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THE NEWS THIS ISSUE

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NEW EU REQUIREMENTS FOR API GMP OVERSIGHT are now in force calling for finished product manufacturers to audit their bulk suppliers and attest to their GMP compliance. With global implications, European regulators and industry have been debating how to create an effective implementation approach, and a flurry of guidances and position papers is emerging. The EU industry views authority inspections as a critical enforcement lever in the effort to achieve fairer competition with Asia and more control over API quality. ***[A detailed explanation by a European regulatory official of the new API GMP legislation and implementing measures and the impact on the obligations of application holders, API manufacturers, and regulatory authorities is provided on pp. 19-23. A recent release from the EMEA focusing specifically on the expectations for API auditing by dosage manufacturers is included on pp.3-4.]***

EU To Begin ICH Q7A Enforcement

GMP inspection clearance of an active pharmaceutical ingredient (API) supplier by the European Union (EU) or its member state authorities will support, but not in itself satisfy, the GMP oversight responsibility placed on the drug product manufacturer under the new EU requirements.

According to a recently released explanation by the European Medicines Agency (EMEA) of the new API GMP oversight requirements, inspection reports or GMP certificates issued by the recognized authorities "can provide useful information to manufacturing authorization holders" but "alone cannot fulfill" the holder's obligation to audit and approve API suppliers.

On the other hand, EMEA notes in the "Q&A" paper that "the results of inspections may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit program of active substance suppliers."

With significant implications for API and dosage form manufacturers marketing in Europe – a large swath of the industry worldwide – European Commission directive 2004 27 called for the new API GMP requirements to be in place among the member states by the end of October.

➢ Effectively, Europe now has the legal/regulatory framework needed to enforce the GMP standards for API manufacturing agreed to in the International Conference on Harmonization (ICH) Guideline Q7A (*see box on pp. 19-23*).

Although creating a solid foundation for API inspections by regulatory authorities, the EU legislative directive and implementing guidance stops short of the U.S. approach of making inspection clearance a marketing prerequisite, but puts the primary responsibility on drug product manufacturers to ensure GMP compliance among their suppliers. Authority inspections at the premises of the API manufacturers are called for when there are grounds to suspect GMP non-compliance and/or upon request of the European Commission (EC), the EMEA, another member state or the manufacturer itself.

In one draft of the new legislation, the EU included a mandatory inspection provision, but it was not carried through into the final version – reflecting in part the resource limitations of the inspectorates.

To accompany the new provisions for API GMP enforcement contained in the 2004 directive, the EMEA issued an "inspection trigger guidance" in March 2005 which essentially provides directions to both regulators and industry on how this expanded authority will be used. In it, the primary role of the dosage manufacturer is explained.

The guidance states that "when an application for a marketing authorization or variation to change or add a new active substance manufacturer is submitted, the applicant will be required to include a declaration from the manufacturing authorization holder that the active substance(s) concerned has/have been manufactured in accordance with" the API GMP guidelines."

The EMEA then explains further the implications for supplier auditing and regulator oversight.

"It is expected that the holder of the manufacturing authorization will base such a declaration on carrying out, or having carried out on his behalf, an audit of the manufacturers/distributors of the active substances concerned. Examination by inspectors of the audit programs used by authorization holders for conducting regular audits (every 2-3 years), including review of audit reports, is one of the primary means by which Competent Authorities will determine if manufacturing authorization holders are in compliance with the above articles."

Third Party Audits Are Acceptable

In the recent Q&A release that further defines the new API GMP auditing requirements, the EMEA addressed three other key issues that have surfaced in its discussions with industry: ● the use of third party auditors ● paper-based vs. on-site audits, and ● the implications for dosage form importers (*see box pp. 3-4*).

➢ EMEA clarifies that sharing of audit reports between different marketing authorization holders using the same active substance supplier is permitted, although the issue of the acceptability of third party audits that are initiated by the API manufacturer is not addressed.

The Active Pharmaceutical Ingredients Committee (APIC) of the European Chemical Industry Council (CEFIC), in cooperation with Concept Heidelberg, has developed a standardized third party program for auditing API manufacturers, distributors and API contract manufacturers and/or contract laboratories based on the Q7A principles. The "turnkey" audit program is being coordinated by the API Compliance Institute (www.api-compliance.org).

The issue of the regulatory scrutiny of information generated by a firm's own GMP auditing program is one that has received attention in the U.S. in the past, and FDA has expressed sensitivity to the need for industry to protect that information. In 1996, FDA issued a compliance policy guide (7151.03) stating its intent not to review internal audit reports except under certain exceptional circumstances ("The Gold Sheet" May 1996).

Noting that FDA has respected the confidentiality of the supplier/customer relationship so far, a participant at the October APIC/CEFIC meeting in Berlin questioned Division of Manufacturing and Product Quality Deputy Director Nicholas Buhay as to whether the agency "may follow the European lead and start evaluating the content of supplier/customer audit reports."

The compliance official responded that he did not "see any such move in the FDA." The agency, Buhay explained, wants the customer to be "very open and very energetic in pursuing evaluation of the site" and is concerned that agency intrusion could act as a brake on that process, "either in finding things or saying things."

➢ European drug product manufacturers have voiced concern with the provision in the new EU approach that API audit reports will undergo regulatory scrutiny.

In April comments on the EMEA inspection trigger guidance, the European Generic Medicines Association (EGA) highlighted its concern "about the statement that the review of audit reports is one of the primary means by which Competent Authorities will determine whether manufacturing authorization holders are in compliance with the new legislative requirements." EGA pointed out that the audit reports and responses "are widely

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EMEA Q&A Paper On Meeting Requirements For Auditing API Suppliers

The following is a set of questions and answers recently published by the European Medicines Agency (EMEA) addressing how manufacturing authorization holders can fulfill their obligations under the directive now in force (2004/28/EC) "to use as starting materials only active substances that have been manufactured in accordance with GMP." The EMEA clarifies its expectations for the required auditing by the manufacturing authorization holder or a designated third party.

The document titled "Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials," published as part of the Compilation of Procedures, states that it is expected that manufacturing authorization holders will gain assurance that the active substances it uses are manufactured in accordance with GMP through audit of the active substance suppliers. Small manufacturers may not have the necessary expertise or resource to conduct their own audits. Is an audit performed by a third party acceptable?

Section 5.25 of the GMP Guide requires starting materials to be purchased from approved suppliers about whom the manufacturer has a particular and thorough knowledge.

An audit conducted by the manufacturing authorization holder itself should be integral to the manufacturer's quality assurance system and subject to the basic GMP requirements, i.e. conducted by properly qualified and trained staff in accordance with approved procedures, should be properly documented, and these aspects can be inspected as necessary by the Competent Authorities. If a third party is involved, the arrangements should be subject to Chapter 7 of the GMP Guide and there should be evidence that the contract giver has evaluated the contract acceptor with respect to the aspects described above. All parties involved should be aware that audit reports and other documentation relating to the audit will be made available for inspection by the competent authorities if requested. This should normally provide sufficient assurance that the results of an audit carried by the third party are credible, thus waiving the need for an audit conducted by the manufacturing authorization holder itself. However, it must also be satisfactorily demonstrated that there is no conflict of interest. Conflicts of interest could arise, for example, from:

- A commercial relationship between the organization performing the audit and the organization being audited; or
- A personal conflict on the part of the auditor where he/she has been employed by the organization being audited in the recent past (i.e. within the last 3 years) or has a financial interest in it.

This topic should also be addressed in the technical contractual arrangements, and any measures taken by the contract giver should be documented, e.g. signed undertakings by the auditors.

Similarly, the principles outlined above could be used to allow sharing of audit reports between different manufacturing authorization holders using the same active substance supplier, provided the scope of the audits can be shown to be applicable to the active substances of mutual interest.

Do I need to perform an audit of an active substance supplier if it has been inspected by an inspectorate from an EEA [European Economic Area] member state and a valid GMP certificate is available?

Manufacturing authorization holders sometimes confuse the role of inspectorates with their own obligations, but nevertheless, when inspection reports or GMP certificates issued by EEA, MRA partners or other recognized authorities are available, these can provide useful information to manufacturing authorization holders. However, these alone cannot fulfill the statutory obligations of the manufacturing authorization holder or the requirements of section 5.25 of the GMP Guide, but the results of inspections may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit program of active substance suppliers.

Is it acceptable to perform a remote assessment based on, for example, questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier?

The EEA inspectorates are not generally in favor of "paper-based audits" *per se* as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy. They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They

cannot replace on-site audits of active substance suppliers but can be a useful interim and temporary measure within the manufacturers audit program.

How do the new requirements affect importers of medicinal products?

Importers are manufacturing authorization holders and so the obligations under Art. 46f/50f of Directive 2001/83(2) apply to them. For importers, the possibility of a "second party" audit performed by the third country manufacturer that uses the active substance as a starting material may be a further option. Importers are already obliged to ensure the third country manufacturer complies with standards of GMP equivalent to those of the European Community and should have established arrangements in line with Chapter 7 of the Guide. They should therefore be fully satisfied that the third country manufacturer has adequately demonstrated that the active substances it uses for products destined for the European Community have been manufactured in accordance with GMP. Importers may of course choose to verify the standards of GMP at the active substance suppliers themselves or through a third party. Whichever option is chosen, the questions and answers given above are also relevant.

considered internal documents" not appropriate for regulatory review.

