I medicinali omeopatici: Aspetti di sicurezza. Il lavoro in Europa.

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Il medicinale omeopatico

Cosa se ne dice?

È naturale;

È sicuro;

Non fa male;

Non causa eventi avversi;

Etc.

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Elenco argomento trattati

1) Il medicinale omeopatico
2) La definizione di sicurezza
3) Il lavoro del gruppo Europeo Homeopathic Medicinal Products Working Group (HMPWG)
4) La prima diluizione sicura

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Come si prepara il medicinale omeopatico?

Materia prima

Animale e biologica

Chimica e minerale

Vegetale

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Il ceppo omeopatico e le diluizioni

Ceppo omeopatico

Diluizioni finali

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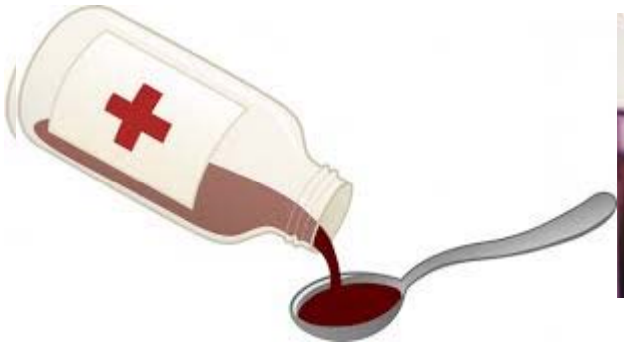
Il medicinale omeopatico finito: i granuli

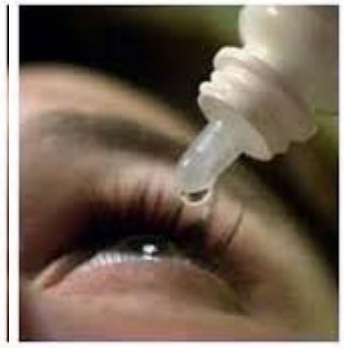
Diluizione

Processo di impregnazione

Medicinale omeopatico finito

Il medicinale omeopatico finito: altri tipi





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Il medicinale omeopatico è definito dalla direttiva europea 2001/83/CE

Homeopathic medicinal product:

Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles.

Article 14

1. Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

— they are administered orally or externally,

— no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto,

La direttiva ha inoltre definito le caratteristiche per una procedura semplificata di registrazione

— there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

Come faccio a dimostrare la diluizione sicura?

Il gruppo europeo

Homeopathic Medicinal Products Working Group (HMPWG):

- È un forum di scambio di expertise regolatorio e scientifico riguardanti la valutazione della qualità, sicurezza e uso omeopatico del medicinale omeopatico per uso umano e veterinario negli Stati UE ;
- Elabora linee guida per la valutazione dei medicinali omeopatici;
- Supporta l'elaborazione dell'elenco di diluizioni sicure dei medicinali omeopatici;
- .....

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Heads of Medicines Agencies - Homeopathic Medicinal Products Working Group - (HMPWG) – 21ST meeting

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Le linee guida relative alla sicurezza

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP
(HMPWG)

POINTS TO CONSIDER ON NON-CLINICAL SAFETY OF HOMEOPATHIC MEDICINAL PRODUCTS OF BOTANICAL, MINERAL AND CHEMICAL ORIGIN

DISCUSSION IN THE HMPWG	April 2002 - November 2005
FIRST COMMENTS OF THE INDUSTRY	October 2005
DISCUSSION IN THE WG HMPWG	December 2005
RELEASE FOR CONSULTATION	January 2006
DEADLINE FOR COMMENTS	31 March 2006
DISCUSSION IN THE HMPWG	June 2006
ADOPTION FOR TRANSMISSION TO HMA	June 2006
DEADLINE FOR COMMENTS	15 January 2007
ADOPTION FOR TRANSMISSION TO HMA	March 2007
ADOPTION BY HMA	July 2007

Guida alla determinazione della prima diluizione sicura per ceppi di origine vegetale, minerale e chimica

Le linee guida relative alla sicurezza

Le caratteristiche principali:

- Utilizzo di un decision tree per il calcolo della FSD
- Considerare il tipo di preparazione utilizzata;
- Metodo di produzione usato;
- Utilizzo del ceppo in altri ambiti (integratore o ad uso alimentare, etc);
- Utilizzo di dati tossicologici noti;

