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MHRA
Regulating Medicines and Medical Devices

[redacted]
Omega Pharma Limited
32 Vauxhall Bridge Road
London, SW1V 2SA.

Our Ref: GPvP 2855/7416989-0001

Date: 9th October 2013

INFRINGEMENT NOTICE
Served pursuant to regulation 206 of the
Human Medicines Regulations 2012

Dear [redacted],

The Secretary of State for Health is serving this Infringement Notice on Omega Pharma Limited under regulation 206 of the Human Medicines Regulations 2010 (the Regulations).

A pharmacovigilance re-inspection conducted on 5th – 7th March 2013 revealed objective grounds for considering that Omega Pharma Limited has contravened the regulations listed in Appendix 1. This was the fifth MHRA pharmacovigilance inspection of Omega Pharma and, despite the commitments previously made by the company, the findings identified during the previous inspections had not been sufficiently addressed, and serious and persistent non-compliance with EU and UK pharmacovigilance requirements was identified at the MHRA re-inspection in March 2013.

Serious and persistent non-compliance with pharmacovigilance requirements has resulted, in part, due to a lack of adequately trained personnel and appropriate resources within the Marketing Authorisation Holder (MAH). The MAH is required to ensure that adequate resources are available in order to ensure complete and appropriate delivery of the approved corrective and preventative action plan, as documented in the MHRA Pharmacovigilance Inspection Report (final version dated 29th August 2013).

You are reminded that a breach of the regulations specified constitutes a criminal offence. Prosecutions may be brought against the company, or its officers, where the breaches are carried out with the officer's consent or connivance or are attributable to their neglect (see regulation 338). In the UK, the penalties for these breaches range from a fine to up to 2 years in prison.

The MAH is requested to respond within 21 working days of the date of this letter to confirm that the measures described in Appendix 1 will be implemented. If the MAH fails to confirm this within 21 days, further action will be considered by the Enforcement Authority, which may include:

- Actions taken against future marketing authorisation applications or marketing authorisations.
- Referral for criminal prosecution.

The EEA qualified person responsible for pharmacovigilance should indicate their approval of the response to this Infringement Notice.

The European Medicines Agency and European Commission will be informed of this notice as specified in Regulations 206(3). Details of Infringement Notices that have been served under regulation 206 may also be published on the MHRA external website. In this event, the MAH will have the opportunity to request that their response is published in conjunction with these details. Please state in your response whether the company agrees to the publication of its response to the Infringement Notice.

Yours sincerely,

David Carter
A person authorised to sign on behalf of The Secretary of State for Health
Email: IAGSecretariat@mhra.gsi.gov.uk

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Appendix 1:

Relevant Provision
The Human Medicines Regulations 2012 (SI 2012/1916), Part 11 Pharmacovigilance: ***Recording obligations on holders*** ***Regulation 187 -*** *(1) Subject to paragraph (2), the holder must record all suspected adverse reactions to the product occurring in the EEA or in third countries which are brought to its attention irrespective of whether the reaction—* *(a) is reported spontaneously by patients or health care professionals; or* *(b) occurred in the context of a post-authorisation study.*
Contravention
In spite of previous commitments made to the UK Licensing Authority, the Marketing Authorisation Holder (MAH) had failed to ensure that there was an adequate system in place to collect suspected adverse reactions relating to Omega Pharma medicinal products from each territory and that appropriate contracts and agreements were in place to support pharmacovigilance activities, including safety data collection. Evidence includes: a) There was no documented pharmacovigilance data reconciliation with Omega Pharma affiliates in Italy, Greece, Portugal, Spain, Switzerland, Romania, Poland, Hungary, Latvia/Lithuania/Estonia, Slovenia and Czech Republic to ensure that any adverse reaction reports received by affiliates had been appropriately transmitted to the Omega Pharma pharmacovigilance department. b) There was no documented pharmacovigilance data reconciliation with Omega Pharma distribution partners to ensure that suspected adverse reaction reports had been appropriately collected from all territories. c) There was no pharmacovigilance agreement with the manufacturers of [redacted] and the [redacted] range of antiseptic medicines [redacted] to ensure appropriate pharmacovigilance data exchange. d) The literature search strategy utilised by the MAH did not support the global collection of all relevant pharmacovigilance data. e) There was no global repository of product quality complaints (failure to perform product quality reviews had been identified as an issue at the previous MHRA GPvP inspection).

