API Audits & Inspections: An APIC Point of View

Chris Oldenhof
DSM / The Netherlands
President of APIC

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Definitions

**API Audit:**

Formal review of GMP compliance and/or Quality status by a customer or by a (non-authority) third party

**API Inspection:**

Formal review of GMP-, Quality- and/or Regulatory compliance by an authority
APIC:  
Active Pharmaceutical Ingredients Committee

- Sector Group of CEFIC  
  (European Chemical Industry Council)
- APIC founded in 1992
- APIC’s Mission:
  - To promote the use of compliant APIs in medicinal products to ensure patient safety
  - To represent the interests of pharmaceutical and chemical companies producing APIs and intermediates in Europe by being recognized experts who advance and influence the global GMP and Regulatory environment.
General APIC Positions on API Audits & Inspections

- Neither is needed: NO
- Only any one of the two is needed: NO
- Only Audit = Sufficient: NO
- Only Inspection = Sufficient: NO / yes
- Both are always needed: YES / no

⇒ Agreement on:
Inspection is always required!
Industry insists upon being inspected...
Which single aspect is of paramount importance in relation to inspections/audits?:

Availability of resources  Low costs
No duplication of work
Patient safety  Workable Guidelines
Competitiveness of the industry
Trade Relations  Harmonization
Better Quality  Profits
Compliance  Legal Aspects
Clear Responsibilities  Regulations
Which single aspect is of paramount importance in relation to inspections/audits?:

- Availability of resources
- Low costs
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- Patient safety
- Workable Guidelines
- Competitiveness of the industry
- Trade Relations
- Harmonization
- Better Quality
- Profits
- Compliance
- Legal Aspects
- Clear Responsibilities
- Regulations
Proposed Priority #1:
No compromises when patient safety is at stake!
Derived Proposed Principle:

Putting patient safety at risk by:

- Tampering, cheating, cutting corners, counterfeiting, not adhering to regulations in the manufacture and trade of APIs - all with the aim of earning more money - is unacceptable.

- A lack of API oversight, enforcement and deterrence is also unacceptable.
What does not work:

A Paper Tiger: Relying solely on checking paperwork => Deterrence: Zero... or worse
Paper Tiger => Lack of oversight, inspection, enforcement:

Opens the door to and even stimulates and attracts the proliferation and escalation of:

- Sloppiness =>
- Cutting corners =>
- Deliberate non-compliance =>
- Cheating =>
- Counterfeiting =>
- Crime…
Example of inspectional weakness: FDA 2003 + 2004 (including PAIs)

![Bar chart showing FDA Registered Firms and Inspections in 2004]

**Number of firms data** taken from the CDER 2005 Compliance Update presented by Kristen Evans at the 29th International cGMP Conference, University of Georgia, March 2005.

**Number of inspections data** taken from the 2004 CDER Report to the Nation published August 2005.
Example of inspectional weakness: FDA 2007 (including PAIs)

China: 18 of 714; India: 54 of 410
Example of overdue inspections: CEPs

- After around 150 inspections worldwide (+65% in Asia, most others in Europe) in ±10 years time EDQM has in total suspended or withdrawn almost 40 CEPs

- This implies: Large quantities of at least around 40 very unsafe APIs have been administered to patients in the EU for years

- From a patient safety perspective the CEPs should never have been granted in the first place

- All the CEP suspensions and withdrawals by EDQM related to API manufacture in Asia (so zero to Europe)

... but APIC has always applauded EDQM because until recently it has been the only European entity arranging for API inspections (*) outside Europe...

