20/06/2018

אל: בעלי רישום של תכשירים רפואיים

<u>הנדון: אימוץ נהלי האיכות של ה- European Medicine Agency (EMA)</u>

הערכת תיקי האיכות במכון לביקורת ותקנים של חומרי רפואה מתבססת מזה שנים רבות על הנחיות בינלאומיות.

חוזר זה מרכז את הנחיות EMA בנושא איכות של תכשירים הומניים ווטרינריים המאומצים ע"י המכון לביקורת ותקנים של חומרי רפואה, וזאת בהמשך למדיניות אימוץ נהלי ICH ו- VICH (חוזר המכון מיום 4.5.2016).

יובהר כי משרד הבריאות פועל בהתאם לנהלים אלו כבר היום ונוהל זה משמש לצורך הבהרה ולנוחות בעלי העניין.

נהלי האיכות העדכניים של ארגון התרופות האירופאי (EMA) המאומצים ע"י המכון מפורטים ברשימה שלהלן:

1. **Quality (Relevant to Chemistry and Biology products):**
   - 1.1. **Active substance**:
     - 1.1.1. Guideline on Active Substance Master File Procedure CHMP/QWP/227/02 EMEA/CVMP/134/02
     - 1.1.2. Guideline on the chemistry of active substances EMA/454576/2016
     - 1.1.3. Investigation of chiral active substances 3CC29A
     - 1.1.4. Guideline on Summary of requirements for active substances in the quality part of the dossier CHMP/QWP/297/97, EMEA/CVMP/1069/02
   - 1.2. **Manufacturing:**
     - 1.2.1. Note for guidance on Manufacture of the finished dosage form CPMP/QWP/486/95
     - 1.2.2. Guideline on process validation for finished products - information and data to be provided in regulatory submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012
     - 1.2.3. Note for guidance on Start of shelf-life of the finished dosage form CPMP/QWP/072/96, EMEA/CVMP/453/01
     - 1.2.4. The Use of ionizing radiation in the manufacture of medicinal products 3AQ4A
     - 1.2.5. Limitations to the use of ethylene oxide in the manufacture of medicinal products EMEA/CVMP/271/01 CPMP/QWP/159/01
   - 1.3. **Impurities:**
     - 1.3.1. Control of impurities of pharmacopoeial substances CPMP/QWP/1529/04

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1.3.2. Specification limits for residues of metal catalysts or metal reagents CHMP/SWP/4446/2000
1.3.3. Setting specifications for related impurities in antibiotics CHMP/CVMP/QWP/199250

1.4. **Specification, analytical procedures and analytical validation:**
1.4.1. Specifications and control tests on the finished product 3AQ11A
1.4.2. Use of near infrared spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations EMEA/CHMP/CVMP/QWP/17760/2009

1.5. **Excipients:**
1.5.1. Excipients in the dossier for application for marketing authorization of a medicinal product_CHMP/QWP/396951/06
1.5.2. Quality of water for pharmaceutical use CPMP/QWP/158/01

1.6. **Packaging:**
1.6.1. Plastic primary packaging materials CPMP/QWP/4359/03, EMEA/CVMP/205/04

1.7. **Stability:**
1.7.1. Declaration of storage conditions for medicinal products particulars and active substances CPMP/QWP/609/96
1.7.2. In-use stability testing of human medicinal products CPMP/QWP/2934/99
1.7.3. Maximum shelf-life for sterile products for human use after first opening or following reconstitution CPMP/QWP/159/96
1.7.4. Note for guidance on Start of shelf-life of the finished dosage form CPMP/QWP/072/96, EMEA/CVMP/453/01
1.7.5. Stability testing for applications for variations to marketing authorisation EMA/CHMP/CVMP/QWP/441071/2011
1.7.6. Stability testing of existing active ingredients and related finished products CPMP/QWP/122/02.
1.7.7. Pharmaceutical Development:
1.7.8. Development pharmaceutics CPMP/QWP/155/96
1.7.9. Decision trees for selection of sterilization methods CPMP/QWP/054/98
1.7.10. Pharmaceutical development of medicines for pediatric use EMA/CHMP/QWP/805880/2012
1.7.11. Quality By Design:
1.7.12. Real time release testing EMA/CHMP/QWP/811210/2009
1.7.13. Use of near infrared spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations EMEA/CHMP/CVMP/QWP/17760/2009

1.8. **Specific types of products:**

1.8.1. Medicinal gases: pharmaceutical documentation (including recommendation on non-clinical safety requirements for well-established medicinal gases) CPMP/QWP/1719/00

1.8.2. Pharmaceutical quality of inhalation and nasal products CHMP/QWP/49313/2005

1.8.3. Quality of oral modified release products EMA/CHMP/QWP/428693/2013

1.8.4. Quality of transdermal patches EMA/CHMP/QWP/608924/2014

1.8.5. Radiopharmaceuticals_CHMP/QWP/306970/2007

1.8.6. Radiopharmaceuticals based on monoclonal antibodies 3AQ21A

2. **Biologics:**

2.1. **Active Substance**

2.1.1. **Manufacture, characterization and control of the active substance:**

2.1.1.1. Allergen products: production and quality issues CHMP/BWP/304831/07

2.1.1.2. Development and manufacture of lentiviral vectors CPMP/BWP/2458/03

2.1.1.3. Development, production, characterization and specifications for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008

2.1.1.4. Gene therapy product quality aspects in the production of vectors and genetically modified somatic cells 3AB6A

2.1.1.5. Human cell-based medicinal products CHMP/410869/06

2.1.1.6. Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer EMA/CHMP/BWP/271475/2006

2.1.1.7. Process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission EMA/CHMP/BWP/187338/2014

2.1.1.8. Production and quality control of animal immunoglobins and immunosera for human use EMA/CHMP/BWP/3354/1999

2.1.1.9. Production and quality control of medicinal products derived by recombinant DNA technology 3AB1A

2.1.1.10. Production and quality control of cytokine products derived by biotechnological process 3AB3aen

2.1.1.11. Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells CHMP/GTWP/671639/2008

2.1.1.12. Quality of biological active substances produced by stable transgene expression in higher plants EMEA/CHMP/BWP/48316/2006
2.1.1.13. Quality of biological active substances produced by transgene expression in animals CHMP/BWP/151897/2013
2.1.1.14. Quality, preclinical and clinical aspects of gene therapy medicinal products CHMP/GTWP/234523/09
2.1.1.15. Note for guidance on the quality, preclinical and clinical aspects of gene transfer of medicinal products CPMP/BWP/3088/99
2.1.1.16. Use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products EMA/CHMP/BWP/429241/2013

2.1.2. **Plasma-derived medicinal products:**
2.1.2.1. Investigation of manufacturing processes for plasma-derived medicinal products with regard to variant Creutzfeldt-Jakob disease risk CPMP/BWP/5136/03
2.1.2.2. Plasma-derived medicinal products CPMP/BWP/706271/2010
2.1.2.3. Replacement of rabbit pyrogen testing by an alternative test for plasma derived medicinal products CHMP/BWP/452081/07

2.1.3. **Plasma Master File:**
2.1.3.1. Requirements for plasma master file certification CPMP/BWP/4663/03[1]
2.1.3.2. Scientific data requirements for plasma master file CHMP/BWP/3794/03
2.1.3.3. Epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008
2.1.3.4. Validation of immunoassay for the detection of antibody to human immunodeficiency virus in plasma pools CHMP/BWP/298388/05
2.1.3.5. Validation of immunoassay for the detection of hepatitis B virus surface antigen in plasma pools CHMP/BWP/298390/05

2.1.4. **Vaccines:**
2.1.4.1. Adjuvants in vaccines for human use CHMP/VEG/134716/04
2.1.4.2. Note for guidance on the development of Vaccinia virus based vaccines against smallpox CPMP/1100/02
2.1.4.3. Influenza vaccines - quality module EMA/CHMP/BWP/310834/2012
2.1.4.4. Note for guidance on pharmaceutical and biological aspects of combined vaccines CPMP/BWP/477/97

[1] למעט הסעיפים המתייחסים ללוחות זמנים ותהליכי עבודה פנימיים.

2.1.4.5. Quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines EMA/CHMP/VWP/141697/2009

2.1.4.6. Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context EMEA/CHMP/VWP/263499/2006

2.1.4.7. Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (revision) EMEA/CPMP/VEG/4717/2003

2.1.4.8. Note for guidance on harmonisation of requirements for influenza vaccines CPMP/BWP/214/96

2.1.4.9. Guideline on quality aspects on the isolation of candidate influenza vaccine viruses in cell culture EMA/CHMP/BWP/368186/2011