Measures to be taken	**Timeframe**
The Marketing Authorisation Holder (MAH) is required to:	
1. Implement agreements with all Omega Pharma affiliates, medicines distributors and manufacturers, which define the roles and responsibilities of the different parties in terms of pharmacovigilance and the reporting requirements for ICSRs (Individual Case Safety Reports).	By end of January 2014
2. Implement reconciliation of pharmacovigilance data with Omega Pharma affiliates and medicines distributors (as described in the company's corrective and preventative action plan).	By end of November 2013
3. Ensure that the literature search strategies utilised for the purposes of weekly identification of ICSRs and for ongoing safety evaluation are adequate and undertake documented tests to confirm this, in order to ensure that pharmacovigilance relevant articles are not missed.	By end of November 2013
4. Establish a global repository of product quality complaints and implement a process for product quality complaint trend analysis.	By end of November 2013

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Relevant Provision	
The Human Medicines Regulations 2012 (SI 2012/1916), Part 11 Pharmacovigilance: ***Obligation on holder to audit pharmacovigilance system*** ***Regulation 184*** *- (1) The holder must—* *(a) perform a regular audit of its pharmacovigilance system;* *(b) place a note concerning the main findings of each audit on the pharmacovigilance system master file on completion of each audit; and* *(c) ensure that an appropriate corrective action plan is prepared and implemented as soon as is reasonably practicable after completion of each audit.*	
Contravention	
The MAH had failed to implement a risk-based pharmacovigilance audit strategy, covering the governance, risk management and internal controls of all parts of the pharmacovigilance system. Evidence included: a) No audits of the Omega Pharma affiliates had been conducted, other than of the UK affiliate (Omega Pharma has affiliate offices in Portugal, Ireland, Italy, Sweden, Greece, Belgium, Germany, UK, France, Spain, Netherlands, Austria, Switzerland, Romania, Poland, Hungary, Latvia/Lithuania/Estonia, Slovenia and Czech Republic). b) The audit of the central pharmacovigilance function did not include any review of the roles and responsibilities of the QPPV, PSUR production, signal detection or training (which are key aspects of the pharmacovigilance system). c) No documented internal audit plan for audits of affiliates or processes within the central pharmacovigilance function existed at the time of the re-inspection.	
Measures to be taken	**Timeframe**
The Marketing Authorisation Holder (MAH) is required to:	
1. Implement a revised global audit standard operating procedure, to include at a minimum: • a description of the risk-based audit programme (the risk-based rationale for audits should be appropriate for the type of pharmacovigilance system operated by the MAH), • a revised auditing scope of the pharmacovigilance global function, • a documented process for managing corrective and preventative actions from audit or inspection.	By end of November 2013
2. Implement an appropriate global internal audit plan for verification of pharmacovigilance activities in line with the approved risk-based audit programme.	By end of November 2013

