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API – the new approach for third countries Perspectives from an acceding country

Anita Filipović Sučić, PhD, MPharm
Agency for Medicinal Products and Medical Devices, HALMED

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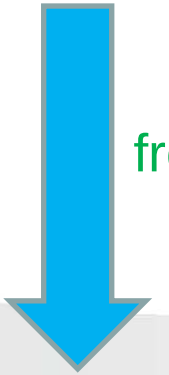
CHANGES IN CROATIAN LEGISLATION

New Croatian Medicinal Products Law and accompanying regulation

HARMONISED WITH



from the day of the accession

Directive 2001/83/EC

►B **DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

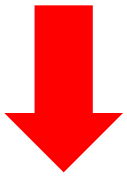
of 6 November 2001

on the Community code relating to medicinal products for human use

(OJ L 311, 28.11.2001, p. 67)

Amended by:

		Official Journal		
		No	page	date
►M1	Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003	L 33	30	8.2.2003
►M2	Commission directive 2003/63/EC of 25 June 2003	L 159	46	27.6.2003
►M3	Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004	L 136	85	30.4.2004
►M4	Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004	L 136	34	30.4.2004
►M5	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006	L 378	1	27.12.2006
►M6	Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007	L 324	121	10.12.2007
►M7	Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008	L 81	51	20.3.2008
►M8	Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009	L 168	33	30.6.2009
►M9	Commission Directive 2009/120/EC of 14 September 2009	L 242	3	15.9.2009
►M10	Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010	L 348	74	31.12.2010
►M11	Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011	L 174	74	1.7.2011



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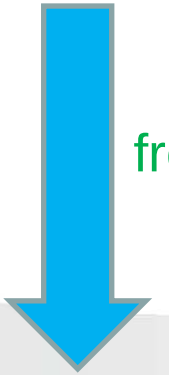
IMPORTATION OF ACTIVE SUBSTANCES

New Croatian Medicinal Products Law

ARTICLE 83

HARMONISED WITH



from the day of the accession

Directive 2001/83/EC

ARTICLE 46b

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IMPORTATION OF ACTIVE SUBSTANCES NEW RULES

Import of active substances (APIs) is only possible if:

- **Option 1**: the consignment is accompanied by a **'written confirmation**' by the authority of the third country that the plant manufacturing active substances operates in compliance with EU-'good manufacturing practice', or with equivalent rules, and is subject to equivalence rules for control and inspections; or
- **Option 2**: the third **country has been listed** by the Commission as a country with an equivalent system of supervision and inspection as in the EU; or
- **Option 3**: exceptionally, and where necessary to ensure the availability of medicinal products, the need for the written confirmation can be waived for a period not exceeding the validity of **GMP certificate**

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WRITTEN CONFIRMATION

Article 46b-Directive 2001/83/EC

Consignment of active substance is accompanied by a „written confirmation" issued by the authority of the exporting third country

≠

Article 8 (ha) and 46 (f)-Directive 2001/83/EC

A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits

↓

MANUFACTURE AND IMPORTATION

↓

AUTHORISATION

Letterhead of the issuing regulatory authority

Written confirmation for active substances exported to the European Union (EU) for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC

Confirmation no. (given by the issuing regulatory authority):

.....

1. Name and address of site (including building number, where applicable):

.....

2. Manufacturer's licence number(s):[3]

.....

REGARDING THE MANUFACTURING PLANT UNDER (1) OF THE FOLLOWING ACTIVE SUBSTANCE(S) EXPORTED TO THE EU FOR MEDICINAL PRODUCTS FOR HUMAN USE

Active substance(s):[4]	Activity(ies):[5]

THE ISSUING REGULATORY AUTHORITY HEREBY CONFIRMS THAT:

The standards of good manufacturing practice (GMP) applicable to this manufacturing plant are at least equivalent to those laid down in the EU (= GMP of WHO/ICH Q7);

The manufacturing plant is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the EU; and

In the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country without delay to the EU.[6]

Date of inspection of the plant under (1). Name of inspecting authority if different from the issuing regulatory authority:

.....

