Import licensing and GMP compliance confirmation by foreign producers

Overview of the Polish system

April 2013
Agenda

• Overview of the current regulations
  • Scope of import authorization
  • Obtaining import license
  • Qualified Person
  • GMP compliance confirmation
  • Import of API
• Planned developments in quality control and assurance
  • Written confirmation
  • Register of manufacturers, importers and distributors of APIs
  • Documentation of the place of business
## Sources of law

<table>
<thead>
<tr>
<th>EU</th>
<th>POLAND</th>
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<tr>
<td>• Directive 2001/83/EC – Community code relating to medicinal products for human use</td>
<td>• Pharmaceutical Act</td>
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<td>• Directive 2003/94/EC – General GMP Guidelines</td>
<td>• Executive regulations issued by the Health Minister including</td>
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<td>• Directive 2011/62/EU – Prevention of the entry into the legal supply chain of falsified medicinal products</td>
<td>• Good Manufacturing Practice requirements (GMP)</td>
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<td></td>
<td>• The Polish law is slightly different to the EU model</td>
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## Defining the terms

<table>
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<th>IMPORT</th>
<th>MANUFACTURING</th>
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<td><strong>Each</strong> action involving import of a <strong>finished</strong> medicinal product from <strong>outside the EU or EEA</strong>, including but not limited to the storage, quality control at batch release and distribution of such medicinal products</td>
<td><strong>Any action leading to the creation of a medicinal product</strong> including purchase of the materials used in production, production packaging and re-packaging, storage, distribution of proprietary medicinal products, and also control activities</td>
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| • finished=packed and ready for consumer use  
• excludes raw materials and unfinished products |
Scope of import authorization (i)

• An import license itself **does not authorize** the placing of a medicinal product on the market – a marketing authorization (MA) must be held

• The MA application should contain *inter alia*:
  
  • name and address of the MA holder
  
  • manufacturer or importer the medicinal product batch is released to
  
  • manufacturing site, including the manufacturing site where the medicinal product batch control takes place, or the site of conducting import operations where medicinal product batch control takes place
  
  • numbers of the medicinal product manufacturing or import authorizations

• MAH and importer may be the same entity – in practice: existence of various operational/distribution structures
Scope of import authorization (ii)

- Import license **authorizes**:
  - sale of imported drugs to manufacturers, distributors (wholesalers), healthcare providers (hospitals)

- Import license **does not authorize**:
  - manufacturing (a manufacturing license required)
  - wholesale distribution of products other than imported (a wholesale license required)
  - sale of imported drugs to patients (retail license required; legal ban on retail and wholesale trade)
Import license application (i)

• Regulator – the Main Pharmaceutical Inspector (GIF)

• Application must include:
  • applicant’s business data
  • product name, type and pharmaceutical form
  • sites where import business activities are conducted
  • control points

• Fees:
  • 1 to 10 medicinal products – ca. €550
  • 11 < medicinal products – ca. €800
Import license application (ii)

• Supplementary quality assurance information required, confirming:
  • compliance with Good Manufacturing Practice (GMP), also by the foreign manufacturer
  • infrastructure for import, control and storage of medicinal products:
    • suitable and sufficient premises
    • technical equipment
    • control facilities
  • a qualified person responsible for batch control before placing on the market
Import license application (iii)

- GIF Inspectorate checks whether the applicant complies with requirements (plus GMP compliance by the foreign manufacturer)
- Decision deadline: 90 days from the filing date
Import license

- Indefinite term
- Content
  - Detailed scope of import subject to authorization
- Inspectorate notifies and sends a copy of the authorization to the European Medicines Agency
Duties of the importer

- Import of only those medicinal products covered by the authorization
- Supporting the Qualified Person’s independence in terms of batch release decision-making
- GMP compliance
- Notification of planned changes involving the terms and conditions of import, especially replacement of the Qualified Person, to the GIF Inspector at least 30 days in advance
- Sending the actual list of imported medicinal products to the Inspectorate
- Keeping archive samples of medicinal products at least a year longer than the product’s expiry date, for at least 3 years
- Cooperation with inspectors during inspections (routine inspections at least once every 3 years)
Qualified Person (QP)

• Certifies a medicinal product batch for release after checking GMP compliance

• Need not be a regular employee so long as the legal form of cooperation ensures constant and stable access to the services of the QP

• Required qualifications:
  • Degree in biology, pharmacy, medical analysis, biotechnology, chemistry, chemical technology, chemical and process engineering, or graduate of medical or veterinary studies
  • two years of experience in quality and quantity analysis of medicinal products or pharmaceutical raw materials at a MP manufacturing plant
  • fluency in Polish

• QP must have unrestricted decision-making autonomy in terms of batch release
GMP compliance (i)

- GMP – a set of standards for production of medicinal products
- Guarantees that medicinal products are manufactured and controlled:
  - adequately in light of intended use
  - as required by their specifications and documents supporting the MA
- General guidelines set at the EU level
- GMP under Polish law is equivalent to the EU GMP and compliant with WHO and PIC/S GMP
- Not all PIC/S GMP compliant manufacturers meet EU GMP requirements
GMP compliance (ii)

- GMP compliance by the foreign manufacturer can be checked by:
  - an inspection at the site conducted by manufacturing inspectors (overseas inspection)
  - a product (product category) inspection report made by another EEA competent authority or information supplied by another EEA state authority
  - either an inspection report or a statement of GMP compliance obtained under an operational Mutual Recognition Agreement (MRA) between the EU and the competent authorities of the third country in which the manufacturer is located
  - inspection report / statement of GMP compliance obtained under an agreement on conformity assessment and acceptance of industrial products (ACAA) concluded between the EU and the third country
Overseas inspections

