SNAS

Testované látky nových technológií, aktuálna legislatíva pre testovanie jednotlivých typov látok

Správna laboratórna prax
Ing. Kvetoslava Forišeková

22.10. 2015
SNAS Bratislava

Požiadavky EU Council Directive 2004/10/EC

- súlad so zásadami SLP je povinný pre laboratóriá vykonávajúce štúdie zdravotnej a environmentálnej bezpečnosti; laboratóriá musia deklarovať súlad so zásadami SLP

Testované látky nových technológií, využitie nových postupov pri testovaní

Nanomateriály

Nanomateriály sú chemické látky alebo materiály, ktorých štruktúry sa v aspoň v jednom rozmere pohybujú v rozsahu približne 1 až 100 nm (10^{-9} m).

Nanomateriály majú unikátne a výraznejšie vlastnosti ako rovnaký materiál bez nanovlastností.

Fyzikálno-chemické vlastnosti nanomateriálov sa preto môžu odlišovať od vlastností veľkoobjemnej látky alebo častíc väčšej veľkosti.

Nanomateriály

Na európskom trhu je už veľké množstvo výrobkov obsahujúcich nanomateriály (napr. batérie, nátery, antibakteriálne odevy, prípravky na ošetrenie povrchov proti zašpineniu, zahmlievaniu, korózii, baktériám, kozmetika, potravinové výrobky - chuť a trvanlivosť).

Nanomateriály

- Fullerenes (C60)
- Single-walled carbon nanotubes (SWCNTs)
- Multi-walled carbon nanotubes (MWCNTs)
- Silver nanoparticles
- Iron nanoparticles
- Titanium dioxide
- Aluminium oxide
- Cerium oxide
- Zinc oxide
- Silicon dioxide
- Dendrimers
- Nanoclays
- Gold nanoparticles

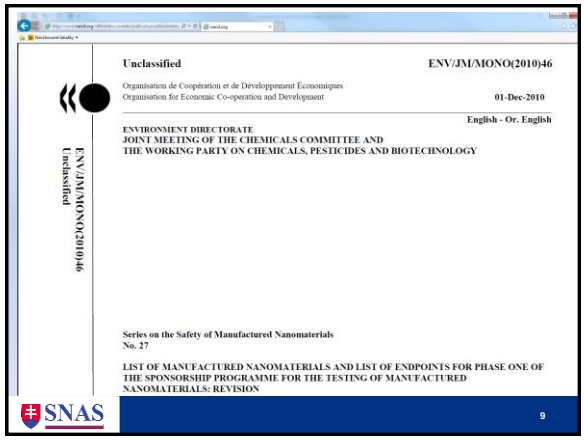
Nanomateriály

Nanomedicína

- Nanodiagnostika
- Nanofarmakológia
- Regeneratívna nanomedicína
- Implantáty

Working Party on Manufactured Nanomaterials
(od 2006, OECD)

- **OECD's Sponsorship Programme for the Testing of Manufactured Nanomaterials**.
- *Guidance Manual for the Testing Manufactured Nanomaterials; OECD Sponsorship Programme; First Revision* [ENV/JM/MONO(2009)20/REV].
- **List of representative manufactured nanomaterials**



Unclassified ENV/JM/MONO(2010)46

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

01-Dec-2010

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Unclassified ENV/JM/MONO(2010)46

Series on the Safety of Manufactured Nanomaterials
No. 27

LIST OF MANUFACTURED NANOMATERIALS AND LIST OF ENDPOINTS FOR PHASE ONE OF THE SPONSORSHIP PROGRAMME FOR THE TESTING OF MANUFACTURED NANOMATERIALS: REVISION

Testovanie nanomateriálov

- **Fyzikálne vlastnosti a charakterizácia materiálu** *(napr. Water solubility/ Dispersability, Crystalline phase, Dustiness, Crystallite size, Particle size distribution – dry and in relevant media, Specific surface area...)*
- **Vplyv na životné prostredie** *(napr. Dispersion stability in water, Biotic degradability, Ready biodegradability, Inherent biodegradability, Simulation testing on ultimate degradation in surface water, Soil simulation testing, Sediment simulation testing, Sewage treatment simulation testing, Identification of degradation product(s), Abiotic Degradability, Adsorption- desorption, Adsorption to soil or sediment, Bioaccumulation potential...)*
- **Ekotoxikológia** *(napr. Effects on sediment species (short term/long term), Effects on soil species (short term/long term), Effects on terrestrial species, Effects on microorganisms, Effects on activated sludge...)*