La prima diluizione sicura stabilisce il margine della presentazione di dati non clinici completi a supporto della sicurezza del ceppo (modulo 4), che rimane necessario per quei prodotti ove non sono disponibili nè dati analitici, nè tossicologici

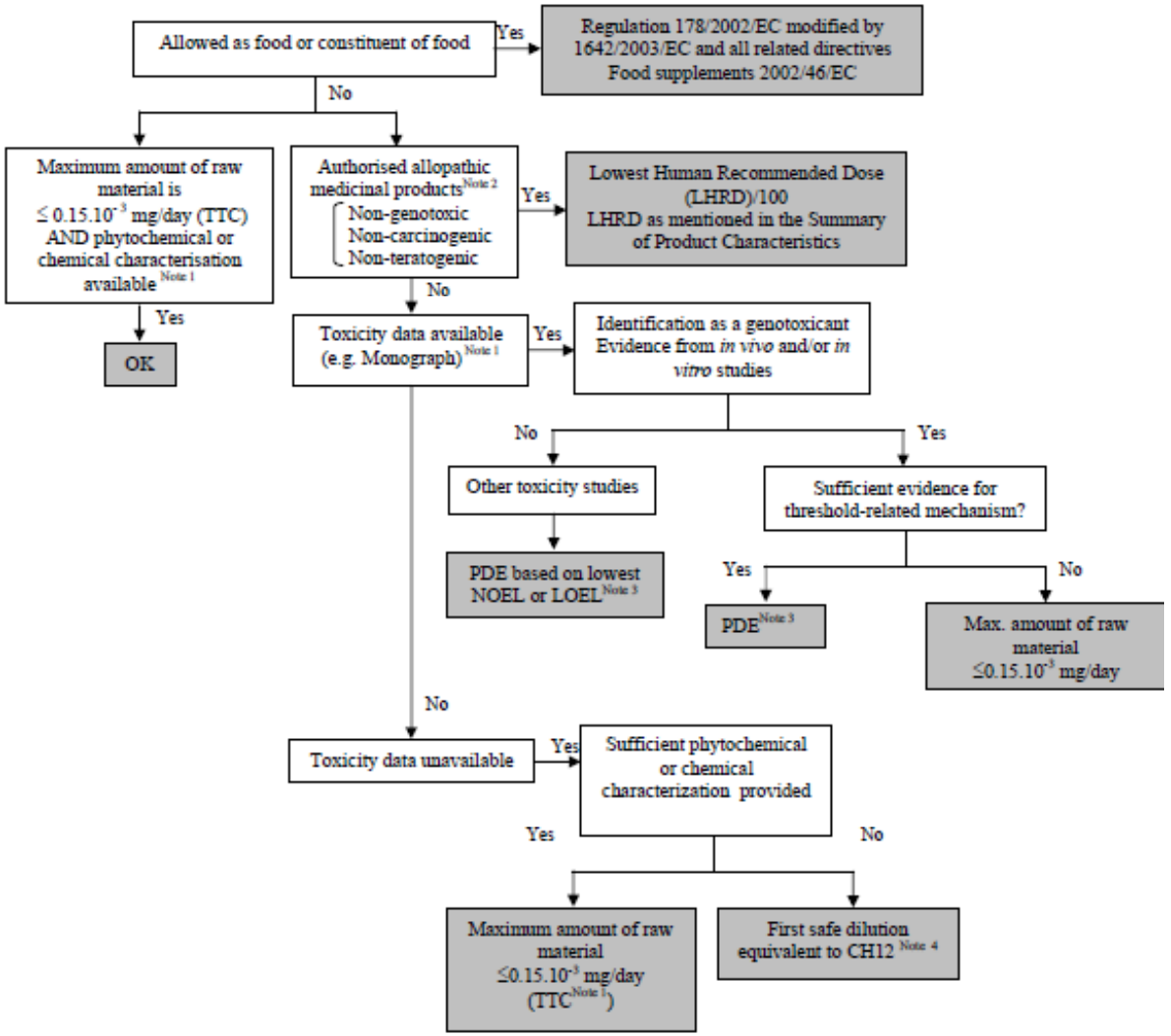
$$FSD = \frac{safe\ content}{10\ g\ or\ 10\ ml}$$

