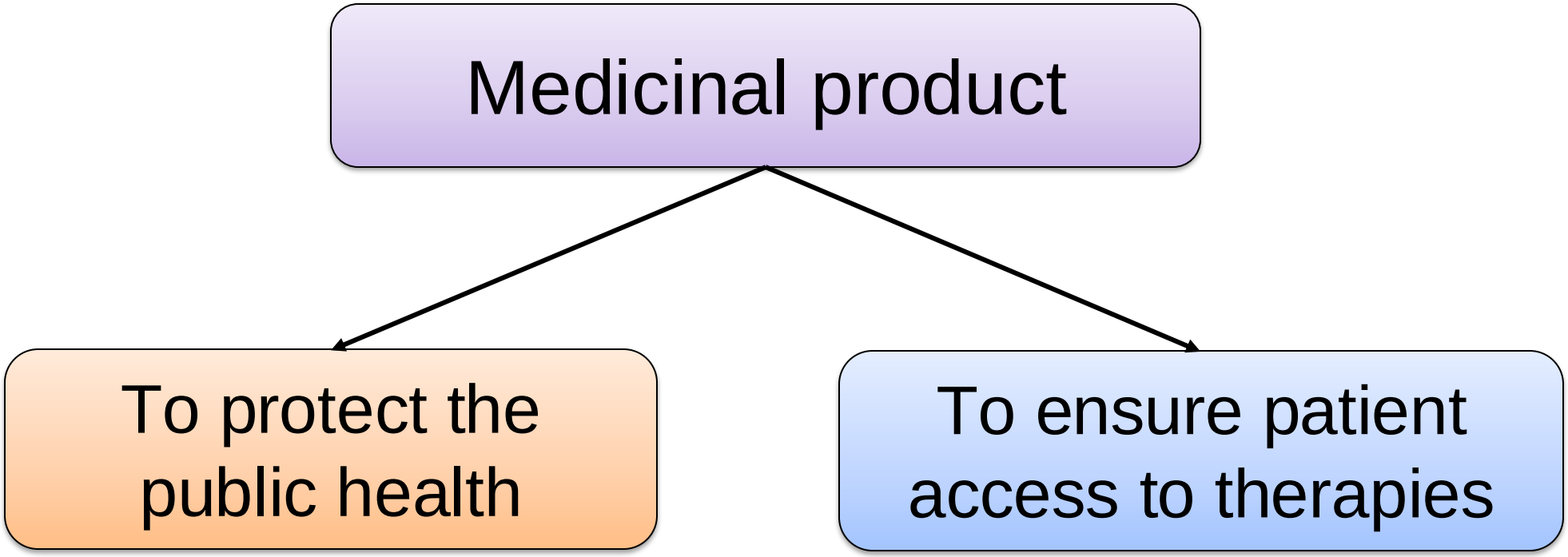
UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE

Are the regulatory aspects of pediatric medicinal products really optimized?

Prof. Paola Minghetti

DiSFarM Dipartimento di Scienze Farmaceutiche


Medicinal product
To protect the public health
To ensure patient access to therapies

Unmet medical need in pediatrics

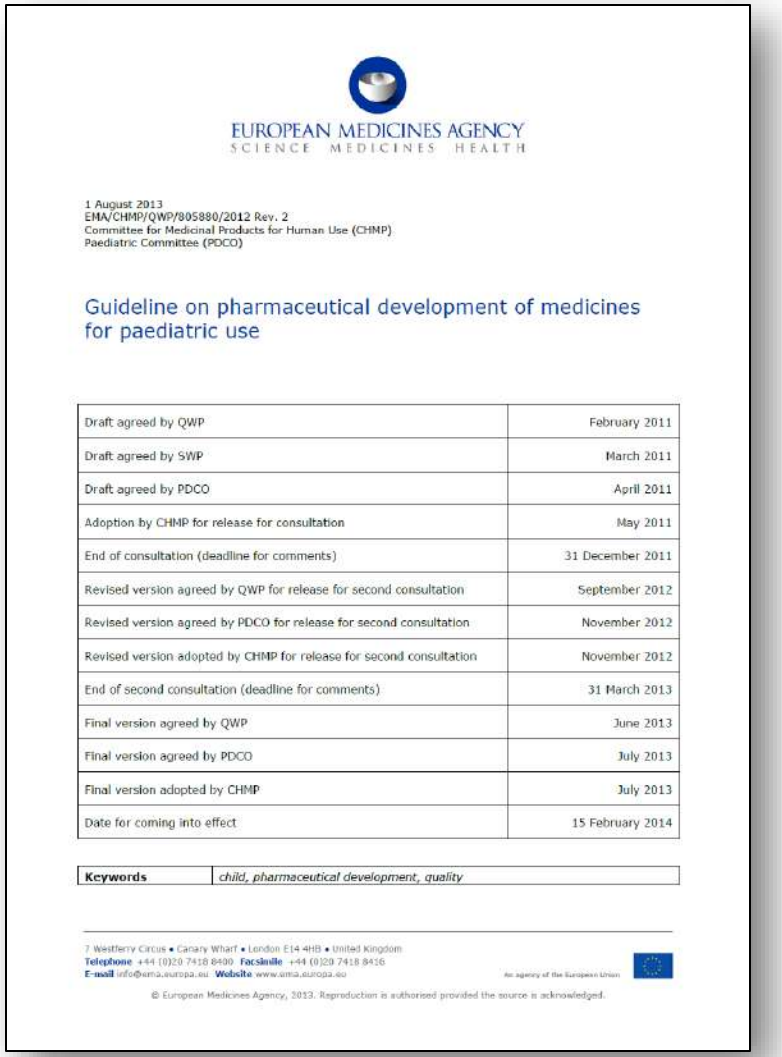
*What can **Pharmaceutical industries** do?*

New MA for first-in-human drugs

New indication for medicinal product already authorized

New MA for new medicinal product containing old API

Patient-centric design of drug product



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

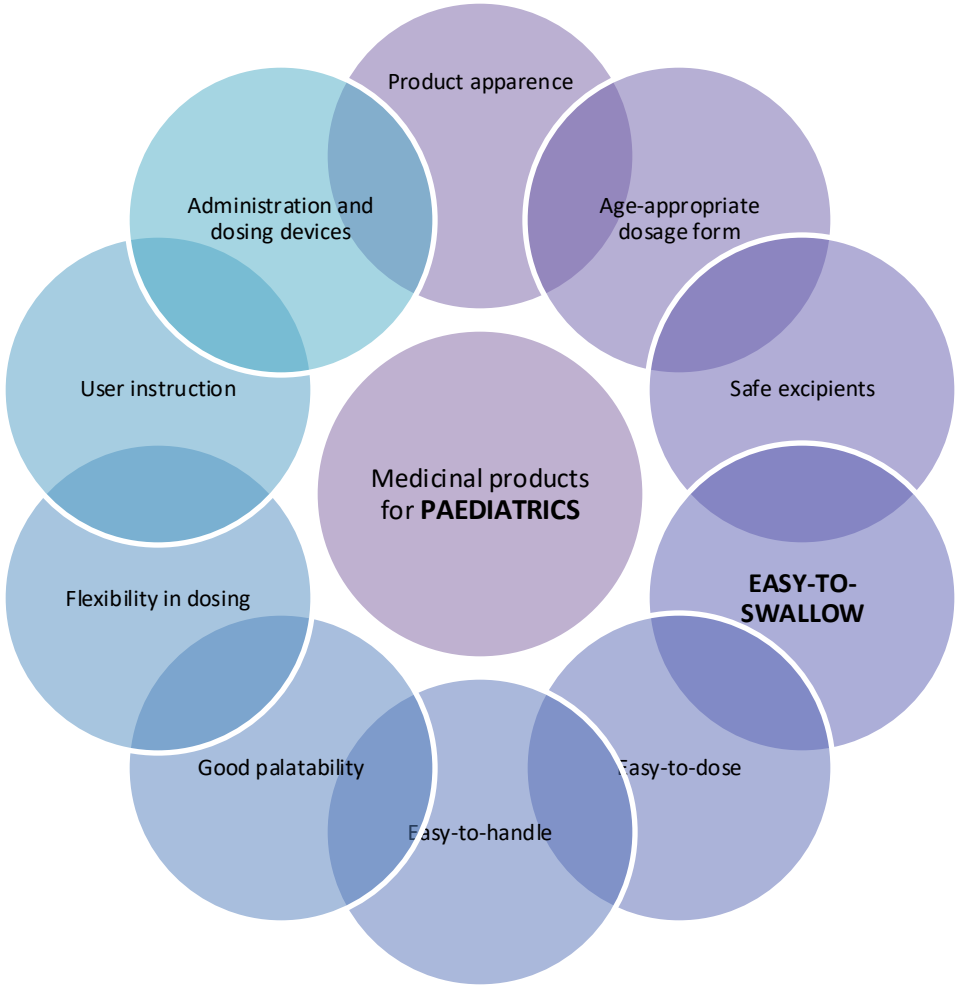
1 August 2013
EMA/CHMP/QWP/805880/2012 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)
Paediatric Committee (PDCO)