➢ The audit program, audit dates and SOPs, on the other hand, are suitable for review, EGA maintained, along with potentially the conclusion regarding the status of the API manufacturer.

The generics association generally welcomed "the new EU legislation regarding mandatory GMP for APIs" and the implementing provisions calling for a declaration in the marketing application of compliance with the GMP guidelines based on the applicant's or a third-party audit.

"This appears to be a very pragmatic approach and will help to avoid a bottleneck in the registration phase of medicinal products." GMP certificates, EGA pointed out, "are indeed not yet available for all APIs used in medicinal products marketed in Europe, and all API manufacturer sites in and outside the EU cannot be inspected within a short period of time."

In stating its support for the move to mandatory API GMP, the generics association expressed the hope that "health authorities use the opportunity of this new legislative framework to staff up their inspection teams to offer the service of voluntary inspection of API manufacturing sites."

➢ While expressing general support for the EU focus on product manufacturer oversight of GMP compliance of their API suppliers, the EGA comments imply the need for careful interpretation of what is really being asked of the manufacturer in making a GMP compliance "declaration" – particularly in terms of putting the quality person, who has to sign off on the declaration, in a tenable position.

The question is more than a semantic one in terms of the viability of the new European approach.

In objecting to regulatory authority review of audit reports, EGA said that it would support the review of the application holder's "conclusion regarding the API manufacturer," offering the terms "acceptable," "provisionally acceptable," "re-audit necessary," and "rejected" as appropriate categories. Such terms are in line with the types of assessments FDA makes in its inspection program, but different from the GMP "certification" imprimatur applied in European regulatory contexts.

There is a tendency in the European dialogue, as witnessed at the Berlin conference, to confuse the FDA inspection process with "certification." FDA does classify inspection results based on a determination of whether follow up enforcement action or application approval withholding is warranted, but does not "certify" GMP compliance.

In turn, placing the responsibility on a "qualified person" at the marketing authorization holder to make a definitive judgment of a supplier's GMP compliance status, rather than a more narrow "acceptability" determination, would be problematic from FDA's point of view given the complex and changing nature of a firm's operations and personnel. Building a system around a "certification" concept based on either regulator inspections or industry audits is a potential pitfall that Europe will need to consider further in refining its regulatory approach.

➢ In commenting on the inspection trigger guide, API manufacturer Hovione pointed to a lack of clarity as to the implications for currently approved marketing/manufacturing authorizations.

"It cannot be the intent of the EMEA/Commission to 'grandfather' current filings and thus enable the majority of EU medicines to escape, or at least to delay significantly, the impact of this landmark requirement that the API used meets GMP," the firm stressed. Accordingly, Hovione suggested that the guidance be revised to

state that approved marketing authorizations need to be updated with the addition of the same declaration that new applicants will now be required to make.

Another issue raised by Hovione was the lack of provision for "random" inspections. Assuring that API firms feel they could be inspected is "imperative" as part of deterrence, which entails "a commensurate probability of identification of non-compliant firms and meaningful sanctions." More generally, Hovione asserted the need for the guidance to communicate "unequivocally that the intent is to make sure that all manufacturers of API, located inside or outside the EU…are likely to be inspected."

Mandatory Inspections Sought By EU API Industry

A prominent concern among the European API industry in assessing the new GMP requirements is that regulatory inspection clearance was not made mandatory for all API suppliers to the European market.

In one draft of the new legislation, the EU included a mandatory inspection provision, but that was not carried through into the final version in view of the resource limitations of the inspectorates.

Since the 1990s, the European industry has been pushing for a centrally-based system of mandatory inspections and routine reinspections by a well-trained EU inspectorate – supported potentially by user fees – in the effort to create a more level playing field with API suppliers from outside the EU that may not be subject to the same intensity of GMP scrutiny and enforcement.

- The issue of a level regulatory playing field is viewed as critical to the overall health and possibly the survival of the European industry, which is facing intense competition from lower-cost producers in Asia. Industry voices like APIC/CEFIC have been urging EU officials to appreciate the importance of the issue – from the perspective of both the quality of European drug products and fair competition – in implementing API GMP requirements.

European industry advocacy of the need for a level playing field is reflective of that heard from U.S. bulk drug manufacturers more than a decade earlier. The concerns U.S. firms expressed about unequal foreign vs. domestic enforcement, together with the evidence of serious quality problems in imported material stemming from GMP non-compliance, caught the attention of Congress and helped spur FDA to ramp up its foreign bulk GMP inspection program and related guidance during the 1990s ("The Gold Sheet" September 1993).

While supportive of the move to require that dosage manufacturers use only APIs from GMP-compliant facilities, the EU firms view authority inspections as a pivotal enforcement lever (*see box below*). Short of the desired across-the-board mandatory inspections, they have been urging EU executors in the European Commission (EC) to expand the conditions under which the licensing authorities will have to conduct them.

APIC On The Need For A Robust Global API Inspection Program

In late 2004, the Active Pharmaceutical Ingredient Committee of CEFIC issued position papers relevant to the EU effort to strengthen the oversight and enforcement of API GMP. The following are excerpts from the papers in which APIC explains the need for a robust global inspection program.

To assist the marketing authorization holders in their obligation to source only APIs made according to GMP, it is essential that reliable information is available on the compliance status of all API producers. Stringent standards are meaningful, provided that they are correctly implemented and enforced through world-wide inspections. The new EU legislation provides for the possibility of also inspecting API producers importing into the EU for GMP compliance, but this is not a mandatory process. APIC fears that these inspections will be fairly limited, considering the limited resources available for such inspections.

Moreover, even companies found to comply at the time of the audit may be tempted to adopt other practices thereafter because of the high costs of GMP compliance and because the chance of re-inspections will be remote. APIC believes that GMP for APIs can only be enforced if inspections will be mandatory and re-inspection will take place regularly.

Inspections should not be limited to the verification of GMP compliance in the facility itself. The distribution chain should also be verified. Traceability to the original manufacturer should be checked, because exchange of API products amongst manufacturers is a regular practice in some countries….

APIC appreciates the incorporation of the GMP principles for APIs into the European drug code. However, a "well-intended" regulation can easily result in the opposite effect if enforcement is not applied and control by the authorities would be absent. The number of API manufacturers is increasing rapidly and EU producers of finished medicines are subject to increased price competition. The European Commission must create conditions that will ensure that competition never leads to sub-standard medicines. Therefore, the need for action is urgent.

The downward pressure on pricing of medicines in Europe urges EU manufacturers to seek new, lower priced API suppliers. However, such lower prices can originate in part from lower costs because of sub-standard GMP and regulatory compliance levels at the supplier. So the serious concern of APIC is that this is resulting in EU pharmaceutical companies – also partly without their knowledge – compromising on quality by sourcing from what appear to be sub-standard suppliers.

Worrying scientific data and other information on APIs that show substantial risks to patient safety in the EU have surfaced in the recent past. Examples are the gentamicin case – giving strong indications that more than 33% of the gentamicin API material on the EU market was produced by unknown manufacturers and is therefore illegal – and the experiences shared by a recognized API trading company at a recent European API conference in Lisbon (October 2004) showing that the traceability of API material back to the manufacturer is frequently lacking. Consequently, the EU's high standards of quality, safety, and efficacy of its medicines, particularly in the highly competitive generic…and OTC markets, are starting to be seriously undermined by current API trends.

Unless control over the API supply to the European market is drastically increased, API manufacturers throughout the world who are applying the strict and costly standards of EU regulations and guidelines will have severe competitive disadvantages against less ethical companies: "Good" APIs and pharmaceutical firms will be pushed out of business by "bad" APIs and pharmaceutical firms.

In order to reduce the risk for the European patients and for the sake of the continuity of API manufacturers who comply with the regulations, the EU must create the legal framework for a uniform level playing field for all API suppliers to the European market based on:

1. A mandatory and effective inspection service that will verify if the API manufacturing process and controls comply with the ICH/Q7A GMP Guideline and are in accordance with the information included in the respective CEP dossiers, DMFs or MAs.

2. A sampling program to assure quality surveillance of medicines and their APIs.

3. The compulsory requirement to include with every Marketing Authorization a current and appropriate Certificate of GMP compliance issued by the EU inspectorate to the producer of the API.

4. Periodic follow-up inspections to reconfirm the validity of the GMP Certificate.

These provisions will also ensure a better level playing field in the EU market for finished medicines whilst also reducing operational costs (e.g., a single authority inspection may avoid the need for multiple client audits).

EU API Industry Fares Better In U.S. Than At Home

The impact of the regulatory environment on the API marketplace in Europe was a key focus of attention at the October APIC conference in Berlin.

Setting the stage for the discussions were presentations at the opening session by three spokesmen for the industry: PharmaChemical Ireland Director Matt Moran; Hovione CEO Guy Villax; and DSM Anti-Infectives External Regulatory Affairs Manager Chris Oldenhof.

Moran and Oldenhof serve on the APIC board and all three are members of the board of CEFIC's European Fine Chemicals Group. EFCG was formed in December 2004 to bring industry executive-level support on explaining and addressing the problems the industry faces and lobbying regulatory authorities to help in creating viable solutions.

