Quality & Risk Assessment of Medicines for Children

23rd Congress of the EAHP
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Disclosure

Conflict of interest: none

Self-assessment questions

1. Risk assessment is possible for Off label use of drugs in children:

a) always b) not always

2. Before approaching an extemporaneous preparation, Risk assessment is necessary:

a) True b) False

3. Excipients never involve metabolism:

a) True b) False

Learning objectives

- Use of Off label drugs must be under control: what to do
- What to assess in an extemporaneous preparation
- How to know the excipients

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Two faces of the same coin

Risk assessment

Safety evaluation

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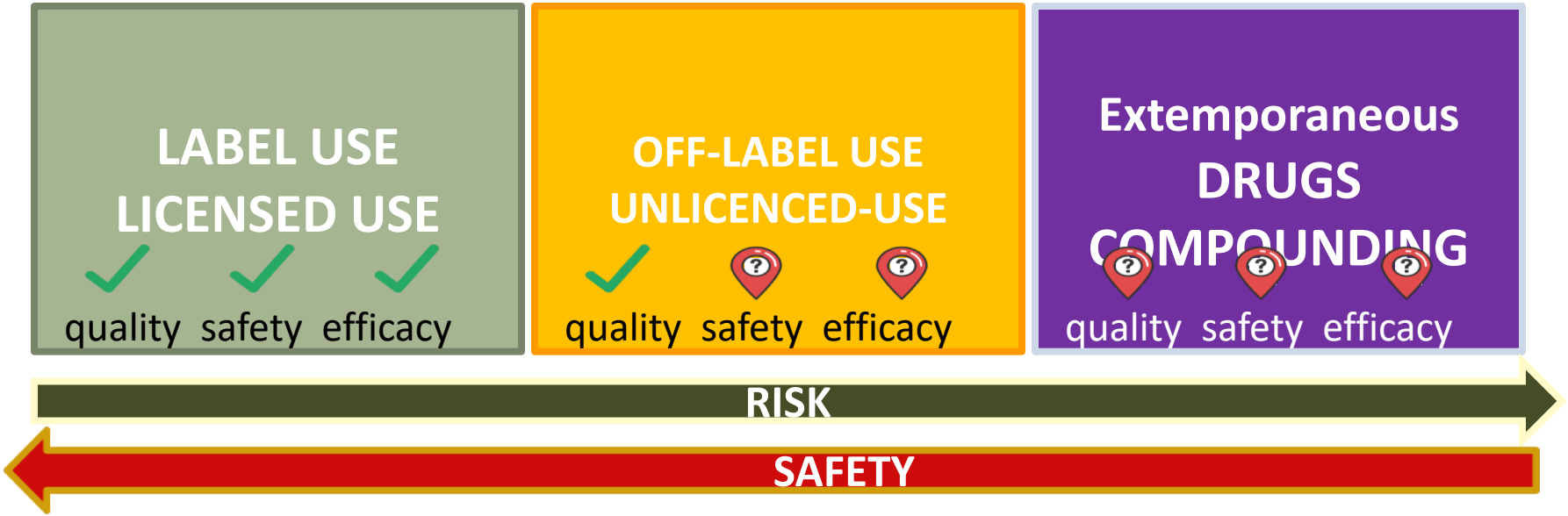
Safety knowledge

3. THE ESSENTIAL ROLE OF SAFETY MONITORING IN THE LIFE-CYCLE OF A MEDICINE

The benefit-risk assessment of any kind of medicine treatment is essential. No assessment of the treatment is, however, possible without safety data and knowledge. The "trial and error" principle is not acceptable in an extremely vulnerable population.

http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf



Drugs & Children: state of art

"There is a gap between the availability of children's medicines and the actual need. That gap is global and must be addressed"

Howard Zucker

BMJ. 2007 Dec 15; 335(7632): 1227.