Guideline on pharmaceutical development of medicines for paediatric use

Draft agreed by QWP	February 2011
Draft agreed by SWP	March 2011
Draft agreed by PDCO	April 2011
Adoption by CHMP for release for consultation	May 2011
End of consultation (deadline for comments)	31 December 2011
Revised version agreed by QWP for release for second consultation	September 2012
Revised version agreed by PDCO for release for second consultation	November 2012
Revised version adopted by CHMP for release for second consultation	November 2012
End of second consultation (deadline for comments)	31 March 2013
Final version agreed by QWP	June 2013
Final version agreed by PDCO	July 2013
Final version adopted by CHMP	July 2013
Date for coming into effect	15 February 2014

Keywords	*child, pharmaceutical development, quality*

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union



Unmet medical need in pediatrics

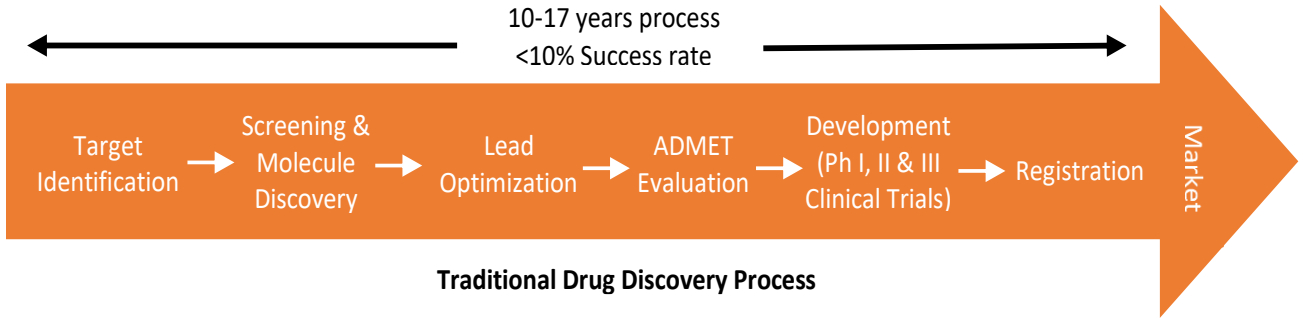
*What can **Pharmaceutical industries** do?*

New MA for first-in-human drugs

New indication for medicinal product already authorized

First-in-human medicines: costs and risks

- The R&D process represents an extremely complex challenge that can discourage the development of new medicines
- It is estimated that only **10-15%** of potential drugs pass the preclinical stage. Only **5%** of remaining products pass the clinical phase reaching approval.
- The total R&D costs have been estimated in **USD 802 million**
- **12-15 years** are required from the selection of the lead compound to the obtainment of a MA.
- **The cost/benefit balance results not favorable in some cases, e.g., orphan medicinal products and pediatric medicinal products**



Traditional Drug Discovery Process

Reed MD. J Pediatr Pharmacol Ther. 2016;21(1):4-6
DiMasi et al. Journal of Health Economics, 2016;47:20-33..

First-in-CHILDREN medicines

Many childhood diseases are rare

Orphan medicinal products

Regulation (EC) 141/2000

Paediatric medicinal products

Regulation (EC) 141/2000 on orphan medicines

Incentives

Medicinal products classified as orphan in accordance with the provisions of this Regulation may benefit from incentives made available by the Community and the Member States for the purpose of promoting research, development and availability of orphan medicinal products, and in particular research aid measures for small and medium-sized enterprises provided for in the framework programs for research and technological development.

Market exclusivity

After granting a centralized marketing authorisation, the Community and its Member States shall:

- do not accept other applications for authorisation,
- shall not grant further authorisations for existing similar medicinal products with the same therapeutic indications for a period of **10 years**. This period may be reduced to 6 years at the end of the fifth.

First-in-CHILDREN medicines

Many childhood diseases are rare

Orphan medicinal products

Paediatric medicinal products

Regulation (EC) 1901/2006

Paediatric Regulation: Reg. (EC) 1901/2006

Three main objectives:

- To promote ***high quality research*** with children to inform on the quality, safety and efficacy of medicines that children (from birth to less than 18 years) will receive;
- To provide more ***information on the use*** of paediatric medicines
- To allow the ***authorisation of medicines*** for diseases that affect children, with age-appropriate pharmaceutical forms and composition (formulation).

EMA Paediatric Committee (PDCO)

Paediatric Investigation Plans (PIPs)

Paediatric-use marketing authorisation (PUMA)

Rewards and Incentives

Paediatric Regulation: Reg. (EC) 1901/2006

Paediatric investigation plan

'**Paediatric investigation plan**' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population

An application for marketing authorisation in respect of a **medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation** shall be regarded as valid only if it includes […] one of the following:

a) the results of all studies performed and details of all information collected in compliance with an **agreed paediatric investigation plan**;

[…]

to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population

The documents submitted shall, cumulatively, cover **all subsets of the paediatric population**.

Paediatric Regulation: Reg. (EC) 1901/2006

Paediatric investigation plan

'**Paediatric investigation plan**' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population

Not required for:

- Generic products
- Well-established medicinal use
- Homeopathic medicinal products
- Traditional herbal medicinal products.

Waivers:

- Medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;
- The disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;
- Medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

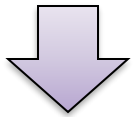
Paediatric Regulation: Reg. (EC) 1901/2006

Paediatric-use marketing authorisation (PUMA)

The PUMA was introduced on for medicines that are:

- already authorised;
- no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC;
- to be exclusively developed for use in children.