3.4 Calculation of the first safe dilution

For the conversion of the PDE (mg/day), TTC (mg/day) or LHRD/1003 (mg/day, see Annex 1) to a first safe dilution, the worst case scenario should be adopted. This implies that the proposed dose of stock is present in 10 ml of oral solution or in 10 g of trituration. This concentration, expressed as a decimal dilution (DH = -log(PDE/TTC/LHRD:100) is taken as the reference for further calculations. The DH can be converted to other dilution types, including centesimal Hahnemannian (CH), Korsakovian (K) or fifty millesimal (LM) by taking into account the specific conversion factor for dilution (CFdilution) as detailed in Table 1.

FSD: First Safe Dilution
LHRD: Lowest Human Recommended Dose
PDE: Permitted Daily Exposure
TTC: Threshold of Toxicological Concern

ANNEX 1. Decision Tree on the Criteria for the establishment of a First Safe Dilution



The Decision Tree

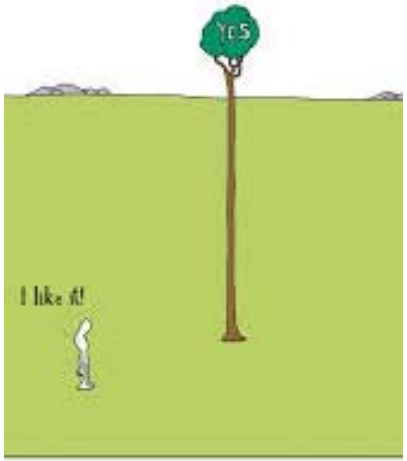


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Table 1. Calculation of the First Safe Dilution and the Conversion Factor for Dilution (CFdilution) taking into account the pharmaceutical form and the type of dilution

FIRST SAFE DILUTION nDH n=-log (concentration of PDE, LHRD/100 or TTC in 10ml solution or 10g trituration)*	**CFdilution for trituration or solution**			**CFdilution for 1% impregnated pharmaceutical forms by a dilution quantitatively equivalent to the first safe dilution (nDH)**			**CFdilution for pharmaceutical forms containing 10% or less than 10% of a dilution or trituration quantitatively equivalent to the first safe dilution (nDH)**		
nDH	**xDH**	**xCH/K**	**xLM**	**xDH**	**xCH/K**	**xLM**	**xDH**	**xCH/K**	**xLM**
n = even	x=n	x=n/2	x=(n-6)/5*	x=n-2	x=(n-2)/2	x=(n-8)/5*	x=n-1	x=n/2	x= (n-7)/5*
n = uneven	x=n	x=(n+1)/2	x=(n-6)/5*	x=n-2	x=(n-1)/2	x=(n-8)/5*	x=n-1	x=(n-1)/2	x=(n-7)/5*
In case of application of the TTC criteria, n=9	**valid for** • oral preparations- liquid forms • oral preparations - solid forms (triturations)			**valid for** • impregnated oral preparations & solids forms			**valid for** • cutaneous and transcutaneous preparations • ear preparations • eye preparations • vaginal preparations • rectal preparations		

* round up to the higher whole number
DH: Decimal Hahnemannian (D, X); CH (C): Centesimal Hahnemannian; K: Korsakovian

PDE, TTC o LHRD/100 devono essere considerati come dose di ceppo. Nel caso di ceppi di origine botanica deve essere considerato il metodo di produzione della TM o 1DH per poter applicare il fattore di conversione del metodo (CF manufacturing method).

CF è relativo alla quantità equivalente di pianta secca nella TM e/o 1DH prodotta secodno un metodo descritto nella Farmacopea Europea.

