CASE AUTH/3624/3/22

COMPLAINANT v PACIRA BIOSCIENCE

Concerns about the promotion of Exparel

CASE SUMMARY

This case concerned claims for Exparel (liposomal bupivacaine) made within emails sent by a sales representative, working on behalf of Pacira BioScience, including: a claim that Exparel could be used as either infiltration or an adductor canal block; two claims for use of Exparel in total knee replacement as day surgery; four claims in relation to the efficacy of Exparel in lower limb arthroplasty; a claim stating that Exparel has an impact on 'social and economic issues'; and an alleged failure to communicate the known risks of Exparel or link to prescribing information.

The Panel ruled breaches of the following Clause of the 2021 Code:

Breach of Clause 5.1	**Failure to maintain high standards**
Breach of Clause 6.1	**Making misleading claims**
Breach of Clause 6.2	**Making unsubstantiated claims**
Breach of Clause 11.2 [One ruling successfully appealed]	**Promotion inconsistent with the SPC**
Breach of Clause 14.4	**Making exaggerated claims**

The Panel ruled no breaches of the following Clause of the 2021 Code:

No breach of Clause 6.1	**Requirement that claims must not be misleading**
No breach of Clause 6.4	**Requirement that claims must reflect the available evidence regarding possible adverse reactions**
No Breach of Clause 11.2	**Requirement that promotion must not be inconsistent with the SPC**
No breach of Clause 14.1	**Requirement that misleading comparisons must not be made**
No breach of Clause 14.4	**Requirement that exaggerated or all-embracing claims must not be made.**
No breach of Clause 17.9	**Requirement that representatives' briefing material must comply with the relevant requirements of the Code**

APPEAL

Pacira BioSciences appealed one of the Panel's rulings of a breach of Clause 11.2 of the 2021 Code in relation to a claim that Exparel could be used as either infiltration or as an

adductor canal block which was overturned by the Appeal Board. The Appeal Board ruled no breach of the following Clause of the 2021 Code:

No Breach of Clause 11.2	Requirement that promotion must not be inconsistent with the SPC

This summary is not intended to be read in isolation
For full details, please see the full case report below.

FULL CASE REPORT

A pharmacy manager at a named health group complained in his/her capacity as a registered pharmacist about the marketing of Exparel (liposomal bupivacaine) by Pacira BioScience.

Exparel was indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small to medium-sized surgical wounds in adults.

The complainant provided correspondence with a named representative**,** working on behalf of Pacira BioScience. In March 2022 the representative emailed another employee at the health group referring to the focus of the named hospital group on reducing LOS [length of stay] and reducing post surgical opioids and queried whether this was a focus for the recipient. The email included the indication for Exparel and described the medicine as being given as a prolonged-release dispersion for injection and offering long-acting local anaesthesia that can be administered as a single dose for patients with post-operative pain in a wide variety of surgical procedures (Shoulder, TKA, Bunionectomy, Laparotomy etc). The email further stated 'Post-surgical pain is managed effectively, and opioid consumption is reduced which further promotes earlier patient mobilization'. The recipient of this email replied that reducing LOS was a focus at his/her hospital and copied in the complainant who was running a project on reducing LOS.

In mid March 2022, the complainant replied to his colleague and the representative as follows:

> 'Thanks for cc/ me in – we're always trying to review ERAS protocol.
>
> Last list price I saw for liposomal bupivacaine was ~£2000/10vials. This would not be feasible for us. Femoral nerve blocks not actively encouraged in our TKR ERAS protocol at the moment with the aim to promote early coordination / mobilisation (at risk of increased pain).
>
> If price more affordable per patient, I can forward to surgeons / anaesthetists – but not at previous list price / current evidence base unfortunately.'

The representative replied as follows:

> 'The indication for EXPAREL allows it to be used as either infiltration or an Adductor Canal block which allow early mobilisation of the patient. EXPAREL is actually used in USA for sameday Total Knee Replacements for this very reason, with TKR patients going home the day of the operation and having 48/72 hrs of pain free mobility – as well as being used in regional anaesthesia in other surgical disciplines.

If EXPAREL is viewed as just a direct replacement as another anaesthetic, then I agree it is expensive, but that is not the place for EXPAREL. It provides extended analgesic efficacy by reducing the bupivacaine diffusion away from the injection site, either in the surgical site or in Regional Block so therefore:

- it provides 48hrs+ pain relief, meaning no middle of night / waking up in pain for the patient.
- there is reduced need for additional pain medication including opioids, and the side effects / additional social & economic issues they can bring
- there is reduced need for catheters / pumps etc

Anecdotally, [another named] Hospital have just started with EXPAREL and their very first patient was having his second Uni Knee done. They used EXPAREL as infiltration and the patient had no pain overnight, walking without crutches, pain level max 1/10 and rates the operation 10/10.

The hospital has continued to implement EXPAREL in their ERAS protocol and have been so impressed with outcomes they are now looking to implement in other disciplines.

[A second named hospital] are doing something similar, and they have stated that switching to EXPAREL is going to be at worst cost neutral although with reduced cost of additional pain medication and nurse follow up time, it should prove cost effective.

I'm happy to come in an run through any data / evidence you wish to see in more detail.'

In response the complainant stated:

'Thanks [name] – very surprised to hear [named hospital] incorporate into their orthopaedic ERAS protocol!

You'll appreciate insignificant evidence to justify use, but we will review if approved by NICE / local Trust as cost-effective benefit to patient outcomes….'

The representative sent two emails in response, as follows:

'Just wanted to add a bit of meat to the bone regarding evidence / guidelines / protocols…

- EXPAREL® liposomal has now been used in more than 10 million patients and it has been incorporated into enhanced recovery protocols at numerous US prestigious institutions

- Published trials and systematic reviews include use in Abdominal surgery, Breast reconstruction, Colorectal procedures, OB/Gynecological/oncology surgery, Urological procedures, TAP block, Orthopaedic procedures & Inpatient and Outpatient procedures

- NICE: NICE considered an EXPAREL review unnecessary as measurement of QALYs is too insensitive a methodology to evaluate post-surgical analgesia of 2-3 days duration.

- ERAS Protocol use in [named area]:

- Used as part of regional anaesthesia for operations in theatre only and restricted for use only in major surgery as part of enhanced recovery protocol

- Utility of EXPAREL liposomal provides the potential to consider earlier mobilisation and discharge of patients undergoing target procedures. Therefore use of this drug as part of an enhanced recovery programme would allow operations which are currently inpatient only to be done as a day case such as total knee arthroplasty as postoperative pain is significantly better controlled.

- As part of their justification for use they stated that there would be “no additional cost” but “significant financial savings”

I’m very happy to come and talk some more about this.’

