turn.

Clause 8.2

Proveca noted that the Panel had ruled that the letter in question was disparaging of the health profession and clinical and scientific opinions of health professionals because it '… highlighted that any pharmacy continuing to dispense unlicensed and off-label preparations for children was in **breach** of the pharmaceutical legal framework' and '**implied** that supplying a special in preference to the use of Sialanar was illegal.'

The Panel further stated '… the letter in question **queried the health professional's decision to prescribe a special** and the pharmacist's action of dispensing against a prescription, **without any knowledge of the clinical circumstances**, stating that such a decision was inconsistent with MHRA Guidelines and law and **implying** that serious consequences could ensue.' (emphasis added by Proveca).

Proveca submitted that these two extracts clearly showed that the Panel misunderstood and misinterpreted the letter. Indeed, not only had Proveca not challenged the clinical or scientific opinion of a health professional, but on the contrary made it very clear that it was for the health professional to make the clinical decision to provide a Special or an off-label product to a patient and this decision must fulfil the legal conditions under which a Special could be provided. The applicable framework was formed of the laws, the guidance issued by the MHRA and jurisdiction of the European Court of Justice, allowing Specials where (i) 'there was a patient 'special need', namely where there was no other available licensed medicinal product; or (ii) 'when there is no authorised equivalent on the national market or which is unavailable on that market' or (iii) 'where there are strong therapeutic arguments in favour of [not supplying the licensed medicinal product and preferring other products not licensed for the specific indication].

Proveca submitted that the letter ensured that pharmacists and Special manufacturers were aware of the legal framework under which they must operate and could assess their compliance under legal, rather than scientific or clinical principles. Therefore, it was incorrect to claim that Proveca had at any point challenged the health professional's opinion or disparaged the health profession.

In addition, Proveca submitted that it had explicitly explained in its letter that an unlicensed product might be supplied '…if there was a *bona fide* unsolicited request from a health professional', ie prescriber, for an individual patient for the indication of excessive sialorrhoea. This was clearly stated without ambiguity in the letter. So, it was incorrect of the Panel, and highly inaccurate, to ignore the clear wording of the letter in its full context and instead to erroneously conclude that Proveca claimed that '…any pharmacy continuing to dispense unlicensed and off-label preparations for children was in breach of the pharmaceutical legal framework'. (emphasis added by Proveca).

Proveca submitted that its argument had always been that in the absence of an identified patient need by a health professional then the applicable legislation, the MHRA guidance and jurisprudence made clear that the dispensing of unlicensed products was not permissible. Proveca had accepted from the onset that a health professional's prescription for a Special or off-label product because of a special need was to be respected as a valid ground for such supply. In further correspondence with the Panel in Case AUTH/3060/8/18, Proveca set out a detailed set of examples and reasons for when it might be suitable for an unlicensed product to be provided. Proveca never questioned a health professional's ability or authority to prescribe a special or off-label product, but merely drew the addressed pharmacists attention to the fact that there must be such a prescription evidencing the patient's special need, as required by the law. Therefore, Proveca was concerned that the Panel's ruling was reached on the wrong grounds, considering that the facts relied on by the Panel were mischaracterised, as illustrated in the above-referenced excerpts from the Panel's letter.

Proveca submitted that all the statements that it had made about the appropriateness of Sialanar for paediatric patients with excessive sialorrhoea were accurate, balanced fair and capable of substantiation. Proveca provided all the relevant references so that the pharmacists and Specials manufacturers would be able to confirm the validity of the information and determine whether their supply practice of Specials was compliant with the applicable legal framework.

Proveca submitted that moreover, the analogy with Case AUTH/2971/8/17 drawn by the Panel was not applicable in the present case. Proveca did not write to either clinicians or prescribers but rather to dispensers who must act upon a prescription. The two should not be confused; there was a difference between a clinician writing a prescription and a pharmacist making a dispensing decision. Therefore, it could not be stated that Proveca disparaged the view or clinical decision of health professional's when simply drawing the dispenser's attention to the need for prescriptions evidencing a special need in order to depart from the licensed product. Furthermore, the Panel noted the additional six complaints received by Proveca and concluded that, implying illegality, putting the recipients on notice and requesting that the recipients would confirm that they would cease this practice, questioned the reader's professional judgement. Again, Proveca submitted that there was no reference to the professional judgement of the addressees of the letter, which aimed to seek confirmation from the addressee that this information had been read and understood and that any supply of off-label or unlicensed glycopyrronium bromide was in accordance with the law.

Proveca submitted that the benefit of this correspondence rather than resolving to take immediate legal action was illustrated by the positive responses that Proveca received from some recipients of the letters, thanking Proveca for bringing this information to its attention (provided). These confirmed that Proveca, rather than assuming wrongdoing or misjudgement by the recipient, instead helped the recipient to ensure that their dispensing activities were in accordance with the law.

Further, Proveca submitted that in this context, it was also important to note that the content of the letter was in line with the views publicly expressed by the ABPI and of the European Federation of Pharmaceutical Industries and Associations (EFPIA) on the matters of prescription of products without a license in respect of the intended indication.

Proveca submitted that the ABPI's position regarding the use of unlicensed medicines was set out in a press release that it issued in May 2012. The press release stated that the '… health and safety of UK patients should always be paramount, and all other considerations, including cost, must be secondary'. In the statement, the ABPI reiterated that use of unlicensed medicines put patients at risk and should be strictly limited to those occasions where there was no licensed alternatives. Proveca's position as expressed in the letter supported and reiterated this point.

In addition, in March 2017 EFPIA made some statements on off-label supply, which applied equally and directly to the supply of unlicensed products beyond the special needs' exemption. Commenting on the European Commission's study report on off-label use, EFPIA stated that:

> 'Indeed, pharmaceutical companies may be less ready to invest in costly and lengthy clinical development and authorisation processes for a given indication if public authorities promote the use of cheaper off-label medicines that have not been subject to the same stringent safety and efficacy assessments as existing on-label medicines, for financial reasons.'

Proveca submitted that these public positions indicated that the industry and trade association bodies considered that supply of a medicine for an indication for which it was not licensed, contained many risks, ranging from public health to reduction in investment and compromise of the regulatory system, resulting in uncertainties and the undermining of the pharmaceutical industry. These considerations were present in and directly applicable to the situation that Proveca had been

facing and in line with the approach Proveca had taken to engage with the potential involuntary infringer by restating the law applicable to off-label and unlicensed medicines and informing them of the fact that there was now a licensed product available to treat those medical conditions in the paediatric population.

Proveca submitted that in the same way that the ABPI's and EFPIA's statement did not disparage the medical profession but rather sought to protect it, Proveca's letter had been aimed at ensuring the safe and lawful operation of supply of medicines. It was not fair for a company to be criticised in trying to ensure that the law was rightly implemented, especially when seeking to discourage the potentially unjustified use of a medicine that had not been subject to the regulatory approval and use for an indication. This undermined the regulatory legal system applicable to medicinal products. Indeed, the use of Specials was a *de facto* circumvention of the pharmaceutical system, only allowed in exceptional circumstances when there was an evidenced patient need identified by a health professional. In the absence of such an identified patient need, the law had established that only authorised medicinal products should be used.

Clause 9.5

Proveca submitted that the Panel noted that the letter, by mentioning the MHRA, implied that it had approved or endorsed the content of the letter, while in fact there was no written follow up with the MHRA and the conversation was nothing beyond a single, general, short, non-product specific telephone conversation.