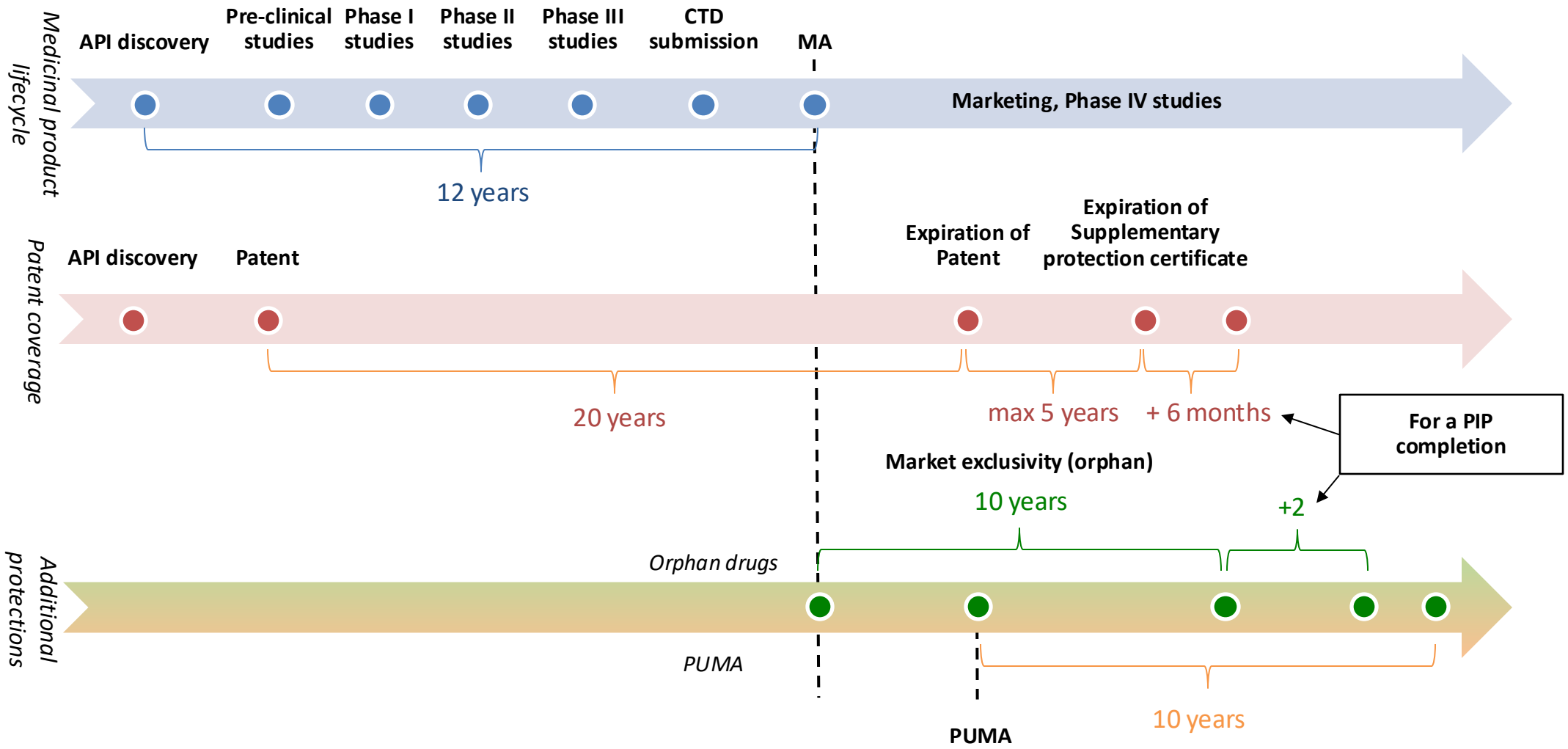
The development of a PUMA must follow a paediatric investigation plan (PIP), to be agreed by the Paediatric Committee (PDCO).



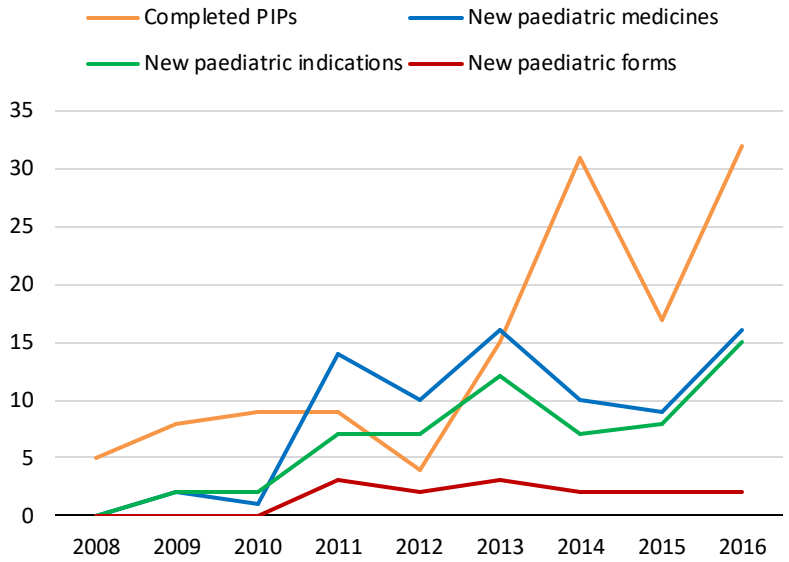
Incentives

- Automatic **access to the centralised procedure** if the applicant chooses this route, even if the application falls outside of the mandatory scope of this procedure.
- **Authorisation under the same name and branding** as the authorised medicine containing the same active substance, if the marketing authorisation holder is the same
- **Partial fee exemption** under the centralised procedure for marketing authorisation and post-authorisation activities for a year.
- **8 plus 2 years of data and market protection**

Incentives for PIPs and new pediatric indications



MP: medicinal product; MS: Member State



The number of PIP and PUMA is increasing year by year

Yes, but....

Are such actions enough?

Still few paediatric product on the market

2020

Among the **97** medicines authorized:

- **22** had orphan designation confirmed
- **0** received a PUMA

2023

Among the ***77*** medicines authorized:

- **17** had orphan designation confirmed
- **2** received a PUMA

NEW

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

NEW

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

Publication date: 26 April 2023
Author: Directorate-General for Health and Food Safety

What may change?

https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0192
https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0193

European Parliament

2019-2024

TEXTS ADOPTED

P9_TA(2024)0220

Union code relating to medicinal products for human use

European Parliament legislative resolution of 10 April 2024 on the proposal for a directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (COM(2023)0192 – C9-0143/2023 – 2023/0132(COD))

(Ordinary legislative procedure: first reading)

PROPOSAL FOR A DIRECTIVE*

Current legislation under revision		Outcome
Directive 2001/83/EC	Community code relating to medicinal products for human use	Repealed and replaced
Directive 2009/35/EC	Colouring matters which may be added to medicinal products	Repealed and replaced
Regulation (EC) No 1901/2006	Paediatric Regulation	Some parts incorporated (General framework for the authorisation and rewarding)
151 articles		*221 articles*

*Annex II to the directive contains the existing text of Annex I. Annex II will be updated by delegated act. The delegated act will be adopted and applied before the deadline for the transposition of the directive.

PROPOSAL FOR A REGULATION

Current legislation under revision		Outcome
Regulation (EC) No 726/2004	Union procedures for the authorisation	Repealed and replaced
Regulation (EC) No 141/2000	Orphan Regulation	Repealed and replaced
Regulation (EC) No 1901/2006	Paediatric Regulation	Repealed
Regulation (EC) No 1394/2007	Advanced therapy medicinal products	Amended
Regulation (EU) No 536/2014	Clinical trials on medicinal products for human use	Amended
Regulation (EU) No 2022/123	reinforced role for the EMA in crisis preparedness and management for medicinal products and medical devices	Amended
144 articles		*181 articles*

Paediatric Medicinal Products

Proposal of Directive		Regulation (EC) No 1901/2006	
GENERAL REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS			
Art. 6	[…omissis…] 5. The marketing authorisation application for a **medicinal product that is not authorised in the Union at the time of entry into force of this Directive and for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products** which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, shall include one of the following: **a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;** b) a decision of the Agency granting a product-specific waiver pursuant to Article 75(1) of [revised Regulation No (EC) 726/2004]; c) a decision of the Agency granting a class waiver pursuant to Article 75(2) of [revised Regulation No (EC) 726/2004]; d) a decision of the Agency granting a deferral pursuant to Article 81 of [revised Regulation No (EC) 726/2004]; e) a decision of the Agency taken in consultation with the Commission pursuant to Article 83 of [revised Regulation No (EC) 726/2004] to temporarily derogate from the provision referred to in points (a) to (d) above in case of health emergencies. **The documents submitted under points (a) to (d) shall, cumulatively, cover all subsets of the paediatric population.** ***In the absence of a paediatric investigation plan in accordance with the first subparagraph, point (a), or where in this regard a comparative study has not been carried out, a justification shall be submitted and where relevant also evidence shall be obtained from postmarketing long-term studies.***	Art. 7	1. An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following: a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan; b) a decision of the Agency granting a product-specific waiver; c) a decision of the Agency granting a class waiver pursuant to Article 11; d) a decision of the Agency granting a deferral. For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application. 2. The documents submitted pursuant to paragraph 1 shall, cumulatively, cover all subsets of the paediatric population. ***Amendments of the Parliament***