COMPLAINT

The complainant alleged that the communications from Pacira did not accurately reflect the robust history of industry-sponsored trials with failure to meet primary/secondary end points compared to placebo or comparator plain bupivacaine (Ilfeld *et al* 2021; Hussain *et al* 2021; Dinges *et al*. 2021).

The following incorrect/misleading comments were of particular concern to the complainant: –

> ‘EXPAREL is actually used in USA for sameday Total Knee Replacements for this very reason, with TKR patients going home the day of the operation and having 48/72 hrs of pain free mobility’.

The complainant stated that there was no evidence of ‘pain free’ mobility post-op; definitely not for 48-72h.

> ‘It provides 48hrs+ pain relief, meaning no middle of night / waking up in pain for the patient.’

The complainant stated that he/she was not aware of any studies accessing the number of times the patient woke in the night.

> ‘There is reduced need for additional pain medication including opioids, and the side effects/additional social & economic issues they can bring’

The complainant stated that trials had not consistently shown a reduction in opioid consumption or time to first opioid dose. There was no evidence that Exparel reduced ‘additional social & economic issues’.

When writing to Pacira BioSciences, the Authority asked it to consider the requirements of Clauses 5.1, 6.1 and 6.2, 6.4, 11.2, 14.1, 14.2, 14.4 and 17.9 of the Code.

Further information from the complainant

The complainant stated that he/she was a UK pharmacist and that in his/her professional view that a representative of Pacira BioSciences provided incorrect and/or misleading statements in email communications promoting Exparel.

The complainant provided further details in response to the case preparation manager's request for further information.

1. Alleged misrepresentation of Exparel marketing authorisation contrary to Clause 11.2

The complainant stated that the marketing authorisation for Exparel 133mg/10mL and Exparel 266mg/20mL indicated that the medicine was for use as 'brachial plexus block', 'femoral nerve block', or 'field block'. In an email sent in March 2022, Pacira BioSciences incorrectly stated the licensed indications as:

> 'The indication for EXPAREL allows it to be used as either infiltration or an Adductor Canal block which allow early mobilisation of the patient'

The complainant stated that Exparel was not indicated for use as adductor canal block. These interventions were not interchangeable or equivalent.

2. Alleged promotion of Exparel inconsistent with the particulars listed in its Summary of Product Characteristics (SPC) contrary to Clause 11.2

The complainant stated that in email communications sent in mid March 2022, Pacira BioSciences referenced the use of Exparel in day case total knee arthroplasty (TKR):

> 'EXPAREL is actually used in USA for sameday Total Knee Replacements for this very reason, with TKR patients going home the day of the operation and having 48/72 hrs of pain free mobility'.

The complainant stated that in email communications sent the following day in March 2022, Pacira BioSciences similarly referenced the use of Exparel in TKR within an Enhanced Recovery after Surgery (ERAS) protocol in [named area]:

> 'Utility of EXPAREL liposomal provides the potential to consider earlier mobilisation and discharge of patients undergoing target procedures. Therefore use of this drug as part of an enhanced recovery programme would allow operations which are currently inpatient only to be done as a day case such as total knee arthroplasty as postoperative pain is significantly better controlled.'

The complainant alleged that this promotion of Exparel in day case TKR was inconsistent with its SPC and potentially harmful:

> *'*EXPAREL liposomal is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan'

Pacira BioSciences similarly failed to disclose that sensory and/or motor loss with Exparel might persist for up to five days.

3. Alleged failure to provide balanced, fair and objective overview of the efficacy of Exparel in lower limb arthroplasty contrary to Clauses 6.1, 14.1, 14.4, and 17.9

The complainant stated that in email communications sent in mid March 2022, Pacira BioSciences made a number of claims regarding the efficacy of Exparel in lower limb arthroplasty:

> 'EXPAREL is actually used in USA for sameday Total Knee Replacements for this very reason, with TKR patients going home the day of the operation and having 48/72 hrs of pain free mobility'.
>
> 'It provides 48hrs+ pain relief, meaning no middle of night / waking up in pain for the patient.'
>
> 'There is reduced need for additional pain medication including opioids, and the side effects / additional social & economic issues they can bring'
>
> 'There is reduced need for catheters / pumps etc'

The complainant alleged that these statements, provided without qualification, were unevidenced, exaggerated, and misleading. Multiple recent meta-analyses have found inadequate evidence and/or no clinical benefit of liposomal bupivacaine on pain severity, analgesic consumption, first analgesic timing, opioid side effects, satisfaction, length of hospital stay, or functional recovery.

4. Stating that Exparel has an impact on 'social and economic issues' alleged to be contrary to Clauses 6.1, 6.2, 6.4, and 14.4

The complainant stated that there was no evidence to substantiate Pacira BioSciences' claim of positive impact on 'social and economic issues'. The lack of evidence regarding Exparel use on opioid consumption further invalidated this claim.

5. Alleged failure to communicate the known risks of Exparel contrary to Clauses 6.1 and 6.4

The complainant alleged that Pacira BioSciences failed to disclose any known risks of Exparel or link to further prescribing information. These were clinically significant risks, including post-marketing reports of 'local anaesthetic systemic toxicity' at greater than 24 hours, which was not a known risk of non-liposomal bupivacaine.

Pacira BioSciences was asked to respond to the additional matters and the clauses cited by the complainant.

RESPONSE

Pacira stated that it was concerned to learn of the complaint about emails sent by the named employee of a third part sales provider to the complainant.

Pacira stated that it was not currently a member of the ABPI, but the company nevertheless accepted the jurisdiction of the Code in respect of this matter.

A. Context of the emails

Pacira stated that the emails sent by the named employee and provided by the complainant were sent in contravention of Pacira's procedures. Those procedures were in place to ensure that all communications about Pacira products were lawful and, in the UK, were compliant with the MHRA Blue Guide and the Code.

Pacira stated that the named employee received a copy of the Pacira European Compliance and Ethics Manual that detailed the requirements and processes in October 2021. He/she received detailed training on Pacira's products, compliance requirements and processes as set out below. Those processes required all emails to be sent for internal review and approval. Had the named employee provided these emails in draft to Pacira, as required, they would not have been authorised for use. In the circumstances, there was therefore no Pacira internal approvals for the emails.

Pacira stated that it had interviewed the named employee who confirmed that he/she was aware that all communications required approval by Pacira Public Communications Review Committee for Europe ('PCRC-Europe') prior to dissemination. He/she also understood that his statements were of opinion and not of fact. His/her explanation was that the emails were an 'absolute genuine error'.

B. Steps taken by Pacira Biosciences to assure compliant sales and promotion in the UK

Pacira stated that it was cognisant of the fact that compliance with the law on advertising and promotion was its responsibility. Being a new entrant to the UK and EU market, Pacira submitted that the responsible step would be to outsource its sales operations to a company experienced in selling pharmaceuticals and who would be well versed in the applicable laws and other requirements across multiple countries and who would therefore help to ensure a successful and compliant launch in this new market.