This written confirmation remains valid until

.....

The authenticity of this written confirmation may be verified with the issuing regulatory authority.

This written confirmation is without prejudice to the responsibilities of the manufacturer to ensure the quality of the medicinal product in accordance with Directive 2001/83/EC.

Address of the issuing regulatory authority:

QUALIFIED PERSON'S DECLARATION CONCERNING GMP COMPLIANCE OF THE ACTIVESUBSTANCE USED AS STARTING MATERIAL AND VERIFICATION OF ITS SUPPLY CHAIN

"The QP Declaration Template"

PART A: Concerned Manufacturing Sites

I confirm that all sites concerned with manufacture of the active substance ***[insert name of active substance]***, and finished product and importation and/or batch certification for product(s) defined in the accompanying application form for the MA application/renewal/variation [***delete as applicable***], are stated below, as applicable.

MANUFACTURING SITES SUBJECT OF THIS DECLARATION[1]		
ACTIVE SUBSTANCE MANUFACTURING SITE [2, 3] AND FUNCTION(S)	**FINISHED PRODUCT MANUFACTURING SITE(S) AND FUNCTION(S)**	**IMPORTATION AND/OR BATCH CERTIFICATION SITE**

1 Where the Applicant has multiple sites for the manufacture of active substance, product or importation and/or batch certification, the QP declaration shall encompass all these sites, as applicable to the regulatory submission defined in the accompanying application form.

No site may be exempted from this list.

All sites concerned with part processing should be listed.

2 State the site name and address in detail, including the building numbers and function.

This information may additionally be provided in a flow chart for clarity.

3 List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material.

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NEW API RULES-Progress report
PHARMACEUTICAL COMMITTEE

Third country	Number of API manufacturing sites supplying EU[2]	Option 1 (written confirmation) or option 2 (listing)	State of play
India	496	Option 1	**Good progress, but more work needed – in particular by industry stakeholders.** IND government has announced that the 'Drug Controller General' (i.e. central agency) is going to issue 'written confirmation'. Implementation guidelines have been published.[3]
China	438	Option 1	**Good progress, but more work needed – in particular by industry stakeholders.** CHN has announced[4] that it will issue written confirmation. A **'notice'**[5] has previously been published. However, SFDA has already informed COM that it would not issue 'written confirmation' for manufacturing sites which are not under SFDA's supervision. This concerns about 30 sites. EMA is coordinating the inspections of these sites (option 3).
U.S.	186	Option 2	**Situation under control.** On-site audit visit by COM in mid-May 2013. The US FDA has issued a supportive public statement. [6]
Japan	108	Option 2	**Situation under control.** On-site audit visit by COM in mid-April 2013.
Switzerland	67	Option 2	**Situation under control.** Listed.
Korea	37	Option 1	**Situation under control.** Korea has issued written confirmation.
Israel	36	Option 1; then 2	**Situation under control.** Listing had to be refused for the time being. Israel has issued written confirmation.
Mexico	35	Option 1, then 2	**Situation under control.** MEX has confirmed in writing that it would issue written confirmation and later apply for listing.
Brazil	23	Option 1, then 2	**Situation under control.** BRA has applied for listing. However, documentation has not been received yet. As soon as COM receives the information, COM starts the 'equivalence assessment'. In the interim, BRA will have to issue written confirmation.
Canada	17	Option 1	**Situation under control.** CAN has informed COM in writing that it would issue written confirmation.
Taiwan	16	Option 1	**Situation under control.** TWN has sent informally a copy of the written confirmation it intends to issue.

