Active Pharmaceutical Ingredients Industry Comments
Generic Drugs User Fee
Food and Drug Administration Docket Nº FDA-2010-N-0381

1. Executive Summary

The European Chemical Industry Council's (CEFIC) fine chemicals group (EFCG) and the Society of Chemical Manufacturers and Affiliates' (SOCMA) Bulk Pharmaceutical Task Force (BPTF) are providing comments to docket number FDA-2010-N-0381. This proposal supports the use of API site registration fees and foreign inspection fees to be used to i) improve the Abbreviated New Drug Application (ANDA) review process and timeline, ii) increase the compliance oversight mechanism to protect patient safety and iii) drive necessary changes to inspectional organization and practice. Details of this proposal, as well as background supporting it, are contained in subsequent paragraphs.

2. Background

CEFIC is the leading trade association of the chemical industry in Europe representing 29,000 large, medium and small companies, which provides 1.3 million jobs and accounts for one third of the world's chemical production. SOCMA is the leading trade association in the United States for the specialty batch and custom manufacturing chemical industry, representing approximately 300 member companies with more than 2000 manufacturing sites and over 100,000 employees. BPTF and EFCG are sector groups of these leading associations whose members include manufacturers of active pharmaceutical ingredients (APIs), excipients and intermediates. One of the primary objectives of both groups is to interact with government agencies on emerging issues that affect members.

EFCG and BPTF thank the FDA for the opportunity to comment on the development of a Generic Drugs User Fee program. We are honored to contribute to the public enquiry and appreciate the fact the EFCG was invited from Europe to provide input and comment on Generic Drugs User Fees. Europe represents the largest concentration of FDA inspected sites dedicated to Active Pharmaceutical Ingredients (APIs) the number of manufacturing sites being several times greater than in the USA. This openness confirms that FDA is operating in the spirit of the 21st century. In response, BPTF and EFCG have sought to demonstrate that industry in several regions of the world is equally aligned and keen to collaborate globally. The need for global collaboration by industry associations as well as drug regulatory agencies has never been more pressing.

Our fundamental concern regarding the risks to public health associated with the use of drugs manufactured at substandard foreign facilities have remained unchanged for a number of years. These concerns are reflected accurately in a large number of documents such as:

- BPTF Citizens Petition of 2005[1]
- BPTF/EFCG joint position paper of 2006[2]
- BPTF and EFCG testimonials at the Congress Sub-Committee on Oversight and Investigations in November 2007[3]

[1] http://www.socma.com/assets/File/socma1/PDFfiles/bptf/Citizens_Petition_Foreign_Inspection_FINAL.pdf (accessed on February 7, 2011)
[2] http://www.socma.com/assets/File/socma1/PDFfiles/bptf/EFCG-SOCMA_common_position_paper.pdf (accessed on February 14, 2011)
[3] http://efcg.cefic.org/isoFILES/publications/items/DOWNLOAD_129.pdf (accessed on February 14, 2011) and http://www.socma.com/assets/File/socma1/PDFfiles/NewsReleases/JohnDubeck_WrittenTestimony.pdf (accessed on February 9, 2011) and

Notwithstanding the comments made in these documents and testimonials, we appreciate and acknowledge that over the past 5 decades FDA has been the driving force behind efforts to ensure the quality and safety of APIs through cGMP, a central component of drug quality outlined in the ICH Q7 guidance in 2001 and more recently enshrined into EU legislation in 2006. Although the FDA system for foreign API oversight needs improvement, FDA requirements are still the standard and far ahead of all other authorities' requirements with respect to API quality and safety.

It is very important to understand that the risks to public health and the solutions proposed are not limited to generic drugs. Although out of the scope of this docket, the recommendations of our groups should be applied to Over-the-Counter (OTC) drugs, as well as to new drugs as applicable.

