EFCG EUROPEAN FINE CHEMICALS GROUP **PHARMACEUTICALS BUSINESS COMMITTEE**	**GMP API COMPLIANCE** **BENCHMARKING QUESTIONNAIRE** For Senior Regulatory Contacts in the HEALTH AUTHORITY INSPECTORATE of EU Member States	cefic European Chemical Industry Council Avenue E. van Nieuwenhuyse 4 B-1160 Brussels Belgium Tel: +32 2 676 7244 Fax: +32 2 676 7301 **abo@cefic.be**

This tabulation reports on the replies received from 6 inspectorates from January to April 2006. Written responses were obtained from Denmark, France, Germany (Hessen and Rheinland-Pfalz-District Office Landau), Portugal and Spain.

Questions	EFCG's summary view of the responses and comments
Q1. 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?	Unequivocal YES. EMEA's "aide-mémoire" is high on the agenda.
Q2. What information on APIs will your inspectors require from dosage form manufacturers during inspections?	Wide disparity of the specific criteria but overall agreement as to "whatever data supports forming an opinion": Examples include: - SOP governing the approval of supplier of starting materials - An audit report with less than 3 years of age - A GMP Certificate - "medicinal product of an API manufacturer who is not audited are quarantined on inspection until the API manufacturer has been audited".
Q3. For API's with a DMF, does the dosage form manufacturer have a letter of commitment or the letter of access to the DMF, which includes such commitment?	Seen by some as a matter for the regulatory assessors. Although there is one indication that this may be changing with the QP requiring to have on hand such a commitment.
Q4. For API's 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?	Ditto - a trend appears to exist that QPs will increasingly rely on commercial assurances such as a "statement of commitment" that cover "change-control" obligations.
Q5. For product supplied through a trader or distributor, does the dosage from 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?	Responses per Q4.
Q6. Will you verify that the dosage form manufacturers purchases API's only from suppliers listed in the marketing application and that the list of approved suppliers present on site is in line with those mentioned in the marketing application? How will you verify that there are no purchases (other than for qualification purposes) from other suppliers (e.g. by review of all purchasing	Unequivocal YES. Verification methods include spot/random checks of batch records versus information in the MAA but are not specified by part of the respondents.

records)?	Again this is an area that needs clarification as to what is the intent and what is the minimum verification.
Q7. What tools are you using to detect fraudulent practices, e.g. where the real origin or the goods are hidden. (e.g. verification of purchasing records).	A variety of methods is mentioned: Reliance on visual checks on site, labels and records at the MA holder. Checking of purchasing records and material acceptance in the information system, analytical records One respondent indicated they would check actual sources of supplies against the approved suppliers as recorded in the MA file. No reliance on 3rd party data except a check of origin of supplier's CofA. No reliance on independent analysis. None of the respondents mentions check of the paper trail: invoice, air waybill, import documentation, VAT records
Q8. What sanction will be applied if the inspector establishes that API's from unauthorized sources are being used?	Unequivocal confirmation of availability and application of sanctions – mention of wide range of sanctions available under the law - such as batch recall, suspension of the manufacturing authorization, suspension of the marketing authorization
Q9. 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?	This question triggers a jurisdiction issue – the trader is usually in EU but in country different from the holder of the MA – as such the agency overseeing the MA has no authority over the relevant trader. Cooperation may be requested from the authority responsible for the trader.
Q10. 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?	Unequivocal YES Some reference to the contractual relationship between user of the API and producer of the API.
Q11. In the event of purchase of API's 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?	Unequivocal YES – but no detailing as to how this complex task is achieved.

Q12. The guidelines say that the dosage form manufacturer should satisfy itself that the API's used meet the GMP requirements, in connection with an audit conducted by or o behalf of the dosage form manufacturer. Have you set any minimum criteria in relation to the audit and the audit report and if so, what are they?	Unequivocal YES, many different criteria expressed – but it is clear that trends seem to be emerging, probably in part thanks to EMEA guidance, also requirements that a contractual relationship evidencing some of the criteria listed is referred.
Q13. What position does your authority take on the acceptability of 3rd party API-supplier audit reports as proof of Q7a-GMP compliance?	Widespread open mind to the concept, some convergence on criteria . Reference is made to EMEA initiatives. Overall the positions on this topic appear to be still developing and far from final despite the fact that EMEA has expressed its views on the basic minimums see #.
Q14. In addition to the items set in Q5, 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?	See response to Q13
Q15. If a 3rd 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?	See response to Q13
Q16. Do your inspectors intend to take samples of API's or will you collect samples via any other channel? If so, how and where do you intend to obtain such samples?	Unequivocal YES. Samples are collected, or may be collected, from various sources by all member states that answered.
Q17. Does your authority intend to maintain "libraries" of analytical results on API samples, including information that can be used as fingerprints of the API's per specific manufacturer?	Consensus that this is a next step, but that it is still in the future.
Q18. 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?	Considered a critical deficiency. Responses include "maybe recall of batches", "fines and suspension of the AM", "withdrawal of the application is possible, withdrawal [from] the market is possible".
Q19. What sanctions are available to your authorities against companies marketing medicinal products in your member state that contain API's not manufactured in compliance with ICH/Q7a GMP (or APIs that are of unknown	Considered a critical deficiency. Some responses states: Recall / Withdrawal of MA. Several responses state: Seizure, fines €37,500 and two years' prison sentence also possible.