Moran commented that EFCG will add a needed business perspective to the technical concerns on which APIC has been focusing.

"Because at the end of the day, all of these issues are very interesting and we can have all of these technical arguments, but if we don't win the arguments, the situation will be quite simple for the business in Europe; it will simply disappear. So it is a business issue," Moran said.

"I think we need to corral all of the forces that we can in trying to defend a European industry, and at the end of

the day, defend European patients. Because ultimately, low quality product means low quality medicines which are being given to our children. And that is an issue which I think Europe has only just started to come to terms with. I think that the work we do with the EFCG will be very important in that regard."

➢ All three speakers referenced the dramatic shift in the sourcing of APIs for the European market since the 1980s.

They drew a contrast with the relative success of European suppliers in the U.S. market vs. Europe in underscoring the importance of creating a level regulatory playing field and the EU industry's vulnerability when facing regulatory hurdles and enforcement oversight that does not extend to the foreign competition.

It is estimated that the percentage of APIs used in the European market supplied by indigenous manufacturers has dropped from greater than 80% in the 1980s to less than 30% today, while material from India and China has risen from less than 10% to more than 70% of the total.

In contrast, although the percentage of European APIs has declined in the U.S. from more than 80% of the total in the 1980s, Europe still supplies more than 50%, according to the recent estimates. The proportion of product from India and China has risen significantly to over 30% of the market, but the region has not yet displaced Europe as the majority provider.

In turn, APIC estimates that there may be 10,000 plants involved in the API supply chain for Europe, of which only a small fraction have actually received an inspection from the EU or the European Directorate for the Quality of Medicines (EDQM). This compares with only several hundred API facilities supplying to the U.S., all of whom are subject to FDA inspections. FDA currently has about 50 experienced inspectors in its foreign inspection cadre and has been performing about 250 inspections abroad a year, two-thirds of which involve API manufacturers ("The Gold Sheet" December 2005).

➢ Ironically, the European industry can compete better with Asian suppliers in the U.S. than it can on its home turf. The evidence indicates, as the European associations point out, that meeting a higher regulatory standard is a significant cost factor.

Oldenhof suggested that the deterrent effect can be viewed as "the main reason for this important difference." Suppliers know that FDA inspections are "very tough" and anticipate being inspected. "So basically that forms a barrier for companies that don't have that GMP level... from entering the U.S. market." By contrast, in Europe "this deterrent is much, much weaker at this point."

EDQM Inspections Result In Seven Suspensions

EU enforcement of API standards in the past has been limited to a paper review by national health authorities or the European Directorate for the Quality of Medicines (EDQM).

EDQM is the EU body that issues "Certificates of Suitability to the Monograph of the European Pharmacopeia" (abbreviated as either CEP or COS) when required for a marketing authorization. More than 20% of CEPs have been granted to non-European countries. Like the U.S., the EU also has an "active substance master file" (ASMF) system applicable as well to non-monograph API filings. Most of the non-EU CEP holders also hold ASMFs.

➢ To help verify the filings, EDQM over the last few years has begun doing inspections, focusing mainly on manufacturers likely to have GMP weaknesses. The inspections can result in CEP suspensions when GMP or filing compliance problems are found.

Citing data from the program at the Berlin conference, EDQM official Helene Bruguera noted that 70 manufacturing sites in 22 countries have been inspected under the five-year-old program. These included 15 sterile APIs, 11 TSE-risk products and six distributors/brokers. Those inspections have resulted in seven suspensions. It was noted at the conference that all these have involved Asian suppliers.

Bruguera reported that about half of the CEPs are held by European manufacturers, about a quarter from eastern Asia and India, and 15% from the U.S. Altogether, about 2,600 applications have been received and 1,800 CEPs granted, with 1,250 involving chemical purity. EDQM staff is fielding an increasing number of revisions – currently about 350-400 a year.

She explained that the assessment of new applications is taking about eight months, three months over the target. To avoid "wasting time on bad dossiers," which may involve "several rounds of questions," EDQM is in the process of introducing "stricter requirements for the treatment of the dossiers," Bruguera said.

Deep Discounts Are A Counterfeiting Red Flag

Moran emphasized that in general, European API manufacturers face a "very challenging" business

environment, with APIs being offered on the European market at a significant discount from other markets such as the U.S. – in some cases as low as 10%.

When discounted at this level, he stressed, both dosage manufacturers and regulators should be "asking some questions as to why....Maybe the supplier is very innovative – that is fine if that could be proved." On the other hand, there may be significant quality/GMP issues reflected in the lower price.

Noting that the EU API firms are being "squeezed from all sides," Moran pointed out that some of the pressure is coming from dosage manufacturers who are being asked "to deliver therapeutics at lower and lower prices [with] more guarantee of safety to the patients" creating the "temptation to use lower cost APIs." The point, he stressed, "is that non-consistent GMP enforcement is going to skew the competitive environment which the industry faces."

➤ It will also spur the expansion of illegal activity such as counterfeiting, Moran emphasized, which is "becoming more and more of a problem to the industry" and a threat to public health.

A recent report by a U.S. think tank, The Center for Medicines in the Public Interest, estimates that sales of counterfeit drugs will "burgeon" at 13% per year through 2010 to $75 billion. Counterfeit estimates for 2005 are $39 billion, or 11 percent of global pharmaceutical commerce.

Moran cited reports that "up to 100,000 patients have died in China as a result of counterfeiting," and that 7-10% of active coming into the U.S. could be counterfeit, even with the tighter regulatory controls in force there. The issue is moving into the mainstream public consciousness as well as the consciousness of those involved with regulation and manufacturing and "needs to be addressed on an urgent basis," he said.

Focusing on problems in the European market, Moran cited the "famous gentamicin case" in which a batch of the antibiotic was analyzed and discovered to have come from eight different sources. The case "makes you ask some questions," he said, and "leads you to believe that at best, we have innovative sub-supply taking place at some parts of the API industry, which is unhealthful for the quality of the product."

The finding was among those derived from a study conducted by the University of Würzburg in Germany after deaths and severe side effects were reported in patients receiving gentamicin that were not explainable except by manufacturing/distribution irregularities.

The study analyzed 39 samples of gentamicin obtained in Germany and the U.S. from a dozen different pharma companies. Of the 21 samples from the German market, 17 had not been made in the plant listed in the DMF. The study team concluded that as many as one third of all APIs on the European market may not have been made by the registered manufacturer.

Counterfeit Survey Points To Regulatory Weakness

The growing problem of pharmaceutical counterfeiting received significant attention at the Berlin conference.

Welding official Karl Metzger pointed to the prevalence in Europe of brokers in the API supply chain as adding to the potential for abuse and making traceability difficult.

➤ At the conference, Metzger reviewed findings from a "stakeholder survey" conducted by the Council of Europe on cooperation practices, measures and experiences applicable to counterfeiting.

Those surveyed saw the problem as reflecting the lack of regulatory supervision and an increasingly competitive environment, which provide a greater incentive to counterfeit medicines.

Fraudulent practices were found to include: ● blending API batches with different qualities from different manufacturers ● 'neutralization' – such as erasing relevant information to decrease the traceability back to the original manufacturer ● submission of or reference to DMFs from a compliant source while using another substandard API for product manufacturing ● purchasing from unidentified manufacturers through non-qualified suppliers, along with many other practices, especially in later steps of the supply chain.

Counterfeiting may appear at any step of the distribution chain, Metzger noted, adding that it does not arise only from active fraud but from passive gross negligence as well.

➤ Survey respondents did not believe that existing regulatory structures are adequate to combat counterfeiting due to the lack of appropriate legislation, appropriate enforcement of the existing legislation, and an adequate definition of responsibilities.

A key part of the fight against counterfeiting was seen to lie in defining the term and its scope more clearly. A "counterfeit" product, Metzger said, is simply any one that is not what it pretends to be. Under this definition, he stressed, every medicinal product in the market that does not comply with its marketing authorization is counterfeit, regardless if the non-compliance was caused by fraud, negligence or accident.

Along with a more clear and unambiguous definition, it was felt that improvements should be made in the current system in terms of: ● legislation ● enforcement, including penalization ● definition of responsibilities ● administrative structures ● cooperative agreements, and ● information exchange/communication networks.

➢ At the Berlin Conference, Hovione's Villax cited the case of the Italian bulk supplier Biochimica Opos as an example of the types of fraudulent activities to which the European supply chain is prone in the relative absence of regulatory oversight and the adverse market impact of these activities.

Some of the problems at Opos were first discovered by the corporate legal department following a merger of Opos' parent company Roussel-Uclaf with Marion Merril Dow in the latter 1990s. The findings resulted in Opos voluntarily withdrawing its filings from the FDA, shutting down production, recalling bulk materials and discontinuing the distribution and sale of the antibiotics, cefaclor, minocycline and clindamycin in the U.S.

Following the internal revelations, FDA followed up with an investigation which revealed that ingredients for cefaclor manufacturing had come from unapproved sources, that false records were kept to hide fraudulent activity, and that the manufacturing of the antibiotics was deviating from the regulatory filing, including using other unapproved facilities in the manufacturing.

