

Implementation of directive 2011/62/EU: what is changed in APIs production and importation in Europe

Università degli Studi di Pavia
Workshop on «Quality and Regulatory: new frontiers in API manufacture»

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Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
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Investigator	X				
Individual's Institution/Organization receives a grant or other funding	X				



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Content of the presentation

- Directive 2011/62/EU (FMD: falsified Medicines Directive)
- Implementation in Europe
- APIs importation mapping exercise
- Implementation in Italy
- Pending issues
- What is changed

European Regulatory Framework before FMD

- Directive 2001/83/CE (as modified before directive 2011/62/EU) introduced the obligation for the manufacturing authorization holder of the medicinal products to use only active ingredients (APIs) compliant with GMP (as defined in ICHQ7A and adopted as EUGMP Parte II in 2005)
- The QP had to declare the GMP compliance of the active substances manufacturer, assessed by an *audit in situ* and any other evidence certifying the quality



European Regulatory Framework before FMD

- According the art. 111 the NCA could carry out an inspection in order to ensure that the obligations were fulfilled
- L'EMA issued a "Guidance on the occasions when it is appropriate for competent Authorities to conduct inspections at premises of manufacturers of active substances used as starting materials" (EMA/INSP/GMP/313538/2006), with the aim to give some «triggers» to select sites to be inspected (part of Compilation of Community procedures on inspections and exchange of information)



European Regulatory Framework before FMD

- Before directive FMD each NCA might have had different approaches for API manufacturers oversight, according to the national legislation:
 - Mandatory registration/authorization
 - No legal requirements for registration/authorization
 - Inspections carried out in EU or extra-EU countries for specific category of APIs (i.e. biological origin/sterile APIs)



European Regulatory Framework before FMD

- Inspections carried out in Europe or extra-EU countries if requested by the manufacturer to grant a GMP certificate
- Inspections carried out if deemed necessary during the assessment (NCA, EDQM and EMA inspections)



Same market, different regulatory approaches

FMD: Background concerns

- Risk to the public health posed by falsified/low quality APIs
- Need to increase GMP compliance for all APIs manufactured or introduced in Europe
- Need to strengthen inspection activities
- Need to harmonize the supervision system for APIs manufacturers, distributors and importers
- QP audit expected but explicit requirement for audits missing
- Lack of provision concerning quality of excipients

FMD: A common legal basis



- EU Member States have to take appropriate measures to ensure that manufacture, import and distribution on their territory of active substances, including that are intended for export, comply with GMP and GDP (art. 46b of directive 2001/83/EC as modified by the FMD)

FMD: A common legal basis



- Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the member State in which they are established (art. 52a)

FMD: A common legal basis

- the NCA shall have a system of supervision including inspection at an appropriate frequency, based on risk, at the premises of the manufacturers, importers or distributors of active substances, located in its territories and effective follow-up thereof (art.111, c.1b)



FMD: A common legal basis

- If there are grounds to suspect non compliance NCAs may carry out inspections at premises of manufacturers or distributors of active substances located in third countries or manufacturers or importers of excipients (in their territory) (art.111).
- EU Compilation of Community procedure procedure 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" under revision

FMD: A common legal basis



- The holder of the manufacturing authorizations:
 - ❖ Ensures GMP and GDP compliance of manufacturers and distributors of APIs, by conducting audits
 - ❖ Formalises a risk assessment for excipients
 - ❖ Informs Authorities in case of suspect of falsification
 - ❖ Verifies that manufacturers, importers or distributors are registered at the NCA of the Member States where they are established (art. 46)

FMD: A common legal basis



- Active substances can be imported if:
 - ❖ GMP at least equivalent to those laid down by the Union
 - ❖ Accompanied by a written confirmation from the NCA of the exporting country declaring that the GMP standards are at least equivalent to EU GMP, effective enforcement including unannounced inspections is in place, information of the Union about findings of non compliance

FMD: Provisions for API business and NCA

- 1) Provisions in EU territory:
 - Manufacturers, importers and distributors of API
 - ➔ Mandatory registration according to a common format
 - NCA have to implement an oversight system, including inspections based on risk
 - ➔ New Guideline on GDP for APIs distributors (7th March 2013)
 - ➔ GMP for APIs will be legally binding after the issuance of the Commission Delegated Regulation (expected to be published end September)

FMD: Provisions for Medicinal Products Manufacturers

- 2) Medicinal products manufacturers:
 - responsibility to verify compliance with GMP and GDP,
 - mandatory audits (exceptional circumstances derogation, i.e. atypical APIs)
 - need to verify that EU manufacturers/importers or distributors are registered at NCA
 - risk assessment and appropriate GMP for excipients