Firstly, Proveca submitted that the Panel had placed significant weight on its view that the letter was promotional. Proveca did not accept this characterisation, as the letter was factual and informative in nature as could be seen from all the parts of the letter with an objective characterisation of the applicable regulatory legal framework. The Code permitted dissemination of informational or educational materials, under Clause 9.7. The letter was informational and educational which was obviously 'inexpensive, directly relevant to the practice of medicine or pharmacy and directly beneficial to the care of patients'. The letter set out the legal framework and explained the difference between the licensed and off label or unlicensed products. As such, it was permissible material under the Code. The informative tone of letter could be corroborated by correspondence that Proveca received from dispensers thanking Proveca for this informative content.

Proveca submitted that the letter aimed to educate the recipients about the legal framework applicable to off-label and unlicensed medicines, with verbatim citations of the guidance by the MHRA, including the quotation that licensed products should be preferred over unlicensed products even when provided off-label. The MHRA was in copy as this exchange of correspondence was the first step undertaken by Proveca to try to resolve this apparent potential breach of the law. The second step was to get back to the MHRA for them to take action. It was therefore essential to copy the MHRA to the letter so that it could see the content and enforce the correct application of the law and the circumvention of the protection afforded to Proveca's product. The third option was to bring a case before the court in order to enforce the protection afforded to the product under the terms of its marketing authorisation and PUMA designation. Therefore, copying the MHRA was for consistency with Proveca's communications and for Proveca to reserve its right to seek damages against offenders at court, being able to transparently show all the relevant steps it took before legal action.

Secondly, Proveca wished to distinguish the present set of circumstances from the ruling in Case AUTH/2971/8/17. In Case AUTH/2971/8/17, the letter at issue implied that the MHRA had endorsed this approach and would take action against recipients and the Panel had taken a similar interpretation on Proveca's letter. However, in Case AUTH/2971/8/17 the letter misleadingly implied that the MHRA would take action against the recipient of the letter, a food supplement distributor which in fact was outside the remit of the MHRA. On the contrary, human medicinal products such as in the present case fell within the remit of the MHRA's jurisdiction. Proveca only sent the letters after contacting the MHRA about the situation and never implied that the MHRA reviewed, approved or endorsed the letters, which besides was something that the MHRA explicitly never did so this would not be possible in any event. Rather, the letter was a courtesy note before Proveca could report this practice and related pharmacies to the MHRA and offer them the opportunity to revisit any potential illegitimate dispensing practices. The MHRA had been consulted about the intended use of 'cease and desist letters' and agreed with the appropriateness of such an approach.

Clause 9.1

Proveca submitted that it disagreed with the Panel's ruling, which was regrettable given the professional way in which Proveca attempted to address a potential serious breach of the law by courteously informing the recipients of the letter of the legal framework applicable to off-label and unlicensed medicines and the existence of a licensed product instead of engaging in contentious practices.

Proveca submitted that the letter was targeted specifically at pharmacists and dispensers of medicinal products, who were presumed to have a certain level of knowledge and expertise in the rules of what products to dispense. The letters were never aimed at or provided to the general public. Therefore, anyone receiving the letter would understand the basis of Proveca's information, rather than, as the Panel held, have felt 'threatened', which might be arguable for a member of the general public with no understanding of the applicable rule and its obligations. The content and tone of the letter was informative, with references to EU and UK legislation, jurisprudence and guidance in order to convey an accurate and complete picture of the applicable framework.

Proveca submitted that the letter addressed professional, sophisticated readers and addressed them in an appropriate tone, without any attempt of concealed promotion or with a 'threatening' manner. It was important to explain the consequences of non-compliance with the law. A company striving to uphold the law, as established by the authorities and the courts, was one which aimed to maintain the high standards of the industry and did not accept their compromise resulting from the uncontrolled supply of unlicensed product, which was the case when there was no specific request for a Special or off-label product by a health professional who had identified a patient need. This was also supported by ABPI and EFPIA, the pharmaceutical industry bodies. Under all circumstances Proveca's conduct was in accordance with the industry's expected high standards, in order to ensure that these very standards were observed by all parties.

Clause 2

Proveca noted that the Panel was '… very concerned about the content and tone of the letter …', which, in the Panel's view, was threatening. The Panel noted that the misleading implication that patients could be switched without any consideration of their clinical circumstances might potentially prejudice patient safety. The Panel was particularly concerned that a health professional '… who had received the letter would be very concerned by the misleading implication that his/her **prescribing decision** was potentially illegal. The tone of the promotional letter could be seen as threatening and, in the Panel's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry'.

Proveca disputed the Panel's rulings and submitted that the factual basis was incorrect. The letter was not directed or addressed to prescribers but to pharmacists and manufactures of Specials. As already explained the letter neither stated that dispensing Specials was *per se* an illegitimate practice nor did it seek to threaten the recipient. Instead, and as explained above in further detail, Proveca stated the law and in particular the conditions under which a Special might be dispensed and explained to the Panel when a patient need might arise.

Proveca submitted that the letter was informational in tone and regretted the fact that it had been perceived by a few recipients as 'threatening'. On the contrary, most of the correspondence that Proveca received following its letter was positive or neutral, with many recipients thanking Proveca for bringing this information to their attention. The overwhelmingly higher number of such positive/ neutral responses 67, compared to the six negative responses and the two complaints, indicated that the communication was perceived by the majority as intended, namely as informational in nature. The attempt by a commercial entity to seek to settle a disagreement by way of correspondence, especially when the disagreement concerned potentially illegal action before resorting to other means, was an honourable practice and not one which could be seen as bringing discredit upon the pharmaceutical industry.

Moreover, Proveca submitted that a recipient who only supplied and/or dispensed unlicensed glycopyrronium bromide when supported by a health professional's unsolicited request for a Special or off-label product in respect of a specific patient need would have no reason to feel threatened upon reading the letter. The letter explicitly stated that a prescription specifically written for an off-label or unlicensed product (where there was a legitimate patient special need) was recognised as a valid reason for providing an off-label or unlicensed medicine instead of the licensed product (e.g. Sialanar). Proveca did not see how a letter setting out the applicable legal framework in a factual and objective manner brought discredit upon and reduced confidence in the industry, especially having regard to the correspondence received by Proveca expressing gratitude for this crucial information. Once a pharmacist was fully informed of the applicable legal framework, he/she could decide whether his/her practice was in line with the applicable rules. It seemed that engaging in a dialogue with potential infringers was the appropriate approach which, to restate, was only undertaken after speaking with the MHRA.

Proveca did not agree with the Panel's rulings that the '… misleading implication that patients could be switched without any consideration of their clinical circumstances might potentially prejudice patient safety'. Firstly, this was a mischaracterisation of Proveca's position by the Panel. Proveca never argued in favour of switching, but only provided information in the event that a pharmacist did not prescribe a licensed product in response to a generic prescription not specifying concentration, formulation or a special need. In the event of uncertainty, the pharmacist was under an obligation to communicate with the prescriber to identify his/her concern and clarify the subject matter of the prescription. This was vastly different from 'switching'.