Villax explained that Opos was the first to offer cefaclor and minocycline API to the market and that when they ran out of capacity, they "found solutions" inconsistent with regulatory filings. In turn, other companies like Hovione not taking the shortcuts were "directly impacted" by the sales of the illegal production. Villax noted that while FDA stepped in, Europe did not take any effective action to stop continued sales by Opos there, reflecting the lack of its enforcement clout in the fraud/counterfeiting area.

GMP Enforcement Draws Industry Attention

Distribution and GMP problems in the supply chain from Asia have been more difficult yet for Europe to get a handle on.

Focusing on the GMP side, Moran clarified that the message from APIC and EFCG is not "that all manufacturing in China and India is sub-par," adding that "there are several very competent and compliant manufacturers in Asia" and that "there is certainly a strong effort by regulators there to transition" to GMP enforcement.

However, he said, given that the number of manufacturers in China may be as high as 20,000, the regulatory challenge is "immense indeed in ensuring that all of their manufacturers are in compliance. And when you have the levels of inspections taking place that we currently do, practically it is just a very difficult task" and "underlies the challenge which the industry" in Europe faces in seeking a level playing field.

➢ Moran also addressed the enforcement problem in terms of its impact on the European citizen.

"If there are substandard APIs coming into Europe – and we know there are – the European citizen is essentially under threat," he said, pointing to the responsibility of industry and regulators to make sure that the standards are met. This responsibility, he stressed, "has to apply right down the value chain – from the doctor through to the manufacturer, through to the distributor, through to those that manufacture the components that go into drugs. It is important that this system is policed and managed correctly…and that all our partners are engaged in what is a battle to defend the European citizen."

While the EU industry may complain about regulations being too severe or bureaucratic, "once they are there, we accept them," Moran said. "But we also need to accept that they have to be enforced globally. And if they are not being enforced globally, potentially this should be considered a trade issue. We are seeing competition from the lower-regulated areas of the world damaging the industry here." Competition that is non-compliant is "unfair," he stressed, "as well as being potentially dangerous."

EFCG Survey Assesses Authority Readiness

Following Moran to the podium at the APIC Berlin conference, Villax discussed in more detail the

competitive challenges in the European market and the quality problems experienced in the API distribution chain.

Villax' firm, Hovione, is a Portugal-based fine chemical manufacturer founded after World War II with API plants located in South China and the U.S. as well as in Europe.

Villax noted that the APIC/CEFIC API conference held a year earlier in Lisbon, Portugal, opened his eyes, leading him to realize "that in Europe, things were not what they seemed to be. I think there were a great number of people in Europe who were convinced that it was law to do things under GMP. And this was not the case."

The conference helped spur Villax' involvement in the formation of the European Fine Chemicals Group (EFCG) under the CEFIC umbrella to bring chief executives to the table "to try and see how the regulatory environment impacts business and what business ought to be doing about it."

➢ EFCG is currently promoting three initiatives related to the enforcement of API GMP in Europe: ● the APIC third party audit process ● a "simple guide" to buying APIs that meet GMP, and ● a benchmarking exercise across the EU to assess the readiness of member states to enforce the new directives with reference to APIs.

Villax explained that the guide is intended to address what manufacturers can do at a "relatively low cost" to supplement audits in helping to ensure that their API suppliers meet GMP (*see box below*). Basically it involves three action points that customers should demand.

EFCG's "Simple Guide" To Ensuring API Supplier GMP Compliance

The following is a "simple guide" from the European Fine Chemicals Group addressing inexpensive steps that dosage manufacturers can take to supplement audits in helping ensure that their API suppliers meet GMP.

For every API/manufacturer you formulate into medicines for sale in the EU make sure that you have on file:

1. A written and signed declaration from each API supplier that certifies that each API it supplies to [your company name] is made under GMP to the requirements of ICH Q7a (Chapter 2 of the EU Guide to GMP, formerly Annex 18), as described in the DMF [filed at the [country health authority] or EDQM CEP N°] and that changes from established production and process control procedures that can impact quality shall be notified to you in writing before their implementation.
2. Annual updates of:
   - A signed summary report evidencing that an Annual Product Quality Review (ICH Q7a 2.50) was performed by the supplier for the API in question.
   - Stability (ICH Q7a 11.54 and 55) – the annual stability report.
   - Change Control (ICH Q7a 13.17) – a record of the correspondence exchange that evidences that changes from established production and process control procedures that can impact quality were considered and discussed prior to implementation.

These should be kept in specific sections of your Product Specification File.

3. Copies of evidence of inspections from reputable health authorities that show that inspectors visited the plant where the API you buy is manufactured and issued a favorable comment on the level of compliance with GMP. This should be included in your API supplier qualification file.

All compliant API producers have such documents and will provide them to you.

In addition to the above, the guidelines issued in Europe indicate that MA holders should have on file for each API an audit report of the manufacturer that is no more than 3 years old. The form, contents, and whether the audit focus is general or product specific, whether it aims to check whether actual operations mirror the operations described in the filed DMF or in other registration documents or not – has not yet been clarified by the Health Authorities. EFCG is expecting guidance on the matter.

The first is a simple declaration that the supplier is indeed that manufacturer, complies with both GMP and what is described in the DMF or the CEP, and that the customer will be informed if there are manufacturing changes. A second point would be yearly updates addressing the annual product quality review, the annual stability study, and change control. And third, copies of any inspection reports by credible health authorities.

Noting that audits are not likely to be done more frequently than once every three years, Villax commented that, for example, "if you get an updated stability study, you will know at least that one extra batch has been done that year. And you will get some data. I think this is important if you are a QP [qualified person]."

- The EFCG benchmarking exercise involves a series of specific questions that the EU and member state health authorities need to consider and address if the API GMP program is going to achieve its intended goals (*see box on p. 12*).

The intention of the survey is to determine authority readiness to enforce the new requirements. It "asks questions such as how many inspectors do you have, what kind of training have they been the object of, what is your plan, how many of you audit, in which geographies, etc.," Villax explained.

Ironically, he pointed out, "those that are supposed to be checked [are] asking whether the police have the resources" to do so. The issue is being raised "because we haven't been given any sense that things are what they ought to be. So we are worried, and we are doing something about it."

The survey is intended to help regulators target "what they should be training their inspectors to do," Villax commented, "because in our contacts with a number of inspectors…it becomes quite apparent that the inspectors don't always know what they should be asking."

EFCG has been raising the types of questions included in the survey "at the European Parliament and most recently the French Parliament," and bringing the issues to the attention of the trade press so that the complexities involved can be better understood and addressed, Villax said. Associations in the member states will help the EFCG executives with the initiative, and EFCG is looking for additional volunteer support in the effort, particularly from Ireland, UK, Belgium and the Scandinavian countries.

- In September 2005, APIC/CEFIC released a comprehensive 70-page guideline for API manufacturers on developing a quality management system.

With references to FDA's systems-oriented 21st century quality initiative, the APIC guideline integrates current GMP requirements as defined in ICH Q7A into the ISO 9001 quality management system framework.

Hovione CEO Analyzes Changing Marketplace

In his presentation at the Berlin conference, Villax provided an in-depth analysis of the changing API marketplace in Europe and how it is being impacted by Asian competition, to help explain the importance of the regulatory issues.

- Villax suggested that the current situation for the European industry was made worse by the exaggerated expectations of the boom mentality that existed in the 1999-2000 period.

At that time, projections were circulating of 15% per annum growth, with companies making aggressive acquisitions and creating inflated goals for expansion over relatively short timeframes. The shorter-term projections did not make sense, the Hovione CEO noted, since "it takes a very long time" to develop a product, get it approved and launch it.

At the same time, Villax noted, there were some contrarians "like Honeywell exiting the business – saying that pharma chemical manufacture is highly capital intensive and is a business plagued by over-capacity, clinical trial failures, limited new drug approvals, new drug marketing disappointments and price wars."

- A review of sales of pharmaceutical fine chemicals by the larger European players shows average growth in the 2002-04 period to have been -14%. "So compared to the expectations and the amount of money spent, the net results were really 180 degrees opposite," Villax pointed out.

He commented that "the stock market bubble really didn't help" the situation. "It made money available for management to do these humungous errors. There was, in my view, huge wealth destruction, only to be followed by job destruction. At a moment when we should have really been building our fine chemicals industry to be strong and lean to put up the fight against Asia, we did the exact opposite – we weakened ourselves dramatically."

EFCG Survey On EU Member State Readiness To Enforce API GMP

The following "Compliance Benchmark Questionnaire" was developed by the European Fine Chemicals Group to assess the readiness of EU member states to enforce the new API GMP oversight requirements. The survey is being distributed through the group's membership, and the results are slated to be presented at the EFCG conference on API compliance in Barcelona in late April. Included are key questions the EU and its member state health authorities will need to consider and address if the API GMP program is going to achieve its intended results.

1. Do you have specific instructions for your inspectors on the API aspects that are to be covered during inspections of dosage form manufacturers as from 30th October 2005?

2. What information on APIs will your inspectors require from dosage form manufacturers during inspections?

3. For APIs with DMF, does the dosage form manufacturer have a letter of commitment or the letter of access to the DMF, which includes such commitment?

For APIs with CEP, does the dosage form manufacturer have a commitment from the API manufacturer that no significant changes were made since the CEP was granted.

For product supplied through a trader or distributor, does the dosage form manufacturer have such declaration made by the original producer to the MA holder, and if not, a copy of the commitment made by the original producer to the trader and by the trader/distributor to the MA holder? Does your authority accept such declarations made by the trader himself?