Paediatric Medicinal Products

Proposal of Regulation		Regulation (EC) No 1901/2006	
PAEDIATRIC INVESTIGATIONAL PLAN			
Art. 74	1. A **paediatric investigation plan** shall specify the timing and all the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the pharmaceutical form, the strength, the route of administration and **the eventual administration device of the medicinal product** so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.	Art. 15	1. [omissis] 2. The paediatric investigation plan shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.
	2. By derogation from paragraph 1, in the following cases an applicant may submit only an **initial paediatric investigation** plan as referred to in the second subparagraph: a) when the active substance concerned is not yet authorised in any medicinal product in the EU and is intended to treat a **novel paediatric condition**; b) following the acceptance by the Agency of a ***duly* justified request** from an applicant in accordance with paragraph 3. An initial paediatric investigation plan shall contain only the details and the timing of the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. This **initial paediatric investigation plan shall also provide a precise timing of when updated versions of the paediatric investigation plan** are to be submitted and when a final paediatric investigation plan complying with all the particulars described in paragraph 1, is expected to be submitted to the Agency.		Missing
	3. When it is not possible, on the basis of scientifically justified reasons, to have a complete paediatric development plan in accordance with the timing given in Article 76(1) an applicant may submit a ***duly*** justified request to the Agency to utilise the procedure mentioned in paragraph 2.		Missing

Amendments of the Parliament

Paediatric Medicinal Products

Proposal of Regulation		Regulation (EC) No 1901/2006	
PAEDIATRIC INVESTIGATIONAL PLAN			
Art. 76	*Validation of a paediatric investigation plan or of a waiver* 4. In consultation with the Commission and with interested parties, **the Agency shall draw up and publish guidelines for the practical application of this Article**.	Art. 16	Missing
Art. 77	*Agreement on a paediatric investigation plan* 1. After the validation of the proposed paediatric investigation plan referred to in Article 74(1) …. the Agency shall adopt within **90 days** a decision as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies proposed.	Art. 17	1. Following receipt of a proposed paediatric investigation plan … the Paediatric Committee shall appoint a rapporteur and shall within **60 days** adopt an opinion as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits justify the studies proposed.

Amendments of the Parliament

Paediatric Medicinal Products

Proposal of Regulation		Regulation (EC) No 1901/2006	
PAEDIATRIC USE MARKETING AUTHORISATION			
Art. 92	1. An application for a paediatric use marketing authorisation shall be submitted in accordance with Articles 5 and 6 and shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including **any specific data needed to support an appropriate formulation, pharmaceutical form, strength, route of administration and eventual administration device for the product, in accordance with an agreed paediatric investigation plan**. The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned. 2. Where a medicinal product is or has been authorised in a Member State or in the Union, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 29 or Article 9 of [revised Directive 2001/83/EC], in an application for a paediatric use marketing authorisation. 3. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same marketing authorisation holder has been granted authorisation for use in adults. […]	Art. 30	[…] 2. An application for a paediatric use marketing authorisation shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including **any specific data needed to support an appropriate strength, pharmaceutical form or route of administration for the product, in accordance with an agreed paediatric investigation plan**. The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned. 3. Where a medicinal product is or has been authorised in a Member State or in the Community, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or Article 10 of Directive 2001/83/EC, in an application for a paediatric use marketing authorisation. 4. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same holder has been granted authorisation for use in adults.

Amendments of the Parliament

Rewards for paediatric medicinal products

Proposal of Directive		Regulation (EC) No 1901/2006	
AGREED PAEDIATRIC INVESTIGATION PLAN			
Art. 86	1. Where an application for marketing authorisation, includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to **a six-month extension** of the period referred to in Article 13, paragraphs 1 and 2 of [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted]. […]	Art. 36	1. Where an application under Article 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a **six-month extension** of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92.
PUMA			
Art. 93	1. Where a paediatric use marketing authorisation referred to in Article 92 is granted and includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the product shall benefit from independent data and marketing protection periods referred to in Articles 80 and 81 of [revised Directive 2001/83/EC]. ⇩ **DATA PROTECTION** 7 years and six months + 12 months (unmet medical need) + 6 months (significant share of research and development) **MARKETING PROTECTION** 2 years	Art. 38	1. Where a paediatric use marketing authorisation is granted in accordance with Articles 5 to 15 of Regulation (EC) No 726/2004, the data and marketing protection periods referred to in Article 14(11) of that Regulation shall apply. ⇩ **DATA PROTECTION** 8 YEARS **MARKETING PROTECTION** 2 years ***Amendments of the Parliament***

Unmet medical need in pediatrics

*What can **Pharmaceutical industries** do?*

New MA for new medicinal product containing old API

New MA/therapeutic indication for an old drug

Drug repurposing

Find new therapeutic indications for existing active ingredients. The process required investments in R&D to develop a new drug products and sustainment of the drug and in supporting MA application for the new indication.

(Sleigh SH, Barton CL, Repurposing Strategies for Therapeutics. Pharm Med. 2010;24(3):151-159)

Intellectual protection for the novel therapeutic indication

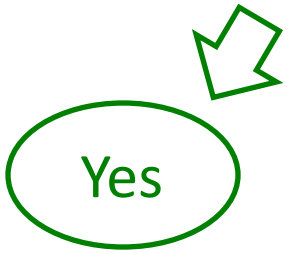
Article 54(5) of the European Patent Convention does not exclude the patentability of any substance or composition for any specific use in a method referred to in Article 53(c) [i.e., methods for treatment of the human or animal body by surgery or therapy and diagnostic methods], provided that such use is not comprised in the state of the art.

In other words, an already known substance/composition may be patented for a second therapeutic indication, if it is new and innovative.

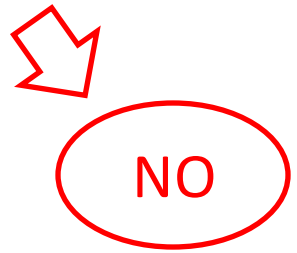
(European Patent Office - Pharmaceutical Directives. www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vi_7_1.htm)

Drug repurposing: how is the old drug identified?

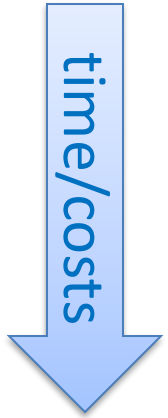
Are there some hypotheses a priori?



- Off-label use
- Literature evidence on new mechanism of action



- text mining (IA)
- in silico screening
- in vitro/ex vivo screening
- study in animal disease models
- observational studies from human trials.