3. Overall Goals for a Generic Drug User Fee Program

The goals of this Generic Drugs User Fee initiative is the increase of funding to FDA to allow for more resources directed at the delivery of ***(1) improved service and predictable timelines in the review process for ANDAs and pre-approval supplements***. However, in light of:

i. The highly complex, fragmented and specialized supply chains
ii. The accelerating globalization of the industry
iii. The intensity of competition in the off-patent segment
iv. The slow pace of adjustment by the governmental bodies charged with oversight over the industry and the protection of patients

EFCG and BPTF find it imperative that two additional critical collateral benefits be secured with this process and that extra funding be raised for ***(2) improvement of the compliance oversight mechanism to the benefit of the safety of patients*** and ***(3) the creation of a validated, transparent and comprehensive database of all FDA-registered API sites.***

To this end user fees should enable a larger number of more thorough compliance inspections. These goals require a radical revamp of the staffing of the foreign inspection service, its funding and autonomy.

4. FDA Performance Goals

Upon implementation of this scheme over a 5 year period, FDA should be able to achieve the following performance goals:

- Timelines for responses to submissions of ANDAs and for any supplement that requires pre-approval should be set respectively at 12 months and 4 months.
- All sites (domestic and foreign) that supply API for drug products consumed in the USA (all drug products: both prescription and OTC) must meet an FDA pre-approval inspection. Thereafter, the maximum length of time between compliance inspections (whether pre-approval inspection or on-going surveillance inspections) must not exceed 3 years.
- A validated database fully transparent to the public and accessible via the internet that lists the companies that have Drug Master Files (DMFs) filed at FDA, the sites that are registered with the FDA and the APIs made at those registered sites and the outcomes of the FDA compliance inspections that have taken place there.

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http://democrats.energycommerce.house.gov/images/stories/Documents/Hearings/PDF/110-oi-hrg.110107.Villax-Testimony.pdf (accessed on February 7, 2011)

5. Overview of Proposal

Starting points for our proposals are to keep it simple and to allow for relatively quick implementation. It will be important that incoming fees be used in full by FDA to fund the critical activities proposed herein. In order to safeguard this simplicity we propose that the installment of fees will be limited to an annual establishment registration fee for each API manufacturing site and a fee for each foreign compliance inspection carried out by FDA. Fees in relation to the review of ANDAs, including the review of API related DMFs and supplements should in their entirety be charged to the ANDA holders, similar to how this has been implemented through Prescription Drug User Fee Act (PDUFA) for New Drug Applications (NDAs).

6. Expected Outcomes Relating to APIs

User fees should be directed at funding additional resources for better oversight over generic drugs. With respect to APIs used in the manufacture of generic drugs, the following outcomes should be expected from the user fee program:

1. In the interest of the FDA and of pharmaceutical companies that purchase APIs it is important to create a true and validated inventory of registered API sites with a list of the APIs they have been satisfactorily inspected for. This database of who is approved to supply should be a public document (serving both USA and non-USA users of APIs). Furthermore if being on the list is a necessary condition for allowing a drug product to be put on the market, being removed from it must trigger the reverse.

2. In order to protect patient safety and the security and authenticity of the API supply chain all inspections should verify Regulatory compliance as well as GMP compliance. However inspections must meet a number of conditions if they are to have the desired effect:

    i. Such inspections need to occur before any drug product (both prescription and OTC) containing API from any site is approved for sale; these are the initial, product specific pre-approval inspection.
    ii. After a product specific pre-approval inspection has taken place, on-going surveillance inspections for that site should occur periodically so that the "acceptable status" remains current with respect to all APIs produced at that site, including the ones for which there have been pre-approval inspections in the past. There has to be a maximum number of years (3 years suggested) before which a re-inspection should take place - however the actual frequency of the on-going surveillance inspections needs to be determined in a risk-based manner. If a site manufactures more than one API for the USA market, an inspection may cover both pre-approval and on-going surveillance. After a successful inspection the document that communicates back the "acceptable status" to the site should list all the APIs with a positive outcome (whether at a pre-approval or on-going surveillance inspection). The issuance of an FDA cGMP certificate for acceptable inspections with validity date would be the preferred method of documentation, as done by EU agencies. Conversely an unsuccessful inspection should result in communicating specifically the "non-acceptable status" of all the involved APIs. This document should be available on-line to the public.