• An inspection is conducted by GIF inspectors or by way of a report from an inspection conducted by a respective body of an EU-EEA country in the last 3 years

• The manufacturing conditions must meet the requirements for producing a medicinal product of a declared quality

• A certified copy of manufacturing authorization issued by an appropriate body in the third country must be presented

• A third country manufacturer has no obligation to submit to an inspection

• The inspection is conducted at the applicant’s expense (MAH/Importer)

• Generally this procedure does not apply to MRA / ACAA countries
MRA / ACAA countries (i)

- Mutual Recognition Agreement (MRA) – mutual recognition of:
  - manufacturing authorizations
  - conclusions of inspections
  - manufacturer’s certification of the conformity of each batch to its specifications without re-control at import

- Similar rules in case of agreements on conformity assessment and acceptance of industrial products (ACAA) concluded between the EU and another country

- Benefits:
  - **GMP certificate** issued by a MRA Partner Country’s authority fulfills the requirements of Art. 20 of Directive 2001/83/EC which relieves the competent authorities of the costs and burdens of overseas inspections
  - An operational MRA allows the Qualified Person to rely on a written **batch certification** from the MRA Partner Country manufacturer instead of repeating costly and time consuming quality control tests
MRA / ACAA countries (ii)

- MRA countries include:
  - Australia (fully operational)
  - Canada (in operation, except for preapproval inspections and medicinal products derived from blood or blood plasma)
  - Japan (operational with limited scope)
  - New Zealand (fully operational)
  - Switzerland (fully operational)
  - ACAA partner country – Israel (from January 2013)
Batch release procedure: MRA v non-MRA

• A batch of medicinal products imported from a non-MRA country is subject to re-testing, which includes:
  • quantitative and qualitative analysis of active pharmaceutical ingredients (API) and other components
  • packaging quality control
  • shipping/storage review
  • documentation of methods and results

• Medicinal products from operational MRA partner countries are excluded from the re-testing procedure

• If the QP approves the results and the batch complies with MA and GMP requirements, the QP certifies the batch. The certification document is kept for 5 years
Import of API under current law

- Import (from outside EU/EEA) of API used as starting materials intended for manufacturing of medicinal products is usually deemed to be part of the manufacturing process
- No import license required
- Manufacturing and importing of API used for the manufacturing of veterinary products is subject to registration in the register
Planned developments

- Implementation of Directive 2011/62/EU on prevention of the entry into the legal supply chain of falsified medicinal products
  - Broadens the definition of import
  - Introduces import of API as a separate category
  - Introduces the “written confirmation” rule
  - Introduces an obligation to supply the documentation of the principal place of business (Polish acronym: DGM)
- At draft legislation stage in Poland
MANUFACTURER
(LOCAL MANUFACTURING LICENSE)
(REGISTRATION OF API IMPORT)

API MANUFACTURER
(WRITTEN CONFIRMATION)
Written confirmation rule

• From 2 July 2013, any API for a medicinal product for human use imported into the EU must be accompanied by a written confirmation:
  
  • Confirms compliance with GMP rules 'equivalent' to the EU rules, the regularity of inspections of the manufacturer and the sanction of manufacturing authorization withdrawal in case of non-compliance
  
  • Issued by the competent authority from the Third Country (exporter), at central, regional or local level (the decision is left to the exporter country) per manufacturing plant
  
  • Other GMP standards equivalent to the EU include WHO’s 44th Technical report, no. 957, 2010, annex 2, or ICH Q7
  
  • Can be based on past inspections
  
  • Independent of the existence of MRAs, EDQM or EU Member State inspections
Written confirmation rule – Exceptions

- The Commission publishes a list of countries which, at their request, were assessed and are considered as having equivalent GMP rules to those in the EU
  - APIs manufactured in these countries do not require a written confirmation
  - Only Switzerland has qualified so far
  - Current assessments: Israel, Australia, Singapore, Brazil, Japan, USA
- Exceptionally and where necessary to ensure the availability of medicinal products, following inspections by a EU member state, the need for a written confirmation for a period not exceeding the validity of the GMP certificate may be waived
Registration of API import

- Conducting business in the importation of API into Poland will require registration in the Register for Active Substance Manufacturers, Importers and Distributors kept by the Main Pharmaceutical Inspector.
- Application to be filed at least 60 days before the planned date of commencing import.
- The application must contain:
  - Applicant’s business data
  - List of API
- Applicant must supply detailed documentation of the principal place of business.
Documentation of principal place of business
(Polish acronym: DGM)

- DGM includes:
  - General information – contact details, description of the business activity, list of active substances subject to import, List of GMP inspections over the last 5 years
  - Quality management system – batch release control procedure, supervision over material suppliers, list of subcontractors, QRM (Quality Risk Management), quality review
  - Personnel – organizational schemes
  - Premises – size, scheme and description of storage rooms. HVAC (heating and ventilation, water supply scheme, other services (steam)
  - Appliances – list of production appliances with an outline of critical parts, cleaning and sanitization, computing systems
  - Documentation – description of the system (paper or electronic), archives
  - Production – block schemes, validation, material management, schemes of the production areas, list of main productive appliances and quality laboratory equipment
  - Quality Control
  - Distribution, monitoring, traceability, preventive measures, recalls, internal audits
Registration procedure

• Prior to registration, the GIF Inspector decides on whether to conduct an inspection on the basis of the risk analysis performed by the manufacturing inspector

• The applicant is not allowed to commence import if the GIF Inspector informs it within 60 days of the filing date that it will conduct an inspection

• Registration fee – ca. €400
Summary

- Tightened GMP standards
- Enhanced recognition of other inspection outcomes
- New initiatives = new levies for market participants, but do they lead to better product safety and availability?
- Practical consequences for the industry
  - Costs / risks v. income
Thank you
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