Testovanie nanomateriálov

- ***Toxikológia*** *(Pharmacokinetics/ Toxicokinetics (ADME), Acute toxicity, Repeated dose toxicity*
  If available: Chronic toxicity, Reproductive toxicity, Developmental toxicity, Genetic toxicity, Experience with human exposure)
- **Material Safety** *(Flammability, Explosivity, Incompatibility)*

Novel Food

„Nová potravina" je každá potravina, ktorá nebola vo významnej miere používaná v Únii na ľudskú spotrebu pred 15. májom 1997 (Regulation (EC) No 258/97), a to bez ohľadu na dátumy pristúpenia rozličných členských štátov do Únie.

Sú to:

- potraviny vyrábané novým výrobným postupom, ak tento výrobný postup spôsobuje významné zmeny v zložení alebo štruktúre potraviny, čo ovplyvňuje jej výživovú hodnotu, spôsob jej látkovej premeny alebo množstvo nežiaducich látok;
- Tradičné potraviny konzumované v tretích krajinách mimo EU

Novel Food – môžu byť poľnohospodárske produkty tretích krajín (**chia semienka, acerola**), novovyrábané požívatiny (**syntetický zeaxanthin, izomaltulóza,**) alebo extrakty z existujúcich potravín (**bielkoviny z repky olejnej, glykozidy steviolu**), potraviny pozostávajúce **z / alebo izolované z mikroorganizmov, húb alebo rias**.

Potravina sa za novú považuje aj v tých prípadoch, keď bola vyrobená výrobným postupom, ktorý sa predtým v potravinárskej výrobe v Únii nepoužíval (klonovanie, génová manipulácia, ožarovanie...), alebo v prípadoch, keď obsahuje umelo vyrobené nanomateriály v zmysle článku 2 ods. 2 písm. t) nariadenia EP a Rady (EÚ) č. 1169/2011 alebo z nich pozostáva.

Nové potraviny by mali byť bezpečné a ich označenie a používanie by nemalo spotrebiteľa zavádzať. Ak má teda nová potravina nahradiť inú potravinu, nemala by sa od nej líšiť takým spôsobom, ktorý by bol pre spotrebiteľa z hľadiska výživy nevýhodnejší.

Nové potraviny by sa mali umiestňovať na trh a používať v potravinách na ľudskú spotrebu len v tom prípade, že sa nachádzajú na únijnom zozname nových potravín povolených na umiestňovanie na trh v rámci Únie.

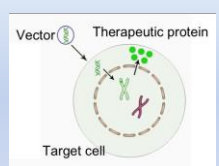
The 'Novel Foods Regulation' (Regulation (EC) No. 258/97) lays out detailed rules for the authorisation of novel foods, ingredients and processes.

V 2013 sa v EU začala diskusia o využívaní klonovania, pripravuje sa návrh nariadenia, zatiaľ neukončené

Gene Therapy Medicinal Product (GTMP)

development of gene and cell therapy for the treatment of genetic diseases

- Biological medicinal product which contains or consists of a recombinant nucleic acid used or administered to human beings with a view to **regulating**, **repairing**, **replacing**, adding or deleting a **genetic sequence**
- Its effect relates to the recombinant nucleic acid sequence or to the transgene expression



Non-clinical safety studies using stem cells (includes hESC/iPSC and genetically modified cells) as the test item

- The GLP requirements for **advanced therapy studies** are not well defined. There are little or no formal specific study guidelines (e.g. OECD Test Guideline) and therefore study designs are custom designed using general guidance to meet the scientific needs and objectives of the study.
- Dialogue with Regulatory Authorities is usually needed to assure regulatory expectations are met.

Use of specialised animal models (e.g. immuno-compromised mice) and surgical techniques (e.g. transplantation of stem cells)

- They are not specifically mentioned in the GLP principles although it is acknowledged that there are sections on test system characterisation and study procedures.
- The GLP principles are designed to be applicable to a variety of techniques used across diverse industrial sectors.
- Specific guidance on specialised techniques and models could be produced but there would have to be a clear need to do so.

During conduct of the 'stem cells study', samples are taken for product specific analyses that require **specialised assays / techniques (e.g. Polymerase Chain Reaction (PCR; real-time or qualitative), In-situ hybridisation (ISH), Immunohistochemistry (IHC), FACS analyses).**

- As some assays are of a specialised nature, there is sometimes no option **but to conduct these in a non-GLP facility.**
- Most receiving authorities will also be aware of these difficulties and assess each situation on a case by case basis.