Proveca submitted that its product was the only approved product for this indication, with a *per se* established safety profile and the only one which might be lawfully dispensed, unless the prescriber requested otherwise, and this would only arise, in very limited cases, on grounds of patient needs. The concern that Sialanar was less safe than unlicensed preparations was never raised by any complainant and did not make sense considering the licensed nature of Sialanar for the age group and indication. In fact, as evidenced in Case AUTH/3060/8/18, one of the complainant's primary concerns was that '… making the switch would pose **an additional cost burden** on the NHS', without any reference to the switch impacting on patient safety. So, the primary and unique concern expressed by the complainant altered to be financial rather than a safety issue. In fact, refusing to provide the licensed product on costs grounds was both an irrelevant consideration to the present matter and had been explicitly held by the European Court in Commission v Poland and by the MHRA in its Guidance Note 14 and by the ABPI itself (as set out above) not to be a valid reason for providing Specials. Once there was a prescription for glycopyrronium bromide, the NHS would pay the standard price cited in the formulary;

the precise profit margin for a dispenser would then depend on the price of the product actually supplied. This should not influence what product was supplied, especially if tilting the position in favour of unlicensed products, in the absence of a clinical need. This confirmed the exact concern that was raised in Proveca's letter in order to inform any recipients who might not be aware of this legal consideration. On the contrary, Proveca stated in its letter that providing Specials instead of Sialanar was acceptable on clinical grounds only; therefore, the Panel's statement that Proveca argued in favour of 'switching without any consideration of the [patients'] clinical circumstances' was simply incorrect.

Proveca did not see how bringing all this information to the recipients' attention brought discredit to the profession, when in fact it had the effect of enabling them to understand the legal limitations and ensure that the supply of medicinal product was conducted in accordance with the applicable legislation. The reference to the decision in Case AUTH/2971/8/17 was inappropriate as in that case the letter misled the recipient about the licensed indications, whereas in the current case Proveca referred specifically to the target indication (excessive sialorrhoea) and patient population (paediatric population) covered by Sialanar's licence. No particular special need for providing unlicensed glycopyrronium bromide on such a wide scale had been evidenced in the case of Proveca.

Overarching reasons to uphold the appeal against the Panel's decision

Proveca submitted that in addition to all the above it was also concerned that the Panel's ruling, had a potential detrimental effect on the patient's safety and clearly undermined the appropriate application of the pharmaceutical legal framework.

Proveca submitted that the Panel did not refer anywhere to the fact that the guidance cited by Proveca was all factually accurate. The letter did not promote Sialanar and all the information was an accurate and objective characterisation of the legal framework. In addition, it was obvious that despite and after Proveca's letter setting out the law, the complainant still thought that it should be entitled to disregard the law for financial considerations (eg, cost burden on the NHS). The direct result of penalising a company for bringing potential breaches of the law to the attention of the other party, was a blatant misapplication of the existing legal framework, which was established to protect public health and safeguard the proprietary rights of the pharmaceutical industry. Within this context, the Panel had not given due consideration to the surrounding circumstances, which had resulted in an unjust ruling, both for Proveca and for the pharmaceutical industry which was rendered incapable of taking action to safeguard its rights in a non-invasive, non-contentious manner.
The detailed provisions in the Code aimed to ensure that pharmaceutical companies operated in a responsible, ethical and professional manner and the promotion of medicines to health professionals and other relevant decision makers was carried out within a robust framework to support high quality patient care. In addition, Clause 1.1 of the Constitution and Procedure stated that the Panel was also responsible for arranging for conciliation between companies when requested to do so.

Proveca stated that in its letter, abided by these principles, aimed peacefully to resolve its disagreement of a practice in order to ensure that off-label and unlicensed products were not provided without a justification, thus possibly compromising the high patient care standards afforded by the marketing authorisation procedure. Observance of the established rules in fact increased confidence in the pharmaceutical industry that the law would be observed and that members of the industry would be monitoring compliance and identifying any possible deviations from the rules.

Proveca submitted that the Panel's ruling as it stood was perverse and provided no recourse outside of litigation or referral to the regulatory authorities to a company which had invested in research and development in getting its medicine approved, especially when it was the only such product on the market and approved for the paediatric population. This decision left no recourse to members of the pharmaceutical industry wishing to safeguard their proprietary rights. Letters, informative in tone, sent to the impacted parties, as discussed with the MHRA before formally reporting suspected wrongdoing to the MHRA, for further action where appropriate, were the most straightforward way for a company to ensure that the applicable rules were observed without involving an enforcement authority. The Panel's ruling effectively deprived pharmaceutical companies of ways to ensure that the legal rules in place to protect their investment in R&D were observed. Moreover, this ruling appeared to support pharmacists and Specials manufacturers which would be infringing the legal framework with impunity.

For the reasons expressed above, Proveca vigorously refuted the Panel's ruling that the content of the letter was in breach of Clauses 2, 8.2, 9.1 and 9.5 of the Code nor did Proveca agree that the message had any other effect beyond informing the recipient of a potentially illegitimate practice.

RESPONSE FROM THE COMPLAINANT

The complainants alleged that the tone and sentiment of this issue of supply of an unlicensed and off-label medicine as expressed in the appeal was more in keeping with how they would have wished it to be communicated, as opposed to the way it was actually written in the letter at issue.

Though the complainants did not have the data they alleged that it was not pharmacists and their prerogative that resulted in an unlicensed medicine being chosen, rather the dispenser was responding to a prescription for a liquid formulation that was of a different strength or formulation to Sialanar. Hence if there was little change in Sialanar prescribing since the March 2018, then Proveca should have

concentrated on communicating with prescribers rather than being aggressive with dispensers.

Though Proveca stated the letter was sent to pharmacies, the complainants alleged that they knew that it was also sent to dispensing doctors and so would have been seen by prescribers and not just dispensing pharmacists or dispensers.

The complainants repeated the initial complaint regarding the relevant clauses in that the letter did read 'Therefore, the provision of unlicensed glycopyrronium bromide preparations for children with chronic drooling when Sialanar is the only available, authorised medicinal product in the UK for that paediatric population is in breach of the law.' and 'We respectfully request that you cease these activities immediately …'.

The complainants disagreed with the appeal that the letter was professionally written and courteous when it also stated '… please consider this letter as officially putting you on notice for illegitimate dispensing practices…' the complainants alleged this was threatening especially as the remainder of that sentence referred to '… significant commercial and financial damage to Proveca'.

The complainant alleged that the appeal was not warranted.

APPEAL BOARD RULING

The Appeal Board noted that prior to the launch of Sialanar in the UK in February 2017, paediatric patients with chronic pathological drooling due to chronic neurological disorders were treated with off-label glycopyrronium bromide products or specials. The Appeal Board noted Proveca's submission that by December 2017, Sialanar's market share of the glycopyrronium bromide paediatric market was only 5% and the company considered that this was due to pharmacists continuing to dispense off label glycopyrronium bromide or specials. The Appeal Board noted that pharmacists would be dispensing prescriptions written by GPs, hospital doctors etc. What was dispensed would depend on what was written on the prescription. It noted the company's position that most of the prescribing was written for the generic medicine and unless features were specified that were not met by Sialanar, such as a different strength or formulation, then Sialanar should be dispensed.

The Appeal Board noted Proveca's submission about its telephone conversation with the MHRA in September 2017. According to Proveca, the MHRA confirmed that although it did not get involved in cease and desist letters, it knew that companies had sent them, reference was made to the MHRA guidance note 14 and it was agreed that a cease and desist letter would be the first step. Consequently, Proveca sent a letter to pharmacists in March 2018 which set out the legal framework for prescribing in relation to Sialanar and unlicensed and off-label glycopyrronium bromide products. Proveca submitted that this letter had had no effect and so the company sent a second letter, the letter at issue, on 10 August. The MHRA was sent one copy of the letter at issue on 17 August. The Appeal Board noted that the content and tone of the second letter was markedly different to the letter sent in March.