4. Will you verify that the dosage form manufacturers only purchase active ingredients from suppliers listed in the marketing application and that the list of approved suppliers present on site is in line with those mentioned on the marketing application? How will you verify that there are no purchases (other than for qualification purposes) from other supplier (e.g. by review of all purchasing records)?

What tools are you using to detect fraudulent practices, e.g. where the real origin of the goods are hidden. (e.g. verification of purchasing records)?

What sanction will be applied if the inspector establishes that APIs from unauthorized sources are being used?

5. If APIs are purchased via traders or distributors, will you extend the inspection to the trader himself to ensure the starting materials are purchased from the declared source?

6. In the event of the inspection of an API producer, do you verify whether the API producer has integrated the EU regulatory requirements into its procedures? For example, does the change control procedure or other documents refer to the EU variations requirements? Do you verify whether procedures are in place to inform the applicant and authorities of any planned change with potential regulatory implications?

7. In the event of purchase of APIs through a trader, do you verify the trader's procedures to ensure that all regulatory requirements (e.g. changes with regulatory impact) are met and how the link is made to the original producer?

8. The guidelines refer that the dosage form manufacturer should satisfy itself that the APIs used meet the GMP requirements – in connection with an audit conducted by or on behalf of the dosage form manufacturer. Have you set any minimum criteria – in relation to the audit and the audit report and if yes, which are these?

9. What position does your authority take on the acceptability of 3rd party API-supplier audit reports as proof of Q7a GMP compliance?

10. In addition to the items set in 5. and if you accept a 3rd party audit report, have you set some minimum criteria in relation to the audit and the audit report:

- Competence of the auditor?
- Credibility of the legal person issuing the audit report?

11. If a third party audit is commissioned by the API producer itself (or on behalf of a number of small or medium size companies), what minimum conditions must be met that such audit reports are accepted as evidence of GMP compliance?

12. Do your inspectors intend to take samples of APIs or will you collect samples via any other channel? If yes, how and where do you intend to obtain such samples?

13. Does your authority intend to maintain "libraries" of analytical results on API samples, including information that can be used as fingerprints of the APIs per specific manufacturer?

14. What actions will your authorities take when testing indicates that the API present in a dosage form marketed in your member state is of a different quality/origin than what has been approved in the marketing authorization?

15. What sanctions are available to your authorities against companies marketing medicinal products in your member state that contain APIs not manufactured in compliance with ICH Q7a GMP (or APIs that are of unknown origin) and when the audited API producer does not propose acceptable corrective actions to the identified deficiencies?

16. What are the criteria for applying the strictest sanctions? What are the strictest sanctions? Are there any precedents?

17. Has your member state in the past withdrawn marketing authorizations for any reason of non-compliance with regulations?

18. In case of a voided CEP certificate, will your member state automatically request that this company be withdrawn as approved supplier by the MAA holder and will the implementation of this decision be verified?

19. What are the maximum sentences/sanctions or what measures are taken in your member state against individuals or companies that are involved in pharmaceutical fraud such as systematic use of APIs that are not known for sure to be GMP-compliant, that are purchased from unapproved sources or use of counterfeit material? Do you have precedents for such convictions or measures? Are such activities considered legal offences in your country?

20. How many inspections of API manufacturing facilities located within the EU will be performed by your member state per year during the coming 5 years?

21. How many inspections of API manufacturing facilities located outside the EU will be performed by your member state per year during the coming 5 years?

22. How many inspections of API trading facilities located within the EU will be performed by your member state per year during the coming 5 years?

23. How many inspections of API trading facilities located outside the EU will be performed by your member state per year during the coming 5 years?

24. How many of your member states' inspectors have been trained in performing API inspections and how many more will be trained in the near future? Doe this training include the detection of fraudulent practices?

25. What is the total number of pharmaceutical inspectors in your member state?

26. Does your authority consider carrying out API inspections in non-EU countries? – What criteria will be used to trigger such audits? Do you intend to re-inspect on a regular basis (e.g. every 3 years) or at a risk-based frequency?

27. Do you impose regular audits by de MA holders, e.g. every three years or at a lower frequency if justified on risk considerations? – What are your minimal expectations from the MA holders?

28. Does your authority have access to API inspection results generated by above-mentioned authorities? If possible, please specify which authorities and the level of detail of the information available to your authority.

In addition to the problem of inflated expectations, the last few years "have been quite tough for our business," Villax stressed, due to other factors such as the limited number of new product launches and the decision by some big pharma firms like Merck, that had been "pushing the outsourcing business," to start moving production back in-house.

Patent And Environmental Rules Also At Play

The regulatory environment – in the patent and environmental areas as well as GMP – has been another dimension of the EU industry problems.

Discussing the patent problem, Villax noted that Bolar-type provisions have only recently been enacted. For the previous two decades, "Europe was at a significant disadvantage over just about everywhere else and couldn't," because of the supplementary patent legislation put in place through big pharma lobbying, "develop generic APIs in time to be competitive."

Environmental legislation passed by the European Parliament has also put the industry at a competitive disadvantage. In 1990, Villax explained, there were 19 pieces of legislation in this area. By 2003 the number had grown to 533. The "avalanche of regulations," he said, has had a dampening effect on chemistry development and application in the EU.

- Looking at the GMP issue, Villax pointed out that "when API producers sell to pharma companies in America, filings and inspections make sure GMP are met. In Europe, you have filings on both sides. You would imagine there are inspections on both sides, but as we all know, there are not."

Under the new directive, control over the quality of APIs in Europe will be in the hands of "this poor gentleman," the qualified person, who will have a tough time "because he is going to be between his sense of responsibility and the purchasing department." EFCG, Villax said, is trying to communicate the ramifications of the problem to the business side of the pharma industry in Europe.

Adding to its competitive problem is the expense European industry faces in producing under GMP.

"It is not just expensive in terms of costs," the Hovione CEO stressed, "it is expensive in terms of business strategy. Because if you do things by the book, it takes quite a bit longer to implement changes. If you do things by the book, it is very tough to be the first one to develop a generic because others take short cuts. So you do have significant disadvantages." The EU does have "a law now, but what is the point of the law if the deterrent is inadequate? This is I think our next big issue."

Asia Presents Threat And Opportunity

After analyzing the regulatory environment in Europe, Villax turned his attention to the manufacturing situation in Asia.

Overall, the Hovione exec views Asia "as a threat as well as an opportunity." He suggested "that if you get to know India and China well, you will see that there are some excellent firms. Then you will see that there are small firms trying very hard to learn. And I think that is one of the most fascinating characteristics of especially China – how eager they are to learn and improve."

- Villax, who has been involved in operations in both India and China, perceives some significant differences between the two.

"Obviously language and communications seems much easier in India than China. I think India has extremely competent and experienced top management. They all seem to have excellent software. China is totally different. The airports are infinitely better, the roads are infinitely better. So it seems that India is much more to do with soft things, software. China has much more to do with infrastructure."

He noted that Hovione has been working successfully in China for more than two decades, Villax noted. "We probably have our own conservative way of approaching business, but the truth is we have never had a disappointment in our work in China. We have been able to build extremely good relationships there. But it is like trying to find needles in a haystack to try and find the good producers, the right partners." However, he cautioned, "if you don't get to know these markets and these areas where there are producers, you will be surprised by very competent competitors."

Villax expanded on where he sees the opportunity in Asia: "It is obvious that in our value propositions, the way we go to our customers, we should be able to make our customers benefit from low-cost building blocks. I think that if we don't do this, we are not running our businesses properly. I think Asia has an amazing sense of speed, they have an amazing can-do mentality. So all our purchasing departments should be making sure they have a big travel budget."

It is necessary to collaborate with and support Asian suppliers, he advised. In Hovione's case, "we transfer technology to them, we help with the quality." On the other hand, the CEO cautioned, "naturally you need to make sure you are not selling the rope that will hang you."

In today's game, he summarized, "the business doesn't really have that many equilibriums any more. You have to constantly be running to stay ahead."

Environmental Controls Also At Issue

In terms of the need for the EU industry to compete with Asia, Villax commented further on the disequilibrium in environmental controls.

➤ Citing some dramatic examples of operational incidents that have found their way into the press, he stressed that the issue of fair competition is significantly involved with environmental as well as GMP standards.

Villax cited a *New York Times* story from late 2003 that focused on "a major producer in China that is very competent, FDA-inspected, with multiple COSs from the EDQM, thousands of cubic meters of reactors doing synthetic steps, and tens of thousands of cubic meters of fermenters." The article focused on deaths among maintenance workers from gross toxic exposures, pointing to the irony that the firm was making products to fight cancer in the West while disregarding the health of its own workers and neighbors.

The article addressed some of the customers of the firm, including an American company, who either lacked knowledge of or was unwilling to discuss the plant's environmental problems. "FDA also isn't terribly keen to answer questions on environment," Villax added.

He further cited reports entered on a Chinese government website of seven serious chemical accidents in the month of April 2004 alone involving environmental degradation, evacuations and severe injury. He sees "some degree of hypocrisy" in Europe's willingness to buy material from such plants, while creating roadblocks for chemical operations "in its own backyard."

➤ In the context of this regulatory disequilibrium, Villax emphasized, "we end up having state-of-the-art GMP plants with state-of-the-art HSE systems sitting idle. We have the best trained operators out of a job while in the Far East, the business is growing" very rapidly.

He noted that earlier in 2005, EMEA asked for comments on a legislative directive which included the statement that issues of health, safety and environment [HSE] aren't really matters for inspectors.

"I wrote back a comment that said this is totally inadmissible," because GMP implementation "really depends very much on the sense of ethics that management has. So if management doesn't think HSE is terribly relevant, what kind of sense of credibility is an inspector going to think this company has? I think inspectors should be allowed to have their judgment biased if they see children working in plants in appalling conditions. I think this kind of thing should be taken seriously."

➤ Another issue is the divergence in Chinese regulatory oversight of domestic manufacturing operations making product for export vs. for the home market.

Companies in China are inspected for their own market and may use "very up-to-date equipment" and standards in domestic production, Villax commented. However, "since the manufacturer is not inspected for Europe, it sometimes uses older equipment which is clearly not up to standard" for the exported material.

In spite of the significant competitive and regulatory challenges faced by the EU API industry, Villax explained the he remains "quite optimistic" about its ability to navigate the technical shoals and take advantage of the opportunities in the evolving regulatory and production environment (*see box below*).

Enforceability Vital To Regulatory Function

In his presentation at the Berlin conference, DSM's Oldenhof focused on "transparency and cooperation in developing regulatory documents" – concerns that are particularly challenging and important in the European context where 25 different national authorities as well as wider international harmonization efforts are now at play.

Oldenhof pointed to five interrelated characteristics that are necessary to develop "a good regulatory document" – either a regulation or a guideline:

● adequately protects the public health – "That is what we are all here for. It doesn't need any discussion."

● is clear – "It must be understandable."

● is reasonable – "It must, in other words, be proportional to the topic and the implicit risk."

● is workable – "You can make a regulation, but if it is really impossible to comply with, it creates serious problems."

● is enforceable – "You must check whether people comply with it, and enforce it if this is not the case. If you don't, it is again a big problem."

Oldenhof pointed to a survey by The Organization for Professionals in Regulatory Affairs (TOPRA), which is based in London, that showed that European legislation was not seen as possessing these characteristics.

The survey recipients were asked if they thought that the practical implications of the new legislation were sufficiently taken into account when the legislation was drafted. Of the 229 responses, 210 (92%) said no, while only 19 (8%) said yes. "A result like this indicates that we really have a problem here," the DSM official commented.

➢ Oldenhof discussed an assessment he performed of a number of key current quality regulatory documents. He scored them either plus or minus based on DSM's experience with their reasonableness and workability.

The variations regulations did not fare well in Oldenhof's assessment.

Being a dedicated API manufacturer, he commented, "it will not surprise you [that] we have huge problems with that. We don't think it is reasonable and we absolutely do not think it is workable. It worries us a lot because in the values of our company it is written that we want to comply with the regulations. We really want to. But if it is impossible, what do you do?"

Other documents that drew minuses in the reasonable/workable categories included both the EU's and FDA's drug substance CMC guidelines, FDA's 314.70 manufacturing change regulations, and the CEP revisions procedure.

On the other hand, the ICH guidelines on residual solvents (Q3C), stability (Q1A), and GMP for APIs (Q7A) all received plus marks.

➢ The assessment led Oldenhof to conclude that "documents resulting from the ICH process are generally regarded as reasonable and workable," while documents resulting from EU and "old paradigm" FDA procedures have problems.

Oldenhof attributed the success of the ICH efforts to the process of guidance development whereby "all stages from the very beginning are executed by the regulators and industry together." The documents that aren't developed in this way, although they may be faster to issue, tend to go through a cycle of major revisions which do not necessarily resolve their problems. By contrast, "when the ICH document is issued it is almost final," with only minor revisions needed afterwards.

Like the ICH documents, FDA's bulk active post-approval change guidance (BACPAC 1) did involve early industry input and contains some "very positive aspects" as a result, Oldenhof said, although it also "contains some things that are not so easy to comply with."

The ultimate consequences of "not good" regulatory documents are that continuous improvement and innovation in pharmaceutical manufacture are blocked – a particular problem for API manufacturers because of the post-approval change authorization regulations in Europe and the U.S., Oldenhof stressed. In addition, "unsafe illegal APIs [are] floating into Europe….and the complying companies cannot compete."

Bad regulations "lose their credibility," Oldenhof stressed, and create a situation where "non-compliance becomes something like an unavoidable fact of life, and I think that is what we should avoid."

Variations Problem Recognized By EMEA

At the Berlin meeting, EMEA Quality Working Party Vice Chair Susanne Keitel (from Germany's Federal Institute for Drugs and Medical Devices) acknowledged industry's concerns with the current variations approach, pointing to the potential offered by the ICH guidelines Q8-Q10 "for a future with a very limited number of variations."

While the EMEA is well-aware of the problems in the current system and discussions about the future of the variation regulation are ongoing, the commission has other pressing priorities "for the time being, and it is difficult, as long as the discussion on the ICH level is ongoing, to come up with a final decision," Keitel said. In the meantime, she noted, the EC has been advising the EU authorities to "use common sense and try to be as flexible as possible."

During the discussion following Keitel's presentation, Oldenhof explained that the manufacturing change problem for the API manufacturer is exacerbated by the complexities of the distribution chain and the lack of knowledge about the customer's application dossier.

The response to letters sent out to inform customers of a desired change is often that the original purchaser "no longer exists, or has moved, or that a business had been sold and we don't know to whom," he said. The authorities may have this information, but the API manufacturer "does not know how" to comply even though it has the intention to do so.

The sale to distributors, who may make commitments on behalf of the API manufacturer without the required approval, adds to the problem. The result is that "we want to inform" the customers, but "at the end of the day we can not inform them."

- In general, Oldenhof asserted that using variations filings as a means of regulatory authority oversight that API manufacturers have informed their clients of a change is "an incredibly complicated and bureaucratic way to check this."

Within the new GMP directive, the DSM official said, dosage form manufacturers will be expected to audit their API suppliers and "there is the possibility for the authorities now to inspect API suppliers." He suggested that this approach is "a better way to check these things instead of creating this humongous avalanche of rather meaningless paper."

- At a U.S.-based API conference sponsored by the Synthetic Organic Chemical Manufacturers Association (SOCMA) in October which paralleled the one in Berlin ["The Gold Sheet" December 2005], participants commented on the importance of the change notification process and the difficulties involved.

Industry consultant Gary Gray recommended that an API producer be "very careful and very aggressive about notifying your customers" when making changes to an API process.

"In my experience, it has been much better to notify a customer of a change that was inconsequential than it is to implement a change and have a customer come back and say, 'something is different about the product, did you make a change?" He added that a change "that you think is pretty inconsequential can turn out to be a significant issue for your customers."

- The change notification process was discussed at the SOCMA conference as an important component of a quality agreement between the API and dosage manufacturer.

Division of Manufacturing and Product Quality staffer Frederick Blumenschein explained that a quality agreement between the API buyer and seller is not a specific GMP requirement but is an important tool in the quality control process ("The Gold Sheet" November 2002).

Blumenschein noted that the agency was working on a guidance for contract manufacturing, but that the effort was in preliminary stages.

The FDA compliance official commented that it made sense to write contracts that spell out each party's responsibilities because "what is increasingly happening is" that FDA ends up dealing with two firms, both of whom "are pointing at the other firm. It is just a mess."

Keller and Heckman attorney John Dubeck pointed out that for the API maker, it is not so much a question of "a given document does not point the finger one way or the other, but that 10 different documents have fingers pointing in different directions for the same thing for different customers."

Dubeck suggested that when dealing with an API supplier that has its own quality agreement, the purchaser may want to adopt the API maker's quality agreement because "an API maker cannot effectively abide by 10 different quality agreements."

Another attendee observed that one problem with this approach is that "it encourages [API makers] to write their own regulations for a single drug supplier who, in the generic world, can be supplying 15 different customers." He described the downside of quality agreements between API makers and finished-dose makers as "catastrophic when you realize that what you are doing is giving individual companies the ability to write their own regulations," which can lead to finished drug makers promulgating requirements that "go far beyond what FDA is saying – and the reason they do that is that they have the opportunity."

Both Flexibility And Enforcement Needed

In summary remarks at the Berlin conference, APIC President Henri Leblanc (Regulatory Affairs Director, Rhodia Organique) pointed to Oldenhof's and other presentations in affirming that the API industry "does not want to be squeezed into a straightjacket. We need some breathing space to be able to innovate. We want to improve our processes, both for quality but also for cost reasons."

On the other hand, Leblanc cautioned that "flexibility without control will inevitably lead to excesses and illegal practices," so an effective enforcement approach is also needed.

➢ By bringing science to bear, the FDA and ICH initiatives "should help" in creating a more workable system, Leblanc said.

However, the Rhodia official emphasized that the industry is global in nature and "is not just selling to Europe, Japan or the States." While there is still some disharmony within the ICH process, the problems get "more and more difficult when you have different types of filings to maintain and different requirements across the globe."

The industry vision is to have "a single global pharmacopeia" and a single regulatory filing system – "not just a format, also the content," Leblanc said, adding that "it should be a goal for all the regulators" to strive for.