Immune assay analysis and neutralising assays associated with GLP studies for anti-viral products

- The specialised nature of these analyses sometimes leaves no option but to use a non-GLP facility and for some analyses there could be limited assay method validation available.
- on some occasions methods are so specialised that they have to be conducted in non GLP facilities.
- Most receiving authorities will also be aware of these difficulties and assess each situation on a case by case basis.

Accelerator mass spectrometry (AMS) - to measure 14C/12C isotope ratios
Quantification of metabolites using techniques such as MALDI

- this sort of work is often carried out by small service providers that operate outside of GLP.
- Most receiving authorities assess each situation on a case by case basis.

New technologies like "NGS" (Next generation sequencing), chip hybridization techniques as well as techniques in the area of toxicogenomics, Large Molecule Analysis

Create questions that are not fully addressed in the existing regulations and definitions:

- Difficulties in defining the complex raw data generated
- Difficulties for QA to find the "specific raw data" out of the huge amount of data acquired using these new technologies
- Validation requirements for specific databases handling these high volumes of data
- Special requirements for characterization of test items

Each of these issues must be addressed on a case by case basis. It is unlikely that it will be possible to provide general guidance which will adequately cover all eventualities.

Legislatíva EU týkajúca sa chemických látok a SLP

Regulation (EC) No 1907/2006 (REACH)

Cieľom systému nazvaného Registrácia, Evaluácia a Autorizácia Chemikálií (REACH) je uplatnenie chemických produktov bezpečnejších pre ľudské zdravie a životné prostredie a:

- **Zlepšenie ochrany ľudského zdravia a kvality ŽP;**
- **Zvýšenie konkurencieschopnosti európskeho chemického priemyslu;**
- **Podpora inovácie chemického priemyslu EÚ;**
- **Vyžaduje sa zodpovednejší prístup od priemyslu pri kontrole rizík;**
- **Poskytovanie informácií dodávateľským reťazcom smerom dole.**

REACH

Článok 13 :

Všeobecné požiadavky na získavanie informácií o skutočných vlastnostiach látok

13.4

Ekotoxikologické a toxikologické testy a analýzy musia byť robené v súlade so zásadami SLP uvedenými v Directive 2004/10/EC.

LEGISLATÍVA SLP v EÚ – testovacie metódy

Council Regulation (EC) No. 440/2008, laying down test methods pursuant to Regulation (EC) No. 1907/2006 of the EP and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

The EU receiving authority for the REACH Regulation is the European Chemicals Agency (ECHA),

Regulation (EC) No 1272/2008 (CLP) on classification, labelling and packaging of substances and mixtures

(Globally Harmonized System of Classification and Labelling of Chemicals).

Article 8.4 - **new ecotoxicological or toxicological tests and analyses,** these shall be carried out in compliance with Article 13(4) of Regulation (EC) No 1907/2006 (REACH), which establishes that:

ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of GLP.

Fyzikálna nebezpečnosť / Physical hazard

Fyzikálna nebezpečnosť je definovaná ako faktor prostredia, ktorý môže poškodiť organizmus bez toho, aby sa ho nevyhnutne dotkol (horľavosť, výbušnosť, chem. reaktivita...).

The EU receiving authority for Regulation (EC) No. 1272/2008 is the European Chemicals Agency (ECHA).

Regulation (EC) No 1272/2008 (CLP)

- Article 8.5 - new tests for physical hazards are carried out for the purposes of this Regulation, they shall be carried out, at the latest from 1 January 2014, in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard:
  1. ***Compliance with the principles of GLP;***
  2. ***Application of EN ISO/IEC 17025;***
  3. *Other internationally recognised standards of comparable scope.*

Legislatíva EU týkajúca sa biocídov a SLP

Regulation (EU) No 528/2012 - requirements for placing biocidal products on the market.

Annex II.:

*Tests performed should comply with the relevant requirements of protection of laboratory animals […] and in the case of **ecotoxicological and toxicological tests, good laboratory practice, set out in Directive 2004/10/EC** […]*

*Tests on **physico-chemical properties** and safety-relevant substance data should be performed at least according to international standards."*

The EU receiving authority is the European Chemicals Agency (ECHA),

Legislatíva EU týkajúca sa pesticídov a SLP

Regulation (EC) No 1107/2009 (plant protection products)

- Article 59(1) in chapter V – requires that tests were certified as **compliant with principles of good laboratory practice (GLP).**
- Article 60(3) in chapter V - on the list of test and study reports requires that those lists shall include information on **whether those test and study reports were certified as compliant with the principles of good laboratory practice**.

The EU receiving authority for Regulation (EC) No 1107/2009 is the European Food Safety Authority (EFSA).

Q&A dokument z januára 2015 (22 strán)

- http://ec.europa.eu/food/plant/pesticides/legislation/docs/qanda_regulation_1107-2009_en.pdf

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Safety of the Food Chain
Chemicals, contaminants, pesticides

SANCO/12415/2013, Rev. 5

30 January 2015

QUESTION AND ANSWERS

Regulation (EC) No 1107/2009 concerning the placing of plant protection product on the market[1]

TABLE OF CONTENTS

1. INTRODUCTION 4

Legislatíva EU týkajúca sa krmovinových a potravinových doplnkov / vrátane GM food and feed a SLP

Regulation (EC) No 429/2008 (feed additives)

- Annex II on general requirements requires that studies shall be performed and documented according to appropriate quality standards (e.g. **Good Laboratory Practice (GLP)).**
- Where *in vivo or in vitro studies are carried out outside the Community, the applicant shall demonstrate that the facilities concerned* ***comply with the OECD principles of Good Laboratory Practice*** *or ISO standards.*

The EU receiving authority for Regulation (EC) No 429/2008 is the European Food Safety Authority (EFSA).

Regulation (EU) No 234/2011 (food additives)

- Paragraph 7 - requires that **toxicological tests should be carried out in compliance with principles of GLP**.
- Article 5(7) on the general provisions on data for risk assessment requires that **toxicological studies shall be conducted in facilities which comply with principles of good laboratory practice.**

The EU receiving authority for Commission Regulation (EU) No 234/2011 is the European Food and Safety Authority (EFSA).

Regulation (EU) No 503/2013 (GM food & feed)

Article 4 :

Toxicological studies shall be conducted in facilities which comply with the:

(a) requirements of Directive 2004/10/EC; or

(b) 'OECD Principles on Good Laboratory Practice' (GLP), *if carried out outside the Union.*

Studies, other than toxicological studies, shall:

(a) comply with the principles of GLP laid down in Directive 2004/10/EC; or

(b) be conducted by organisations accredited under the relevant ISO standard."

Recommendation 97/618/EC (novel foods)

- Section 3.10 on allergenic potential specifies that studies **to test the allergenic potential of novel foods** should be **compliant to principles of GCP and GLP**.
- Chapter XI **on nutritional information on the novel foods** requires that studies **should be compliant to principles of GLP**, in particular regarding the numbers involved in study groups.

The EU receiving authority is the European Food Safety Authority (EFSA).

Iné typy látok sa nepokladajú za „novel food":

- geneticky modifikované potraviny patria do rozsahu pôsobnosti nariadenia EP a Rady (ES) č. 1829/2003,
- enzýmy patria do rozsahu pôsobnosti nariadenia EP a Rady (ES) č. 1332/2008,
- potraviny používané výlučne ako prídavné látky patria do rozsahu pôsobnosti nariadenia EP a Rady (ES) č. 1333/2008,
- arómy patria do rozsahu pôsobnosti nariadenia EP a Rady (ES) č. 1334/2008,
- extrakčné rozpúšťadlá patria do rozsahu pôsobnosti smernice EP a Rady č. 2009/32/ES.

Legislatíva EU týkajúca sa medicínskych produktov a SLP

Directive 2003/63/EC - human medicinal products (dopĺňa 2001/83/EC)

- Paragraph 9 - **non-clinical (pharmaco-toxicological) studies** shall be carried out in conformity with the provisions related to **GLP**.
- Section 2.2 Module 4 (Part III) on **radio-pharmaceutical precursors for radio-labelling purposes** requires that for single dose and repeated dose toxicity, the results of studies carried out in conformity with the provisions related to GLP.

The EU receiving authority for Commission Directive 2003/63/EC is the European Medicines Agency (EMA).

Regulation (EU) No 536/2014 (clinical trials) - bude platiť od 2016

- Article 25: *"**non-clinical information submitted in an application dossier shall be based on data derived from studies complying with Union law on the principles of good laboratory practice**, as applicable at the time of performance of those studies."*
- Annex III of the Regulation requires the **inclusion of *„a statement of the good laboratory practice status*** *or equivalent standards, as referred to in Article 25(3)" in the investigational medicinal product dossier (IMPD).*

Directive 2009/9/EC - veterinary medicinal products (dopĺňa 2001/82/EC)

- Paragraph 6 - **pharmacological, toxicological, residue and safety tests shall be carried out in conformity with the provisions related to GLP** laid down in Directive 2004/10/EC and Directive 2004/9/EC.
- Chapter II on the presentation of particulars and documents specifies that **each study report shall include a statement of compliance with GLP**.

The EU receiving authority for Commission Directive 2009/9/EC is the European Medicines Agency (EMA).

Legislatíva EU týkajúca sa kozmetiky a SLP

Kozmetika - Regulation (EU) No 1223/2009

- Article 10(3) of Chapter III on safety assessment - *"**Non-clinical safety studies referred to in the safety assessment** for the purpose of assessing the safety of a cosmetic product **shall comply with Community legislation on the principles of good laboratory practice**, as applicable at the time of performance of the study.*

The receiving authorities for Regulation (EC) No 1223/2009 are the Member State competent authorities.

Detergenty - Regulation (EC) No 648/2004

- Recital 30 - tests specified for the biodegradability of surfactants should be carried out in laboratories meeting an internationally recognised standard, namely EN **ISO/IEC17025 or the principles of good laboratory practice.**
- Article 5(2) The tests shall be carried out on the basis of an approach defined in a technical guidance document, which will specify those tests for which **the principles of good laboratory practice should be applied.**
- Article 7 on the testing of surfactants requires that tests on detergents shall be conducted in compliance with EN ISO/IEC standard or the principles of good laboratory practice, except for those tests for which the principles of good laboratory practice have been made mandatory.
- Annex I defines standards of accreditation, good laboratory practice and animal protection concerning the laboratories that are competent and authorised to provide the necessary service for checking compliance of detergents with the requirements of this Regulation and its Annexes.

The receiving authorities for Regulation (EC) No 648/2004 are the Member State competent authorities.

Pôvodná EÚ legislatíva týkajúca sa SLP

- **Industrial Chemicals** (Directive 67/548/EEC, rozšírenie o podmienky testovania 88/379/EEC nahradená 199/45/EC)
- **Existing Industrial Chemicals** (Directive 793/93/EEC)
- **Medicinal Products** (Directive 2001/83/EC)
- **Veterinary Medicinal Products** (Directive 2001/82/EC)
- **Plant Protection Products** (79/117/EEC, 91/414/EEC)
- **Biocides** (98/8/EC)
- **Feed Additives** (87/153/EEC a doplňujúca 2001/79/EC)
- **Food Additives** (89/397/EEC; a doplňujúca 93/99/EEC)
- **Cosmetics** (76/768/EEC, 93/35/EEC a konsolidovaná verzia 2009/36/EC)

Aktuálna legislatíva na Slovensku

Zákon platný od 1. 4. 2010

Zákon č. 67/2010 Z. z. o podmienkach uvedenia chemických látok a chemických zmesí na trh a o zmene a doplnení niektorých zákonov (chemický zákon)

Zákon č. 67/2010 Z. z.

o podmienkach uvedenia chemických látok a chemických zmesí na trh a o zmene a doplnení niektorých zákonov (chemický zákon)

I. Všeobecné ustanovenia

II. **Klasifikácia, označovanie a balenie látok a zmesí, testovanie látok a karta bezpečnostných údajov**

III. **Uvedenie látok, zmesí, výrobkov a detergentov na trh**

IV. **SPRÁVNA LABORATÓRNA PRAX**

Zákon č. 67/2010 Z. z., problematiky SLP sa týka Štvrtá časť zákona – Správna laboratórna prax

- § 9 - **Zásady SLP**
- § 10 - **Testovacie pracovisko**
- § 11 - **Monitorovanie zásad SLP**
- § 12 - **Národný program**
- § 13 - **Konanie o vydaní osvedčenia**
- § 14 - **Zrušenie osvedčenia**
- § 15 - **Konanie o námietkach**

Na rozdiel od akreditácie sa na § 13, 14 a 15 (udelenie, osvedčenia, zrušenie osvedčenia, námietky) nevzťahuje všeobecný predpis o správnom konaní.

Nariadenie vlády č. 320/2010 Z. z.
z 23. júna 2010,
ktorým sa upravujú činnosti testovacích pracovísk a činnosti inšpektorov vykonávajúcich inšpekcie, audit a overovanie dodržiavania zásad správnej laboratórnej praxe
doplnené o nariadenie vlády č. 92/2012 Z. z.

s účinnosťou od 15. 3. 2012

Otázky ???

SNAS

55