In addition to the above quantitative element of "frequency" of inspections that we propose to be determined by a risk-based assessment, there are two other qualitative elements that need to be considered.

iii. The Degree of Depth of the Inspection: The signatories of this document believe that any inspection done under a new user fee regime should be more than just a general GMP inspection. It should not only be product specific for all APIs that the site supplies for drug products consumed in the USA but the inspection must also positively verify that what happens in reality in the production line, the QC labs, the sourcing of materials, etc. mirrors what is described in the current DMF. Our sense is that the current variability of the depth of API inspections is too great, and the mandatory need to compare reality with the contents of the DMF (or ANDA) is vague and needs explicit definition. Currently far too many inspections are only focused on GMP compliance and do not give sufficient weight to the verification of actual compliance with the submitted information and data in the regulatory filings. There should be no disconnects between the filing and the operations.

iv. The Structure of FDA's Foreign Inspection Service: FDA's Foreign Inspection service under its current structure cannot be expected to meet the requirements of the role this proposal demands. The Foreign Inspection Service was designed and structured several decades ago and the 21st century requires something entirely different. The inspection effort is now radically different in terms of: a) sheer number of inspections, and b) the locations where these inspections take place present far greater diversity and are often not in the "comfort zone" of the current cadre of inspectors. In addition, to meet the criteria described in i., ii. and iii., inspections must become lengthier and demand more resources. The Foreign Inspection Service needs to have a permanent cadre of inspectors that are recruited and compensated specifically for performing foreign inspections. They need the appropriate qualifications and training to be able to inspect in environments that differ substantially from those in the USA with regard to culture, climate, development level, values, language and writing. The data are showing that priorities within both the US and European inspection programs are still based on proximity and not on risk. This must change, and a dedicated corps of purpose-recruited, trained and compensated inspectors is a necessary part of the solution. FDA inspectional obligations must not be delegated to 3rd parties; this activity is at the core of FDA's mission. Nevertheless FDA should establish a rich level of dialogue, all the way up to and including Mutual Recognition Agreements, with other government agencies such as European Medicines Agency (EMA), European Directorate for the Quality of Medicines & HealthCare (EDQM), the EU Member States' medicines' agencies, PMDA Japan and TGA Australia. Such dialogues should include reciprocal access to compliance inspections related data enabling an improved risk-assessment process without incurring further cost.

3. A further concern of the API industry is that the current state of affairs is very detrimental to compliant companies and very favorable to others: the playing field is not level. If the above measures could be achieved it would be a giant step forward in rebalancing the competitive environment. Failing to do so would lead to yet further delocalization of API production to areas where inspections are much less frequent because arranging for and performing inspections there presents material additional hurdles. Generally speaking, absent an arbiter of quality, compliant quality suppliers are increasingly unable to compete. This is a trend that urgently needs to be stopped and turned around in the interest of patients.

7. Proposal

Our associations welcome the principle of user fees for API manufacturers. EFCG's parent association CEFIC has been communicating this position via its sector group Active Pharmaceuticals Ingredients Committee (APIC) since 2004[4], endorsed by EFCG.
We propose:

- **An Annual Establishment Registration Fee**: Foreign and domestic sites applying for or renewing an establishment registration would be required to pay an annual fee. The annual registration procedure should also involve listing the relevant APIs (those currently approved, and those for which a submission is likely to be made in the coming year). This would also allow for a data base to be created that would list all registered sites together with an indication of what APIs the site has been inspected and found acceptable for. Our proposed fee lies in a range from $1,000 to $10,000 (to be determined by the FDA, taking into account the monetary requirements to maintain an accurate database). A forgery proof "receipt" of the payment should identify the site unambiguously (street address, DUNS number and/or Establishment Registration number, latitude and longitude), the year, and the inspected APIs it produces together with the matching NDC labeler code. Furthermore, FDA should be mandated to display on the FDA website such data so that auditors of API plants and purchasing departments of pharmaceutical companies can confirm the FDA inspection status of the site. Such information would be a central contributor to supply chain security
- **A fee per inspection**: Every foreign inspection should require payment of an inspection user fee. The payment needs to be made prior to the start of the inspection. The level of the user fee should be variable and should be based on the actual costs incurred and for the resources needed for its execution. We expect that the cost of inspections may vary significantly based on size of site, number of APIs, geography, travel costs, number of inspectors, need for translators, etc. That said, it may be simpler to have standard inspection fees per region that take into account geographic distance/travel, need for translators etc. When the inspection process has been closed and FDA has formulated a conclusion, in case of a positive outcome FDA should issue a GMP certificate for the site and the certificate should list the APIs that the site has been inspected for, and what is the period for which such certification remains valid. This proposal will bring FDA into line with best practice.

Exhibits 1, 2 and 3 present examples of GMP certificates that leading agencies already issue after successful GMP compliance inspections. In Exhibit 4 we present an FDA certificate that has been used in the past and that we propose should -as a minimum- be routinely issued after every inspection both domestic and foreign.

Finally we would highlight the fact that EMA's EudraGMP database has now gone live and can be visited on http://eudragmp.ema.europa.eu/inspections/logonGeneralPublic.do this database aims to list publicly all GMP certificates issued by a EU member state medicines' agency. Our expectation is that FDA will offer a similar service soon. However the public will be better served if the EudraGMP database would migrate into becoming a supra-national GMP certificate database that would carry all legitimate GMP certificates issued by any competent authority that is mutually recognized by its peers.

[4] No Safe Medicines Without Safe Ingredients, APIC, Sector Group of Cefic, 24 December 2004, http://apic.cefic.org/pub/No%20safe%20medicines%20without%20safe%20ingredients1%5B1%5D.doc.PDF (accessed on February 7, 2011)

8. Additional Considerations

We would like to take this opportunity to highlight three additional issues that FDA should consider addressing:

- Many API sites, that are not inspected by FDA and may even not be suppliers of APIs to the USA at all, are known to file DMFs for APIs at FDA. These may be DMFs that will never be reviewed because no ANDA sponsor will ever refer to them. However, such companies often use the DMF number, assigned by FDA, on their websites or in their catalogues or other promotional material to convey the false perception of quality and "FDA approval" that FDA should not permit. We believe that the Annual Establishment Registration Fee proposed will address the matter satisfactorily.
- We do not believe that it makes sense to have multiple pre-approval inspections for the same site for the same compound (API/DMF), unless justified by use in a different formulation or requested by a different FDA Center (CDER, CBER, CDHR or CVM). We know of multiple cases where the same site was the object of 3 pre-approval inspections for the same API in the same plant on an essentially unchanged DMF. This seems a poor use of resources, and this is precisely what frequent and thorough on-going surveillance inspections should be addressing – whether the API is used in one ANDA, or many – it needs regular checking. If this state of affairs occurs because it is mandated by law or regulations, this should be revisited.
- A collateral effect of the Generics Drug User Fees is to deter non-compliance, to make sure deliberate non-compliance does not pay. Therefore it would be appropriate for FDA to consider adopting some positive elements to reward and motivate compliance as well as innovation. We propose that:
    i. DMFs that embrace Quality by Design approaches and demonstrate that an investment has been made that brings forward a notable understanding of the design space of the API process should be singled out and encouraged. The inherent benefit should be that changes considered "major" in the traditional approach - whenever occurring within a demonstrated design space- will be considered not to require prior- approval. It would be important that FDA clarifies that such a benefit is tangible and can be relied upon.
    ii. For sites where a risk-based assessment indicates a low risk, and where inspectors after several inspections report back positively in terms of a) high and consistent level of compliance and b) a management and personnel demonstrate consistently a high level of maturity in its quality culture, FDA should issue a statement to indicate that the frequency of on-going surveillance inspections will be reduced. This would also provide the site with a valuable public accolade, it would motivate everyone at the site, it would differentiate the site and would free up inspection resources to address more pressing needs elsewhere.[5]

[5] There is precedent in US regulatory agency practice for this approach: Occupational Safety & Health Administration's (OSHA's) VPP Star Program is such a reward system. EFCG and SOCMA are proud that its members have sites that have been so recognized by OSHA, participants in OSHA's VPP star program are removed from the inspection roster and are used as best-practice examples.