Table 2. Calculation of Conversion Factor for Different Manufacturing Methods

($CF_{manufacturing\ method}$)

Manufacturing method	$CF_{manufacturing\ method}$ of mother tincture (MT) and D1 (1DH) (European pharmacopoeia)[4] calculated with reference to the dried plant material	
	Ratio raw material (stated in dried plant)/MT	Ratio raw material (stated in dried plant)/D1
Eur. Ph.method 4c . (1/10)	1 part dried plant + 9 parts ethanol, equivalent to **1/10** part dried plant/part MT	1 part MT + 9 parts ethanol= 1/10MT, equivalent to **1/100** part dried plant/part D1
Eur. Ph method. 4d . (1/20)	1 part dried plant+ 19 parts ethanol, equivalent to **1/20** part dried plant/ part MT	1 part MT + 9 parts ethanol = 1/10 MT, equivalent to **1/200** part dried plant/part D1
Eur. Ph. , method 1		
1a	1 part expressed juice + 1 part ethanol = 1/2 part juice/part MT, equivalent to **((100-T)/2T)** part dried plant/part MT	2 parts MT + 8 parts ethanol = 2/10 MT, equivalent to **2/10*((100-T)/2T)** part dried plant/ part D1
1b	1 part fresh plant latex + 2 parts ethanol = 1/3 part juice/part MT, equivalent to **((100-T)/3T)** part dried plant/part MT	3 parts MT + 7 parts ethanol=3/10 part MT/part D1, equivalent to **3/10*((100-T)/3T)** part dried plant/part D1
Eur. Ph. , method. 2a,2b	1 part of fresh plant + (1*T/100) parts ethanol = (100/100+T) part fresh plant part /MT, equivalent to **[(100-T)/(100+T)]** part dried plant/part MT	2 parts of MT + 8 parts ethanol = 2/10 MT, equivalent to **2/10 * [(100-T)/(100+T)]** part dried plant/part D1
Eur. Ph. , method 3a,3b	1 part of fresh plant + (2*1*T/100) parts ethanol = [100/(100+2T] part fresh plant / part MT, equivalent to **[(100-T)/(100+2T)]** part dried plant/part MT	3 parts of MT + 7 parts ethanol = 3/10 MT, equivalent to **3/10 * [(100-T)/(100+2T)]** part dried plant/part D1
Eur. Ph. , method 4a,4b	1 part of dried plant+ 10 parts ethanol = **1/11** part dried plant/part MT mentioned as D1	D1 equivalent to MT

T: loss on drying (%); D1: first decimal dilution (1DH)

Working hypothesis for Eur. Ph., methods 1: the % of juice/latex is equivalent to T

Note: $CF_{manufacturing\ method}$ is only valid if the same part(s) of the plant and similar alcohol strength are used for the manufacturing of MT.

Es: Sodio Cloruro

Ceppo omeopatico: sodio cloruro NaCl

Metodo di produzione: ceppo= materia prima

Concentrazione del componente tossico: 10 g di ceppo= 10 g NaCl

Basi per il calcolo FSD: media dell'assunzione al giorno per la maggioranza di neonati a sei mesi di vita

Riferimento bibliografico: Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union, EFSA Journal 2013;11(10):3408

Quantità ammessa: 120 mg Na/day - 300 mg Cl/day

Calcolo della FSD

Ceppo omeopatico: Chimaphila umbellata MT (French Pharmacopoeia)

Metodo di produzione: Metodo 1.1.10

Concentrazione del componente tossico: pianta intera (derivati naftochinonici)

Es: Chimaphila umbellata

Basi per il calcolo FSD: TTC

Riferimento bibliografico: TTC

Quantità ammessa:0.15 µg/day

Metodo di calcolo: 1ml stock = 1 g dried RM

Calcolo della FSD

Osservazioni: l'uso del TTC è idoneo ove non ci sono prodotti farmaceutici o alimentari autorizzati; sono presenti dati di tossicità

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Heads of Medicines Agencies

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP
(HMPWG)

Questions and Answers on
First Safe Dilutions

Sono state pubblicate linee guida esplicative per il calcolo di FSD

Working out of structure and content of a Question and Answers document 1-6 by the FSD-subgroup	7 March 2013
Adoption of Question and Answers document 1-5 for public consultation on the HMA website by the HMPWG	21 November 2013
Adoption of Question and Answers document 6 for public consultation on the HMA website by the HMPWG	05 June 2014
Public consultation of Question and Answers document 1-5 on the HMA website until	20 June 2014
Public consultation of Question and Answers document 6 on the HMA website until	31 October 2014
Adoption of Question and Answers document 1-6 by written procedure by HMPWG for transmission to HMA	June 2015
Adoption by HMA-MG for publication on HMA website	October 2015

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Nel caso di medicinali omeopatici contenenti materiali di partenza di origine biologica