FMD: Provisions for importation of APIs

- 3) Provisions for third countries: Systematic inspection not feasible ➔ Need to build mutual trust and cooperation
 - Mandatory requirement for "written confirmation" (WC) issued by the NCA of the exporting country
 - Exceptions to the WC:
 - ❖ Country "listed" as equivalent (art. 111b) (1st waiver)
 - ❖ Exceptionally for sites holding an EU GMP certificate if needed to avoid shortages (2nd waiver)

FMD: Registration

- 1) Provisions in EU territory: Registration



FMD: Registration

1) Provisions in EU territory: Registration

Union Format for Registration¹ of Manufacturer, Importer or Distributor of Active Substances

1. Registration number
2. Name or corporate name of registrant
3. Permanent or legal address of registrant
4. Address(es) of site(s) where registered activities take place
All relevant sites should be listed if not covered by separate registrations
5. National legal basis of registration
6. Name of responsible officer of the competent authority of the member state validating the registration²
7. Signature³
8. Date



19

FMD: Registration

1) Provisions in EU territory: Registration for manufacturers (Part 1)

Registration for manufacturers (Part 1)

1. Identification of the product to be registered

2. Identification of the manufacturer

3. Identification of the importer or distributor

4. Identification of the site(s) where registered activities take place

5. Identification of the responsible officer of the competent authority of the member state validating the registration

6. Identification of the signature of the responsible officer of the competent authority of the member state validating the registration

7. Identification of the date of registration



20

FMD: Registration

1) Provisions in EU territory: Registration for Importers and Distributors (Part 2)

Registration for Importers and Distributors (Part 2)

1. Identification of the product to be registered

2. Identification of the importer or distributor

3. Identification of the site(s) where registered activities take place

4. Identification of the responsible officer of the competent authority of the member state validating the registration

5. Identification of the signature of the responsible officer of the competent authority of the member state validating the registration

6. Identification of the date of registration



21

FMD: EudraGMDP database

1) Provisions in EU territory: Public database of registered sites

EudraGMDP

API Registration

The Company hereby registers the API (Active Pharmaceutical Ingredient) in the EudraGMDP database.

The Company hereby registers the API (Active Pharmaceutical Ingredient) in the EudraGMDP database.

The Company hereby registers the API (Active Pharmaceutical Ingredient) in the EudraGMDP database.



22

FMD: EudraGMDP database

1) Provisions in EU territory: Public database of registered sites

Site ID	Site Name	Site Address	Site Type	Site Status	Site Date
1000000001	Site 1	Address 1	Site Type 1	Active	2014-01-01
1000000002	Site 2	Address 2	Site Type 2	Active	2014-01-01
1000000003	Site 3	Address 3	Site Type 3	Active	2014-01-01
1000000004	Site 4	Address 4	Site Type 4	Active	2014-01-01
1000000005	Site 5	Address 5	Site Type 5	Active	2014-01-01
1000000006	Site 6	Address 6	Site Type 6	Active	2014-01-01
1000000007	Site 7	Address 7	Site Type 7	Active	2014-01-01
1000000008	Site 8	Address 8	Site Type 8	Active	2014-01-01
1000000009	Site 9	Address 9	Site Type 9	Active	2014-01-01
1000000010	Site 10	Address 10	Site Type 10	Active	2014-01-01



23

FMD: Eudra GMDP database

1) Provisions in EU territory: Public database of Certificates

EudraGMDP

Public database of Certificates

Search for certificates by:

Search for certificates by:

Search for certificates by:



24

GMP certificate for API manufacturers

- 1) Provisions in EU territory: GMP certificate and Statement of GMP non compliance according to the registration format



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25

GDP certificate for API distributors/importers

- 1) Provisions in EU territory: GDP certificate Union format



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26

GDP certificate for API distributors/importers

- 1) Provisions in EU territory: GMDP certificates database and non compliance statement



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27

QP role

- 2) Medicinal products manufacturers: QP declaration form revised



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28

Importation of APIs

- 3) Provisions for Third Countries:
- If not "listed" as equivalent (so far Switzerland, Australia, Japan and USA are listed) the NCA of the exporting Country has to issue a WC for APIs exported to Europe
 - the WC certifies that: the APIs are manufactured in accordance to standards at least equivalent to those valid in Europe, European NCA will be informed in case of non compliance (can be issued also if the inspection is carried out by trusted international Authorities)



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29

Written Confirmation is..

- A certificate legally binding
- It is not a "standard" GMP certificate; it is an endorsement of responsibility by the issuing NCA because the commitment to inform receiving countries about GMP non compliance
- It is requested also in case of MRA



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30

Written Confirmation is..

