THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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Supply Chain Management and Surveillance

Introduction

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Lessons learnt exercise – Amsterdam 4/11/2019

Sampling and testing by OMCLs

- EDQM is coordinating the General European OMCL Network
- Official Medicines Control Laboratories (OMCLs) are

  public institutions which test medicinal products independently from manufacturers (no conflicts of interest, guarantee of impartiality, respecting confidentiality)
- The network comprises OMCLs from countries that are members or observers of Ph.Eur. Convention.

Sampling and testing in the OMCL Network

EDQM activities

- Coordinated Sartan testing group of 13 OMCLs
- Supported method development and validation
- Sourced contaminated material for validation
- Developed a common format for communication of sampling plans and testing results
- Developed a risk-oriented sampling plan in discussion with EMA, NCAs, inspectorates and a CMDh representative
- Exercise initially focused on detection of NDMA, NDEA or both, in APIs and/or drug products

Sampling and testing in the OMCL Network (2)

- Testing purposes:
  - ➢ Confirm levels of NDMA in contaminated products, already recalled (Art. 31 referral request, verification of MAH results, confirm patient exposure)
  - ➢Market surveillance of products and APIs
  - ➢Market surveillance of other sartans than valsartan
  - ➢Analysis of samples from GMP inspections

Later

- Testing was extended to other N-Nitrosamines (DIPINA,EIPNA, NDBA,NMBA) in the sartans
- Testing was extended to other APIs manufactured at concerned sites

Sampling and testing - Challenges

- Increased demand for analytical capacity
- Availability of suitable equipment
- Availability of validated methods
- Availability of reference standards

- Setting priorities and coordination of sampling and testing
- Access to samples (fragmented supply chain, in particular when produced outside EU)
- Overview of which API source was used for manufacture of a given batch of medicinal product

Analytical challenges: ppm-ppb

nitrosamine
(0.03 ppm = 30 ppb):

«usual» impurity
(500 to 1000 ppm):

1ml in 1L solution

1ml in 33'000 L solution

Analytical methods used

	DE_BW CVUA	IE_PAL PALG	CH_Swissmedic	DE_BY LGL	DE_BY LGL	FR_ANSM
Analytical technique	LC-MS/MS	GC-MS (HS)	GC-MS (liquid DI) limit test	GC-MS (DI)	LC-MS/MS	HPLC-UV
Analytes(s)	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA
Sample (DS and/or DP)	DS and DP	DS and DP	DS and DP	DS	DS and DP	DS and DP

- Methods published on EDQM website:

https://www.edqm.eu/en/ad-hoc-projects-omcl-network

LOQs for NDMA

	DE_BW CVUA LC-MS/MS (DP)	CH_Swissmedic GC-MS (liquid DI) limit test (DS and DP)	DE_BY LGL GC-MS (DI) (DS)	DE_BY LGL LC-MS/MS (DS and DP)	FR_ANSM HPLC-UV (DS)	Health Canada GC-MS/MS (DI)
Valsartan limit: 0.300 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	0.236 ppm	0.04 ppm	0.005 ppm (DS and DP)
Irbesartan limit: 0.320 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	0.079 ppm	0.04 ppm	0.005 ppm (DS and DP)
Losartan limit: 0.640 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	0.492 ppm	0.05 ppm	0.005 ppm (DS and DP)
Candesartan limit: 3.000 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	-	0.25 ppm	0.005 ppm (DS)
Olmesartan limit: 2.400 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	-	0.25 ppm	0.005 ppm (DS)

HS: Head Space; DI: Direct Injection; DP: Drug Product; DS: Drug Substance

In green: suitable sensitivity
In black: borderline sensitivity
In red: insufficient sensitivity

LOQs for NDEA

	DE_BW CVUA LC-MS/MS (DP)	CH_Swissmedic GC-MS (liquid DI) limit test (DS and DP)	DE_BY LGL GC-MS (DI) (DS)	DE_BY LGL LC-MS/MS (DS and DP)	FR_ANSM HPLC-UV (DS)	Health Canada GC-MS/MS (DI)
Valsartan limit: 0.082 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	0.061 ppm	0.08 ppm	0.007 ppm (DS and DP)
Irbesartan limit: 0.088 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	0.0195 ppm	0.09 ppm	0.007 ppm (DS and DP)
Losartan limit: 0.177 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	0.149 ppm	0.10 ppm	0.007 ppm (DS and DP)
Candesartan limit: 0.820 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	-	0.40 ppm	0.007 ppm (DS)
Olmesartan limit: 0.663 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	-	0.50 ppm	0.007 ppm (DS)

HS: Head Space; DI: Direct Injection; DP: Drug Product; DS: Drug Substance

In green: suitable sensitivity
In black: borderline sensitivity
In red: insufficient sensitivity

Samples tested by OMCLs

…for NDMA

	DP	DS
Valsartan	612	141
Losartan	312	16
Olmesartan	313	13
Candesartan	434	10
Irbesartan	260	20
Telmisartan	69	49
Total	**2000**	**249**

…for NDEA

	DP	DS
Valsartan	246	200
Losartan	188	149
Olmesartan	194	43
Candesartan	204	85
Irbesartan	175	160
Total	**1007**	**637**

The testing was carried out by 13 OMCLs

OMCL OOS Findings

NDMA

VALSARTAN	API	DP
Manufacturer A	55	240
Manufacturer B	14	10
Manufacturer C	-	3
Manufacturer D	1	-

NDEA

VALSARTAN	API	DP
Manufacturer E	38	22
Manufacturer F	14	9
Manufacturer A	1	5
LOSARTAN		
Manufacturer G	-	2
Manufacturer A	1	-
Irbesartan		
Manufacturer F	25	28
Manufacturer A	1	1

OMCL testing triggered/supported batch recalls and suspension of CEPs

GMP inspection key findings (1)

API manufacturer:

- The joint assessors/GMP inspectors for cause inspections revealed insufficient knowledge of API process development and the manufacturing process
- Therefore potential impurities were not identified and the impact on the commercial manufacturing was not considered
- Missing link between the pre-GMP activities and the GMP manufacturing environment

GMP inspection key findings (2)

API manufacturer:

- Poor application of GMPs contributed to spreading the impurities
  - ➢Inadequate follow up of complaints and Out Of Trend results
  - ➢Problematic solvent recovery procedures
  - ➢Unsatisfactory cleaning procedures
  - ➢Cross contamination

GMP inspection key findings (3)

- Marketing authorisation holder / Medicinal product manufacturer

- Quality agreement with API manufacturers not adequate to allow them to take their full responsibilities

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