2.1.4.10. Testing for simian virus 40 (SV40) in polio virus vaccines CPMP/BWP/1412/02

2.2. **Finished Product**

2.2.1. **Pharmaceutical development:**

2.2.1.1. Development pharmaceutics for biotechnological and biological products CPMP/BWP/328/99

2.2.2. **Adventitious agent's safety evaluation**

2.2.2.1. Adventitious agent safety of urine-derived medicinal products EMA/CHMP/BWP/126802/2012

2.2.2.2. Use of bovine serum in the manufacture of human biological medicinal products_CHMP/BWP/457920/2012

2.2.2.3. Use of porcine trypsin used in the manufacture of human biological medicinal products EMA/CHMP/BWP/814397/2011

2.2.2.4. Virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses CPMP/BWP/268/95

2.2.2.5. Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products EMEA/410/01

2.2.3. **Biosimilarity**:

2.2.3.1. Similar biological medicinal products CHMP/437/04

2.2.3.2. Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues CHMP/BWP/247713/2012

2.2.3.3. Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins EMEA/CHMP/BMWP/118264/2007

2.2.3.4. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues
2.2.3.5. EMEA/CHMP/BMWP/32775/2005

2.2.4. **Cell based Therapy**:
2.2.4.1. Human cell-based medicinal products CHMP/410869/06
2.2.4.2. Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer EMA/CHMP/BWP/271475/2006
2.2.4.3. Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products EMA/CAT/CPWP/686637/201

2.2.5. **Gene Therapy:**
2.2.5.1. Quality, preclinical and clinical aspects of gene therapy medicinal products CHMP/GTWP/234523/09
2.2.5.2. Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells CHMP/GTWP/671639/2008
2.2.5.3. Development and manufacture of lentiviral vectors CPMP/BWP/2458/03
2.2.5.4. Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products EMA/CAT/CPWP/686637/201

2.2.6. **Herbal Medicinal Products:**
2.2.6.1. Good agricultural and collection practice for starting materials of herbal origin EMEA/HMPC/246816/05
2.2.6.2. Quality of combination herbal medicinal products/traditional herbal medicinal products EMEA/HMPC/CHMP/CVMP/287539/05
2.2.6.3. Quality of herbal medicinal products/traditional herbal medicinal products CPMP/QWP/2819/00
2.2.6.4. Specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products CPMP/QWP/2820/00

3. **Veterinary**:
3.1. Development pharmaceutics for veterinary medicinal products EMEA/CVMP/315/98
3.2. Excipients in the dossier for application for marketing authorisation for veterinary medicinal products EMEA/CVMP/004/98
3.3. Declaration of storage conditions: 1. in the product information of pharmaceutical veterinary medicinal products, 2. for active substances (Annex) EMEA/CVMP/422/99

3.4. In-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products) EMEA/CVMP/424/01
3.5. Additional quality requirements for products intended for incorporation into animal feeding-stuffs (medicated premixes) EMEA/CVMP/080/95
3.6. Quality aspects of pharmaceutical veterinary medicines for administration via drinking water EMEA/CVMP/540/03
3.7. Quality aspects of single-dose veterinary spot-on products EMEA/CVMP/QWP/544461/2007
3.8. Quality of modified release dosage forms for veterinary use EMEA/CVMP/680/02
3.9. Inclusion of antioxidants and antimicrobial preservatives in medicinal products CPMP/CVMP/QWP/115/95
3.10. Limitations to the use of ethylene oxide in the manufacture of medicinal products EMEA/CVMP/271/01

4. כאשר קיימת בהנחיות EMA הפנייה לחקיקה האירופאית (EC Directives and Regulations), יש להתייחס לחקיקה המתאימה בישראל (פקודת הרוקחים [נוסח חדש] התשמ"א – 1981, ותקנות הרוקחים (תכשירים) התשמ"ו – 1986, תקנות הרוקחים (תנאי ייצור נאותים לתכשירים) התשס"ט - 2008).

5. כאשר יש סתירה בין הנחיות EMA וחקיקה או נהלים ישראליים, החקיקה והנהלים הישראלים גוברים.

6. בהנחיות בהן ישנה התייחסות לנושאי איכות, בטיחות ויעילות, יש להתייחס לנושא האיכות.

7. למרות האמור לעיל, בקשות לרישום שיוגשו ע"פ הנחיות FDA יבחנו לגופו של ענין.

8. ההנחיות זמינות באתר EMA. בקישור הבא: אתר EMA
רשימת ההנחיות יפורסמו באתר המכון ויעודכנו מעת לעת.

תחולה:

01.07.2018

תחולתן של הנחיות EMA
"Guideline on process validation for finished products - information and data to be provided in regulatory submissions" - 01.01.2020.

בכבוד רב,

ספרה אקסלרוד

דר' עפרה אקסלרוד,
מנהלת המכון וסגנית מנהל מערך הרוקחות והאכיפה.

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