



EFCG

EUROPEAN FINE CHEMICALS GROUP

Press Conference APIs Update

**CPhI – Frankfurt
30th September 2008**

Guy Villax

Member of the EFCG Board
CEO of Hovione, Portugal



Pharmaceuticals Business Committee Agenda

- **API GMP & Regulatory Compliance**
 - Policies are rapidly changing
 - Heparin disaster has been a tough lesson for industry and authorities alike
 - Regulators are preparing to take action
 - On both sides of the Atlantic and in Japan
 - Agents / Traders / Brokers are also targeted
 - New legal initiatives being prepared in EU & US

- **REACH**
 - Enforcement ?



Regulators are taking action

- **EU's changing policies on APIs: Commission's Concept Paper in preparation of a legislative proposal to combat counterfeit medicines**
- EU's intentions include:
 - Mandatory API inspections in third countries without equivalent GMP and inspection standards
(See e.g. European Commission's presentation of April 2008, next sheet)
 - Licensing system for Traders / Brokers
 - Mandatory API fingerprinting at receiving end (dosage form manufacturers)
 - Severe penalties for violations



European Commission

3. Manufacture & Placing on the market of active substances

- Notification of manufacture and import of active substances
- Obligation to perform audits
- Obligation to apply fingerprint technologies for testing
- Legally binding principles for GMP
- Mandatory inspections in third countries without equivalent GMP and inspection standards



Regulators are taking action

- **EDQM letter dated 27th August 2008**
 - **Proposal that Traders holding CEPs will have to disclose to the public domain the names of the plants where the API is made**



Certification of substances Division

IFAH
Mr CLAYTON Rick
1 rue Defacqz
B – 1000 Brussels

Ref: RZ/PH/2008-4941L
CP/cb

Strasbourg, 27 August 2008

Dear Colleagues,

You are certainly informed of the policy for mentioning manufacturing sites on CEPs implemented last year and advertised on the EDQM website (www.edqm.eu / Certification Pharm.Subst./ News & General Information / New Applications).

For the sake of transparency, CEPs now mention all manufacturing sites involved in the synthesis of the substance, starting from the declared starting material. In comparison with the former policy the main difference is that, when the manufacturer of a substance purchases the 'crude substance' or a late intermediate and performs only a final purification or salification, the site(s) of manufacture of these purchased materials is (are) mentioned on the CEP.

Having already received strong support from users of CEPs, from authorities and from industries, in particular through the APIC and EFCG, we would like to now go further and include on the publicly available CEP database the name and address of the manufacturing sites mentioned on CEPs. Thus, this information will not only be limited to the direct users of the substance and its CEP, answering the continuous request for improvement of the transparency of the pharmaceutical supply chain.

Could you please give us a feed-back by 1st October on the opinion of your association members regarding this proposal that is warmly welcomed by authorities and is already expected from some Industries (namely the APIC and EFCG).