- The availability of the WC doesn't exonerate the EU NCAs from the responsibility to carry out risk based inspections (art. 111)
- More info about importation of APIs and written confirmation can be found at the Q&A version 5.0 issued by the European Commission



31

Importation of APIs

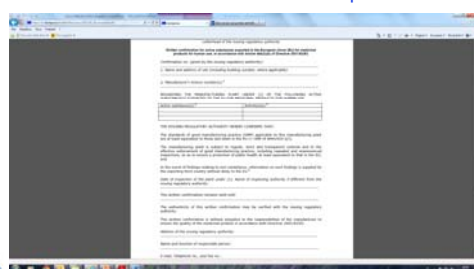
3) Provisions for third countries: WC template



32

Importation of APIs

3) Provisions for third countries: WC template



33

Imported APIs Mapping

- Uncertainties about future impact of the new rules (WC starting 2nd July 2013, in Italy mandatory from 8th March 2014)
- Possible shortages of medicines
- EU Commission initiatives and contacts with the major exporters
- HMA taskforce on FMD implementation
- January 2013: mapping exercise (AIFA webpage: <http://www.agenziafarmaco.gov.it/it/content/officina-di-produzione-di-medicinali-utilizzo-di-api-importati-da-paesi-extra-eu>)



34

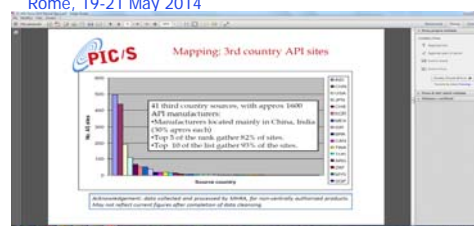
Imported APIs Mapping



35

Outcome of the API Mapping Imported to Europe

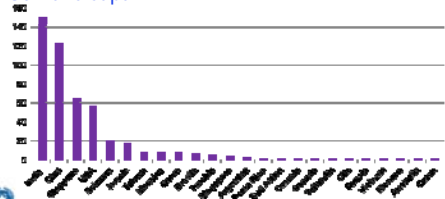
Presentation of Manuel Ibarra (Spain), 6th expert circle on APIs, Rome, 19-21 May 2014



36

Outcome for API Mapping Imported to Italy

- About 500 sites identified. 24 Countries represented, but the API are mostly imported from India, China, USA and Japan



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Post Mapping: Risk mitigation

- Identification of sites potentially lacking of WC
- EMA request addressed to the importing NCA to carry out a risk assessment of the potential shortage and eventually plan an EU inspection
- Table collecting information for all NCA was circulated /updated by EMA on a weekly basis and later monthly basis or for any change of information regarding the need to inspect the sites



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38

Post Mapping: Risk mitigation

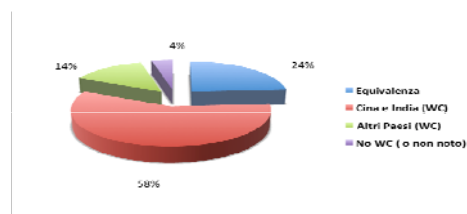
- Establishment of the EMA's Rapid Reaction Team (July 2013) to facilitate urgent inspection
- Need to inform the EU Commission on the use of the «second waiver»
 - Will use the second waiver:
 - Spain, Italy, UK, Ireland, Germany, Romania, Malta, France, Croatia, Netherlands, Cyprus, Latvia
 - Will not use the second waiver:
 - Belgium, Sweden, Norway, Czech Republic, Liechtenstein



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Shortage risk evaluation, end 2013



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Document EMA/367664/2013 Compliance and Inspection

- Guidance on how to deal with an API imported from a MS and used by other MS (implementation of the FMD was not contemporaneous in all MS)
- User MS has to plan an inspection and inform EMA if the WC is not available and second waiver not applicable
- The API imported without WC and not covered by a EU GMP certificate cannot be used until the certification is available



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Imported APIs Mapping

- So far minimal impact:
 - some change of the API supplier (variation)
 - Stockpiling
 - Very few planned inspections



no product shortages have been observed .. So far..



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Italian Regulatory Framework before FMD

National decree n. 219/2006 provisions:

- 1) In Italy there was a mandatory authorization system and production and importation had to be authorized by the Italian Medicines Agency (AIFA) (art. 50, comma 1, art. 54 comma 1 and 2). The authorization is granted after an inspection
- 2) In Italy the authorized sites were subject to a monitoring system, according to which routine inspections are performed to check compliance with EU GMP Part II every three years as maximum (art.53)

Italian Regulatory framework after FMD (D.Lgs. n.17/2014): AIFA registration

D.Lgs 17/2014 modifies the decree n. 219/2006 and introduces the FMD into the national legislation:

- Art 52 *bis*: manufacturers (including partial manufacture, repackaging and relabeling) and importers (including active substances used as starting materials for production or extraction of other active substances) register their activity to AIFA.
- Within 60 days from the registration AIFA may decide to carry out an inspection on a risk based approach

D.Lgs. n.17/2014:AIFA registration

- After the inspection notification the inspection is carried out within 60 days; operations can start not before 30 days after the inspection
- If the inspection is not carried out within 60 days the company can start the activity
- a clock stop can be taken into consideration (i.e. the closure of the company for the annual shutdown) but this is subject to agreement/communication
- AIFA inspection can be carried out after the activity is started and the activity can be suspended in case of critical findings

D.Lgs. n.17/2014:AIFA authorization

The above mentioned provisions don't apply to biological and sterile products because they remain under the authorization system → an express authorization from AIFA is needed ↓

The operations cannot start until the authorization is granted (inspection or evaluation of the submitted documentation); this applies to new API, new production lines, major changes

Change Management for registered APIs

❖ Major changes having an impact on the quality of the APIs have to be immediately notified (for registered APIs) and within 60 days AIFA may decide to ask for additional documentation or for an inspection → If an inspection is deemed necessary the deadline are those defined for the registration of the API

❖ Minor changes will be notified to AIFA on annual basis

Implementation guidance

<http://www.agenziafarmaco.gov.it/it/content/aifa-rilascia-una-guida-alle-nuove-norme-su-sostanze-attive-ed-eccipienti>



Double system: authorization & registration

A double system in place, for sites under the authorization the rules are the same as before the decree n.17/2014



- ❖ Form A: extension of the authorization for biological and sterile API (category already authorized)
- ❖ Form B: extension of the authorization for new production area/lines for biological and sterile APIs
- ❖ Form C: extension of authorization for biological and sterile API (category not authorized yet)

Double system: authorization & registration

Under registration systems are new and old sites manufacturing APIs typically through a synthesis process:

- ❖ Form D: registration of manufacturers of APIs (which are not sterile and not biological)
- ❖ Form E: Registration of importers of APIs (which are not sterile and not biological)
- ❖ Form F: Major changes for manufactured APIs (which are not sterile and not biological)

Routine Inspection Program Risk Based

- Development of a procedure which will be used to "score" the API manufacturing sites and importers (which don't manufacture the finished products)
- The program will be based on the risk mapping
- The GMP certificate validity needs to be readjusted to the inspection deadline
- Transitional period in which the routine program will be kept on the three years basis

extra-EU Inspections

- Extra-EU sites will be mainly inspected if:
 - Deemed relevant in a risk profile
 - Absence of WC
 - GMP non compliance issued by non EU NCA
 - If requested during the importation registration process
 - If requested during the assessment
 - If under the interest of International programs (i.e. EDQM)
- Use of the module "inspection Planning" of Eudra-GMDP database to share information among NCAs

Pending issues

- Atypical API/herbal API: WC missing and standards applicable
- API name in WC: i.e. micronized, compacted..
- APIs which imported from a MS and fractionated to other MS: need to improve communication about the acceptance of the waiver
- Completion of registries and uploading into Eudra-GMDP

Pending issues

- Harmonization on inspection strategy in EU (triggers and frequency)
- Classification of changes to be notified by API manufacturers, importers, distributors and decision upon the inspection
- Risk assessment of excipients manufacturers
- Brokers of APIs not concerned by the directive: is this a big mistake??

What is changed?

- Common rules in Europe
- Still some differences on the practices adopted by the NCAs (i.e. check point of the WC, importation registration enforcement, GMP/GDP certificates for importers) but managed at national level
- Full traceability of the supply chain: importation, distribution, manufacturing
- Importation from extra EU sites only if registered and inspected by the local authority

What is changed?

- Increase of the awareness that API quality is a major concern
- A number of CEP suspensions and GMP Non-compliance statements issued by EU MS are the proof that the system is more under control than in the past
- Contribution to contrast counterfeiting medicines
- The level of protection of the European citizens is increased

Conclusions and Perspectives



- The quality standards for APIs are increasing
- Need to promote the Joint Audit Program for API inspectorates within Europe
- Need to continue and reinforce the International API Inspection Cooperation Programs (API International Program, EDQM inspection, PIC/S joint inspections, exchange of information), to keep the global supply chain under control

Conclusions and Perspectives



This regulatory framework might not be perfect and it might need to be improved/enforced, but in a long term perspective benefits of harmonization and mutual trust and cooperation in the field of API oversight are expected (not only in Europe!)

Grazie per l'attenzione!

CONTATTI

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