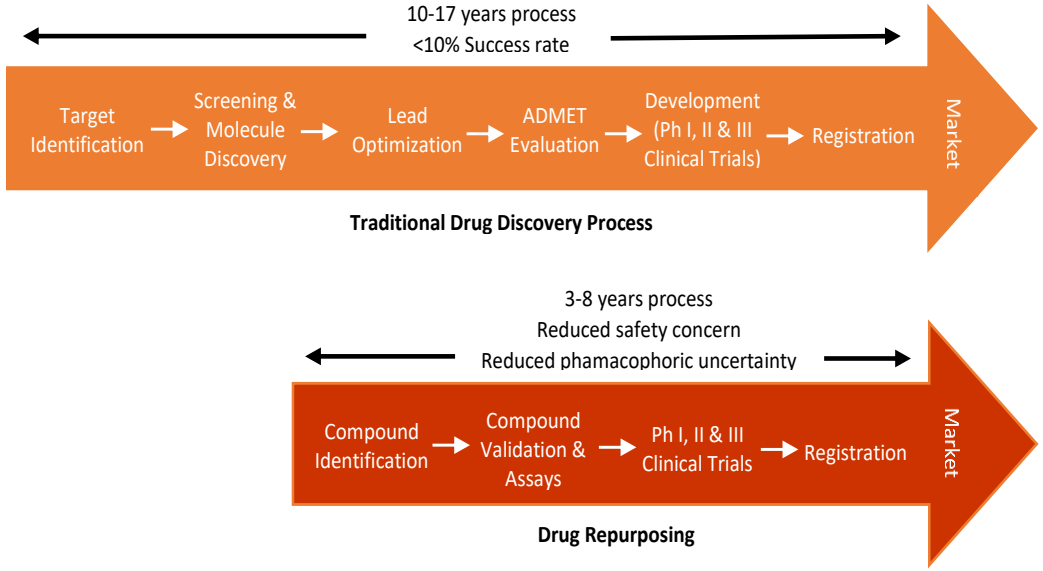


Oprea TI, Overington JP. Assay Drug Dev Technol. 2015;13(6):299-306.

Repurposing vs off-label use vs new entities

Developing repurposed medicines may be worth since:

- Availability of solid and public medical evidence on product efficacy and safety (derived from off-label use or post-marketing clinical trials;
- Investment in economic terms and time in R&D is moderate;
- No need for phase I studies that represent the greatest obstacle in the success of a new molecule (45% of new active substances fail phase I studies) (**hybrid CTD**)
- The new therapeutic indication may get a patent protection



Naylor S, et al. Drug Discovery World. 2015;16(2):57-72.

Repurposing vs off-label use vs new entities

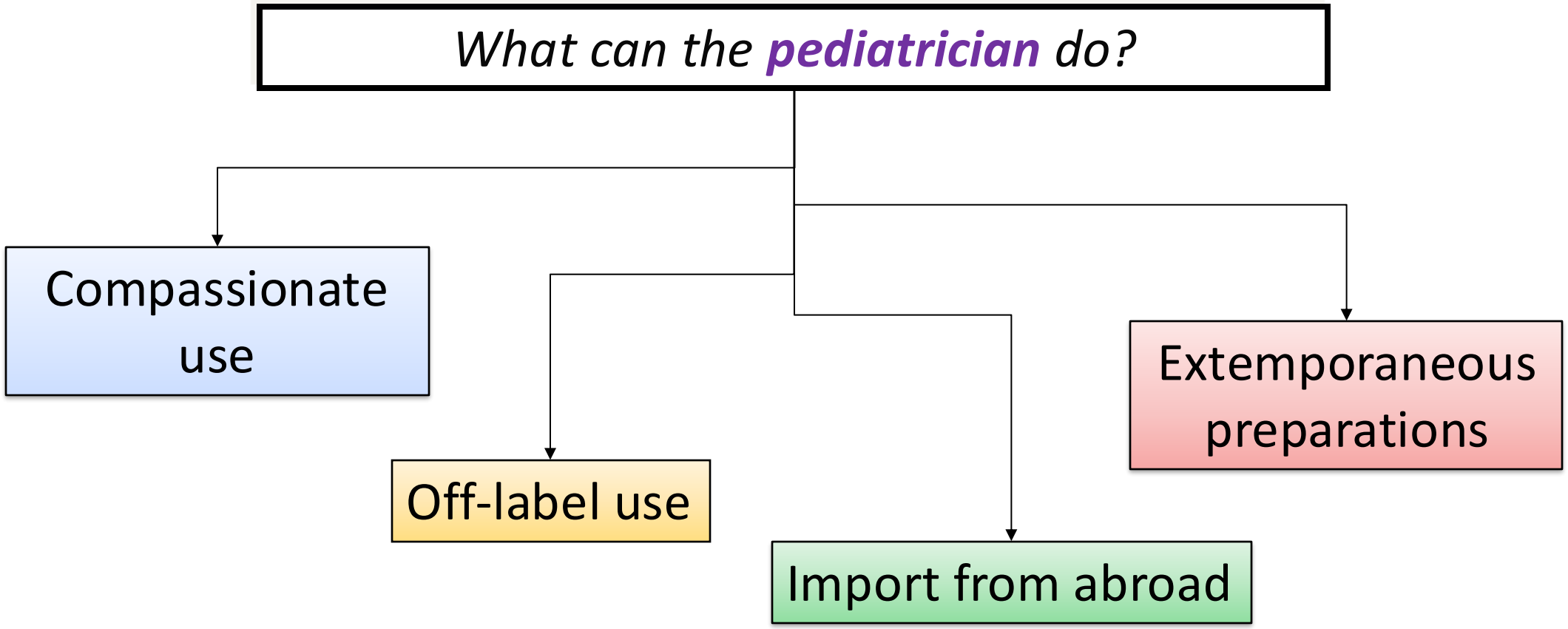
Developing repurposed medicines may not be worth since:

- It can be difficult to get the recognition, in terms of price, of the R&D costs and added value;
- Even if R&D costs for repurposed medicines are lower that first-in-humans ones, the economic sustainability may not guarantee for complex formulations.
- Some countries promote off-label use of drugs/compounded preparation rather than repurposing medicines.

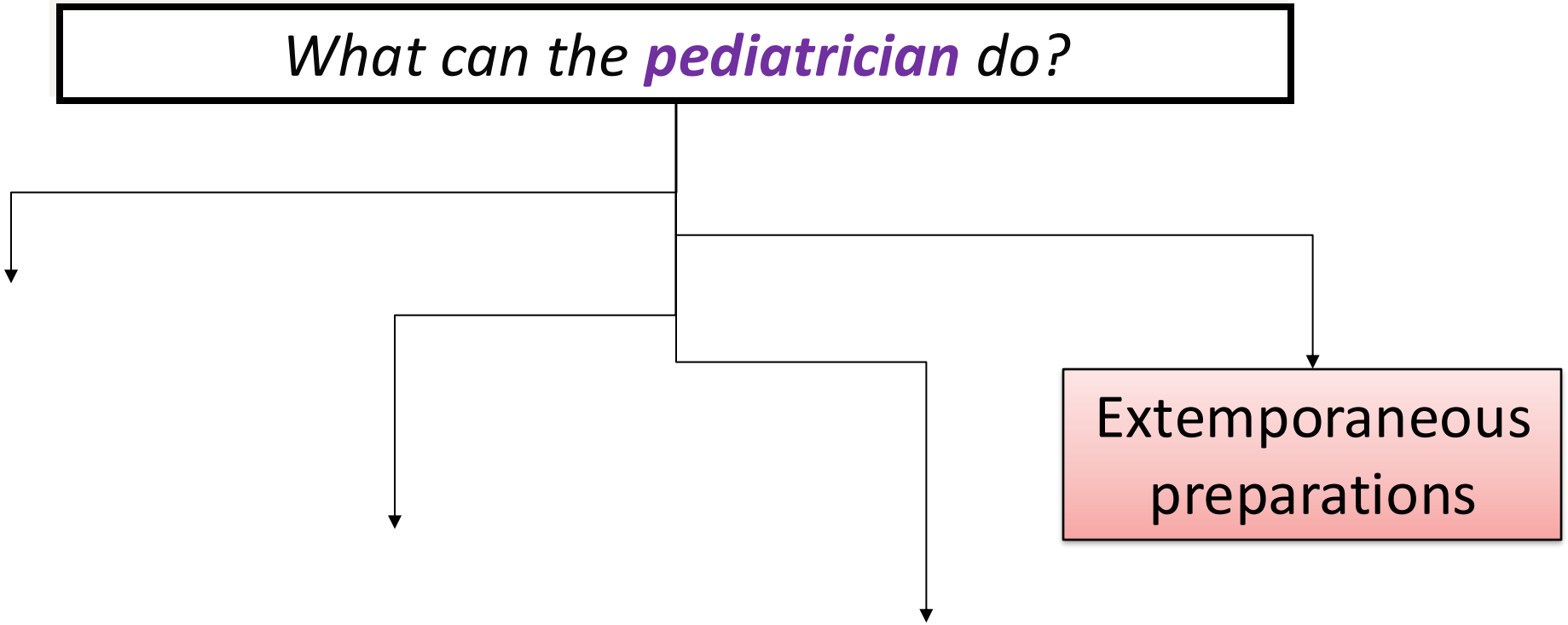
In the Netherland, chenodeoxycholic acid capsules mainly **compounded** (**€ 20,000/patient/year**) for treating patient affected by Cerebrotendinous Xanthomatosis due to the too high cost of the **authorized** medicinal product (**€ 170,000/patient/year**).