Yours sincerely,



Corinne POUGET
Head

Division Certification of Substances



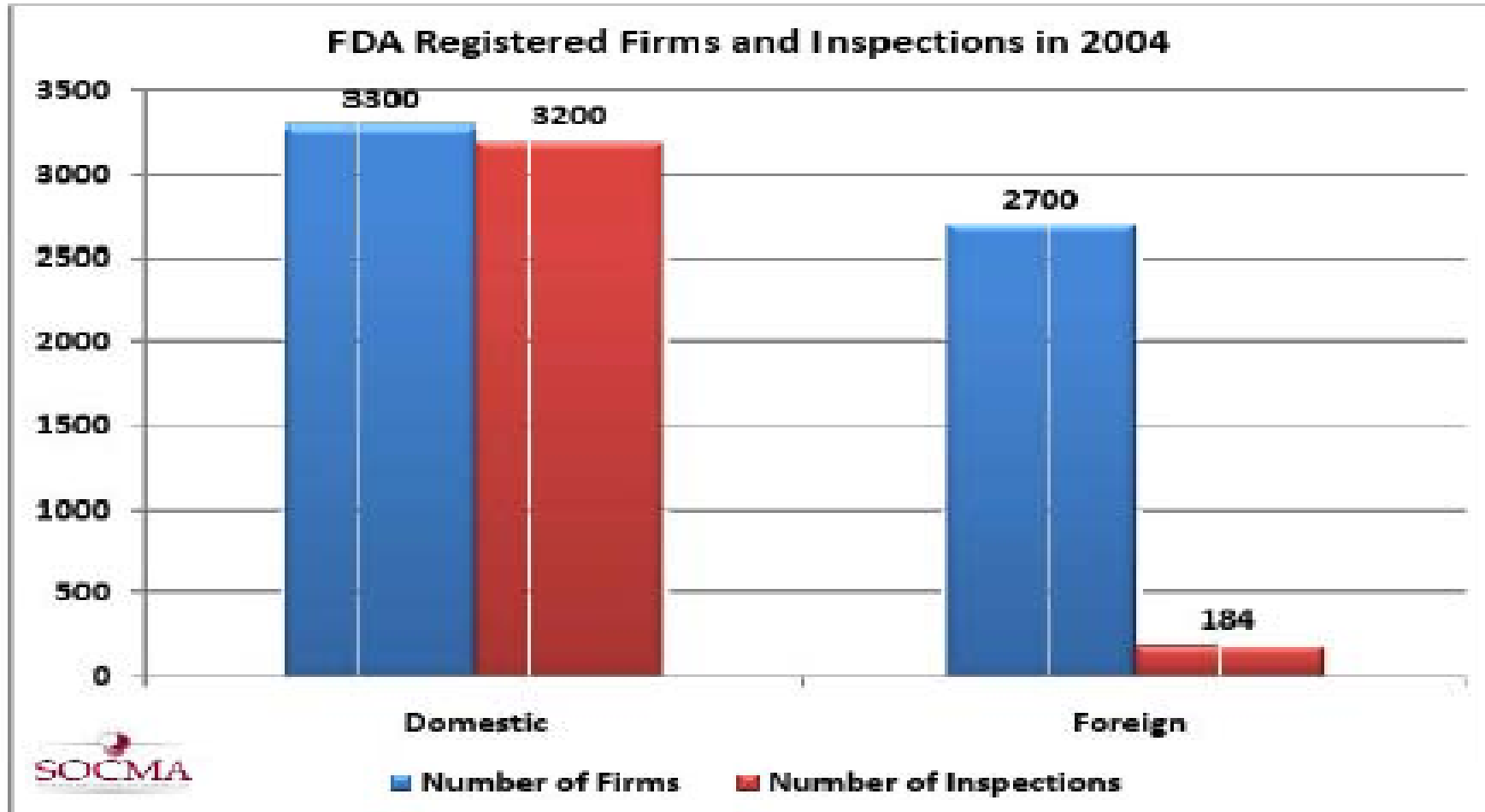
Regulators are taking action

- **US Congress: Draft “FDA Globalization Act” bill proposing:**
 - Frequency of inspections to be same for foreign as domestic
 - Annual inspection user fees
 - API country of origin on drug product label
 - Severe penalty system for violations

will take 3 years to phase in



Compare with current frequencies: FDA Inspections 2003 + 2004



Number of firms data taken from the CDER 2005 Compliance Update presented by Kristen Evans at the 20th International cGMP Conference, University of Georgia, March 2005.

Number of inspections data taken from the 2004 CDER Report to the Nation published August 2005.



Regulators are taking action

- **More frequent foreign inspections**
 - Will become truly risk-based on a global basis: Hence high rate expected of “problems” to be uncovered. Includes:
 - suspected non-compliance and
 - whistle-blowing
 - EU agencies + EDQM now close to 50 - 60 foreign API inspections per year
 - EDQM gets the EFCG top prize for doing a good job !
 - France and Italy lead in EU’s international action, and provide most of the resources
 - FDA will double its foreign inspections in 2009 but FDA Globalization Act will lead to... 15-fold increase!
 - FDA opening branch offices in China, India, South America etc...
 - EU, US/FDA & TGA/Australia starting up cooperation and coordination on worldwide API inspections
- **Some existing triggers to identify non-compliance**
 - Suspended and withdrawn CEPs
 - Check the EDQM database, SCRIP ads...
 - Rapid alerts
 - But no information on or link to European DMFs (will these remain a low-compliance back-door ?)



Regulators are taking action

- **Japan has implemented the DMF/CTD system, and is even inspecting in China**
- **2007 & 2008: FDA inspects in India, issues warning letters, followed e.g. by Raids by Federal Agents at US Offices and Import Alert that blocks 33 of Ranbaxy's dosage forms and 6 of its APIs – share price drops 10%**
- **Non-compliant companies are slowly excluded from the USA and Europe, sales of compliant firms are up**



Compliance: Today

- **Standards still getting tougher**
- **But enforcement, and the perception of enforcement, the news of sanctions is now becoming much more effective**
- **We start to have Deterrence but it needs to be increased yet further**

Flight to quality!

Non-compliance is ceasing to be a competitive advantage.

Safe ingredients => Safe medicines



Compliance: Near Future

A large wave of US- and EU API inspections will hit Asia within the coming few years

- What will be the outcome with today roughly 1% of all API manufacturers in China and India complying with EU / US standards?
- What will be the outcome with ca. 3,000 API manufacturers in China that do not comply with any GMP, not even Chinese GMP?
- What will be the outcome for the ca. 15,000 API manufacturers in India?
- How will all this affect the availability of APIs and of medicines in Europe and the USA???



REACH Enforcement

- **REACH is the single most significant piece of legislation to impact the Chemicals industry – over 1000 pages of legislation**
 - **How unreasonable is it getting ?**
 - **Is it going to be enforced ?**
 - **What are the sanctions ?**
 - **Is it another boost to the competitive advantage of non-compliance ?**



REACH

- **Remarks: Interesting positions by ECHA:**
 - **Article 2(5)(a) ... the exemption is clearly limited to medicinal products within the scope of the medicines rules and while the manufacture and import of active substances for use as starting materials is covered therein (Chapter IV of Directive 2001/83 and Directive 2001/82), the manufacture and import of excipients is not**
Helsinki, 14 August 2008
Doc: REHCORN/16/2008
- **So excipients - that are currently not even subject to GMP (because most of them are so safe) MUST comply with REACH !**



REACH

- **There are about 4000 APIs, they are mostly poisons, and they are for human consumption: GMPs are Law... Industry struggles to get its Regulators to do their enforcement job.**
- **REACH covers upwards of 30.000 compounds... mostly not for human or animal consumption – is anyone going to bother with enforcement ?**
 - **Was it just lip-service to the green lobby ?**
 - **Is it going to be more profitable to comply or to cheat ?**



Thank You

**In the past 5 years
-Brussels, Madrid, Paris, Milan, Frankfurt-
the press has been instrumental
in getting our word across**

**We appreciate your support
and continue to count on you.**

Presentations can be found on www.efcg.cefic.org