Pacira provided the named the third party sales provider's credentials and submitted that after reviewing a short list of other vendors, Pacira chose the third party sales provider based on recommendations from leaders in the industry, experience with other contract sales organisations, interviews with the third party's leadership and having gained a good understanding of the sophistication and market specificity of their offering and approach.

Pacira stated that it nevertheless took steps to ensure that the third party sales provider and its representatives would be aware of the law and would comply with it. These steps included:

- Imposing contractual provisions on the third party sales provider to ensure regulatory requirements were met by their staff and including requirements that the third party sales provider:

- provided a professional, fully trained and appropriately credentialled sales force;
- provided support in compliance with applicable laws;
- provided training on applicable regulatory requirements and ensured that all staff attend such training as well as training on the products, on Pacira internal policies and on applicable regulatory requirements provided by Pacira, and that attendance was recorded and participation assessed;
- ensured staff adhered to Pacira policies; and
- ensured that staff only used approved materials.

- Provided the third party sales provider with an extensive European Compliance and Ethics Manual ('Manual') whose content was drawn from the EFPIA and ABPI Codes as well as local laws of other countries. A senior Pacira employee worked with various counsel in the UK and Europe to ensure that the content of the Manual properly reflected local laws. This included section 3.1 that required all external communications to be approved, and section 3.4 which clearly stated that emails making product claims were subject to review by the PCRC-Europe.

- The above mentioned senior Pacira employee provided training to all the new hires at the third party sales provider and Pacira Europe on the Compliance Manual and the applicable laws in October 2021 to the third party sales provider sales team dedicated to Pacira's activities.

The named representative's training and profile

Pacira submitted that the representative in question completed the following training and assessments:

- A full week of training in October which included a workshop by the senior Pacira employee above on the Compliance Manual and the applicable laws as well as multiple training sessions on the SPC and approved product claims for EXPAREL liposomal (Core New Hire Training schedule);

- Pacira online modules and assessments, all of which were completed by early November 2021, including Pacira Europe Compliance & Ethics Manual (COM-EU-00001)1.0, which included the Manual with a ten-question assessment to test for understanding, and twelve modules on or related to EXPAREL liposomal, including EU Module 8 – EXPAREL (bupivacaine liposome injectable suspension) SPC (EU-EXPAREL-0008)1.0 and EU Module 7 – Introduction to EXPAREL(EU-EXPAREL-0007)1.0, all twelve of which were followed by a final exam, the EU EXPAREL liposomal Final Exam (PP-EX-EU-0033)1.0 (Report 23 March 2022);

- Pacira live certification on EXPAREL liposomal product knowledge completed in late November 2021 (EXPAREL Dosing Guide In-service Presentation Certification Check List);

- the third party sales provider online modules, including Communications with Healthcare Professionals v9 validation and ABPI Overview Induction Validation, both of which were completed on 9 November 2021 (SAP Success Factors and Greenhouse report 25 March 2022 and the third part sales provider); and

- the third party sales provider Induction Training in October 2021, which included training on the Code (See pages 3, 4 and 6 from the third party sales provider ABPI training deck).

Furthermore, the representative had completed ABPI training in 2003.

C. Steps Pacira had taken to prevent a reoccurrence

Pacira stated that it had taken steps including immediate communications and training dealing specifically with email communications.

An email was sent in March 2022 addressed to the whole European team (Pacira and the third party sales provider), noting the letter from the PMCPA and reiterating the requirements applicable to making any product claims, including the internal processes for approval.

Pacira had written a presentation on 'Compliant Email Communications & Approved Product Claims' setting out the laws, the requirements in the Manual and Pacira processes, as well as scenario-based explanations, which was delivered to the whole European team (Pacira and the third party sales provider) on 30 March 2022.

Acting on Pacira's request, the third party sales provider had removed the named employee from its account, and he/she would no longer be engaged in any activities for Pacira.

The third party sales provider would be undertaking regular audits of its team's emails.

The Veeva system was in the process of being fully rolled out and would be the conduit for controlling communications between the sales team and healthcare professionals (HCPs). This would ensure that all materials were properly authorised but would also provide a mechanism for regular data reviews of sales team activities, including communications sent to healthcare professionals.

In addition to training provided by the third party sales provider to its team, Pacira would be providing quarterly compliance training.

D. Claims made

Pacira submitted that had the representative complied with the Pacira processes as he/she was aware he/she ought to, none of the emails sent to the complainant would in fact have been sent

Pacira nevertheless wished for the PMCPA to note as a matter of record that some of the claims were capable of substantiation and some of these had been approved. The company provided a spreadsheet which included a list of those claims and the evidence supporting their substantiation.

E. Applicability of ABPI Code and certification requirement

Pacira stated that it accepted the jurisdiction of the PMCPA in respect of this matter, Pacira was not a member of the ABPI and was therefore not subject to the Code of practice to the extent that it included additional requirements above and beyond applicable law.

On that basis, Pacira could not be found to be in breach of Clause 17.9 with respect to certification requirements, which were solely a Code requirement and not a legal one and which was therefore only applicable to ABPI members. The company referred to the MHRA Blue Guide, paragraph 4.4:

> Although it was not a legal requirement, the appointment of qualified signatories to certify advertising material is a requirement of both the ABPI Code of Practice and of the PAGB Medicines Advertising Codes.

F. Conclusion

Pacira stated that it had taken all possible steps to engage a sales team that was qualified for the role and had invested heavily in training that sales team in the products, Pacira's processes and the applicable legal and other requirements. Pacira's readily available Manual clearly stated that emails required authorisation, and this process was not followed by the representative. The representative acknowledged that he/she knew and understood this to be the process, and that he/she unilaterally chose not to follow the process before sending the emails at issue. Had he/she followed the Pacira processes, these emails would never have been sent.

Pacira stated that it anticipated therefore that this was an isolated incident by an individual who for reasons of their own, and despite extensive training, chose to take matters into their own hands and ignore the requirements and Pacira's processes, both of which they knew and understood.

Pacira stated that its immediate follow-up actions would, it anticipated, definitively prevent a reoccurrence.

PANEL RULING

The Panel noted that Pacira was not a member of the ABPI. It appeared that the company had agreed to comply with the Code and accept the jurisdiction of the PMCPA. There were a number of companies which were not members of the ABPI in a similar position and the Code applied to these companies as well as to member companies of the ABPI.

The Panel considered the allegations in the second communication from the complainant as follows. The Panel noted that Pacira were asked to respond to Clause 14.2, which appeared to be in error, and that Pacira did not respond to Clause 14.2. The Panel therefore made no ruling in this regard.