origin) and when the audited API producer does not propose acceptable corrective actions to the identified deficiencies?	
Q20. What are the criteria for applying the strictest sanctions? What are the strictest sanctions? Are there any precedents?	One response states maximum €37500 fine and 2 years' imprisonment. Another mentions withdrawal of MA. Several mention recall of batches of final medicinal product. Two respondents reported the existence of such precedent.
Q21. Has your member state in the past withdrawn marketing authorizations for any reasons of non-compliance with regulations? What was the nature of such non-compliance?	Wide disparity MAs have been withdrawn in some countries. One country replied "No"
Q22. In case of a voided CEP certificate, will you member state automatically request that this company be withdrawn as an approved supplier by the marketing authorization holder and will the implementation of this decision be verified?	It is of concern that we do not have an "unequivocal YES" and that the responses suggest a lack of clear policies; with some respondents indicating that the matter would still be subject to their inspectorate's view. When a CEP is voided as the result of an inspection (normally because of severe non-compliance or fraud) forceful, consistent measures would be the expected consequences, also because the involved medicinal product may pose a danger to patients. Also scrutiny of other outlets (e.g. registered via ASMFs) would be expected.
Q23. 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 API's that are (1) not certain to be GMP-compliant, (2) hat are purchased from unapproved sources, or (3) use of counterfeit material? Do you have precedents for such convictions or measures? Are such activities considered legal offences in your country?	Unequivocal confirmation of availability and application of sanctions. Two countries report fines of €500.000 fine, and in one additionally up to 5 years' imprisonment Withdrawal of manufacturing licence also mentioned.
Q24. 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?	4 Respondents indicate they will perform in total 58 API inspections in their MS. Note: This may include APIs already subject to inspection under the former legislation (biotech, steriles) – so may not correspond to increased enforcement of the larger volume small molecule APIs. Focus appears to be national inspections.

Q25. 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?	4 Respondents indicate they will perform in total >40 inspections of API manufacturers located outside of the EU. Note: Ditto - This may include APIs already subject to inspection under the former legislation (biotech, steriles). So not encouraging.
Q26. 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?	This question triggers a jurisdiction issue – the trader is usually in EU but in a member state different from the holder of the MA – as such the agency overseeing the MA has no authority over the relevant trader.
Q27. 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?	No respondent intends to perform routine inspections on API trading facilities located outside of the EU.
Q28. How many of your member state's inspectors have been trained in performing API inspections and how many more will be trained in the near future? Does this training include the detection of fraudulent practices?	All respondents refer specialized API training for the inspectors. Little focus on fraud detection. A majority of the inspectorates responding indicate an intent to recruit more inspectors.
Q29. What is the total number of pharmaceutical industry inspectors in your member state?	4 Responses add up to a total of 73 inspectors. One response had "160" that we don't understand.
Q30. 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 on a risk-based frequency?	The responses make clear that in some member states much focus will remain on the APIs already inspected under the former legislation (so biotech APIs…). Member states appear to have or are developing sets of criteria but the responses show a lack of uniformity.
Q31. 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?	Some member states have a clear position ("2-3 years") but others not (yet) while one mentions the required frequency depends on previous results. Reference made to the imminent updating of 5.25 and 5.26 of the EU GMP.
Q32. 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.	Currently there is access to inspection conclusions / summaries / statements from other EU member states. For the future emphasis is placed on "In 2006, we will have access to the European GMP database (Eudra-GMP)."

#: The EFCG summary also makes reference to the EMEA's **Questions & Answers on audits of active substances manufacturers** per http://www.emea.eu.int/Inspections/GMPfaqAS.html as at 8th April 2005.
The Danish responses also benefited from data extracted from their web site on http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=8127 they are marked ".." in the responses above.