(*) Centralised procedure APIs are inspected globally through EMEA coordination
Victims of counterfeited / non-inspected pharmaceutical ingredients

Heparin

Haiti

Panama

Gentamicin
A worrying pattern emerges:

<table>
<thead>
<tr>
<th>Product</th>
<th>Origin</th>
<th>Deliberate</th>
<th>Where Deaths</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin/OSCS (Counterfeit)</td>
<td>China</td>
<td>Yes</td>
<td>US, not in EU</td>
<td>Side effects in Germany</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Mimics in analyses</td>
</tr>
<tr>
<td>Pet Food/Melamine (Counterfeit)</td>
<td>China</td>
<td>Yes</td>
<td>US, not in EU</td>
<td>Mimics in analyses</td>
</tr>
<tr>
<td>Gentamicin sulfate (Counterfeit)</td>
<td>China</td>
<td>Yes</td>
<td>US, not in EU</td>
<td>Only seen with special analyses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Germany reacts: Würzburg project</td>
</tr>
<tr>
<td>Glycerin/DEG (Counterfeit)</td>
<td>China</td>
<td>Yes</td>
<td>Not in US/EU</td>
<td>But found in US/EU: In toothpaste</td>
</tr>
<tr>
<td>L-Tryptophan (Not a counterfeit)</td>
<td>Japan</td>
<td>No</td>
<td>US, not in EU</td>
<td>Trace impurity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Side effects in Germany</td>
</tr>
</tbody>
</table>

Note: Ketek® affair includes similar discrepancies between EU and US casualties data
Rogue APIs in Europe

Quotes from a presentation by French/Chinese trading company on frequently occurring trade situations with APIs from China as a result of lack of oversight (*):

- “COS/DMF is disconnected with reality of GMP level, even of existing of site

- “Producers submit false documents and refuse any audits, visits to site” (If Audit or Inspection announced => Immediate close-down)

- “Competition mainly focused on price, bring the sector going down - destroying pharmaceutical European industry in generics”

- “In fact, no respect of European laws and regulations”

- “Europe becoming the last served market after USA / Japan and the rest of the world”

⇒ Bad news for the safety of patients in Europe…

(*) Charles Hu (Bim Sifram Group), EFCG Conference Lisbon, 29-30 May 2008
Rogue APIs in Europe

Contrast of Mr. Hu’s view with the recent EMEA report:

“Community project on the practical implementation of the new obligations for manufacturing authorisation holders (Art. 46f/50f Directive 2001/83(2)/EC)” (14 July 2008)

on MA holder inspection outcomes on EU API compliance in 2005 - 2006 is difficult to understand.

Note: Recent trader statement at same Lisbon Conference that “+90% of APIs entering EU via traders and brokers (about 40% of total API volume) does not comply with ICH Q7” confirms the concerns as expressed by Mr. Hu.
The survey, carried out between May 2005 and May 2006, reveals that manufacturing authorisation holders are aware of their new obligations and have taken measures to comply.
Rogue APIs in Europe

Quote from the EMEA Report’s conclusions:

and although the performance of manufacturing authorisation holders was expected to improve in this new area of compliance, the European Commission is planning legal proposals to improve the regulatory framework to protect patients from the growing threat from counterfeit medicinal products.

- Is the word “although” suggesting that the legal initiative may not be necessary because everything is under control?
- With patient safety being at stake serious concern and zero tolerance should prevail
Rogue APIs in Europe

But also coming from EMEA:

(Press Conference, 5 June 2008)

“EMEA urges more collaboration after heparin scandal”

...EMEA Head Thomas Lonngren said:

"This is a new scenario for us as regulators on both sides of the Atlantic. Suddenly we discover that we have important manufacturing far away that we don't have any control of."

See: http://www.reuters.com/article/governmentFilingsNews/idUSL065880782008080606
and: http://www.reuters.com/article/governmentFilingsNews/idUSL065880782008080606
Why Inspect?