1. Alleged misrepresentation of Exparel indications in the claim 'the indication for EXPAREL allows it to be used as either infiltration or an Adductor Canal block which allow early mobilisation of the patient'

The Panel noted that the indication in Section 4.1 of the SPC for Exparel was:

> 'EXPAREL liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults'

The Panel noted the complainant's allegation that Exparel was indicated for use as 'brachial plexus block', 'femoral nerve block', or 'field block' and not indicated for use as adductor canal block. The complainant stated that these interventions were not interchangeable or equivalent and cited a publication by Wang *et al* 2017.

The Panel noted that Wang *et al* 2017 was a meta-analysis of randomised controlled trials (RCTs) that compared adductor canal block to femoral nerve block and referred to adductor canal block as an alternative femoral nerve block.

The Panel further noted that according to the Introduction to EU & UK Compliance New Hire Training slides, dated 18 October 2021, use of Exparel liposomal in any nerve block procedure other than brachial plexus block or femoral nerve block was considered to be off label.

The Panel noted that according to Pacira, this claim could be substantiated.

Pacira referred to Section 4.2 of the SPC, Posology and method of administration, which stated that Exparel liposomal was for administration by infiltration or perineural use only.

The Panel noted Pacira's further provided a letter of explanation which stated that anywhere on its course from the pelvis to the periphery, it was still the femoral nerve, or what remained of it, until it eventually became nerve endings in the tissue it innervates. As such, Pacira submitted that the human anatomy of the knee was such that the block could be performed anywhere along the course of the femoral nerve depending on the needs of the patient for a particular surgery. Specifically included in this would be at the inguinal level, mid-femoral level, or femoral triangle, or in the adductor canal.

The Panel noted that the email dated 10 March referred to the Exparel indication as set out in the SPC. The email of 15 March included the claim at issue.

Clause 11.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics.

The Panel noted that the SPC did not refer to the adductor canal. Noting the training slides dated 18 October 2021 and that Wang *et al* 2017 made a distinction and comparison between adductor canal block and femoral nerve block, the Panel considered, on balance, that the claim was therefore likely to be inconsistent with the SPC for Exparel and ruled a **breach of Clause 11.2.** This ruling was appealed by Pacira.

APPEAL FROM PACIRA BIOSCIENCE

Pacira BioSciences submitted that it accepted all of the Panel's rulings of breaches of the Code, save for the breach of Clause 11.2 at point 1 in relation to the alleged misrepresentation of Exparel indications in the claim 'the indication for Exparel allows it to be used as either infiltration or an Adductor Canal block (which allow early mobilisation of the patient),' which

Pacira BioSciences disputed in its appeal, as set out below. The ruling regarding the portion of matter 1 that Pacira BioSciences had shown in parentheses above ('which allow early mobilisation of the patient'), was not being appealed.

Pacira noted that the Panel noted that the SPC did not refer to the adductor canal and noted the training slides dated 18 October 2021 and that Wang *et al* 2017 made a distinction and comparison between adductor canal block and femoral nerve block, and it had considered, on balance, that the claim was therefore likely to be inconsistent with the SPC for Exparel and ruled a breach of Clause 11.2. Pacira BioSciences submitted that it was not a misrepresentation to state that: 'the indication for Exparel allows it to be used as either infiltration or an Adductor Canal block'.

Pacira BioSciences submitted that in the SPC for both dosages of Exparel, under section 4.1 Therapeutic Indications, it stated (with Pacira's emphasis):

> 'Exparel liposomal was indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults.'

Pacira BioSciences noted that under section 4.2 Posology, that for patients undergoing total knee arthroplasty, Exparel liposomal was administered as a femoral nerve block.

Pacira BioSciences submitted that the SPC for Exparel included an indication for use as a 'femoral nerve block'.

i) The femoral nerve was a large nerve which originated from the lower spine and had several branches which extend through the lower pelvis, and further down into the lower limbs. It controlled motor activity from the hip to the knee, as well as sensation from the thigh to the big toe (hallux). When performing the block typically described as a 'femoral nerve block,' the anaesthetic was administered in the crease between the thigh and the pelvis above the divisions of the nerve so that the blockade would cover the entire distribution of the femoral nerve, including all branches.

ii) Over recent years, variations on the traditional femoral nerve block had evolved so that the local anaesthetic could be administered to a specific branch, rather than the entire femoral nerve. This allowed the blockade to be limited to target sensation in a specific area rather than the full length of the leg. This was preferable, for example, when a patient required optimal motor ability in order to ambulate shortly after surgery. Examples of block techniques which targeted specific branches of the femoral nerve include supra-inguinal, infra-inguinal, femoral triangle, sub-sartorial, and adductor canal blocks. While these were different techniques at different anatomical points along the path of the femoral nerve, they were all blocks of the femoral nerve and the branches the femoral nerve.

iii) The saphenous nerve was a branch of the femoral nerve, which provided sensation to the knee, calf, ankle and foot arch. It was the branch that was blocked in a distal approach to a femoral nerve block, closer to the knee, known as an 'adductor canal

block.'. Therefore, by definition, the branch blocked by an adductor canal block was a component of the nerve blocked by a femoral nerve block, and therefore, the adductor canal block was included in the indication for femoral nerve block.

iv) Clinicians had an interest in comparing the adductor canal block, a distal approach to the femoral nerve block, to the traditional femoral nerve block approach to evaluate how effectively each approach provided pain relief for the patient, while also allowing the patient to mobilise after surgery. This was the focus of many studies and meta-analyses comparing the all-encompassing femoral nerve block to the more localized adductor canal block.

v) By way of illustration, the SPC for Exparel also included an indication for use as a 'brachial plexus block,' but in the case of the brachial plexus, there was no single block typically referred to as a 'brachial plexus block.' Rather, there were multiple anatomical sites where the branches of the brachial plexus could be blocked, and each was identified by the anatomical site along the brachial plexus where the block was performed, ie, interscalene brachial plexus block, supraclavicular brachial plexus block, infraclavicular brachial plexus block and axillary brachial plexus block. The terminal branches of the brachial plexus could also be blocked further down the arm at the level of the elbow, mid-forearm, and wrist. While clinicians choose among these different anatomical sites along the pathway of the brachial plexus to perform a block, these were all blocks of the brachial plexus or the branches from the brachial plexus.

Pacira BioSciences submitted that the SPC included the indication for both the brachial plexus block (about which there was no claim complained of) and the femoral nerve block. It was the anatomy around the femoral nerve block that Pacira BioSciences would like to explain in support of its appeal as set out above.

Pacira BioSciences submitted that as background, Exparel liposomal was presented in a vial and was injected to produce local analgesia. Exparel used a multivesicular liposome technology, which encapsulated Exparel's API, bupivacaine, in a suspension of multivesicular liposomes, so that after injection, bupivacaine, an analgesic, was released over time. Regional anaesthesiologists might administer local anaesthetics and analgesics, like Exparel, to prevent or relieve pain by interrupting nerve conduction. When administered as 'nerve blocks,' local anaesthetics temporarily block nerves from delivering signals to the brain.

All blocks of the femoral nerve were included in the indication for Exparel

Pacira BioSciences submitted that Exparel liposomal was indicated as a femoral nerve block for treatment of post-operative pain in adults. The femoral nerve was a large nerve which originated from the lower spine and had several branches which extend through the lower pelvis, and further down into the lower limbs. It controlled motor activity from the hip (major hip flexor muscles) to the knee (extension muscles). It also controlled sensation, such as pain, over the anterior (front) and medial (mid) thigh and the medial leg down to the big toe (hallux) (Refai *et al* 2022).

Pacira BioSciences submitted that for many surgical procedures a full blockade of the femoral nerve was not necessary, therefore blocking a branch of the femoral nerve might be preferable to provide adequate pain relief, without blocking the motor nerves. There were multiple

anatomical sites where the branches of the femoral nerve could be blocked depending on the surgical area and movement requirements for a particular procedure, including but not limited to, supra-inguinal, infra-inguinal, femoral triangle, sub-sartorial, and adductor canal.

Anatomy and the femoral nerve

Femoral nerve and its branches

Pacira BioSciences submitted that the femoral nerve originated from the L2 to L4 nerve roots from the spinal cord and descended through the back of the pelvis, through the muscle fibres of the **psoas muscle** and then passing the pelvic bones under the **fascia iliaca** to the midpoint of the inguinal ligament. The nerve continued to traverse below the inguinal ligament, where it l next to the femoral artery and vein in the femoral crease. As soon as the femoral nerve passed underneath the inguinal ligament it divided into anterior and posterior divisions and gave off branches to the hip joint, the muscles and skin of the upper thigh continuing over the knee and down the inside of the lower leg and eventually terminated as the **saphenous nerve** on the inner side of the lower leg (Refai *et al* 2022). The **saphenous nerve** was a terminal **branch** of the **femoral nerve** (Bendtsen 2017)).

Femoral nerve and surrounding anatomy

Pacira BioSciences submitted that from the top of the leg in the femoral crease (**infra-inguinal**), the **femoral nerve** passed through the **femoral triangle** and then branched into the terminal branch known as the **saphenous nerve** and as such, passed through the **adductor canal**.

This was supported by Refai *et al*, which stated (with Pacira BioScience's emphasis):

> 'The sensory nerve was called the **saphenous nerve** and was the **largest cutaneous branch of the femoral nerve**. It was responsible for sensory innervation along the anteromedial and posteromedial aspects of the leg into the medial foot. The **femoral nerve** becomes the **saphenous nerve** when it passed through the **adductor canal**.'

As noted previously, regional anaesthesiologists referenced anatomical points to indicate locations along the **femoral nerve** where the application of anaesthetic would block the activity of that nerve.

A 'femoral nerve block' included a saphenous (adductor canal) block

Pacira BioSciences submitted that when performing the block typically described as a 'femoral nerve block,' the anaesthetic was administered in the crease between the thigh and the pelvis above the divisions of the nerve so that the motor and sensory blockade would cover all branches. As a result, a traditional 'femoral nerve block' resulted in anaesthesia of the anterior and medial thigh down to and including the knee, as well as skin on the medial leg and foot (Atchabahian, *et al* 2017). The saphenous nerve was a branch of the femoral nerve, which provided sensation to the knee, calf, ankle and foot arch. (Refai, *et al*). For knee procedures, such as a knee replacement, rather than injecting local anaesthetic near the pelvis and blocking sensation from the hip to the foot and motor activity of the thigh, as in a traditional 'femoral nerve block,' it had become preferable to administer the local anaesthetic to the saphenous branch of the femoral nerve only, lower, closer to the knee, so that pain in the surgical area was blocked, but the motor nerves of the thigh were spared and the patient might

begin ambulating immediately after surgery. (Hussain, *et al* 2016). See further, Bendtsen 2017 (p.615) which stated (with Pacira BioScience's emphasis):

> 'The **saphenous nerve** was a **terminal sensory branch of the femoral nerve**. It supplied innervation to the medial aspect of the leg down to the ankle and foot. It also sent infrapatellar branches to the knee joint.
>
> The block had also been reported as a supplement to [opioid-minimizing pain management regimens] in patients having knee [replacement]. Typically, a more proximal (mid-thigh) approach and a larger volume of local anaesthetic was used for this '**adductor canal block**'.

Pacira BioSciences submitted that by definition, the nerves blocked by an adductor canal block were a component of the nerves blocked by a traditional 'femoral nerve block' and therefore, the adductor canal block was included in the indication for femoral nerve block.

Pacira BioSciences submitted that Physiopedia 2018, a cadaveric dissection of the relevant anatomy clearly showed the femoral nerve passing through the adductor canal.

Evolution of femoral nerve blocks with advances in ultrasound guidance

Pacira BioSciences submitted that prior to the widespread use of ultrasound-guided techniques to visualise the nerve in real time within the patient in order to locate anatomical sites along the femoral nerve, the femoral nerve could only be blocked at a limited number of anatomical locations. With older landmark and nerve stimulation techniques, the femoral nerve was usually blocked in the psoas muscle, or just above the inguinal ligament (supra inguinal) or below the inguinal ligament in the femoral crease, next to the femoral artery.

Pacira BioSciences submitted that the introduction of ultrasound guided techniques had produced more opportunities to block the femoral nerve at different anatomical locations, such as the femoral triangle block, the sub-sartorial block, the adductor canal block or further along the terminal branch of the femoral nerve, the saphenous nerve. All these techniques were nevertheless applied along the femoral nerve, which was the use indicated in the SPC for Exparel.

Similarly, all blocks of the brachial plexus were included in the indication for Exparel

Pacira BioSciences submitted that to illustrate this further, it was helpful to look to the brachial plexus as a comparison to the femoral nerve. Exparel liposomal was also indicated as a brachial plexus block for treatment of post-operative pain in adults. The arm (upper limb) was innervated by the nerves of the brachial plexus, much like the leg was innervated by the femoral nerve. The brachial plexus includes the nerve roots (nerves from spinal cord) of C5, C6, C7 and T1 and extends all the way from the neck, underneath the collarbone through the armpit to the arm, elbow and hand where the terminal branches end.

Pacira BioSciences submitted that a diagram from Neal *et al*. 2008 illustrated the anatomical sites for multiple blocks of the brachial plexus, including an interscalene brachial plexus block, a supraclavicular brachial plexus block, an infraclavicular brachial plexus block and an axillary brachial plexus block. The terminal branches of the brachial plexus could also be blocked further down the arm at the level of the elbow, mid-forearm and wrist. While clinicians choose among these different anatomical sites along the pathway of the brachial plexus to perform a

block, these were all blocks of the brachial plexus or the branches from the brachial plexus. Similarly, clinicians choose among the different anatomical sites along the femoral nerve to perform a block of the femoral nerve.