Naylor S, Kauppi DM, Schonfeld JM. Drug Discovery World. 2015;16(2):57-72.
Sheldon T. BMJ 2018;361:k2103

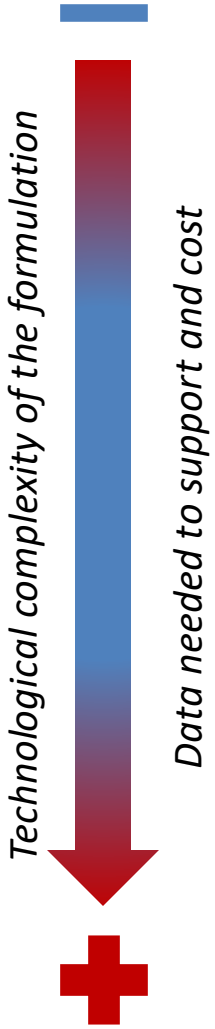
Unmet medical need in pediatrics



Unmet medical need in pediatrics



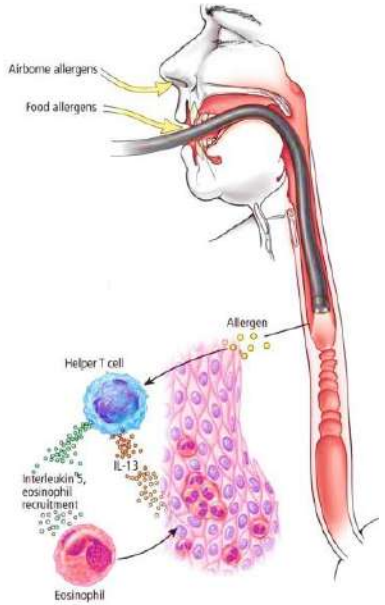
Some examples…



- **Cholic Acid (Capsules)**
- **Budesonide (Orodispersible tablets/oral gels)**

Important role of compounding

Budesonide



Eosinophilic esophagitis (<13/100.000/year)

It is a chronic immune/antigen-mediated oesophageal inflammatory disease associated with oesophageal dysfunction resulting from severe eosinophil-predominant inflammation.

Viscous oral gel

(extemporaneous preparation compounded in hospital pharmacy)

Table 1. Composition (expressed in grams) of the formulations for 240 mL (four doses each of 60 mL).

Excipients	F1P	F1	F2P	F2	F3P	F4P	F4
Budesonide (BU)	-	0.06	-	0.06	-	-	0.06
Xanthan gum (XG)	4.80	4.80	2.40	2.40	3.60	1.80	1.80
Guar gum (GG)	-	-	2.40	2.40	-	1.80	1.80
Sodium saccharin	0.24	0.24	0.24	0.24	0.24	0.24	0.24
Glycerin	29.74	29.74	29.74	29.74	29.74	29.74	29.74
EDTA	0.24	0.24	0.24	0.24	0.24	0.24	0.24
Sodium benzoate	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Water up to (mL)	240	240	240	240	240	240	240

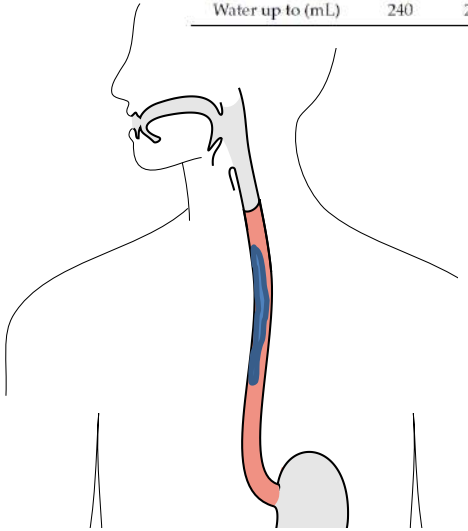


Table 5. Chemical and technological characterization of the modified preparation.

Batch	pH T = 0	Permanence Time (min)	BU Penetrated the Mucosa	
			(mg/g mucosa)	(%)
F1	4.976	28 ± 4	0.790 ± 0.192	0.610 ± 0.132
F2	5.156	29 ± 2	0.783 ± 0.231	0.562 ± 0.152
F4	5.068	25 ± 5	0.901 ± 0.367	0.682 ± 0.270

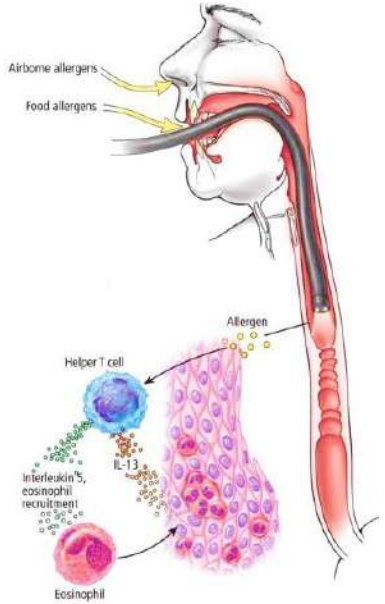

pharmaceutics

MDPI

Article

Mucoadhesive Budesonide Formulation for the Treatment of Eosinophilic Esophagitis

Budesonide



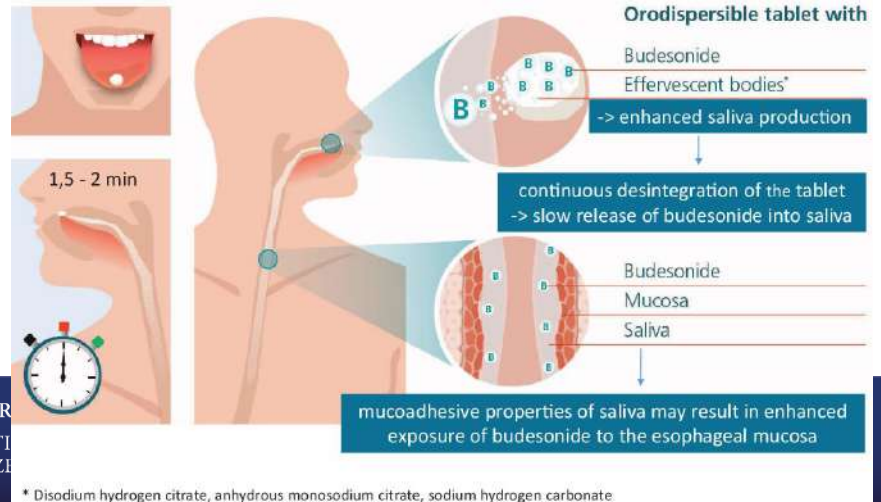
Eosinophilic esophagitis (<13/100.000/year)

It is a chronic immune/antigen-mediated oesophageal inflammatory disease associated with oesophageal dysfunction resulting from severe eosinophil-predominant inflammation.