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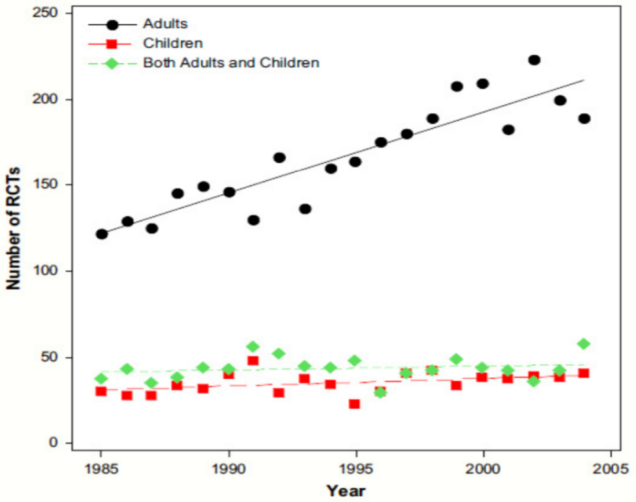
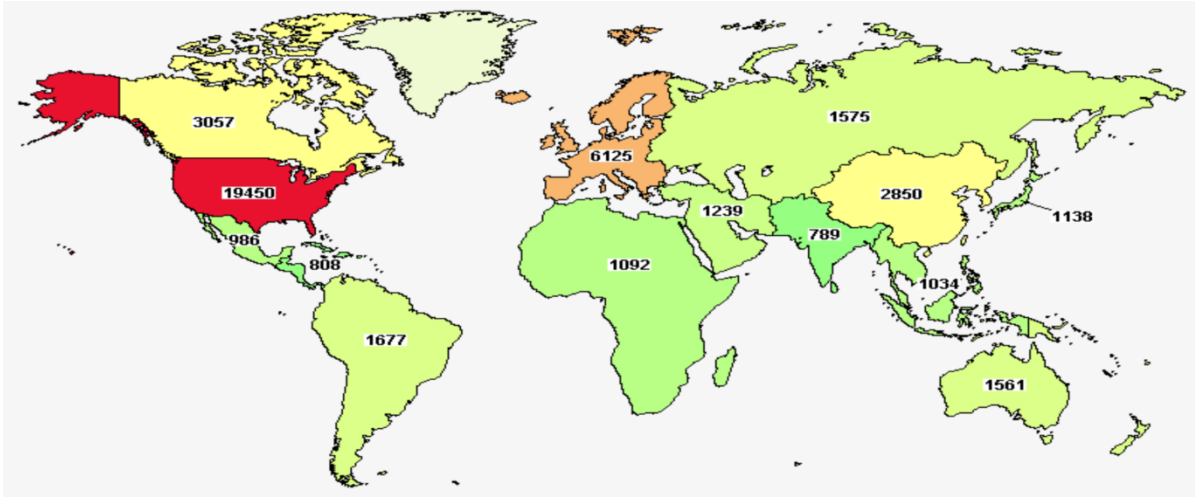
Pediatric RCTs: a photography



1985-2004 (Cohen E., 2007)



Interventional Clinical Trial with results: **4972 (birth to 17); 26398 (>17).** Clinical trials.gov (last access 20 feb 2018)

2006-2011: 59.9% of the disease burden was attributable to children, but only 12.0% (292/2440) of trials were pediatric ($P < .001$). Among pediatric trials, 58.6% were conducted without industry funding compared with 35.0% of adult trials ($P < .001$).

Bourgeois, F. T., Murthy, S., Pinto, C., Olson, K. L., Ioannidis, J. P. A., & Mandl, K. D. (2012). Pediatric Versus Adult Drug Trials for Conditions With High Pediatric Disease Burden. *Pediatrics*, *130*(2), 285–292. http://doi.org/10.1542/peds.2012-0139

Off Label use

Off-Label Category	Description
Age	Drug not recommended in the SmPC below a certain age
Weight	Drug not recommended in the SmPC for children below a certain weight
Absence of Paediatric Information	No mention at all in the SmPC regarding paediatric use
Lack of paediatric clinical data	Stated lack of evidence of efficacy and safety in paediatric patients in the SmPC
Contraindication	Statement in the SmPC that the drug is contraindicated in children
Indication	Drug prescribed for indications outside of those listed in the SmPC
Route of Administration	Drug administered by a route not described in the SmPC

Mir AN, Md. Geer I: Off-Label Use of Medicines in Children. Int J Pharm Sci Res 2016; 7(5): 1820-28.doi: 10.13040/IJPSR.0975-8232.7(5).1820-28.

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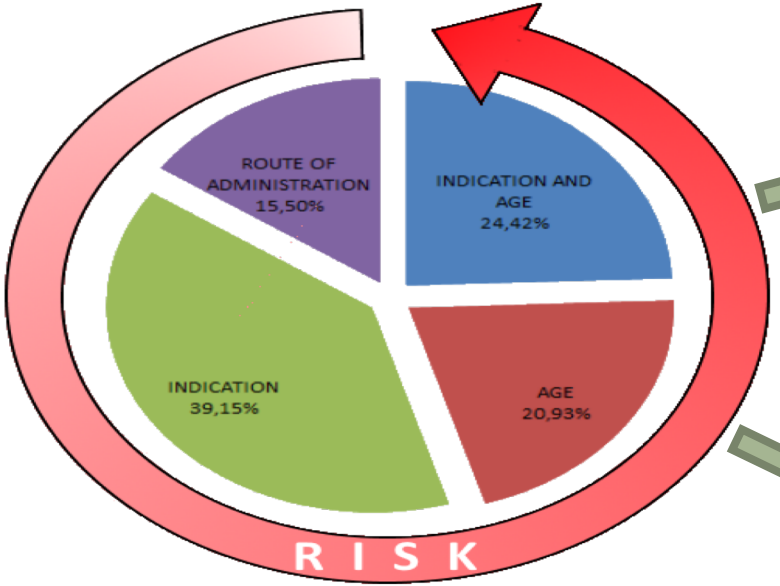
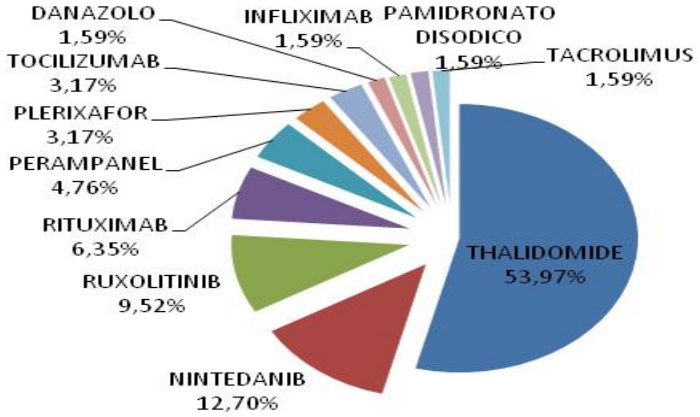
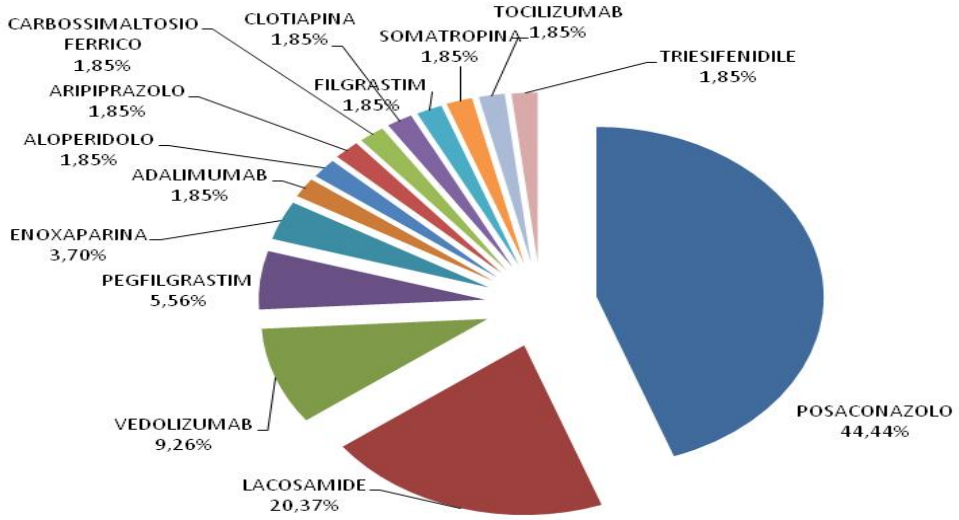
Our off-label experience (2017)