9. Conclusion

In closing, we emphasize that solutions should not be limited to generic drugs and note that our proposal is a starting point that may be enhanced over time. A proposal for an optimal solution would have involved proposing far more ambitious plans. For instance, inspections across the globe should be unannounced as they are within the USA. Joint (FDA and foreign government agency) unannounced inspections in lower compliance zones would provide the ideal inspection scheme in a globalized industry.

The signatories of this document believe that the current state of affairs in terms of global cGMP compliance in the manufacture of APIs requires prompt attention. Generic Drug User Fees are a way to achieve a more level playing field and to bring patient risk back to an acceptable level, these are critical matters that must be addressed with urgency. To that end, we believe the proposal found herein could be implemented relatively quickly and would address the major concerns that Industry has raised for a number of years.

We appreciate the opportunity to express our views and look forward to participating in the next phase of the process.

Brussels and Washington, February 18th, 2011.

Brian Murphy	Lawrence Sloan
President and Chairman of the Board	President and CEO
European Fine Chemicals Group	SOCMA
a CEFIC sector group	Society of Chemicals Manufacturers and Affiliates

Exhibit 1

infarmed
Autoridade Nacional do Medicamento
e Produtos de Saúde, I.P.

INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

CERTIFICATE NUMBER: ***F007/S1/H/AF/ME/068/2008***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Portugal confirms the following:
The manufacturer: ***Hovione FarmaCiência, S.A.***
Site address: ***Sete Casas, Loures, 2674-506, Portugal***

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation:
Art.176.º n.º 1 a) of Decree-Law n.º 176/2006, 30 of August

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2010-01-08*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC
- The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC .

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted. The authenticity of this certificate may be verified with the issuing authority.

Part 2

1 Manufacturing Operations

- authorised 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;

- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;

- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides,cytotoxics,cephalosporins,substances with hormonal activity or other potential hazardous active ingredients this should be stated under the relevant produce type and dosage form;

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1749-004 Lisboa - Portugal
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infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

1.2	**Non-sterile products**
	1.2.1 Non-sterile products (list of dosage forms) 1.2.1.17 Other: Other(en)
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility 1.6.3 Chemical/Physical

Manufacture of active substance. Names of substances subject to inspection :

- ***DEXAMETHASONE 17, 21 - DIPROPIONATE(en)***
- ***CLOBETASOL 17 - PROPIONATE(en)***
- ***FLUTICASONE PROPIONATE(en)***
- ***MOMETASONE FUROATE(en)***
- ***MOMETASONE FUROATE MONOHYDRATE(en)***
- ***HALOBETASOL PROPIONATE(en)***
- ***BETAMETHASONE 17, 21 - DIPROPIONATE(en)***
- ***BECLOMETHASONE DIPROPIONATE(en)***
- ***IOHEXOL(en)***
- ***IOPAMIDOL(en)***
- ***HYDROCORTISONE ACEPONATE(en)***
- ***BETAMETHASONE 21 - DISODIUM PHOSPHATE(en)***
- ***SUMATRIPTAM(en)***
- ***BETAMETHASONE 21 - ACETATE(en)***
- ***SINVASTATINE(en)***
- ***BECLOMETHASONE(en)***
- ***BETAMETHASONE 17 - VALERATE(en)***
- ***[12366] MINOCYCLINE HYDROCHLORIDE(en)***

2010-06-02

Name and signature of the authorised person of the Competent Authority of Portugal

Maria Fernanda Ralha

Ms Fernanda Ralha
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Exhibit 2
(English Translation)

Letter of GMP conformity study Result

PMDA

name	Name in General	
	Brand name (formulation)	Iohexol injection 300mg/ml [redacted] 10mL And other 6 formulations
Applicant Name		[redacted]
Date of application or date of approval		As attached
Date of apply for GMP conformity study		July 30th., 2008
Name of manufacturer for GMP conformity study		ZHEJIANG HISYN PHARMACEUTICFAL CO., LTD
Address of manufacturer for GMP conformity study		ZHEJIANG PROVINCE CHEMICAL AND MEDICAL MATERIALS BASE, LINHAI PARK POSTAL CODE: 317016(China)
Name of the Company		ZHEJIANG HISYN PHARMACEUTICFAL CO., LTD
Address of the Company		ZHEJIANG PROVINCE CHEMICAL AND MEDICAL MATERIALS BASE, LINHAI PARK POSTAL CODE: 317016(China)
Classification of approval or accreditation		Clause36 No.1-4 of Pharmaceutical implementing regulations
Number of approval or accreditation		AG10500265 July 23rd., 2008
Result of GMP conformity study		Examination held by PMDA according to Pharmaceutical law Clause 14 No.6, it is stated that there is no issue to be observed.
Others		This is a GMP conformity study results related to API/Iohexol

We hereby notice the result of the examination.
March 26th., 2010

PMDA

Attention to: Minister of MHLW

Exhibit 2

写

独立行政法人
医薬品医療機器総合機構

医薬品適合性調査結果通知書

名称	一般的名称	
	販売名	イオヘキソール注３００ｍｇ／ｍＬ「[redacted]」１０ｍＬ 他　６件（別紙のとおり）
申請者名		[redacted]
承認申請年月日又は承認年月日		別紙のとおり
適合性調査申請年月日		平成２０年　７月３０日
調査を行つた製造所の名称		ZHEJIANG HISYN PHARMACEUTICAL CO., LTD.
調査を行つた製造所の所在地		ZHEJIANG PROVINCE CHEMICAL AND MEDICAL MATERIALS BASE, LINHAI PARK POSTAL CODE: 317016（中国）
製造業者の氏名（法人にあつては、名称及び代表者の氏名）		ZHEJIANG HISYN PHARMACEUTICAL CO., LTD.
製造業者の住所（法人にあつては、主たる事務所の所在地）		ZHEJIANG PROVINCE CHEMICAL AND MEDICAL MATERIALS BASE, LINHAI PARK POSTAL CODE: 317016（中国）
製造業の許可区分又は外国製造業者の認定区分		薬事法施行規則第３６条第１項第４号
製造業の許可番号又は外国製造業者の認定番号及び年月日		ＡＧ１０５００２６５ 平成２０年　７月２３日
調査結果		医薬品医療機器総合機構における薬事法第１４条第６項の規定に基づく適合性調査の結果、特に問題としなければならない事項はないと判断する。
備考		原薬「イオヘキソール」についての適合性調査

上記により、医薬品の適合性調査の結果を通知します。

平成２２年　３月２６日

独立行政法人医薬品医療機器総合機構理事長

厚生労働大臣　殿

EFCG
EUROPEAN FINE CHEMICALS GROUP

SOCMA

（別紙）

名称		承認申請年月日
一般的名称	販売名	
	イオヘキソール注３００ｍｇ／ｍＬ「　」１０ｍＬ	平成１９年　７月３１日
	イオヘキソール注３００ｍｇ／ｍＬ「　」２０ｍＬ	平成１９年　７月３１日
	イオヘキソール注３００ｍｇ／ｍＬ「　」５０ｍＬ	平成１９年　７月３１日
	イオヘキソール注３００ｍｇ／ｍＬ「　」１００ｍＬ	平成１９年　７月３１日
	イオヘキソール注３５０ｍｇ／ｍＬ「　」２０ｍＬ	平成１９年　７月３１日
	イオヘキソール注３５０ｍｇ／ｍＬ「　」５０ｍＬ	平成１９年　７月３１日
	イオヘキソール注３５０ｍｇ／ｍＬ「　」１００ｍＬ	平成１９年　７月３１日