Jorveza® orodispersible tablet 0.5, 1 mg

(Authorized by EMA in 2018 following an accelerated assessment based on a mix of clinical trials and literature)

[IT price: € 4.13/tablet (1 mg)]



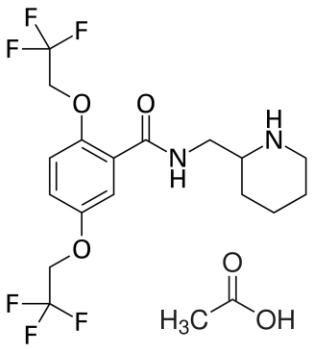
Viscous oral gel

(extemporaneous preparation compounded in hospital pharmacy)

[IT price: € 0.84/gel 4 mL (1 mg)]

Lucendo et al., Therapeutic Advances in Gastroenterology, 2020, 13.

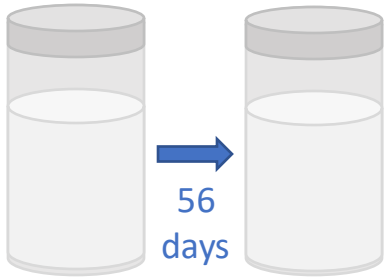
Optimization of oral flecainide formulation



Flecainide acetate

sucrose

methylparaben

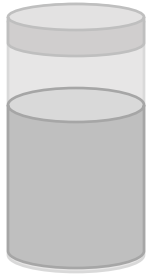


56 days

Chemically, physically and microbiologically stable at 4-40 ° C (10-20 mg/ml).

citrate buffer (or)

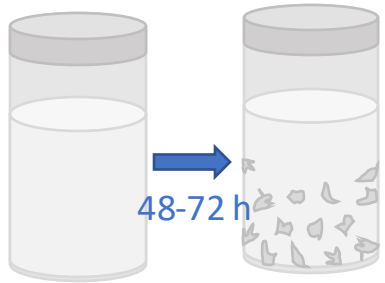
phosphate buffer



Relevant impact on solubility and formation of different salts.

methylparaben

citrate buffer



48-72 h

Development of large non-resuspendable crystals, potential risk of dosing errors.

RE: Flecainide

Dear Davide,

I am pleased to be able to share some good news with you. We have had the results back from the microbiological challenge testing of both F2 and F3:

	10 mg/mL	
Formulation	(F2)	(F3)
Flecainide acetate (Ph. Eur. 1324)	1.00 g	1.00 g
Sucrose	40.00 g	40.00 g
Methyl parahydroxybenzoate	-	0.07 g
Purified water	74.50 g	74.50 g

The results showed that both formulations complied with Ph. Eur. 5.1.3 for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus brasiliensis* and *Zygosaccharomyces rouxii* (<25 UFC/g at Day 14 and Day 28). We will proceed with the preservative-free formulation (F2) and are now arranging for the verification of the HPLC Assay method. If all goes well, we will have a draft monograph ready for publication in Pharmeuropa PaedForm from 1 October - 31 December. I will keep you informed of our progress.

Casiraghi, A. et al. Pharmaceutics. 13.11 (2021)

Cholic acid

Congenital defects of primary bile acid synthesis caused by **3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency** or **Δ4-3-oxosteroid-5β-reductase deficiency** in infants, children, and adolescents 1 month to 18 years of age, and in adults (0.06/10,000)

Extemporaneous preparation

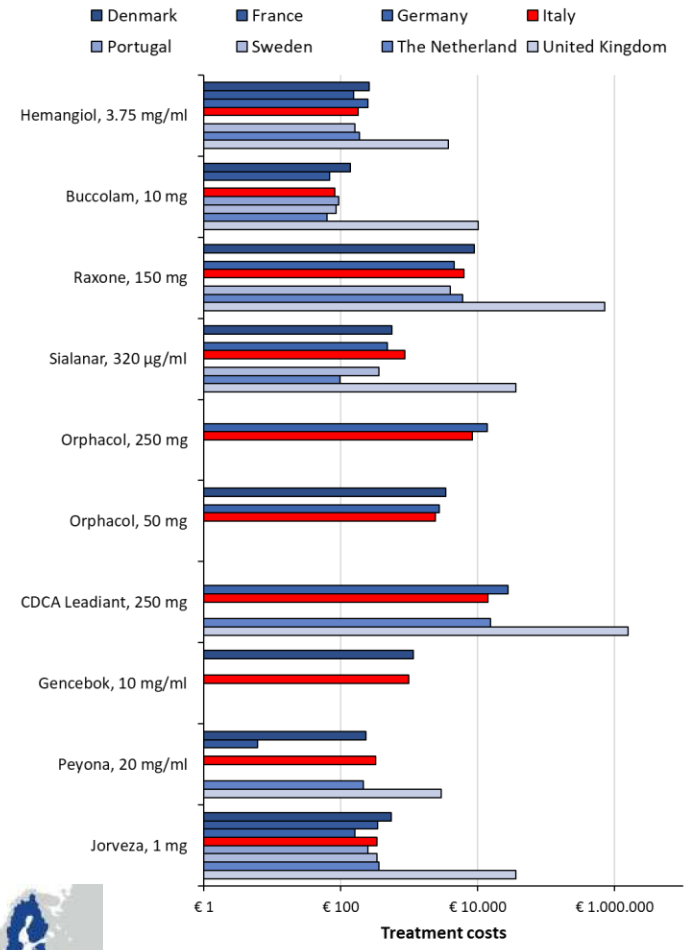
Developed in Early 90s' at the Bicetre Hospital (France) for the treatment of inpatients

250 mg capsule

(Authorized by EMA in 2013 on the basis of literature)

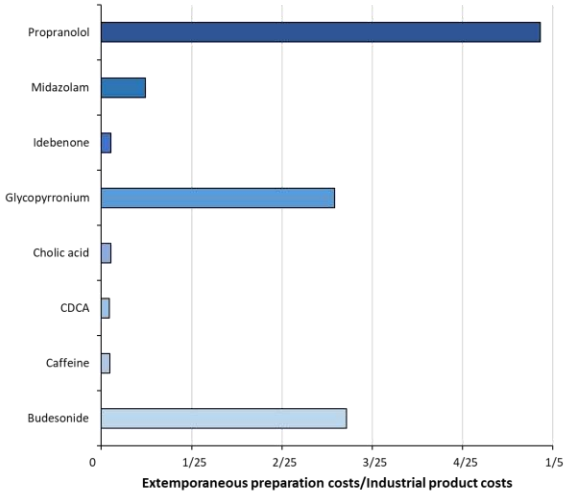
Authorised medicinal development

Repurposing vs compounding



Paediatric medicinal products

API	MEDICINAL PRODUCTS	STRENGTHS, PHARMACEUTICAL FORM
Budesonide	Jorveza	1 mg, orodispersible tablet
Caffeine	Peyona (previously Nymusa)	20 mg/ml, solution for infusion and oral solution
	Gencebok	10 mg/ml, solution for infusion and oral solution
CDCA	Chenodeoxycholic acid Leadiant	250 mg, capsule
Cholic acid	Orphacol	50 mg, capsule
Glycopyrronium	Sialanar	320 µg/ml, oral solution
Idebenone	Raxone	150 mg, tablet
Midazolam	Buccolam	10 mg, oral solution in a pre-filled syringe
Propranolol	Hemangiol	3.75 mg/ml, oral solution



Journal of Drug Delivery Science and Technology 82 (2023) 104349

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Cases of drug repositioning in children's orphan drugs: Licenced drugs versus unlicenced magistral preparations

Davide Zanon [a], Umberto M. Musazzi [b,*], Mario Cirino [a], Giada Bennati [a], Antonella Casiraghi [b], Natalia Maximova [a], Egidio Barbi [a,c], Paola Minghetti [b]

[a] Institute for Maternal and Child Health IRCCS Burlo Garofolo, via dell'Istria, 65, 34137, Trieste, Italy
[b] Department of Pharmaceutical Sciences, Università degli Studi di Milano, via G. Colombo 71, 20133, Milan, Italy
[c] Pediatric Department, University of Trieste, Trieste, Italy

Key recommendations for organisations of healthcare professionals

Extemporaneous preparations

Organisations (in cooperation with pharmacists and national authorities) should liaise with health authorities to **issue guidance on safe extemporaneous preparations of medicines** which are in short in supply and when there are no remaining alternatives left in the market and to help develop protocols where needed.