Distinguishing/Explaining Wang *et al* and Similar Studies

Pacira BioSciences submitted that clinicians had an interest in comparing more recent approaches to the femoral nerve block to a traditional femoral nerve block to evaluate how effectively each approach provides pain relief for the patient, while also allowing the patient to mobilise after surgery. This was the focus of the Wang *et al* article, and the many other meta-analyses comparing the all-encompassing femoral nerve block to the more localized adductor canal block. The complainant referenced *Wang et al*, which was referred to as followed in the Panel's ruling:

> 'The Panel noted the complainant's allegation that Exparel was indicated for use as "brachial plexus block", "femoral nerve block", or "field block" and not indicated for use as adductor canal block. The complainant stated that these interventions were not interchangeable or equivalent and cited a publication by Wang *et al*. The Panel noted that Wang *et al* was a meta-analysis of randomised controlled trials (RCTs) that compared adductor canal block to femoral nerve block and referred to adductor canal block as an alternative femoral nerve block.'

Wang *et al* was a meta-analysis comparing adductor canal block with femoral nerve block for post operative pain management in total knee arthroplasty.

Pacira BioSciences questioned what Wang *et al* meant by 'femoral nerve block' if a block placed in the adductor canal in fact itself blocked a branch of the femoral nerve? Wang *et al* stated that 'anatomical study of adductor canal showed that an adductor canal contained multiple afferent sensory nerves (*e.g.*, saphenous nerve…)'. This showed that Wang *et al* understood that a block applied at the anatomical location known as 'the adductor canal' was a block applied to a branch of the femoral nerve. A similar meta-analysis, entitled, 'Adductor Canal Block Versus Femoral Nerve Block for Analgesia After Total Knee Arthroplasty,' (Gao *et al.* 2017), made this clear stating, with respect to an adductor canal block, that:

> 'usually, it blocks the largest sensory **branches from the femoral nerve to the knee, the saphenous nerve**' (emphasis added).

Pacira BioSciences submitted that the reference to 'femoral nerve block' by Wang *et al* referred to the traditional femoral nerve block where anesthetic was administered in the crease between the thigh and the pelvis that was more commonly used prior to the use of ultrasound. The block applied to the adductor canal had only been possible with the use of ultrasound and hence the distinction used in the article, although it was objectively a poor use of nomenclature given that both blocks were in fact blocks of the femoral nerve. Wang *et al.* 2017, stated that:

> 'Adductor canal block (ACB) is a relatively new alternative for post-TKA pain management. Regional anesthesia is deposited within an adductor canal that can be easily visualised at the middle third of the thigh with use of ultrasonography'.

RESPONSE FROM COMPLAINANT

The complainant acknowledged the decision of Pacira BioSciences to appeal the Panel's ruling of a breach of Clause 11.2 in relation to the claim 'the indication for Exparel allows it to be used as either infiltration or an Adductor Canal block (which allow early mobilisation of the patient)'.

'Femoral nerve block' was a medical procedure

The complainant noted that in its appeal Pacira BioSciences stated "When performing the block typically described as a 'femoral nerve block," the anaesthetic is administered in the crease between the thigh and the pelvis…'. The complainant stated that 'Femoral nerve block' was a well-defined medical procedure. An 'adductor canal block' was a distinct medical procedure, also involving branches of the femoral nerves as explained in the appeal references submitted. This was noted by Pacira BioSciences in its 'Introduction to EU & UK Compliance New Hire Training slides' dated October 2021, for which any other 'procedure' was considered 'off-label'.

Adductor canal block includes the anterior division of obturator nerve

The complainant alleged that Refai *et al*, Burckett-St *et al*, and Gao *et al* submitted by Pacira BioSciences noted adductor canal blocks included the anterior division of obturator nerve. In relation to adductor canal block, Burckett-St *et al*, stated 'previous clinical studies that suggest ON (obturator nerve) block contributes to knee analgesia.'. The obturator nerve was not the femoral nerve. At licensed Exparel dose of 20mL, adductor canal block could not reasonably be expected to only affect the femoral nerve.

Concerns regarding product licence must be referred to the MHRA to prevent unintentional promotion or endorsement of Exparel

The complainant alleged that it was not the responsibility of the Panel to clarify the indications for which a medicine was licensed. Pacira BioSciences must instead seek clarification from the MHRA before further promoting the use of Exparel in adductor canal block.

Conflict of interest disclosure

The complainant alleged that Pacira BioSciences must be required to disclose any compensation and/or conflicts of interest for expert contributors. The complainant accepted Pacira BioScience's response that breaches of the Code were an isolated incident and it had since taken steps to prevent recurrence.

APPEAL BOARD RULING

The Appeal Board welcomed the quality and clarity of submissions in this case.

The Appeal Board considered the narrow grounds of the matter of appeal which was solely in relation to the claim 'the indication for Exparel allows it to be used as either infiltration or an Adductor Canal block …'. The Appeal Board noted that the second part of that claim '…which allow early mobilisation of the patient' which related to the effect of Exparel, had already been covered by the Panel's ruling of a breach of Clause 11.2 at point 2 which had been accepted by Pacira.

Pacira explained in detail that it was more clinically appropriate to perform a nerve block further down the leg if it met the needs of the procedure and was the best care for the patient. The

Appeal Board referred to the wording of Section 4.1 of the Exparel SPC, Therapeutic indications, which stated that 'EXPAREL liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults'. Section 4.2, Posology and method of administration, referred to 'Peripheral nerve block (femoral and brachial plexus)'.

The Appeal Board considered the MHRA approved wording of the indication of Exparel and in the Appeal Board's view, it would be unlikely for an SPC to list the sites on every point of a nerve where a block could be performed. Section 4.4 of the Exparel SPC, referred to different sites of injection in relation to use as a femoral nerve block. The Appeal Board had been provided with no evidence that a separate indication was required for performing a block at the saphenous nerve branch of the femoral nerve in the adductor canal region. The Appeal Board noted Pacira's submission that a wider indication was the case for Exparel and its competitor regional anaesthetics. Without any further qualification, it appeared to the Appeal Board that there was no evidence before it that the indication for Exparel did not allow it to be used as a nerve block anywhere along the femoral nerve including as an adductor canal block.

The Appeal Board considered Pacira's submission that the nomenclature of sites on the femoral nerve for regional nerve blocks had not been standardised and work in this area was due to be published shortly. The complainant had alleged on appeal that the adductor canal block also included the anterior division of the obturator nerve (Burckett-St. Laurant *et al*). However, the Appeal Board noted Pacira's submission that the paper concluded that 'No terminal branches of the ON [obturator nerve] were found to directly innervate the capsule of the knee joint. In only 2 specimens, we found an anterior branch of the ON [obturator nerve] entering the adductor canal and anastomosing with the SN [saphenous nerve], one in the proximal third and one in the distal third of the canal'. The Appeal Board did not consider on the evidence provided that, on the balance of probabilities, the adductor canal included the obturator nerve as submitted by the complainant.

The Appeal Board considered that as it accepted the saphenous nerve branch of the femoral nerve was part of the femoral nerve, there was no evidence that use of Exparel as an 'Adductor Canal block' was inconsistent with the Exparel SPC as alleged. The Appeal Board thus ruled **no breach of Clause 11.2** in relation to the claim 'the indication for Exparel allows it to be used as either infiltration or an Adductor Canal block …'. **The appeal was successful.**

2. Alleged inconsistency with the Exparel SPC in two claims for total knee replacement as day surgery

The Panel noted that two claims were made in relation to the use of Exparel for same day total knee replacements. The Panel noted the first claim, which was made in an email dated 15 March 2022, was that

> 'EXPAREL is actually used in USA for sameday Total Knee Replacements for this very reason, with TKR patients going home the day of the operation and having 48/72 hrs of pain free mobility'.

The second claim, which was made in an email dated 16 March 2022, was that

> 'Utility of EXPAREL liposomal provides the potential to consider earlier mobilisation and discharge of patients undergoing target procedures. Therefore use of this drug as part of an enhanced recovery programme would allow operations which are currently inpatient only to be done as a day case such as total knee arthroplasty as postoperative pain is significantly better controlled.'

The Panel noted that it appeared that neither of these claims had been approved by Pacira but according to Pacira could be substantiated.

The Panel noted Pacira's submission that EXPAREL was used as part of an Enhanced recovery after surgery (ERAS) pathway and provided references that supported same day discharge (Dysart *et al* 2018; Weiser *et al* 2018; Parcells *et al* 2016; Hutchins *et al* 2015; Van Horne *et al* 2019; Van Horne *et al* 2022).

Nonetheless, the Panel noted the SPC did not refer to use of Exparel in total knee replacements as day cases and noted Sections 4.2 and 4.4 of the SPC.

Section 4.2 of the SPC, Posology and method of administration, Peripheral nerve block (femoral and brachial plexus), stated that

> 'In patients undergoing total knee arthroplasty (TKA), a total of 266 mg (20 mL) of EXPAREL liposomal was administered as a femoral nerve block.'

Further, Section 4.4 of the SPC Special Warnings and precautions for use, Warnings and Precautions specific to EXPAREL liposomal, stated that

> 'EXPAREL liposomal is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan.'

The Panel, noting the contents of the SPC highlighted above, considered that the two claims promoting same day discharge and early mobilisation were likely to be inconsistent with the particulars listed in the SPC. The Panel therefore ruled, on balance, a **breach of Clause 11.2** of the Code in relation to each claim.

With regard to the allegation that Pacira BioSciences failed to disclose that sensory and/or motor loss with Exparel might persist for up to five days, the Panel noted that Section 4.7 of the SPC, Effects on ability to drive and use machines stated that

> 'Bupivacaine could have a major influence on the ability to drive and use machines. Patients should be informed in advance that bupivacaine liposomal dispersion can cause temporary loss of sensation or motor function. The potential sensory and/or motor loss with EXPAREL liposomal is temporary and varies in degree and duration depending on the site of injection, route of administration (i.e. field block or nerve block) and dosage administered, and may last for up to 5 days as seen in clinical trials.'

Section 4.8 of the SPC, Undesirable effects, listed motor dysfunction and sensory loss as uncommon adverse drug reactions (ADRs).

The Panel noted that this information was not included in the email sent on 16 March by the named representative. Whilst the Panel was concerned that the information was not provided,

the Panel, noting its rulings regarding day case surgery, did not consider that the absence of possible sensory loss and or motor dysfunction in the email at issue meant that it was inconsistent with the SPC in this regard. The Panel, on the narrow allegation, ruled **no breach of Clause 11.2.**

3. Alleged failure to provide balanced, fair and objective overview of the efficacy of Exparel in lower limb arthroplasty in four claims

The Panel noted the following claims were made in an email dated 15 March.

a. 'EXPAREL is actually used in USA for sameday Total Knee Replacements for this very reason, with TKR patients going home the day of the operation and having 48/72 hrs of pain free mobility'.

b. 'It provides 48hrs+ pain relief, meaning no middle of night / waking up in pain for the patient.'

c. 'There is reduced need for additional pain medication including opioids, and the side effects / additional social & economic issues they can bring'

d. 'There is reduced need for catheters / pumps etc'

The Panel noted the information provided by the complainant to support the allegations (Hamilton *et al* 2016; Hamilton *et al* 2017; Hussain *et al* 2021; Dinges *et al* 2021). Pacira had not commented on the data provided by the complainant but had provided other material to support the claims.

With regard to claim a, the Panel noted its comments and rulings in point 2 above regarding total knee replacement as day cases. The Panel also noted that Pacira did not provide material to substantiate the claim for 48/72 hours of pain free mobility in relation to knee surgery; the company instead submitted data to substantiate the claim for 48+ hours pain relief which had been approved, including Section 5.1 of the SPC as well as Patel *et al* (2019) and Mont *et al* (2018) and stated that there were many studies contained in the heatmaps that demonstrated reduced pain following the use of EXPAREL to 48 hours and beyond e.g. L. EXPARELOB-GYN Heatmap.

The Panel noted that Patel *et al* referred to brachial plexus block in shoulder surgery and reduced opioid consumption and Mont *et al* referred to local infiltration analgesia after total knee arthroplasty.

The Panel noted that Patel *et al* 2019 analysed the percentage of pain-free patients as a tertiary efficacy end point, defined as VAS [visual analog scale] pain intensity score less than or equal to 1.5 without prior rescue medication, which showed significantly more patients were pain-free post surgery compared with placebo, at each time point up to 48 hours. The Panel noted the publication was in relation to brachial plexus block in shoulder surgery; the claim at issue referred to total knee replacement and thus the Panel did not consider this paper to be suitable to substantiate the claim.

The Panel noted that Mont *et al* referred to local infiltration analgesia after total knee arthroplasty. Mont *et al* was a Phase IV study and its coprimary efficacy endpoints were the

AUC of VAS pain intensity scores from 12 to 48 hours after surgery (AUC $_{12\text{-}48}$) and total opioid consumption from 0 to 48 hours after surgery. The Panel noted the study concluded that local infiltration analgesia with liposomal bupivacaine significantly improved postsurgical pain, opioid consumption and time to first opioid rescue with more opioid free patients. The Panel noted there did not appear to be an analysis or reference in relation to pain-free mobility.