More Flexible Approach Proposed For API Changes

FDA is looking to revamp its guidance approach in the API CMC area. Rather than revising the relevant guidance efforts including BACPAC 1 and 2 and the drug substance CMC guidance on a piecemeal basis, the agency has decided to take a unified approach that will embody the science- and risk-based principles of the agency's new quality assessment paradigm ("The Gold Sheet" December 2005).

➢ At the SOCMA conference, participants reviewed the problems in the current FDA regulatory paradigm for API manufacturing changes and compared ideas on what a more flexible approach might entail.

One of the participants in the debate was SST Technical Affairs Executive Director Arthur Fabian. Fabian has been among those in industry over the past several years who have stressed the importance of revamping the agency's regulatory scheme for changes in API production if bulk drug manufacturers are to improve quality and efficiency without incurring undue filing burdens for themselves and their customers.

In a presentation entitled "Brainstorming BACPAC II," Fabian filled in further the outlines of a proposal he began developing in response to FDA's BACPAC effort in the late 1990s for a less restrictive regulatory system that would more clearly reflect the ability of manufacturers to determine the equivalence of API materials at various stages of production ("The Gold Sheet" April 1997).

The SST official explained that such a system would call for FDA preclearance of a change "only for the case of the initial appearance of non-equivalence" and/or when the final API is impacted. Filing requirements would be proportional to the actual impact of any changes as opposed to the potential impact, and would relate not to "the location of the change, but where one shows equivalence." As such, the system would be driven by science and data rather than by an *a priori* judgment of changes, allowing industry more flexibility.

➢ In mapping out a way to get beyond the encumbrances of the current BACPAC I/II scheme, Fabian's SOCMA presentation lined up with the intentions expressed by FDA Office of New Drug Quality Assessment Director Moheb Nasr at the APIC meeting to develop a more integrated and forward-looking guidance approach rather than amending the existing documents.

Fabian's proposed approach also echoes the recent paper by a task group of the Pharmaceutical Research and Manufacturers of America (PhRMA) which advocates that knowledge of the effects on critical quality attributes should obviate the need for regulatory oversight of changes ("The Gold Sheet" December 2005).

Fabian framed his proposed regulatory reductions in terms of dropping down a level in the supplement filing from the current preapproval supplement (PAS) default mode. However, under the push of the quality initiative, the supplement filing requirements could be eliminated altogether if equivalency criteria are met.

Consideration of a fresh approach is appropriate, Fabian pointed out, "because on the one hand FDA has not yet issued their final draft guidance on the topic, and on the other hand, several industry trade groups have submitted proposals to the FDA as to what they would like BACPAC II to look like."

FDA published BACPAC I in 1998, which covered filing expectations for changes upstream of the final intermediate. While proposals have been forthcoming from industry and the agency had a committee working on the document, a draft of BACPAC II, extending through the final API product, has not been issued ("The Gold Sheet" September 2003). ♦♦

Impact of New EU Pharmaceutical API Quality Regulations/Guidance

The following is a discussion by European Commission pharmaceutical official Sabine Atzor at the October APIC/ CEFIC conference in Berlin in which she reviews the implications of the new EU pharmaceutical legislation and implementing measures that strengthen the oversight of API GMP. Atzor explains how the new legislation is being implemented in the EU through its system of directives, guidelines and guidances, and the impact on the obligations of manufacturing authorization holders, API manufacturers, and the competent authorities.

With the important date approaching, the end of October, which is such an important date for the active substance manufacturers and also the pharmaceutical manufacturers regarding the new legislative requirements, I am really happy to take this invitation for a presentation today….It is new to all of us, [including] the regulators. Coming from the European Commission I will be able to present you with the regulatory framework, but I will not be in the position to give you an answer to all questions related to the practical implementation of this legislation. But I will be happy to take on board your questions…and bring them to the attention to the team of experts located at the EMEA, which is the GMP inspectors group, and have all the questions discussed there, and responded to in a harmonized way. I think that is what you are interested in as well in the European industry.

To start with my presentation, I would like to deliver a brief overview of what you can expect today from me. I will give you an outline on what is new in terms of legislation and regulatory requirements. Then I will link this to different responsibilities of the stakeholders in the whole system, which includes the manufacturers of medicinal products, of active substances, and also the competent authorities.

Just to give you a brief overview as a starter: What do we have on the regulatory side? ● We have directives, which are addressed to the member states – our member states have to make sure that those directives are implemented into national legislation ● we have guidelines which are based on those directives, and ● we have guidances, practical arrangements.

You are familiar probably with the human medicinal products directive and the veterinary medicinal products directive, which have been amended last year to include specific provisions for manufacturers of active substances and also for manufacturers of finished products – to include GMP on the API side.

The human medicinal products directive also includes the provision for an additional directive, a GMP directive for excipients. We are currently working on this directive, but I don't want to go into details during this presentation.

Then we have the guidelines. One of the most important ones in this whole discussion is the new GMP Part II for active substances used as starting materials, which replaces the former GMP Annex 18. It was just published [October 10] by the European Commission. It will become applicable for member states to implement into national legislation at the end of October by the latest.

For this new GMP Part II, we have restructured the GMP guide to give a better explanation of how this work will have realized the introduction to the GMP guide in general, and have made this public on our web site at the European Commission [pharmacos.eudra.org].

The restructuring of the GMP guide and the inclusion of the GMP Part II on active substances makes it necessary to revise certain GMP annexes. That is what we have on our work list for the future.

I would also like to talk about guidances and practical arrangements. Here we have quite a lot. There is the "Compilation of Community Procedures" on harmonizing inspection aspects and exchange of information between the member states. [It] is mainly addressed to member states' competent authorities. The Compilation has been in existence for a couple of years already and has always been published by the EMEA on behalf of the European Commission, and has just now been revised to included additional procedures relating to active substances and also relating to the realized legislation. These revisions refer to the inclusion of an important document which we call the "inspection trigger guidance" – if you take the complete name, "guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials." And the new Compilation also includes a format of the GMP Certificate, the GMP Inspection Report Format, and a Manufacturing Authorization.

Talking about guidances and guidelines, and I will go into details later on through my presentation, we also have the Notice to Applicants: Volume 2b currently in revision to include specific requirements regarding GMP for active substance manufacturers and the obligations of the qualified person of the finished product manufacturer. And finally, the EMEA is

currently preparing a question-and-answer document on audits and the interpretation of what can be acceptable. And that document is currently still in preparation and expected to be public during this month on the EMEA web site.

GUIDELINE REVISIONS

The legislation entitles the European Commission to publish detailed guidelines on: ● the form and content of the authorization (only for medicinal products) ● inspection reports, and ● GMP certificates. Let me give you some of the main discussion points which came up during the development of these three documents:

The authorization and inspection report format already existed even before this legal requirement was implemented into the directive. The revision includes practical considerations with the experience of this document. Considering the **authorization format,** we had a discussion as to whether or not the process of sterilization of active substances should be included in the authorization. Most of the member states considered the sterilization process of the active substance to be part of the manufacturing process of the finished product. Therefore they decided to include it in the authorization format and we have…a specific section for that.

As regards the inspection reports, we have now one report format which is applicable both to inspections at medicinal product manufacturers as well as active substance manufacturers. I would like to draw your attention to the fact that deficiencies are classified in three categories: We have critical deficiencies, which relate to deficiencies which can cause serious public health issues and concerns, then we have major deficiencies, and others. To the major deficiencies belong noncompliances of the product with the marketing authorization, and also noncompliances of the qualified person with his obligation. The qualified person of the manufacturer of the medicinal product is responsible for ensuring that this product has been manufactured in compliance with GMP and in compliance with the marketing authorization, and that also includes in compliance with GMP for active substances. So it is the qualified person of the medicinal product manufacturer who has significant responsibility, ultimate responsibility, on ensuring that active substances have really been manufactured in compliance with GMP.

The **GMP certificate** is a new format which is now published because we have a new system, and we will talk about this later….We will include in the future an inspection date of the manufacturer. The certificate also includes a statement [that] it should be referred to only within a period of three years after this inspection was performed.

The detailed guidance, which had to be published by the European Commission, [contains] the **principles of the GMP**, which I already mentioned – the principles on GMP concerning manufacturing of active substances used as starting materials. And those, as I said, were just published last Monday by the Commission. It replaces Annex 18, and I would like to emphasize that the new Part II does not include changes of the technical requirements of the former Annex 18 or the ICH Q7A. However, it includes a revised introductory section. This revised introductory section emphasizes that these GMP requirements are now applicable for active substances to be used in the manufacture of human and veterinary medicines and products, and that is a very new aspect which is vested in the new legislation.

With the Annex 18 having been switched to the GMP Part II, it was necessary to restructure the GMP guide. We have explained that in the revised introductory section of the GMP guide. The former basic principles for medicinal products now have become Part I. The active substance basic principles are Part II. And the former GMP annexes remain, and they will be applicable as necessary both to active substances and medicinal products. So it was considered necessary that with this revised structure, the annexes will have to be adjusted accordingly to make sure that they match to both parts. For that reason the EMEA has crafted a concept paper to announce a revision of the GMP annexes, and that includes the GMP Annex 2 on biologicals, 3 on radiopharmaceuticals, 6 on medicinal gases, and 7 on…medicinal products. It is intended that these revisions of the annexes will be finalized in 2007.