The Appeal Board noted that the letter at issue was sent to 16,154 UK pharmacies, primarily consisting of community pharmacists and hospital outpatients pharmacists. The Appeal Board noted from the Proveca representatives at the appeal that the letters were sent in envelopes which were personally addressed to named individuals whose details were obtained from a database. Each letter started 'Dear Sir/Madam' and included 'Copy sent to the Medicines Healthcare products Regulatory Authority'. In the Appeal Board's view as the letters were sent to named individuals, recipients would probably assume that their individual letter had been specifically highlighted to the MHRA. There was no indication to the recipient that the letter at issue had been sent to over 16,000 pharmacies.

The Appeal Board noted that recipients were asked to confirm via email to Proveca that they had ceased such activities.

The Appeal Board noted the content of the letter including the references to breaching the pharmaceutical legal framework and breaches of the law. In the Appeal Board's view, there was also an implication that a claim for damages might ensue.

The Appeal Board was concerned about the tone of the letter in question and, in that regard, it noted that the complainant and five of the six negative responses from recipients to the letter in question, provided by Proveca, stated that they found it to be threatening.

The Appeal Board noted that there was a difference between writing to all pharmacies as opposed to those whose dispensing was the subject of Proveca's concern. The Appeal Board noted the company's submission that it had chosen to send the letter to all pharmacies as it did not consider that it was possible for the company to identify which were dispensing glycopyrronium bromide off-licence or as specials. The Appeal Board questioned if this was an acceptable approach. This was compounded by the fact that the treatment of chronic pathological drooling in paediatric patients with chronic neurological disorders was likely to be a niche area and the majority of pharmacists on the mailing list would not be dispensing glycopyrronium bromide products for paediatric use.

The Appeal Board noted that it was not necessarily unacceptable to draw the attention of pharmacists to the legal framework, however, such material had to comply with the Code. The Appeal Board queried the company's submission at the appeal that the letter in question was an essential step if it wished to pursue court action. In the Appeal Board's view, a *bona fide* letter before action would be sent solely to those individuals whose dispensing was the subject of concern and would certainly not bear prescribing information. The Appeal Board, therefore, did not accept Proveca's submission that upholding

the Panel's decisions would have dangerous consequences and prevent companies from enforcing the law and protecting their rights. The Appeal Board understood the company's position. It was the content and tone of the letter that was the issue for consideration not the principle that a letter had been written to address the commercial situation.

The Appeal Board considered that the letter in question which bore prescribing information was clearly promotional and it queried how Proveca could consider it to be anything else.

The Appeal Board noted the complainant's concern that pharmacies and dispensaries in surgeries were being disparaged for dispensing what was prescribed by other health professionals such as GPs hospital doctors etc. The Appeal Board noted that whilst the letter in question did deal with some of the exceptions, overall the letter implied that supplying off label glycopyrronium bromide or a special rather than Sialanar would always be in breach of UK law which was not so. The Appeal Board noted, as acknowledged by Proveca, that the supply of an unlicensed medicine was legally permissible in certain circumstances where there was a patient with a 'special need'.

The Appeal Board considered that the letter in question implied that pharmacists did not know the legal requirements regarding the dispensing of specials. The Appeal Board further noted the negative responses received from at least six recipients of the letter at issue. It appeared that the recipients considered that the content of the letter at issue was such that it questioned the reader's professional judgement. In the Appeal Board's view, the content and tone of the letter was such that it disparaged the professional opinion of health professionals and it upheld the Panel's ruling of a breach of Clause 8.2. The appeal on this point was unsuccessful.

The Appeal Board noted that Clause 9.5 stated that promotional material must not include any reference to, *inter alia*, the Medicines and Healthcare products Regulatory Agency, unless this was specifically required by the licensing authority. The exception in the relevant supplementary information in relation to factual safety information and the MHRA Drug Safety Update did not apply to the letter at issue. The Appeal Board noted that the letter in question referred to the MHRA's Guidance Note 14 on the supply of unlicensed medicinal products (specials) and the hierarchy for the use of unlicensed medicines, an appendix to this guidance note. The letter in question stated that Proveca had brought the dispensing practices at issue to the attention of the MHRA which was copied into the letter, albeit 7 days after it had been sent. In the Appeal Board's view, the implication was that the MHRA approved or otherwise endorsed the content of the letter. The Appeal Board did not consider that Proveca's account of the conversation between it and the MHRA in September 2017 meant that the wording in the letter in question was specifically required by the MHRA as stated in Clause 9.5 and thus it upheld the Panel's ruling of a breach of that Clause. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings above and considered that Proveca had failed to maintain high standards and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board considered that pharmacists who had received the letter would be very concerned by the misleading implication that his/her dispensing practices were potentially illegal and that legal consequences including an implication that a claim for financial damages might ensue. The Appeal Board noted that the majority of the recipients of the letter would not have dispensed glycopyrronium bromide. The tone of the promotional letter could be seen as threatening and, in the Appeal Board's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Case AUTH/3060/8/18

COMPLAINT

The complainant stated that he/she had received a letter from Proveca asking that the dispensing of an unlicensed product should cease when there was a licensed alternative available. The prescription originated from a secondary care consultant and was a historic one. The complainant stated that the crux of his/her complaint was that the tone of the letter was quite threatening; it had been copied to the MHRA and alleged that illegitimate dispensing practices were being followed.

The complainant had had a discussion with colleagues at a local surgery about the issues surrounding the letter to remedy any issues following clinical review from a local GP. The complainant alleged that the letter was unnecessarily threatening towards the pharmacy and making the switch would pose an additional cost burden on the NHS. An additional concern was that the original prescriptions were initiated in secondary care so there might be clinical reasons for prescribing the original unlicensed special. The complainant had sought clarification from a local primary care clinician who would hopefully feedback at the appropriate time.

When writing to Proveca, the Authority asked it to consider the requirements of Clauses 9.1 and 2.

RESPONSE

Proveca submitted that it was a small independent pharmaceutical company which specialised in the development and licensing of off-patent medicines through the paediatric – use marketing authorization (PUMA) regulatory route. The law and guidelines from the MHRA were very clear as to when an off-licensed medicine could be dispensed to patients. It was not the prerogative of the pharmacists to choose an unlicensed medicine where a licensed alternative

existed. It was the prerogative of the health practitioner in accordance with the law. Proveca stated that it had noted this in an earlier letter of March 2018 which resulted in very little change in practice. Rather than considering legal action, the company thus sent the letter in question to reiterate the position as a courtesy to the pharmacists.

Proveca noted that the complainant considered the letter in question to be threatening in tone. Proveca submitted that the letter at issue was intended to inform all pharmacists of the licensed status of Sialanar and the legal requirement for the dispensing and supply of unlicensed products. Proveca stated that the MHRA agreed with its proposal to write to pharmacists to remind them of their legal obligations with a 'cease and desist' letter. If this was not successful, the MHRA suggested that the company get back in touch to see how the Agency might be further involved. Despite the March 2018 letter informing pharmacists that there was now a licensed product available, significant off-label and unlicensed dispensing of glycopyrronium bromide continued to be widespread for children with chronic drooling. Proveca took legal advice to ensure its communications were aligned with UK law and sent the letter at issue to remind pharmacists of their obligations around supply of unlicensed medicines.