To protect patient safety by:

Not only
- Detecting GMP non-compliance
- Detecting RA non-compliance

But also by
- Detecting Fraud
- Detecting Counterfeiting

Note:
And as has now been proven by the outcomes of EDQM’s inspection program: A system based on trusting on MA holder audits only does not work!
A recent example of what may be found during API-focused inspections

- February 2006: FDA inspection at an Indian top-of-the-bill generics company’s (*) API plant in India resulted in severe Warning Letter in June 2006
- February 2007: US Federal Agents’ raids at the company’s US headquarters and manufacturing facilities
- July 2008: US Government court filings make reference to “a pattern of systemic fraudulent conduct” at the company (including sourcing of APIs from unapproved sources, fraudulent API stability testing, use of rapidly degrading APIs)
- July 2008: US Congress Subcommittee on Oversight and Investigations launching investigation on possible FDA failures to stop involved unsafe products from entering the USA.
- September 2008: FDA bans 33 of the company’s generic drug products and 6 of its APIs from the US market.

Impact on Europe…?

(*) The company exports >25% of its drug products output to the USA and ca. 17% to Europe
How to inspect / audit for API fraud?

Tips and tricks: At the API manufacturer (1)

- Check location and details of site up front on Google Earth
- Check for large discrepancies between annual output and sales (Indicates purchase API elsewhere and re-labeling)
- Check the label book for labels from other manufacturers (Indicates labeling own API as if produced by others)
- Check if any API is shipped in neutrally labeled packaging (Indicates illegitimate re-labeling at receiving end)
- Check if API warehouse inventory is lower than theoretically (Indicates hidden API may be stored in other warehouses)
How to inspect / audit for API fraud?

Tips and tricks: At the API manufacturer (2)

- Do not only check first rows of drums (Other rows may be unlabeled)
- Do not follow the company’s agenda; ask to see things that were not expected by the company
- Only inspect when manufacture of the API is running
- Check for compliance of all data included within the API registration documents (e.g. CEP dossier or DMF)
- Check any reports of inspections of the site performed by other reputed authorities
How to inspect / audit for API fraud?

Tips and tricks: At the API manufacturer (3)

- Check on EDQM’s website if the manufacturer holds any CEPs that have been suspended or withdrawn by EDQM
- Check purchasing records and sales records for illicit transactions
- Take API samples and have them analytically fingerprinted vs. an original sample from the company and/or compare with registered API quality in CEP dossier or DMF
- Obtain a list of shipped batches, dates and clients and later cross-check these during inspections of clients’ sites
How to inspect / audit for API fraud?

Tips and tricks: At the Exporting API trader

- Check for discrepancies between volumes of API purchased from companies vs. volumes sold under the labels of those companies
- Check for traces of activities of replacing original labels by different labels (e.g. equipment to remove labels: e.g. a burner)
- Check for the presence of API in warehouses with labels from producers not included in official documentation
- Scrutinize entire labels production, management and reconciliation system for irregularities
- Take API samples for analytical fingerprinting as above
How to inspect / audit for API fraud?

Tips and tricks: At the Importing API trader

• Same points as for Exporting API trader
• Check information on the origin of the API material at customs vs. data on file at the importing trader
How to inspect / audit for API fraud?

Tips and tricks: At the API user / Dosage Form manufacturer (1)

- Check for fraudulent actions with documentation aimed at hiding the true origin of the material
- Check the purchasing records on sourced APIs from specific companies vs. the volumes of API from these specific companies actually used in production of the dosage forms
- Check if API with labels from producers not included in official documentation is present in warehouses
How to inspect / audit for API fraud?

**Tips and tricks: At the API user / Dosage Form manufacturer (2)**

- Take API samples for analytical fingerprinting vs. authentic samples of the approved API supplier and check fingerprint vs. registered API quality
- Compare information obtained from the approved API supplier on the API volume sold annually to the inspected dosage form manufacturer and compare vs. volume used annually in production of the dosage forms
- Verify also that batch numbers and dates match those of the ones obtained from the API manufacturer
What is needed to solve Europe’s Rogue API Problem?:

CEFIC’s submitted 10 Points to the European Commission

1. Mandatory API GMP Certification from European inspectorate
2. Global prioritization of API inspections
3. Central European Unit to coordinate API inspections worldwide
4. Including focus on fraud and counterfeiting within GMP inspections
5. Resolve resource problems for inspections through user fees
What is needed to solve Europe’s Rogue API Problem:

CEFIC submitted 10 Points to the European Commission

6. Use of analytical technologies by authorities and industry to detect counterfeit APIs (e.g. NIRS)
7. IT system to help customs to stop importation of Rogue APIs
8. Introduction of tough sanctions and penalties for API counterfeiting
9. Introduction of licensing system for traders and brokers
10. Clarify legal liability of Qualified Persons
A Fatal Example: Heparin

- Heparin use: Heart surgery, kidney dialysis, angioplasty: millions of patients per year
- Q1 2008: In USA 149 patients reported dead and ca. 800 adverse reactions (partly life-threatening) due to contaminated heparin
- The involved heparin manufacturer in China was never inspected
- Contaminated heparin detected in 11 countries but no casualties in Europe...
- Europe: Only in Germany 80 adverse reactions
- Massive recalls but we appear to be trapped: availability vs. risk! (vide infra)
Heparin

- FDA identifies contaminant: 5% - 45%
- Oversulfated chondroitin sulfate (OSCS)
- OSCS molecular structure closely resembles heparin
- OSCS mimics heparin in standard testing
- OSCS is not a natural compound => synthesized!
- Chondroitin sulfate origin: animal cartilage
- OSCS is cheap (< $80 vs. heparin $500-1500)
- OSCS most likely added deliberately
- Contaminated heparin comes from 12 different sources located all throughout China
- Profit: $ 1 - 3 million
- Proof obtained that OSCS caused the toxic effects
- Heparin API price > tripled by end of 2007 (blue ear pig disease)
Heparin & Europe

Due to:

- The very high incidence of OSCS contamination
- Our high dependency upon Chinese supply of heparin API resulting in shortage of uncontaminated heparin
- The life-saving aspects of heparin use…

EMEA and EU Member States’ Health Authorities issued declarations stating that low molecular weight heparin contaminated with OSCS should continue to be used until the shortage will be resolved.

But the pharmacological properties of OSCS are completely unknown…

See e.g.:
http://www.mhra.gov.uk/Publications/Safetywarnings/Drugalerts/CON017989
A reaction to the Heparin disaster

William Hubbard, former Deputy Commissioner of the US / FDA:
(US Congress Hearing, May 2008)

“These APIs are a string of ticking time bombs. Heparin has gone off and there will be more until we fix the problem”

“We’re inspecting where the drugs aren’t being made and not where the drugs are being made”
Inspections

- Do not give guarantees for safe APIs
- Do not give guarantees against counterfeit & fraud
- But the more frequent and the more deterrent they are the smaller the chance for health catastrophes
- Without them the doors are wide open to... anything

“FDA inspections at Changzhou SPL would not have prevented the heparin disaster”

Hmm, probably an incorrect conclusion...?
Is it “impossible to inspect all API manufacturers”?

A rough calculation:

**China:**
Ca. 1% of ca. 5,000 API producers operate at EU standards = **+50** (Includes the 3,000 illegal manufacturers not licensed by SFDA. If excluded: only **+20**)

**India:**
Ca. 1% of ca. 10,000 API manufacturers operate at EU standards = **+100**

Many other manufacturers in China / India will refuse inspection and/or will close down upon announcement of inspection (cf. Hu)
Is it “impossible to inspect all API manufacturers”? 

⇒ The number of inspections will be feasible to do, especially when also global priorities will be set in a risk-based manner and coordination between US, EU, Australia etc. will be in place

⇒ Very strong deterrent effect!

⇒ To protect patients: Consider not “to inspect those who supply APIs for EU medicines” but “to only allow API in EU medicine from inspected and certified API manufacturers”
Does deterrence really work?
Deterrence works!
Deterrence works!
Thank you for your attention!