Quality Assurance

The quality and consequently the safety and efficacy of the preparation depend on the correct use of the **components**, the calculations performed, the accuracy and precision of the weighings and volumes, the adherence to the **procedures** and the **appropriate operating conditions**.

Good compounding practice

Good Preparation Practices are technical guidelines to be respected in order to obtain a medicinal product of the required quality

Good practice guidance for patient and healthcare professional organisations on the prevention of shortages of medicines for human use - 2022

Key recommendations for healthcare professional organisations

Extemporaneous preparations

Organisations (in cooperation with pharmacists and national authorities) should liaise with health authorities to issue guidance on safe extemporaneous preparations of medicines which are in short in supply and when there are no remaining alternatives left in the market and to help develop protocols where needed.

Guidelines and operating instructions - Italian scientific compounding pharmacists society

Compounding when an industrial medicine is not available:

- DIAZEPAM for rectal use: national shortage Micropam® formulations for magistral preparations – *Rev.01 of 19/03/2021*
- Operational Instruction for the preparation of CAPSULES OF MEXILETINA HCl 200 mg – *Rev.01 of 20/10/2022*
- Operational Instruction for the compounding of ONDANSETRON LIQUID PREPARATION FOR ORAL USE– *Rev.01 of 26/09/2022*
- Operational Instruction for the preparation of IBUPROFENE ORAL SUSPENSION– *Rev.01 of 29/07/2022*
- *…..and more*

Manipulation a medicine to change the dosage form:

- Operational Instruction for the preparation of master's preparations based on HYDROXYchloroquine – *Rev.01 of 01/02/2021*
- Operational Instruction for the preparation of chloroquine-based magistral preparations– *Rev.01 of 29/01/2021*
- Operational Instruction for the preparation of suspensions containing Darunavir + Cobicistat – *Rev.00 of 26/03/2020*
- Operational instruction for the preparation of magistral preparations based on antiretrovirals to be administered to patients unable to swallow whole solid forms – *Rev.01 of 18/03/2020*

DIAZEPAM PER USO RETTALE: CARENZA NAZIONALE Micropam®
FORMULAZIONI PER PREPARAZIONI MAGISTRALI

Rev.01 del 19/03/2021

DIAZEPAM for rectal use: national shortage Micropam® formulations for magistral preparations

Since 2020, the industrial medicine Micropam® (Aurobindo Pharma s.r.l.) has been included in AIFA's list of medicines in shortage as it is available in quantities that are not sufficient to fully satisfy the national demand.

SOP containing 6 possible formulation alternatives and related preparation, stability and packaging processes

*«Alternatively, if your pharmacy carries out galenic production, **it is possible to support patients by proposing to prepare a galenic medicine, referring to the Information reported on** "DIAZEPAM PER USO RETTALE: CARENZA NAZIONALE Micropam® FORMULAZIONI PER PREPARAZIONI MAGISTRALI" prepared by the SIFO and SIFAP Clinical Galenic Area-Rev.01 of 19/03/2021-, which provides technical and practical indications on the preparation of galenic preparations for rectal administration based on diazepam.»*

AIFA
Agenzia Italiana del Farmaco
Ufficio Qualità dei Prodotti e Contrasto al Crimine Farmaceutico

Roma, 21 maggio 2021

NOTA INFORMATIVA PER LA GESTIONE DELLA CARENZA DI MICROPAM®

Gentile Dottoressa, Egregio Dottore,
con questa lettera l'Agenzia Italiana del Farmaco, con il supporto delle Associazioni di categoria, intende condividere importanti informazioni utili a supportare i pazienti in questa fase di carenza dei medicinali Micropam® 10 mg/2,5 ml soluzione rettale, 4 contenitori monodose (AIC 029417021), e Micropam® 5 mg/2,5 ml soluzione rettale, 4 contenitori monodose (AIC 029417019), di titolarità di Aurobindo Pharma (Italia) S.r.l.
Come riportato nell'elenco dei medicinali carenti pubblicato sul portale dell'Agenzia (disponibile alla pagina: https://www.aifa.gov.it/farmaci-carenti), i due medicinali su citati sono attualmente carenti per problemi produttivi; al momento non è ancora nota la data di ripristino della produzione e della distribuzione.
Ulteriori informazioni sono state fornite dall'Agenzia con la pubblicazione di un comunicato, costantemente aggiornato, rinvenibile al seguente link: https://www.aifa.gov.it/-/informazioni-sulla-carenza-dei-medicinali-buccolam-e-micropam-.
In considerazione della criticità della carenza di Micropam® 10mg/2,5ml soluzione rettale AIC 029417021 e Micropam® 5mg/2,5ml soluzione rettale AIC 029417019, l'Agenzia ha autorizzato il titolare AIC Aurobindo Pharma (Italia) S.r.l. all'importazione dall'estero di confezioni per entrambi i dosaggi; tali confezioni possono essere distribuite nel territorio nazionale solo attraverso il canale ospedaliero o i servizi farmaceutici territoriali facenti capo alle ASL.
La preghiamo, quindi, di voler condividere le informazioni su riportate con i pazienti che dovessero rivolgersi alla sua farmacia per l'approvvigionamento di Micropam®.

Agenzia Italiana del Farmaco · Via del Tritone, 181 - 00187 Roma · (+39) 06.59.78.401 · www.aifa.gov.it

*How to **compound** an extemporaneous preparation?*

SOP containing information on the correct preparation of medicines in shortage

Some example…

Diazepam
for rectal use


DIAZEPAM PER USO RETTALE: CARENZA NAZIONALE Microgram®
FORMULAZIONI PER PREPARAZIONI MAGRISTRALI

Rev.01 del 19/03/2021

Ondansetron,
liquid for oral use


Istruzione Operativa per l'allestimento di Ondansetron liquido per uso orale
(4 mg/5 mL in flacone da 50 mL)

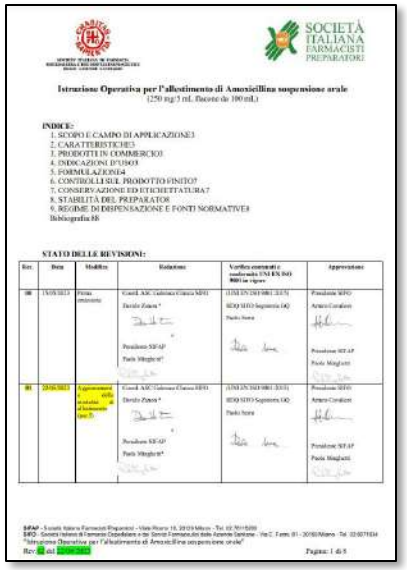
Rev.01 del 19/03/2021

Ibuprofen
oral solution


Istruzione Operativa per l'allestimento di Ibuprofene sospensione orale

Rev.01 del 29/07/2022

Amoxicilline
oral suspension


Istruzione Operativa per l'allestimento di Amoxicillina sospensione orale
(250 mg/5 mL flacone da 100 mL)

Rev.01 del 29/07/2022

Mexiletina HCl,
capsules


Istruzione Operativa per l'allestimento di capsule di Mexiletina HCl 200 mg

Rev.01 del 20/10/2022

Thank you for your kind attention!

DRUG DELIVERY &
REGULATORY AFFAIRS
UNIMI GROUP

Paola Minghetti
Francesco Cilurzo

Antonella Casiraghi
Chiara Gennari
Francesca Selmin

Silvia Franzè
Umberto M. Musazzi
Andrea Marcelluzzi
Paolo Rocco
Sara Manellari
Giulia Anderluzzi
Elisa Vettorato

Paola Volontè
Chiara Meazzini
Giorgia Frigerio
Camilla Pozza
Marta Madeo

All the PhD and master degree students joined us in these more than 20 years