Medicines and Healthcare Products Regulatory Agency

Report No: ***INSP GMP 22917/8721389-0002 NCR***

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer [1]

Part 1

Issued following an inspection in accordance with :
Art. 15 of Directive 2001/20/EC

The competent authority of United Kingdom confirms the following:
The manufacturer: ***PHARMACEUTICS INTERNATIONAL INC***
Site address: ***103 BEAVER COURT, COCKEYSVILLE, 21030, United States***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-02-26*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC

[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

Part 2

Human Investigational Medicinal Products

1 NON-COMPLIANT MANUFACTURING OPERATIONS

Include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;

1.1	**Sterile products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.2 Lyophilisates 1.1.1.4 Small volume liquids
	1.1.2 Terminally Sterilised (processing operations for the following dosage forms) 1.1.2.3 Small volume liquids
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.2 Capsules, soft shell 1.2.1.13 Tablets
1.4	**Other products or manufacturing activity**
	1.4.2 Sterilisation of active substance/ excipients/ finished product 1.4.2.1 Filtration 1.4.2.2 Dry heat 1.4.2.3 Moist heat
1.5	**Packaging**
	1.5.2 Secondary packing
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility*

Clarifying remarks (for public users)

The scope of this statement of non-compliance is limited to medicinal products considered non-critical to public health. Where manufacture and/or testing is continued for critical products, this should be supported by a documented risk assessment containing sufficient information to support activity on a risk management basis. The statement of non-compliance also applies to all investigational medicinal products (IMPs) manufactured by Pii and the manufacture and supply of these products should cease. The only exemption to this is where a trial sponsor can demonstrate that the benefit risk ratio remains positive and supports the continuation of a particular trial. Pii is required to carry out a risk assessment, in conjunction with the sponsor of each trial for which they manufacture IMP, to discuss such continuation of supply on a batch by batch basis.

Part 3

1. Nature of non-compliance:

The inspection identified two critical deficiencies: (1) failure of organisational and technical measures to minimise the risk cross-contamination between hazardous and non-hazardous products manufactured in the same manufacturing facilities using shared equipment. (2) Failure of the quality unit to ensure the effective operation of the quality system. This included a gross failure of change management, permitting the use of an unqualified HPLC system and unacceptable approach to production equipment qualification. Quality investigations also lacked implementation of quality risk management principles. Three major deficiencies were also identified: (1) organisational data governance failures, particularly relating to generation and checking of analytical data obtained from electronic systems, and inadequate investigation into previous data integrity failures. (2) deficiencies in sterilisation and depyrogenation processes, and (3) insufficient control of aseptic operations to provide the required level of sterility assurance.

Action taken/proposed by the NCA

Recall of batches already released
Based on the identified GMP deficiencies, recall of product is recommended, where market alternatives and medical criticality permits.

Prohibition of supply
No future batches of non-critical product to be supplied to the EU while this statement of non-compliance remains in force

Suspension of clinical trials
The proposal to continue supply individual batches of investigational medicinal product should be submitted as a substantial amendment, supported by a risk assessment and demonstrating a positive benefit risk ratio for trial subjects. This should be authorised by the National Competent Authority.

Additional comments
National Competent Authorities should evaluate the criticality of products being supplied by this manufacturing site and enact measures to ensure continued supplies where appropriate. Marketing authorisation holders are requested to contact the relevant National Authority to verify whether their products are considered medically critical to public health in their territory and therefore outside the scope of the non-compliance statement. The scope of this statement of non-compliance also applies to chemical / physical quality control testing (GMP in-process and stability analysis) at the adjacent site; 10950 Beaver Dam Road, Hunt Valley, MD 21031 USA.

Products manufactured at site, if known	Products	EudraCT nos
Investigational Medicinal Products	EU clinical trials impacted	EudraCT numbers not available.