Proveca explained that it was only by a narrowly drawn exemption expressed in Article 5(1) of Directive 2001/83/EC, implemented in the UK Regulation 167 of the Human Medicines Regulations 2012 (SI/2012/1916), that the supply of an unlicensed drug was legally permissible. This was where a patient had a 'special need' ie where there was no other available licensed medicine and a company received a *bona fide* unsolicited request from a prescriber for a specific individual patient.

Proveca noted that where there was a prescription for an unlicensed product it had not suggested that it was not dispensed; if there was a *bona fide* reason for the prescription this was the prescriber's prerogative.

Proveca submitted that several pharmacists had emailed the company following receipt of the letter. In total 65 emails had been received; 59 confirmed receipt of the letter, advising the company of actions taken and/or thanking it for the information; 6 expressed some level of concern at the letter but acknowledged its content. Proveca had met with or called everyone who contacted it. The overwhelming response to the calls was that, now they were aware of their obligations, the pharmacist was keen to comply with the law and move away from dispensing specials in situations where their use was not warranted, justified or prescribed by a health professional. Some pharmacists stated that the communication had been helpful in allowing them to ensure good governance.
Proveca denied a breach of Clause 2.

With regard to high standards, Proveca submitted that the letter at issue was professionally written and courteous. It provided, in a clear and comprehensive manner, the legal position which it appreciated pharmacists might not be familiar with. The company denied a breach of Clause 9.1.

FURTHER INFORMATION FROM PROVECA

In response to a request for further information Proveca provided details of a telephone call with the MHRA in September 2017, which consisted of a short discussion around the extent of the MHRA's involvement in cease and desist letters sent by companies. The MHRA explained that whilst the MHRA was not involved in the issue or drafting of cease and desist letters (and therefore had no templates or examples to share), it was aware of this practice by companies sending such letters referring to MHRA Guidance Note 14. Proveca suggested drafting a letter along these lines and the MHRA agreed. Proveca considered reference to the relevant guidance crucial for informing the recipients of the applicable rules and their obligations by reference to national guidance, instead of risking being perceived as suggesting its own rules and interpretation of the applicable framework. Proveca considered this an objective and factual reference to the applicable national rules and in line with the informative tone that it sought to adopt.

According to Proveca, the MHRA suggested that once Proveca had taken a number of steps, including a cease and desist letter, to remedy the situation it considered wrong, it could then contact the MHRA explaining the position and the steps that Proveca had taken, so that the MHRA could then take a view on whether there was scope for the Agency's involvement.

Proveca submitted that it was clear that it could not have consulted the MHRA more specifically about the letter, seeking any pre-approval, and Proveca did not consider it appropriate to take up the Agency's time considering that they did not issue such letters. Proveca submitted, however, that it did promptly send copies of the finalised letter to the MHRA. No comments or correspondence were received from the MHRA in response to the letter.

The MHRA responded to a pharmacist who complained about the letter that it was not an enforcement matter and it would be handled by either the regulatory affairs or customer services teams, if appropriate.

Whilst the MHRA suggested that Proveca contact the Agency if its approach was unsuccessful, Proveca wished to exhaust all possible avenues of informing the concerned parties of the illegitimacy of the specials dispensing practice without justification, before involving the Agency. Given the recency of the letters sent by Proveca, Proveca wanted to wait for an appropriate time to elapse in order to assess the success of its effort to inform pharmacists.

Proveca provided anonymised copies of the 6 emails setting out concerns following receipt of the letter at issue. Proveca also provided a copy of the letter that it sent to pharmacists in March 2018 informing them of the existence of a licensed product. No responses to this letter were provided.

Proveca considered that it might be suitable to prescribe an unlicensed product instead of Sialanar when:

- the concentration of Sialanar was too low and a much lower volume of product would be required (provided by a higher concentration of special eg 5mg/5ml). This would be unusual but there could be the rare occasion.

- The child had an allergy to one of the excipients of Sialanar, where a special might exclude the excipient. Again, this would be highly unlikely since Sialanar contained very few ingredients. The lack of such ingredient would need to be assured in the special formulation.

PANEL RULING

The Panel noted that the letter urged pharmacies to refrain from dispensing glycopyrronium bromide 'specials', and off-license preparations for children with chronic drooling and ensure that Sialanar was dispensed. The letter in question stated Sialanar's licensed indication in the second paragraph on the first page, namely that it was the only product licensed in the UK for the symptomatic treatment of severe drooling in the paediatric population (children aged 3 - 17 years).

The Panel noted that the letter in question was promotional and bore prescribing information. The Panel noted that it was not necessarily unacceptable to draw the attention of prescribers to the prescribing legal framework, however such material had to comply with the Code. In the Panel's view there was a difference between writing to all pharmacists as opposed to those whose dispensing was the subject of Proveca's concern. The Panel noted the company's submission that it was not possible for the company to know which pharmacists were dispensing glycopyrronium bromide.

The Panel noted the complainant's submission that the original prescriptions were initiated in secondary care so there might be clinical reasons for prescribing the original unlicensed special.

The Panel noted that Clause 8.2 stated that health professions and the clinical and scientific opinions of health professionals must not be disparaged. Paragraph 2.2 of the MHRA guidance on 'The supply of unlicensed medicinal products ("specials")' allowed a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or other prescriber to decide whether an unlicensed medicine should be supplied in preference to a licensed medicine where the licensed product could not meet an individual patient's special needs. The Panel noted that the letter highlighted that any pharmacy continuing to dispense unlicensed and off-label preparations for children was in breach of the pharmaceutical legal framework. The Panel noted Proveca's response that if there was a *bona fide* reason for the prescription of an unlicensed product then it was the prerogative of the prescriber and Proveca was not suggesting that it was not dispensed.

The Panel noted Proveca's submission that it might be suitable to prescribe an unlicensed product instead of Sialanar when the concentration of Sialanar (2mg/5ml) was too low and a much lower volume of product would be required (provided by a higher concentration of special eg 5mg/5ml). However, the Panel considered that the letter in question misleadingly implied that the activity was illegal by stating that if a pharmacy was supplying unlicensed or off-label preparations of glycopyrronium bromide for the indication of chronic drooling in paediatric patients then it should consider the letter as officially putting it on notice for illegitimate dispensing practices which might be a contravention of legally established rights and have caused Proveca significant commercial and financial damage. The Panel noted, as acknowledged by Proveca, that the supply of an unlicensed medicine was legally permissible in certain circumstances where there was a patient with a 'special need'. The Panel considered that the letter in question queried the health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances, stating that such a decision was inconsistent with MHRA Guidance and law and implying that serious consequences could ensue. The Panel noted that the letter in question stated that Proveca had brought the dispensing practice at issue to the attention of the MHRA which was copied into the letter. In the Panel's view the implication was that the MHRA approved of or otherwise endorsed the content of the letter which was not so. The Panel further noted the negative responses received from at least six recipients of the letter at issue. It appeared that the recipients considered that the content of the letter was such that it was threatening and questioned the reader's professional judgement. In the Panel's view Proveca had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel considered that the letter in question queried a health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription, without any knowledge of the clinical circumstances which in the Panel's view might potentially put patient safety at risk. The letter stated that such a decision was inconsistent with MHRA Guidance and law and implied that serious consequences could ensue if the letter was not adhered to. The Panel was very concerned about the content and tone of the letter and noted its comments and rulings above. In the Panel's view, pharmacists who had received the letter would be very concerned by the misleading implication that his/her dispensing practices were potentially illegal and that legal consequences including an implication that a claim for financial damages might ensue. The Panel noted that not all recipients of the letter would have dispensed glycopyrronium bromide. The tone of the promotional letter could be seen as threatening and, in the Panel's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its ruling of a breach of Clause 2 which would mean that brief details of the case would be the subject of an advertisement. The

Panel therefore decided on balance taking all the circumstances into account not to report Proveca to the Appeal Board for it to consider in accordance with Paragraph 8.2 of the Constitution and Procedure.