OBLIGATIONS OF THE STAKEHOLDERS

As I said I would like to talk about: ● the authorization holders of the manufacturing and the marketing authorization holders ● the manufacturers of active substances, and ● the competent authorities. With the competent authorities, we have obligations both for the [assessment] authorities as well as the inspection authorities in the member states.

Let me start with **authorization holders**. One of the basic provisions in the legislation is listed in Article 46 and Article 50 of the human and veterinary directives. It says that the holder of the manufacturing authorization 'shall at least be obliged to comply with the principles and guidelines of GMP for medicinal products,' and 'to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on GMP for starting materials.' Probably you are all aware of this legal provision, but I have put it on the screen to emphasize that the final ultimate

responsibility is with the holder of the manufacturing authorization here. So it is the holder of the authorization and the qualified person who really have to ensure GMP for active substances.

Now, easy said, and how done? There is already the provision given in the GMP, now Part I, basic requirements for medicinal products. And then chapter 5, which says, 'Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer.' The question is: What are approved suppliers? What should be the elements of our contractual agreement? What about audits? When do they have to be done? How should they be conducted? Do the results have to be transparent? To answer all these questions, this Chapter 5.26 is currently under revision. The lead has been taken by the UK on this. And a corporation has been established to revise this chapter with PIC/S, who has just recently installed an expert working group on active substances. That group met a couple of days ago and I think they probably developed a first draft.

To give some answers to the questions raised in the previous slide, the EMEA has sat down together with the member states to discuss these questions. How should audits be performed in practice? What can be accepted? It is clear what I said in my previous slides about the obligations of the manufacturing authorization holder – that GMP certificates issued by competent authorities, by inspection authorities, cannot replace their own evaluation of the manufacturer. It is the manufacturer's responsibility to do this on his own. And at the manufacturer is the qualified person. So he must perform an evaluation….

However, GMP certificates can be taken into account for a risk-based strategy in this evaluation. It has to be made sure that audits in this evaluation are one part of the measures to monitor the quality. The question is: How often do they have to be repeated? How often do they have to be done? The regulators consider that here a risk-based approach should be applied.

Third party audits can be acceptable. However, contractual agreements are necessary between the contract giver and the contract acceptor. And the contract giver has to evaluate this third party to be acceptable for the purposes. It is important that there is no conflict of interest between the third party and the API manufacturer, which means there must be no commercial relationship between the two. And there must be no personal conflict of interest, which means auditors of the third party should not have worked for the API manufacturer within the last two or three years.

How does GMP factor into the dossier assessment? We have two documents under revision, as I just mentioned: the Notice to Applicants, which will be published soon in a revised version, and the Inspection Trigger Guidance, which is already public. According to the Notice to Applicants, in the revised version the QP…of the manufacturing authorization holder will have a new obligation. He will have to state that the active substance manufacturer [is] in compliance with the detailed guidelines on GMP for starting materials.

Now how does it work? Here the Inspection Trigger Guidance has an answer and says: 'It is expected that the holder of the manufacturing authorization will base such a declaration on carrying out, or having carried out on his behalf,' which includes third party audits, 'an audit of the manufacturer or distributor of the active substances concerned.' So it is the holder of the manufacturing authorization who needs to provide such a document on the basis of these audits. And the applicant for the marketing authorization needs to submit this declaration with the dossier. Finally, it is up to the assessment authorities to check that this declaration is included, and to check it also for consistency.

Here let me frame up a perspective: I think here it is important that in the future, GMP inspectors and assessors will cooperate more, and this was done in the past, in terms of information exchange, in terms of mutual input for inspections and assessment. And maybe, question mark, joint inspections between the two….

Coming to the **obligations for the manufacturers of the active substances**: I would like to point out that with the new legislation we have a definition now on what is manufacturing of active substances. Article 46 (A) and 50 (A) of both directives gave a very clear definition. Manufacturing of active substances is: total and partial manufacture or import; dividing up; packaging; and presentation prior to its incorporation into a medicinal product, including repackaging and re-labeling, such as carried out by the distributor – which means manufacturer in certain cases includes the distributor as well.

Now what are the obligations of the active substance manufacturer? He has an obligation concerning the manufacturing authorization holder, so he has to manufacture in compliance with GMP Part II. This is part of the contractual agreement, in compliance with chapter 7 of the GMP guide. He has to allow audits and he has to allow audit reports to be shared with the authorities.

Concerning the competent authorities, he has to allow inspections and sampling by the competent authorities, under the centralized application system, and under the CEP [Certificate of Suitability to the Monograph of the European Pharmacopeia] inspection system. This is applicable both for manufacturers inside or outside the EU.

Talking about the **obligations of competent authorities**, I would like to limit my comments here to the inspection services of the member states. For the assessment, I have already said some things before.

With the new legislation we have inspection revisions of the manufacturer of medicinal products. [The obligation to inspect them] is not really new – that existed before. But we have new practices concerning the qualification of active substance manufacturers as I outlined before. We have, however, a new legal provision to inspect manufacturers of active substances and marketing authorization holders in that context....

Let me briefly outline what is new. For the manufacturer of the medicinal products it is new, as I said before, that the QP has to give a declaration based on an audit of the manufacturer/distributor. Inspectors now have to examine the audit programs used by the authorization holder for conducting regular audits. This includes the review of the audit reports. This is considered to be one of the primary means by which competent authorities will determine if manufacturing authorization holders are in compliance with the legislation. This is a very new area for the inspectors to consider during their regular inspections.

Concerning the manufacturers of active substances, we have a … provision now which says that a competent authority may carry out inspections at premises of the manufacturer and marketing authorization holder. This is linked to certain conditions: This inspection can take place whenever the competent authority considers that there are problems for suspecting non-compliance with GMP provisions. They may also carry out inspections at the request of another member state, the European Commission, the agency, which is the EMEA, or within the CEP inspection program at the request of the European Commission and the agency, or finally, at the request of the manufacturer himself. But I would like to emphasize that also for requests of the manufacturer himself, the legislation provides [that] it is up to the member state to decide as to whether or not they will perform an inspection on the request of the manufacturer.

Now, what are **grounds for suspecting GMP non-compliance**? [EU] inspectors have discussed this question and set up a list of criteria which is published in the inspection trigger guidance:

● Any information which comes to the attention of the inspectors or the manufacturers on GMP non-compliance would be a trigger.

● Secondly, EDQM [European Directorate for the Quality of Medicines] performs its inspections under the CEP program. If major or critical deficiencies come up [and] follow-up inspections are considered necessary, this would be a reason [for] a follow-up inspection by the relevant authorities [on behalf of EDQM].

● Sample analysis results in significant non-compliance with a specification would also be an inspection trigger. Inspection triggers also refer to serious adverse reactions or recalls related to quality impairment, or to recurrent problems with the quality of the individual batches. Suspicions regarding authenticity of data are also inspection triggers.

● Bearing the gentamicin case in mind, an inspection trigger was added relating to the change of the pharmacopeia for safety reasons. So whenever there are grounds of suspecting that these changes have not sufficiently been implemented, this could be an inspection trigger.

● Biological substances and manufacturer may not be subject to routine inspection, and then this would be a ground to perform inspections here as well.

● I indicated earlier that different member states have different legislation on how to deal with the sterilization process of active substances. So whenever sterile active substances are incorporated aseptically and are not covered by a manufacturing authorization, this would still be a trigger for performing an inspection at the active substance manufacturer.

● We have the inspections under the CEP system of the EDQM. I already indicated this. The commission has now mandated the EDQM to plan and perform such inspections. The EDQM in practice cooperates here with the EMEA and the member states to make sure that this planning fits into the overall system. And the inspections which are performed have the scope to verify that the data submitted conforms with the monographs of the European Pharmacopeia, which does not mean that with every CEP application an inspection is performed.

● Once a certificate has been issued, there may be grounds for suspending or withdrawing a certificate. This would also be an inspection trigger for EDQM.

● Inspections at the active substance manufacturer may also be conducted under the centralized system. There are provisions in the regulation that the committee, which is a committee for human or veterinary medicinal products at the EMEA, may request inspections at the manufacturing site for medicinal products for GMP-related or assessment-related aspects. That could also cover the active substances produced at that site. Apart from that, the EMEA has the mandate to specifically request an inspection of the active substance manufacturer.

The new legislation for the human and veterinary sector foresees that each inspection, whether at the manufacturer of the medicinal product or the manufacturer of the active substance, should be completed with a GMP certificate. The certificate shall be issued within 90 days of an inspection if the company is in compliance with GMP.

[Certificates will be entered into the *EudraGMP* database.] Information on negative inspection results will also be entered into the GMP database. This database is currently under development by the EMEA and is expected to be running [by the end of next year].

I have presented to you a very complex system of [legislation and] regulatory provisions which assigns responsibilities to all the stakeholders, [including] the API manufacturer, the finished product manufacturer, the inspection authorities, the marketing authorization holder, and EDQM. It is important now that the system starts running and that we watch it carefully for its implications for patient safety and competitiveness to the European industry. It has to be clear, however, that there is one stakeholder sitting in the driver's seat and that is the medicinal product manufacturer. He is the one having the ultimate responsibility and he is the one to watch this system very carefully.

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