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP (HMPWG)

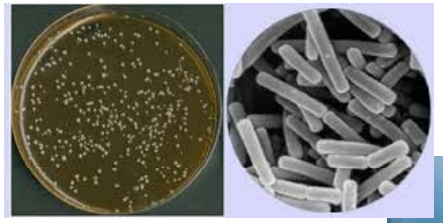
POINTS TO CONSIDER ON SAFETY OF HOMEOPATHIC MEDICINAL PRODUCTS FROM BIOLOGICAL ORIGIN

DISCUSSION IN THE HMPWG	January 2001-April 2005
RELEASE FOR CONSULTATION	March 2005
DISCUSSION IN THE HMPWG	December 2005
ADOPTION FOR TRANSMISSION TO HMA	March 2007
ADOPTION BY HMA	July 2007

I materiali di origine biologica

Materiali ottenuti da:

- Prodotti di origine umana come linee cellulari umane, tessuti o fluidi sani, o materiali/lesioni infette;
- Prodotti di origine animale come animali interi, tessuti, secrezioni animali, tossine, tessuti e estratti (nosodi) da tessuti patologici o sani, emoderivati, parassiti, linee cellulari animali;
- Microrganismi come batteri, virus, funghi microscopici, parassiti di piante;



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Definizione della prima preparazione sicura

5. Manufacturing process and safety of the Homeopathic Medicinal Product and of the first safe preparation

5.1 First safe preparation

The first safe preparation should be defined on a case-by-case basis. First safe preparation can be defined at any level of the manufacturing process up to the last removal/inactivation step introduced in the process.

Only first safe preparations may be used to produce the homeopathic medicinal products, which should comply with the principles of minimization the risk of transmission of pathogenic agent, taking into account the species infection potential other than the homeopathic therapeutic agent.

For manufacturing of human and/or animal derived homeopathic medicinal products, both pathogenic and healthy, an adequate determination of what shall be considered as the first safe preparation, for each stock is essential. This determination ensures the correct definition of viral studies to be applied in order to evaluate putative infectivity.

Safety studies, taking both viral and non-viral adventitious agents into consideration, should be performed at this lowest level prior to manufacturing further dilutions and/or other homeopathic preparations.

Caso per caso

Solo la prima preparazione sicura può essere usata nella produzione del medicinale

Gli studi di sicurezza devono tenere in considerazione agenti virali e non virali effettuati al livello più basso di diluizione

La produzione della FSP

5.2 Manufacture of the homeopathic medicinal product and first safe preparations

Dilutions alone and *per se* do not ensure biological safety of the first safe preparation. Manufacturing steps at the level of homeopathic dilutions such as solvent/detergent, filtration or pasteurisation may contribute to the safety of the first safe preparation. First safe preparations should be properly characterised in terms of microbiological, viral and TSE safety. Viral validation studies should be performed on the production of this first safe preparation. The effectiveness of the manufacturing process to inactivate or remove adventitious agents is important for the biological safety of the first safe preparation of the homeopathic medicinal product. Adequate measures are to be taken to minimise the risk of agents of infection in the homeopathic preparations - it must comply with the requirements of the European Pharmacopoeia monograph on Homeopathic Preparations.

Validation of the process of viral inactivation/removal should be addressed in specially designed viral validation studies with model viruses performed according to the Guideline CPMP/BWP/268/95 "The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses".

Le diluizioni non assicura la sicurezza della prima preparazione sicura

La prima preparazione sicura deve essere ben caratterizzata

Devono essere effettuati studi di validazione virale secondo le linee guida EMA

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CONCLUSIONI

- ✓ Il medicinale omeopatico è costituto da componenti di origine diversa;
- ✓ I ceppi omeopatici possono essere costituiti da componenti tossici di *per se*;
- ✓ La definizione della diluizione del ceppo omeopatico affinché la diluizione sia sicura è definita da linee guida europee;
- ✓ Il gruppo europeo HMPWG è impegnato nella valutazione della prima diluizione sicura con un gruppo di lavoro specifico.

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP
(HMPWG)

MANDATE, OBJECTIVES AND RULES OF PROCEDURE OF THE HMPWG SUB-WORKING GROUP ON FIRST SAFE DILUTIONS