During its consideration of these cases, the Panel noted that the promotional letter at issue stated that not only is it not allowed to dispense an unlicensed medicine where there is a licensed alternative, but a licensed product should be the preferred option for other indications outside of its marketing authorization given it had already been assessed for safety and efficacy. The Panel queried whether this was in line with Clause 3.2 and asked that Proveca be advised of its concerns.

APPEAL BY PROVECA

Proveca submitted that the Panel had misunderstood and mischaracterised what the letter in question was saying, to whom it was addressed and why; in doing so it has erroneously concluded that Proveca was in breach of Clause 2 and 9.1.

Proveca submitted that firstly, the letter in question concerned the application and operation of the applicable legal framework concerning Specials and off-label products. It was informative in nature and aimed to enable the pharmacists and manufacturers of Specials to assess whether they were in compliance when dispensing a product without an identified special need in the prescription. At no point did the letter either 'queried a health professional's decision to prescribe a special and the pharmacist's action of dispensing against a prescription …' or that any supply of off-label or unlicensed products was illegal as the Panel mistakenly stated. Secondly, Proveca submitted that the letter was addressed to dispensers and not prescribers. Proveca did not discuss, let alone challenge the clinical assessment or scientific opinion conducted by a health professional about the treatment of a patient. The clinical judgment of the recipient was never at stake; on the contrary, the letter clearly stated that prescribers could decide to prescribe a Special (or off-label product) to a particular patient if the health professional considered that there was a specific patient need. Thirdly, Proveca submitted that the parallel drawn with Case AUTH/2971/8/17 was inappropriate, as the present case differed on a number of significant grounds, such as that (a) the MHRA was not the competent authority and its involvement was entirely mischaracterised in Case AUTH/2971/8/17, as opposed to the present case in which the MHRA were consulted by Proveca about the general situation and (b) in Case AUTH/2971/8/17 the letter at issue misled the recipient about the licensed indication.

Proveca submitted that it was an innovative company with micro SME status that was engaged in the development and licensing of medicinal products for the paediatric population with chronic and life-limiting conditions. Proveca's product, Sialanar, was the only oral glycopyrronium product licensed for children on the UK market and the only one licensed for severe chronic drooling. Sialanar was first launched in the UK in February 2017, and prior to its approval, the needs of the market were fulfilled by off-label and unlicensed glycopyrronium bromide products within the 'Specials' legal framework. By December 2017, Sialanar's market penetration was very limited and accounted for less than 5% of the paediatric market compared to unlicensed and off-label oral glycopyrronium bromide.

Proveca noted that it had become aware of a disproportionately high supply of off-label and unlicensed products compared to its own licensed product, due to its limited market share. This discrepancy could neither be justified nor explained on medical or clinical grounds for preferring unlicensed products in the vast majority of cases. This would only be the case where Sialanar was contraindicated as a result of its excipients or where a significantly different concentration leading to a much lower volume was required. Currently there was no evidence of a patient need on the market in respect of glycopyrronium bromide for the licensed indication in children. Considering that there was no shortage of supply of Sialanar, it was obvious that at least some of the off-label and unlicensed products were dispensed outside of the strict conditions established by the applicable legal framework; including the legal framework applicable to the dispensing and supply of Specials.

Upon becoming aware of the extent of the widespread supply of off-label and unlicensed glycopyrronium bromide products, Proveca in the first instance sought to discuss this with the MHRA on a general basis. The MHRA agreed with Proveca approaching the potentially infringing specials manufacturers and pharmacists to explain the rules around off-label and unlicensed supply and to inform them that there was now a licensed glycopyrronium bromide product available to treat severe sialorrhoea in the paediatric population. Proveca was told by the MHRA that if the recommended approach was unsuccessful, it should contact the MHRA again and it would assess whether Proveca should take action.

The issue that Proveca wanted to raise was in the event where the prescription did not specify the product form and/or strength, in which case it was up to the pharmacist to determine what to dispense in order to fulfil the prescription. The legal framework imposed on the pharmacist the obligation to dispense the licensed product, unless there were evidenced medical grounds to dispense an unlicensed or off-label product. With variability in the preparation of Specials and the lack of any regulatory oversight on unlicensed products, there were serious public health concerns that had led to the established legal framework. This was precisely what Proveca wanted to ensure was brought to the pharmacists' and specials manufacturers' attention.
Therefore, Proveca submitted that it had written to pharmacists and specials manufacturers alike to inform them that a licensed product was now available and reminding them about the legal framework applicable to Specials, in a balanced and proportionate manner.

Clause 9.1

Proveca submitted that it disagreed with the Panel's finding, which was regrettable given the professional way in which Proveca attempted to address a potential serious breach of the law by courteously informing the recipients of the letter of the legal framework applicable to off-label and unlicensed medicines and the existence of a licensed product instead of engaging in contentious practices. The letter ensured that pharmacists and Specials manufacturers were aware of the legal framework under which they must operate and could assess their compliance under legal, rather than scientific or clinical principles.

All the statements that Proveca had made about the appropriateness of Sialanar for paediatric patients with excessive sialorrhoea were accurate, balanced, fair and capable of substantiation. Proveca provided all the relevant references so that the pharmacists and Specials manufacturers would be able to confirm the validity of the information and determine whether their supply practice of Specials was compliant with the applicable legal framework. The benefit of this correspondence rather than resolving to take immediate legal action was illustrated by the positive responses that Proveca received from some recipients of the letters, thanking Proveca for bringing this information to their attention. A selection of the correspondence was quoted. Those confirmed that Proveca helped the recipients to ensure that their dispensing activities were in accordance with the law.

Further, Proveca submitted that in this context, it was also important to note that the content of the letter was in line with the views publicly expressed by the ABPI and EFPIA on the matters of prescription of products without a licence in respect of the intended indication.

Proveca submitted that the ABPI's position regarding the use of unlicensed medicines was set out in a press release that it issued in May 2012. The press release stated that the '… health and safety of UK patients should always be paramount, and all other considerations, including cost, must be secondary'. In the statement, the ABPI reiterated that use of unlicensed medicines put patients at risk and should be strictly limited to those occasions where there was no licensed alternative. Proveca's position as expressed in the letter supported and reiterated this point.

In addition, in March 2017 EFPIA made some statements on off-label supply, which applied equally and directly to the supply of unlicensed products beyond the special needs' exemption. Commenting on the European Commission's study report on off-label use, EFPIA stated that:

> 'Indeed, pharmaceutical companies may be less ready to invest in costly and lengthy clinical development and authorisation processes for a given indication if public authorities promote the use of cheaper off-label medicines that have not been subject to the same stringent safety and efficacy assessments as existing on-label medicines, for financial reasons.'