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COUNTRIES REQUESTED LISTING

Country	Date of request	Status, Date of publication in the *Official Journal of the European Union*
Switzerland	4 April 2012	Adopted, Commission implementing Decision (OJ L 325, 23.11.2012)
Israel	9 May 2012	No listing for the moment (the relevant Israeli legislation covers only active substances used for the manufacture of finished products manufactured in Israel). Contacts ongoing.
Australia	18 September 2012	Adopted, Commission implementing Decision (OJ L 113, 25.4.2013)
Singapore	17 September 2012	No listing for the moment (the relevant Singapore legislation provides for a non-mandatory GMP certification scheme). Contacts ongoing. In the meantime, Singapore issues written confirmation.
Brazil	4 October 2012	Equivalence assessment ongoing
Japan	6 December 2012	Equivalence assessment ongoing
United States	17 January 2013	Equivalence assessment ongoing

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MEDICINAL PRODUCTS (MPs) MANUFACTURERS IN CROATIA

16 medicinal products manufacturers

11 manufacturers use the active substance as a starting material

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IMPORTATION OF APIs FROM THIRD COUNTRIES

MANUFACTURE OF MPs WITH ONE API IN CROATIA

-94 APIs imported from 75 API manufacturing sites

Country	Number of API manufacturing sites
India	39
China	18
Switzerland	7
USA	5
Taiwan	3
Israel	2
Mexico	1
TOTAL	**75**

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IMPORTATION OF APIs FROM THIRD COUNTRIES

MANUFACTURE OF COMBINATION MPs IN CROATIA

-27 APIs imported from 24 API manufacturing sites

Country	Number of API manufacturing sites
India	9
China	7
Israel	5
USA	2
Taiwan	1
TOTAL	**24**

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IMPORTATION OF APIs FROM THIRD COUNTRIES

MANUFACTURE OF MPs IN CROATIA

-IN TOTAL 92* API manufacturing sites from third countries

Country	Number of API manufacturing sites
FROM COUNTRIES ISSUING WRITTEN CONFIRMATION (INDIA; CHINA; ISRAEL, TAIWAN; MEXICO)	79 (1 ISSUED, 1 PENDING)
FROM COUNTRY WHICH IS LISTED (SWITZERLAND)	7
FROM COUNTRY CANDIDATE FOR LISTING (USA)	6
VALID EU-GMP CERTIFICATE	18 from 92

*92 = 75 (mono-component MP) + 24 (combinations) - 7 (same API plant for mono-component MP and combination)

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CROATIAN MARKET

4803 MARKETING AUTHORISATIONS
(on 26/4/2013)

230 AUTHORISATIONS FOR MPs
manufactured in Croatia
with APIs from third country

188 MPs WITH PARALLEL PRODUCTS*

13 MPs WITH PARALLEL MPs IN ANOTHER PHARM. FORM AND STRENGTH

29 MPs WITHOUT PARALLEL PRODUCT

***Parallel product is MP with same API/same strength/farm. form and has marketing authorisation in Croatia**

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CROATIAN MARKET

29 MPs WITH APIs FROM THIRD COUNTRIES WITHOUT PARALLEL PRODUCT

17 API MANUFACTURING SITES FROM THIRD COUNTRIES

Country	Number of API manufacturing sites	Status
Switzerland	5	Listed
India	5 (1 has alternate, 1 EU-GMP)	
China	5 (2 have alternates/EU-GMP)	
USA	1	Candidate for listing
Israel	1	

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FURTHER STEPS

1. Contact Croatian manufacturers of MPs using APIs from manufacturing sites in third countries, without parallel product:

-to check will written confirmation be issued on time

-organisation of inspection of API site (if necessary)

-organisation of exceptional import (if neccessary)

2. Analysis of API manufacturing sites of parallel products, analysis of availability of parallel products on the Croatian market

3. Analysis of APIs from third countries used for manufacture of MPs in Croatia for other EU markets

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CONCLUSION

- new rules for API importation from third countries will be introduced into Croatian legislation from the day of the accession

- analysis of Croatian manufacturers of MPs showed:
  - -92 API manufacturing sites from third countries
  - -230 MPs with APIs from third countries
  - -29 MPs with APIs from third countries without parallel product

- further analysis will be conducted


Obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos