The competitive advantage of non-compliance

Recently the QA responsible for one of the Leading German Generic firms was heard saying she now travelled as much in the Far East as in Europe auditing API suppliers. This was at the recent Lisbon APIC/CEFIC meeting of QA and Regulatory professionals that addressed quality topics and the possibility of GMP Certificates for plants that sells APIs in, or into, Europe as from 30th October 2005.

The lady felt that if she did not go out of Europe looking to qualify competitive API suppliers, then the Other Leading German Generic firms would... this auditor did come across genuinely pained by the current absence of a mandatory level playing field – and complained how the inexistence of policing of compliance made her job tougher. Ethical dilemmas are quickly imagined.

The new EU Directive describes a certificate of GMP compliance for the API as an option to assure compliance to GMP standards as set out in ICH Q7a – this is not water-tight for 4 key reasons i) it is not mandatory, ii) it does not require a clear link between the inspection and a specific Marketing Approval Application (MAA) (so a company inspected for oral products will be "certified" for inhalation or injectable products), iii) there is talk of allowing 3rd parties (such as consultants) to do this inspection, and iv) there is no credible effort to make sure that the inspectors that issue such certificates are trained to follow the same standards and best practices (a matter only achievable with centralization given the heterogeneity of the European Union).

We all know that those firms that supply APIs for the USA are in a different league from those that supply the EU – the FDA and its Foreign Inspection Service makes sure of that – and prices of APIs destined for the US are consistently higher. So much for the current policy in the EU that the EMEA / Member States Regulators "trust" the formulator to make sure that the APIs they use meet GMP standards…

The countries that have fewer controls: absence of DMFs, absence of compliance inspections would find that they end being the recipients of 2nd class material. Pharmacies in Berlin and Lisbon for instance sell medicines produced with APIs made in far away places in plants that have never been inspected by an EU official, using a certificate of conformity (CEP) owned by a trader whose only assets are a rented office and contracts, and, even if -say the UK- tries to set a higher standard, parallel imports will make sure the lowest common denominator wins across the 25 member states.

Many of us in Europe are disappointed of the lack of GMP standards and regulatory compliance enforcement in Europe – the EU Commission needs to act. As far as APIs are concerned the mentioned Directive (2004/27/EC) could be the solution we need provided detailed regulation made it watertight: and inspections of API manufacturers and -traders would become the rule rather than an exception. Indeed the Directive contemplates *"guidelines to be published … on the form and content of the certificate of GMP"* and further mentions *"unannounced inspections … grounds … for suspecting non-compliance…"*.

For the sake of the future of the EU API industry, for the peace of mind of QA responsibles and Qualified Persons of the generic firms of Europe and to avoid further disgraces such as the BSE scare, the GM debacle, HIV tainted blood in blood banks, dioxin in Belgian chicken feed, or the amounts of illicit API (eg gentamicin) imported into the EU and used in EU medicines - the EU must create the legal framework for, and specifically fund, an API inspection service. This should be a central organization, located within the EMEA or the EDQM, drawing on the vast expertise that exists in Europe. The inspections should be triggered by MAAs, and the inspection should be based on the referred DMF. The approval of such MAAs should be dependent on reports of such specific inspections.

The US FDA today has decades of historical data on the compliance track-record of API manufacturers, and can therefore perform risk-based assessments and focus inspections on the newer or less reliable companies. This year one of Hovione's Fluticasone API customers had an ANDA approved by the FDA without a Pre-Approval Inspection to the API plant. That's the kind of "no-inspection" the industry wants.

An EU inspection service would be welcomed not just by the European patient, but also by all those manufacturers whether European, Indian, Chinese or from elsewhere that take quality seriously and are committed to making quality products. In all these geographic spaces there are too many free-riders that hurt prices, benefit from the competitive advantage of non-compliance, and, over the long-run jeopardize the future of quality firms.

Earlier this month a handful of European API manufacturers got together to plan on voicing their concerns to the Commission and asking for this Inspection Service to be set up. If you would like to join us please email me on ceo@hovione.com. We welcome the support of all industrial firms that produce APIs, whether you are located in the EU or not.

Without a regulatory-based, state enforced, level-playing-field you cannot be sure to have quality medicines. GMP inspections cannot be optional, they must be mandatory.

Guy Villax, Chief Executive - Hovione

The following associations/companies have expressed support for the view expressed: Orgamol, FIS, CPA (Chemical Pharmaceutical Generic Association, Italy), APIC/CEFIC and Afaquim (Spanish Fine Chemical Association/ APIs producers).