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Relevant Provision
The Human Medicines Regulations 2012 (SI 2012/1916), Part 11 Pharmacovigilance: ***Obligation on holder to submit periodic safety update reports: general requirements*** ***Regulation 191*** *- (4) Each PSUR must contain -* *(a) summaries of data relevant to the benefits and risks of the product, including results of all studies, with a consideration of their potential impact on the authorisation for the product;* *(b) a scientific evaluation of the risk-benefit balance of the product; and* *(c) all data relating to the volume of sales of the product and any data the holder has relating to the volume of prescriptions, including an estimate of the population exposed to the product.*
Contravention
The MAH had failed to submit periodic safety update reports (PSURs) containing appropriate scientific evaluation of the risk-benefit balance of the product and all data relating to the volume of sales of the product. Evidence relating to [redacted] 1% PSUR (1st August 2009 to 31st July 2012) includes: a) Section 6 (Patient Exposure) included an estimate of total exposure of 65,644 units per month. However, Omega's Swiss subsidiary [redacted] did not provide sales data for the PSUR, even though there had been Swiss sales for [redacted] in the PSUR period. b) Section 9 (Other information) stated "Efficacy-related information: not relevant". This was incorrect as 61 cases of lack of efficacy were received during the PSUR period. Although this represented a small number of cases in comparison to exposure for the product, the MAH did not comment on whether this represented an increase in reporting of lack of efficacy since the previous PSUR or on whether concerns have been identified relating to increasing resistance to [redacted]. c) Section 10 (Overall safety evaluation) stated "nonserious unlisted reactions: none". This statement was incorrect because four cases relating to hair loss/baldness were received during the period of the PSUR and these events were unlisted. There was no discussion in the PSUR concerning the significance of these cases and no background information was included to provide context for these events e.g. the number of events of this type that had previously been reported.

Measures to be taken	**Timeframe**
The Marketing Authorisation Holder (MAH) is required to:	
1. Conduct documented training of PSUR writers on the requirements set out in The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 191 and Good Pharmacovigilance Practice Module VII – Periodic Safety Update Report.	By end of November 2013
2. Implement a revised PSUR standard operating procedure, to include at a minimum: • process for accurate compilation of PSURs and scientific evaluation of the risk-benefit balance of the product, • process for quality checks of PSURs.	By end of November 2013

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Relevant Provision
The Human Medicines Regulations 2012 (SI 2012/1916), Part 11 Pharmacovigilance: ***Obligation on holder to operate a pharmacovigilance system*** ***Regulation 182*** *- (4) the holder must use its pharmacovigilance system to—* *(a) evaluate scientifically all information relevant to the product;* *(b) consider options for minimising and preventing the risk presented by the use of the product; and* *(c) take appropriate measures as soon as is reasonably practicable to—* *(i) investigate the potential risks of the product,* *(ii) communicate the risks, and* *(iii) implement actions for minimising and preventing the risks, including updating the risk management system for the product.*
Contravention
Delays and deficiencies in the implementation of compliant signal detection processes for ongoing safety evaluation had been identified at previous MHRA GPvP inspections of the MAH. At this re-inspection, it was identified that signal detection was not being performed using all available safety data. Evidence included: a) The data reviewed during signal detection activities only included UK origin cases that were received in the period under review; there was no review of global, cumulative data. b) There was no overall review of safety data for products with common active substances; for example, the cases for [redacted] and [redacted] (active ingredient, [redacted]) were not reviewed in conjunction. c) The literature searching strategy that was utilised would not identify articles of interest for ongoing safety evaluation of medicinal products. d) Signal detection was not being performed for products authorised in other EU Member States that were not authorised in the UK, i.e. the MAH had limited its corrective action to products authorised in the UK.

Measures to be taken	**Timeframe**
The Marketing Authorisation Holder (MAH) is required to:	
1. Implement evaluation of global safety data for the purpose of signal detection for all products.	By end of November 2013
2. Implement a revised standard operating procedure, to include at a minimum: • all global sources of safety data used for ongoing safety evaluation, • frequency and methodology of signal detection activities.	By end of November 2013
3. Conduct documented training for those staff performing signal detection activities on the requirements set out in The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 182 and Good Pharmacovigilance Practice Module IX – Signal Management.	By end of November 2013
4. Ensure that the literature search strategies utilised for the purpose of ongoing safety evaluation are adequate and undertake documented tests to confirm this, in order to ensure that pharmacovigilance relevant articles are not missed.	By end of November 2013