Exhibit 3

LÄÄKELAITOS
LÄKEMEDELSVERKET
NATIONAL AGENCY
FOR MEDICINES

Inspectorate

Certificate No: FI/051H/2009

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER[1]

Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Finland confirms the following:

The manufacturer: PCAS Finland Oy
Site address: Messukentänkatu 8, FI-20210 Turku

Is an active substance manufacturer (authorization number: 6312/4.2.1.2./2008) that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation: Medicines Act and Medicines Decree, Finland

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 28th - 30th January 2009, it is considered that it complies with the Good Manufacturing Practice requirements [1] referred to in The principles of GMP for active substances[2] referred to in Article 47 of Directive 2001/83/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted. The authenticity of this certificate may be verified with the issuing authority.

Helsinki 27th February 2009

Kari Lönnberg, Senior Pharmaceutical Inspector,
National Agency for Medicines of Finland,
Inspectorate
Tel. +358 9 473 341, Fax. +358 9 47334 267

[1] The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.
[2] These requirements fulfil the GMP recommendations of WHO

EFCG
EUROPEAN FINE CHEMICALS GROUP

SOCMA

LÄÄKELAITOS
LÄKEMEDELSVERKET
NATIONAL AGENCY
FOR MEDICINES

Inspectorate

Certificate No: FI/051H/2009

Part 2

☒ Human Medicinal Products	
1 MANUFACTURING OPERATIONS	
1.4	**Other products or manufacturing activity**
	1.4.1 Manufacture of: 1.4.1.4 Others: Manufacture of non-sterile solid, powder or liquid Active substances:
1.6	**Quality control testing**
	1.6.3 Chemical/Physical

Any restrictions or clarifying remarks related to the scope of this certificate:

This certificate is requested by PCAS Finland Oy on 22nd January 2009 for European Union.

Helsinki 27th February 2009

Kari Lönnberg, Senior Pharmaceutical Inspector,
National Agency for Medicines of Finland, Inspectorate
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Proceeding fee
MSAH 1252/2007, PCAS Finland Oy

EFCG
EUROPEAN FINE CHEMICALS GROUP

SOCMA

Exhibit 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DECLARATION of Betty L. Jones

I, Betty L. Jones, declare the following:

1) I am Acting Director, Division of Manufacturing and Product Quality, Office of Compliance, Center for Drug Evaluation and Research, the United States Food and Drug Administration.

2) In this capacity, I issue Certificates of Pharmaceutical Products to foreign governments for export purpose concerning the manufacture, preparation, and marketing of drugs in the United States and the GMP status of the plant which produces them.

3) The manufacturing facility of Albemarle Corporation, located at 725 Cannon Bridge Road, Orangeburg, South Carolina 29115, is subject to periodic inspections by the FDA. The latest inspection showed that the plant, at this time, is in substantial compliance with current Good Manufacturing Practices (cGMPs) as required by the Federal Food, Drug, and Cosmetic Act and as recommended by the World Health Organization.

4) The registration number for the above facility is: 1045166.

5) Pursuant to 28 U.S.C. § 1746, I declare under a penalty of perjury that the foregoing is true and correct.

Betty L. Jones

Betty L. Jones, Deputy Director
Office of Compliance
Center for Drug Evaluation and Research

State of Maryland) ss

Subscribed and sworn to before me this 29th day of September 2004.

TRUE AND CERTIFIED COPY
OF ORIGINAL
Margaret W Wendt
Margaret W. Wendt
La. Notary Public ID #54241
Lifetime Commission

Roxana L Newquist
Notary Public
Roxana L. Newquist
NOTARY PUBLIC
How[illegible]ty, Maryland
My Com[illegible] Expires 01/01/2008