The Panel noted the data in Section 5.1 of the SPC referred to efficacy being assessed in acute pain 72 hours after total knee arthroplasty. This was a longer time period than the claim in the email for 48-72 hours post surgery. Section 5.1 of the SPC included statistically significant pain intensity score data (AUC of pain intensity score) and opioid use. It appeared that in some uses of Exparel, including Brachial Plexus Nerve Block, there were data of subjects being opioid free whereas in the example of femoral nerve block for total knee arthroplasty, no subjects were opioid free at 72 hours in either the placebo or the Exparel groups.

The Panel considered that no data were provided to support claim 3a in relation to pain-free mobility nor in relation to 'no middle of night / waking up in pain for the patient' in the context of knee surgery in 3b.

The Panel considered that the claims did not reflect the evidence before it clearly and exaggerated the medicine's properties. The Panel ruled each claim in **breach of Clauses 6.1 and 14.4** of the Code**.**

The Panel noted that Clause 14.1 was in relation to comparisons. The Panel did not consider that the complainant had established that claims 3a and 3b were comparisons and thus on that narrow ground, ruled **no breach of Clause 14.1** of the Code in that regard.

With regard to the claim 'There is reduced need for additional pain medication including opioids, and the side effects / additional social & economic issues they can bring' (claim 3c), the Panel noted Pacira's submission that there were many studies contained in the heatmaps that demonstrated reduced opioid use following the use of Exparel to 48 hours and beyond. The Panel noted that the heat maps referred to six randomised controlled trials in gynaecologic oncology. In three out of the six trials listed in the EXPARELOB-GYN Heatmap (Enclosure L; copy provided), opioid consumption was significantly lower up to 48 hours after use of liposomal bupivacaine; the other three found no statistical difference.

Nedeljkovic *et al* 2020 stated that 'Total opioid consumption through 72 hours was reduced with LB [liposomal bupivacaine] plus bupivacaine HCl versus bupivacaine HCl alone (least squares mean [LSM] [standard error (SE)] MED, 15.5mg [6.67 mg] vs 32.0 mg [6.25 mg]). This corresponded to an LSM treatment difference of -16.5 mg (95% confidence interval [CI], −30.8 to −2.2 mg; P = .012).

Baker *et al* 2018 stated that 'Of 201 patients, 101 were treated with LB TAP [transversus abdominis plane] block (LB-TAPB) and 100 without LB-TAPB. Treatment with LB-TAPB vs without LB-TAPB significantly reduced mean post-surgical opioid consumption.' The table of adverse events listed a lower number of opioid-related adverse events in patients treated with KB-TAPB versus without, however these were not significant.

The Panel further noted that Section 5.1 of the SPC listed statistically significant reductions in opioid medications.

In relation to the aspect of the claim that 'there is reduced need for additional pain medication including opioids', the Panel considered there was evidence to show a reduction in opioid use and thus did not consider that the complainant had established that claim 3c was misleading or exaggerated as alleged. The Panel therefore ruled **no breach of Clauses 6.1 and 14.4** in this regard. The Panel did not consider that the complainant had established there was a comparison so the Panel ruled **no breach of Clause 14.1 of the Code** accordingly.

With regard to claim 3d and the use of catheters which had not been approved, Pacira submitted that Exparel provided a single administration of long lasting liposomal bupivacaine without the need for continuous infusion of local anaesthetics which required a catheter and management of the infusion and the site. Pacira referred to some of the problems with the use of ambulatory infusion pumps including the need for 24/7 availability of health care provider to address any complications. The Panel noted that the data in this regard related to the US.

The Panel did not consider that the complainant had discharged his/her burden of proof that there was not a reduced need for catheters with Exparel nor that the claim was misleading or exaggerated. The Panel therefore ruled **no breach of Clauses 6.1 and 14.4**. The Panel did not consider that the complainant had established that the claim was a misleading comparison and therefore ruled **no breach of Clause 14.1.**

The Panel noted that there was no briefing material for representatives and at the time of the emails, the company had not agreed to comply with the Code and accept the jurisdiction of the PMCPA. The Panel therefore ruled **no breach of Clause 17.9.**

4. Claim stating that Exparel has an impact on 'social and economic issues'

The Panel noted that the phrase 'social and economic issues' was part of claim 3c above which was in the email of 15 March 2022.

> 'There is reduced need for additional pain medication including opioids, and the side effects / additional social & economic issues they can bring'

The Panel noted Pacira's submission regarding reduced opioid use as set out in point 3 above.

The Panel noted that Pacira had not provided any additional data to substantiate the claim at issue with regards to the effects on social and economic issues. However, the Panel noted that if Exparel reduced the need for additional pain medication including opioids as noted at Point 3 then there would potentially be a reduction in side effects and any social and economic issues arising from opioid use. Whilst in the Panel's view, use of opioids was likely to be less expensive than using Exparel based on the cost of the medicines, it noted that there was no evidence before it that the use of Exparel in total knee replacement, and the resultant reduced use of opioids, would directly result in reduced social and economic issues as implied by the claim.

The Panel considered, on the evidence before it, that the claim was misleading, not capable of substantiation and exaggerated the properties of Exparel and therefore, on balance, ruled a **breach of Clauses 6.1, 6.2 and 14.4.**

The Panel noted Clause 6.4, *inter alia,* stated information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no adverse reactions, toxic hazards or risks of addiction or dependency.

The Panel did not consider that implying that if patients were not using opioids then they would not experience the side effects of opioids was unreasonable in relation to the requirements as set out in Clause 6.4 and thus ruled **no breach of Clause 6.4** in that regard.

5. Alleged failure to communicate the known risks of Exparel or link to further prescribing information

The Panel noted that prescribing information must be provided in a clear and legible manner in all promotional material as per Clause 12.1.

The Panel noted that no prescribing information was provided as part of the emails in question, nor was there information about adverse reactions. However, the Panel noted that Clauses 6.1 and 6.4 were raised by the complainant.

Clause 6.1 of the 2021 Code stated that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

Clause 6.4 stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification.

The Panel did not consider that the omission of prescribing information and information about adverse events amounted to breaches of Clauses 6.1 and 6.4 as alleged. Therefore, **no breach of Clauses 6.1 and 6.4** were ruled.

6. **Overall**

The Panel noted its rulings and comments above, including that prescribing information and information about reporting adverse events was not provided. The Panel considered that both were paramount to patient safety and considered it was crucial that health professionals could rely completely upon the industry for up-to-date and accurate information about their medicines. The Panel considered therefore that high standards had not been maintained and **a breach of Clause 5.1** was ruled.

Complaint received **16 March 2022**

Case completed **23 March 2023**