2016-06-15

Name and signature of the authorised person of the Competent Authority of United Kingdom

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Confidential
Medicines and Healthcare Products Regulatory Agency
Tel: ***Confidential***
Fax: ***Confidential***

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Report No: ***Insp GMP 22917/37149-0007 NCR***

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer [1]

Part 1

Issued following an inspection in accordance with :
Art. 111(7) of Directive 2001/83/EC as amended
Art. 15 of Directive 2001/20/EC

The competent authority of United Kingdom confirms the following:
The manufacturer: ***PHARMACEUTICS INTERNATIONAL INC***
Site address: ***10819 GILROY ROAD, HUNT VALLEY, 21031, United States***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-02-26*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC

[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

Part 2

Human Medicinal Products Human Investigational Medicinal Products

1 NON-COMPLIANT MANUFACTURING OPERATIONS Include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.2 Capsules, soft shell 1.2.1.6 Liquids for internal use 1.2.1.13 Tablets 1.2.1.17 Other: Vaginal tablets (pessaries) and granules/powders(en)
1.5	**Packaging**
	1.5.2 Secondary packing
	1.5.1 Primary Packing 1.5.1.1 Capsules, hard shell 1.5.1.2 Capsules, soft shell 1.5.1.6 Liquids for internal use 1.5.1.13 Tablets
1.6	**Quality control testing**
	1.6.3 Chemical/Physical

Clarifying remarks (for public users)

The scope of this statement of non-compliance is limited to medicinal products considered non-critical to public health. Where manufacture and/or testing is continued for critical products, this should be supported by a documented risk assessment containing sufficient information to support activity on a risk management basis. The statement of non-compliance also applies to all investigational medicinal products (IMPs) manufactured by Pii and the manufacture and supply of these products should cease. The only exemption to this is where a trial sponsor can demonstrate that the benefit risk ratio remains positive and supports the continuation of a particular trial. Pii is required to carry out a risk assessment, in conjunction with the sponsor of each trial for which they manufacture IMP, to discuss such continuation of supply on a batch by batch basis.

Part 3

1. Nature of non-compliance:

The inspection identified two critical deficiencies: (1) failure of organisational and technical measures to minimise the risk cross-contamination between hazardous and non-hazardous products manufactured in the same manufacturing facilities using shared equipment. (2) Failure of the quality unit to ensure the effective operation of the quality system. This included a gross failure of change management, permitting the use of an unqualified HPLC system and unacceptable approach to production equipment qualification. Quality investigations also lacked implementation of quality risk management principles. Three major deficiencies were also identified: (1) organisational data governance failures, particularly relating to generation and checking of analytical data obtained from electronic systems, and inadequate investigation into previous data integrity failures. (2) deficiencies in sterilisation and depyrogenation processes, and (3) insufficient control of aseptic operations to provide the required level of sterility assurance.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. UK GMP 22917 Insp GMP 22917/37149-0006
Withdrawal of UK GMP 22917 Insp GMP 22917/37149-0006

Recall of batches already released
Based on the identified GMP deficiencies, recall of product is recommended, where market alternatives and medical criticality permits.

Prohibition of supply
No future batches of non-critical product to be supplied to the EU while this statement of non-compliance remains in force

Suspension of clinical trials
The proposal to continue supply individual batches of investigational medicinal product should be submitted as a substantial amendment, supported by a risk assessment and demonstrating a positive benefit risk ratio for trial subjects. This should be authorised by the National Competent Authority.

Additional comments
National Competent Authorities should evaluate the criticality of products being supplied by this manufacturing site and enact measures to ensure continued supplies where appropriate. Marketing authorisation holders are requested to contact the relevant National Authority to verify whether their products are considered medically critical to public health in their territory and therefore outside the scope of the non-compliance statement. The scope of this statement of non-compliance also applies to chemical / physical quality control testing (GMP in-process and stability analysis) at the adjacent site; 10950 Beaver Dam Road, Hunt Valley, MD 21031 USA.

Products manufactured at site, if known	Products	Dosage Form	Reference Member State, National or EMA
Human Medicinal Products	Ammonaps	Tablets 500mg	EU/1/99/120/001 and 002
	Ammonaps	Oral powder	EU/1/99/120/003 & 004
	Lutigest	Vaginal tablets	UK PL 03194/0103

Products manufactured at site, if known	Products	EudraCT nos
Investigational Medicinal Products	EU clinical trials impacted	EudraCT numbers not available.

2016-06-15

Name and signature of the authorised person of the Competent Authority of United Kingdom

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