Proveca submitted that these public positions indicated that the ABPI and EFPIA considered that supply of a medicine for an indication for which it was not licensed, contained many risks, ranging from public health to reduction in investment and compromise of the regulatory system, resulting in uncertainties and the undermining of the pharmaceutical industry. These considerations were present in and directly applicable to the situation that Proveca had been facing and in line with the approach Proveca had taken to engage with the potential involuntary infringer by restating the law applicable to off-label and unlicensed medicines and informing them of the fact that there was now a licensed product available to treat those medical conditions in the paediatric population.

Proveca submitted that the letter was targeted specifically at pharmacists and dispensers of medicinal products, who were presumed to have a certain level of knowledge and expertise in the rules of what products to dispense. The letters were never aimed at or provided to the general public. Therefore, anyone receiving the letter would understand the basis of Proveca's information, rather than, as the Panel held, have felt 'threatened', which might be arguable for a member of the general public with no understanding of the applicable rule and its obligations. The content and tone of the letter was informative, with references to EU and UK legislation, jurisprudence and guidance in order to convey an accurate and complete picture of the applicable framework.

Proveca submitted that the letter addressed professional, sophisticated readers and addressed them in an appropriate tone, without any attempt of concealed promotion or with a 'threatening' manner. It was important to explain the consequences of non-compliance with the law. A company striving to uphold the law, as established by the authorities and the courts, was one which aimed to maintain the high standards of the industry and did not accept their compromise resulting from the uncontrolled supply of unlicensed product, which was the case when there was no specific request for a Special or off-label product by a health professional who had identified a patient need. This was also supported by ABPI and EFPIA. Under all circumstances Proveca's conduct was in accordance with the industry's expected high standards, in order to ensure that these very standards were observed by all parties.

Clause 2

Proveca noted that the Panel was '… very concerned about the content and tone of the letter …', which in the Panel's view was threatening. The Panel noted that the misleading implication that patients could be switched without any consideration of their clinical circumstances might potentially prejudice patient safety. The Panel was particularly concerned that a health professional '… who had received the letter would be very concerned by the misleading implication that his/her prescribing decision was potentially illegal. The tone of the promotional letter could be seen as threatening and, in the Panel's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry'.

Proveca disputed the Panel's ruling and submitted that the factual basis was incorrect. The letter was not directed or addressed to 'prescribers' but to pharmacists and manufactures of Specials. As already explained the letter neither stated that dispensing off-label or unlicensed medicines was *per se* an illegitimate practice nor did it seek to threaten the recipient. Instead, and as explained above in further detail, Proveca stated the law and in particular the conditions under which an off-label or unlicensed product might be dispensed and explained to the Panel when a patient need might arise.

Proveca submitted that the letter was informational in tone and regretted the fact that it had been perceived by a few recipients as 'threatening'. On the contrary, most of the correspondence that Proveca received following its letter was positive or neutral, with many recipients thanking Proveca for bringing this information to their attention. The overwhelmingly higher number of such positive/neutral responses, 67 compared to the 6 negative responses and the two complaints, indicated that the communication was perceived by the majority as intended, namely as informational in nature. The attempt by a commercial entity to seek to settle a disagreement by way of correspondence, especially when the disagreement concerned potentially illegal action before resorting to other means, was an honourable practice and not one which could be seen as bringing discredit upon the pharmaceutical industry.

Moreover, a recipient who only supplied and/or dispensed unlicensed glycopyrronium bromide when supported by a health professional's unsolicited request for a Special or off-label product in respect of a specific patient need would have no reason to feel threatened upon reading the letter. The letter explicitly stated that a prescription specifically written for an off-label or unlicensed product (where there was a legitimate patient special need) was recognised as a valid reason for providing an off-label or unlicensed medicine instead of the licensed product (e.g. Sialanar). Proveca did not see how a letter setting out the applicable legal framework in a factual and objective manner brought discredit and reduced confidence in the industry, especially having regard to the correspondence received by Proveca expressing gratitude for this crucial information. Once a pharmacist was fully informed of the applicable legal framework, he/she could decide whether his/her practice was in line with the applicable rules. It seemed that engaging in a dialogue with potential infringers was the appropriate approach which, to restate, was only undertaken after speaking with the MHRA. Proveca did not agree with the Panel's ruling that the '… misleading implication that patients could be switched without any consideration of their clinical circumstances might potentially prejudice patient safety'. Firstly, this was a mischaracterisation of Proveca's position by the Panel. Proveca never argued in favour of switching, but only provided information in the event that a pharmacist did not prescribe a licensed product in response to a generic prescription not specifying concentration, formulation or a special need. In the event of uncertainty, the pharmacist was under an obligation to communicate with the prescriber to identify his/her concern and clarify the subject matter of the prescription. This was vastly different from 'switching'.

Proveca stated that its product was the only approved product for this indication, with a *per se* established safety profile and the only one which might be lawfully dispensed, unless the prescriber requested otherwise, and this would only arise, in very limited cases, on grounds of patient needs. The concern that Sialanar was less safe than unlicensed preparations was never raised by any complainant and was legally unsound considering licensed nature of Sialanar for the age group and indication. In fact, as evidenced in Case AUTH/3060/8/18, one of the complainant's primary concerns was that making the switch would pose **an additional cost burden** on the NHS, without any reference to the switch impacting on patient safety. So, the primary and unique concern expressed by the complainant seems to be financial rather than a safety issue. In fact, refusing to provide the licensed product on costs grounds was both an irrelevant consideration to the present matter and had been explicitly held by the European Court in Commission v Poland and by the MHRA in its Guidance Note 14 and by the ABPI itself (as set out above) not to be a valid reason for dispensing and supplying Specials. Once there was a prescription for glycopyrronium bromide, the NHS would pay the standard price cited in the formulary; the precise profit margin for a dispenser would then depend on the price of the product actually supplied. This should not influence what product was supplied, especially if tilting the position in favour of unlicensed products, in the absence of a clinical need. This confirmed the exact concern that was raised in Proveca's letter in order to inform any recipients who might not be aware of this legal consideration. On the contrary, Proveca stated in its letter that providing off-label and unlicensed glycopyrronium instead of Sialanar was acceptable on clinical grounds only; therefore, the Panel's statement that Proveca argued in favour of dispensing '… without any consideration of the [patients'] clinical circumstances' was simply incorrect.

Proveca did not see how bringing all this information to the recipients' attention brought discredit to the profession, when in fact it had the effect of enabling them to understand the legal limitations and ensure that the supply of medicinal product was conducted in accordance with the applicable legislation. The reference to Case AUTH/2971/8/17 was inappropriate as in that case the letter misled the recipient about the licensed indications, whereas Proveca referred specifically to the target indication (excessive sialorrhoea) and patient population (paediatric population) covered by Sialanar's licence. No particular special need for providing unlicensed glycopyrronium bromide on such a wide scale had been evidenced in the case of Proveca.

Overarching reasons to uphold the appeal against the Panel's decision

Proveca submitted that in addition to all the above it was also concerned that the Panel's ruling, had a potential detrimental effect on the patient's safety and clearly undermined the appropriate application of the pharmaceutical legal framework.

Proveca submitted that the Panel did not refer anywhere to the fact that the guidance cited by Proveca was all factually accurate. The letter did not promote Sialanar and all the information was an accurate and objective characterisation of the legal framework. In addition, it was obvious that despite and after Proveca's letter setting out the law, the complainant still thought that it should be entitled to disregard the law for financial considerations (e.g. cost burden on the NHS). The direct result of penalising a company for bringing potential breaches of the law to the attention of the other party was a blatant misapplication of the existing legal framework, which was established to protect public health and safeguard the proprietary rights of the pharmaceutical industry. Within this context, the Panel had not given due consideration to the surrounding circumstances, which had resulted in an unjust ruling, both for Proveca and for the pharmaceutical industry which was rendered incapable of taking action to safeguard its rights in a non-invasive, non-contentious manner.

The detailed provisions in the Code aimed to ensure that pharmaceutical companies operate in a responsible, ethical and professional manner and the promotion of medicines to health professionals and other relevant decision makers was carried out within a robust framework to support high quality patient care. In addition, Clause 1.1 of the Constitution and Procedure stated that the Panel was also responsible for arranging for conciliation between companies when requested to do so.

Proveca submitted that its letter, abided by these principles, aimed peacefully to resolve its disagreement of a practice in order to ensure that off-label and unlicensed products were not provided without a justification, thus possibly compromising the high patient care standards afforded by the marketing authorisation procedure. Observance of the established rules in fact increased confidence in the pharmaceutical industry that the law would be observed and that members of the industry would be monitoring compliance and identifying any possible deviations.

Proveca submitted that the Panel's ruling as it stood was perverse and provided no recourse outside of litigation or referral to the regulatory authorities to a company which had invested in research and development in getting its medicinal product approved, especially when it was the only such product on the market and approved for the paediatric population. This decision left no recourse to members of the pharmaceutical industry wishing to safeguard their proprietary rights. Letters, informative in tone, sent to the impacted parties, as discussed with the MHRA before formally reporting suspected wrongdoing to the MHRA, for further action, where appropriate, were the most straightforward way for a company to ensure that the applicable rules were observed without involving an enforcement authority. The Panel's ruling effectively deprived pharmaceutical companies of ways to ensure that the legal rules in place to protect their investment in R&D were observed. Moreover, this ruling appeared to support pharmacists and Specials manufacturers who would be infringing the legal framework with impunity.

For the reasons expressed above, Proveca vigorously refuted the Panel's ruling that the content of the letter was in breach of Clauses 2 and 9.1 of the Code, as the letter's message had no other effect beyond informing the recipient of a potentially illegitimate practice.

RESPONSE FROM THE COMPLAINANT

The complainant had no comments on the appeal.

APPEAL BOARD RULING

The Appeal Board noted that prior to the launch of Sialanar in the UK in February 2017, paediatric patients with chronic pathological drooling due to chronic neurological disorders were treated with off-label glycopyrronium bromide products or specials. The Appeal Board noted Proveca's submission that by December 2017, Sialanar's market share of the glycopyrronium bromide paediatric market was only 5% and the company considered that this was due to pharmacists continuing to dispense off label glycopyrronium bromide or specials. The Appeal Board noted that pharmacists would be dispensing prescriptions written by GPs, hospital doctors etc. What was dispensed would depend on what was written on the prescription. It noted the company's position that most of the prescribing was written for the generic medicine and unless features were specified that were not met by Sialanar, such as a different strength or formulation, then Sialanar should be dispensed.

The Appeal Board noted Proveca's submission about its telephone conversation with the MHRA in September 2017. According to Proveca, the MHRA confirmed that although it did not get involved in cease and desist letters, it knew that companies had sent them, reference was made to the MHRA guidance note 14 and it was agreed that a cease and desist letter would be the first step. Consequently, Proveca sent a letter to pharmacists in March 2018 which set out the legal framework for prescribing in relation to Sialanar and unlicensed and off-label glycopyrronium bromide products. Proveca submitted that this letter had had no effect and so the company sent a second letter, the letter at issue, on 10 August. The MHRA was sent one copy of the letter at issue on 17 August. The Appeal Board noted that the content and tone of the second letter was markedly different to the letter sent in March. The Appeal Board noted that the letter at issue was sent to 16,154 UK pharmacies, primarily consisting of community pharmacists and hospital outpatients pharmacists. The Appeal Board noted from the Proveca representatives at the appeal that the letters were sent in envelopes which were personally addressed to named individuals whose

details were obtained from a database. Each letter started 'Dear Sir/Madam' and included 'Copy sent to the Medicines Healthcare products Regulatory Authority'. In the Appeal Board's view as the letters were sent to named individuals, recipients would probably assume that their individual letter had been specifically highlighted to the MHRA. There was no indication to the recipient that the letter at issue had been sent to over 16,000 pharmacies.

The Appeal Board noted that recipients were asked to confirm via email to Proveca that they had ceased such activities.

The Appeal Board noted the content of the letter including the references to breaching the pharmaceutical legal framework and breaches of the law. In the Appeal Board's view, there was also an implication that a claim for damages might ensue.

The Appeal Board was concerned about the tone of the letter in question and, in that regard, it noted that the complainant and five of the six negative responses from recipients to the letter in question, provided by Proveca, stated that they found it to be threatening.

The Appeal Board noted that there was a difference between writing to all pharmacies as opposed to those whose dispensing was the subject of Proveca's concern. The Appeal Board noted the company's submission that it had chosen to send the letter to all pharmacies as it did not consider that it was possible for the company to identify which were dispensing glycopyrronium bromide off-licence or as specials. The Appeal Board questioned if this was an acceptable approach. This was compounded by the fact that the treatment of chronic pathological drooling in paediatric patients with chronic neurological disorders was likely to be a niche area and the majority of pharmacists on the mailing list would not be dispensing glycopyrronium bromide products for paediatric use.

The Appeal Board noted that it was not necessarily unacceptable to draw the attention of pharmacists to the legal framework, however, such material had to comply with the Code. The Appeal Board queried the company's submission at the appeal that the letter in question was an essential step if it wished to pursue court action. In the Appeal Board's view, a *bona fide* letter before action would be sent solely to those individuals whose dispensing was the subject of concern and would certainly not bear prescribing information. The Appeal Board, therefore, did not accept Proveca's submission that upholding the Panel's decisions would have dangerous consequences and prevent companies from enforcing the law and protecting their rights. The Appeal Board understood the company's position. It was the content and tone of the letter that was the issue for consideration not the principle that a letter had been written to address the commercial situation.

The Appeal Board considered that the letter in question which bore prescribing information was clearly promotional and it queried how Proveca could consider it to be anything else.

The Appeal Board noted the complainant's concern that pharmacies and dispensaries in surgeries were being disparaged for dispensing what was prescribed by other health professionals such as GPs hospital doctors etc. The Appeal Board noted that whilst the letter in question did deal with some of the exceptions, overall the letter implied that supplying off label glycopyrronium bromide or a special rather than Sialanar would always be in breach of UK law which was not so. The Appeal Board noted, as acknowledged by Proveca, that the supply of an unlicensed medicine was legally permissible in certain circumstances where there was a patient with a 'special need'.

The Appeal Board considered that the letter in question implied that pharmacists did not know the legal requirements regarding the dispensing of specials.

In the Appeal Board's view, the implication was that the MHRA approved or otherwise endorsed the content of the letter in question and that was not so.

The Appeal Board noted its comments above and considered that Proveca had failed to maintain high standards and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board considered that pharmacists who had received the letter would be very concerned by the misleading implication that his/her dispensing practices were potentially illegal and that legal consequences including an implication that a claim for financial damages might ensue. The Appeal Board noted that the majority of the recipients of the letter would not have dispensed glycopyrronium bromide. The tone of the promotional letter could be seen as threatening and, in the Appeal Board's view, brought discredit upon, and reduced confidence in, the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **21 August 2018**

Case completed **11 December 2018**