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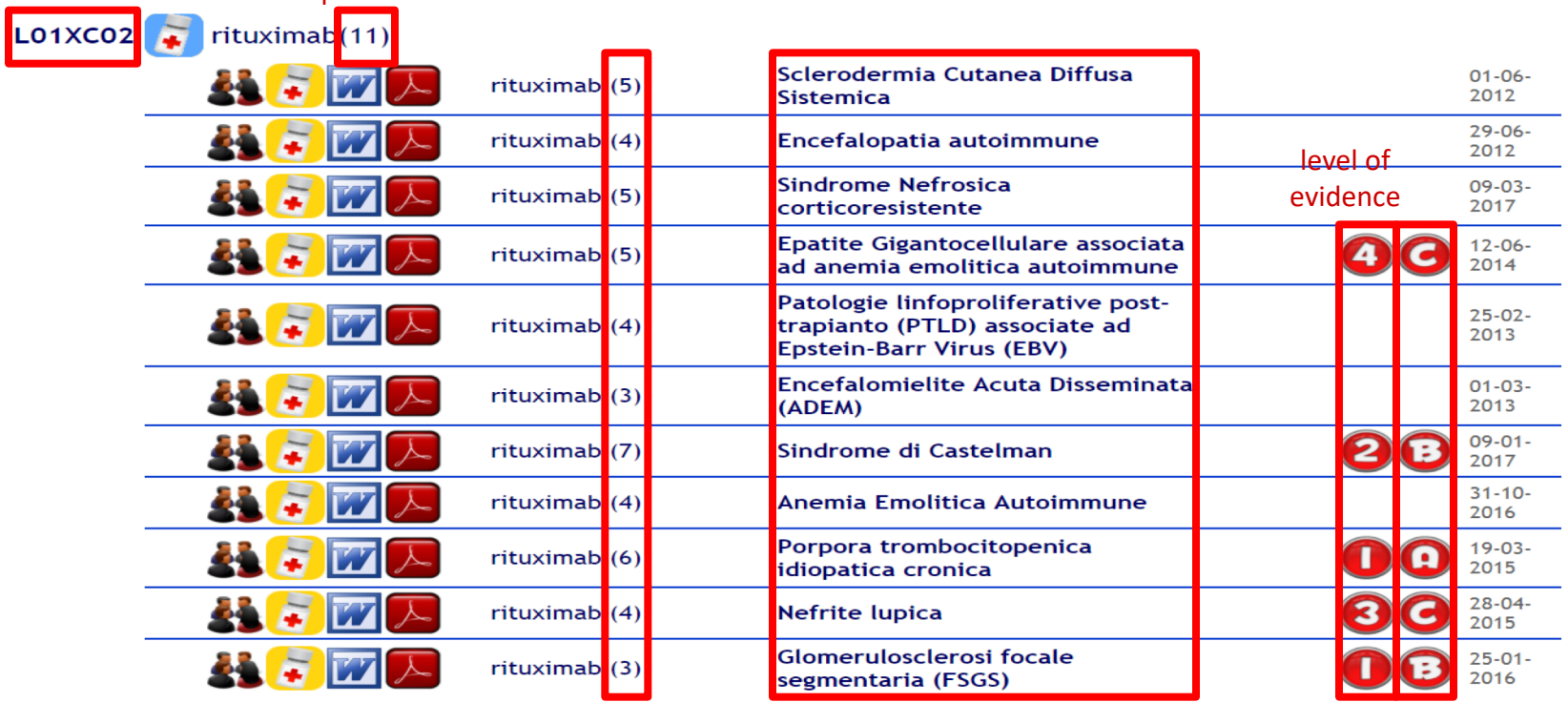
Step 1: build the database

LABEL USE LICENCED USE quality safety efficacy
OFF-LABEL USE UNLICENCED-USE quality safety efficacy
extemporaneous DRUGS COMPOUNDING quality safety efficacy

ATC

Number of different indications for which the drug is prescribed



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LABEL USE LICENCED USE quality safety efficacy
OFF-LABEL USE UNLICENCED-USE quality safety efficacy
extemporaneous DRUGS COMPOUNDING quality safety efficacy

Which data?

Sirolimus

Indicazione Off Label: **Sindrome autoimmune linfoproliferativa(ALPS)**

Titolo dello studio	Autoimmune Lymphoproliferative Syndrome (GeneReviews)	Advances in the management and understanding of autoimmune lyphoprolifertaive syndrome (ALPS) (2009, Br J Haematol)	Rapid Regression of Lymphadenopathy upon Rapamycin Treatment in a Child With Autoimmune Lymphoproliferative Syndrome (2009, Pediatr Blood Cancer)	Treatment with sirolimus results in complete responses in patients with autoimmune Lymphoproliferative syndrome (2009, Br J Haematol)	Immunomodulatory drugs in autoimmune lymphoproliferative syndrome (ALPS). Tommasini A et al. Pediatr Blood Cancer. 2012 Feb;58(2):310.	New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Teachey DT. Curr Opin Pediatr. 2012 Feb;24(1):1-8	Sirolimus is effective in relapsed/refractory autoimmune cytopenias: results of a prospective multi-institutional trial (Blood, 2016)
Tipo di patologia	Sindrome Linfoproliferativa Autoimmune (ALPS)	Sindrome Linfoproliferativa Autoimmune (ALPS)	Sindrome Linfoproliferativa Autoimmune (ALPS)	Sindrome Linfoproliferativa Autoimmune (ALPS)	Sindrome autoimmune linfoproliferativa (ALPS)	sindrome autoimmune linfoproliferativa (ALPS)	Citopenie autoimmuni, tra cui la Sindrome autoimmune linfoproliferativa (ALPS)
Fase sperimentale	No	No	No		No	no	II/III
Disegno dello studio	Review	Review	Case report	Case series	Letter to editor	review	Studio prospettico multicentrico in aperto
Intention To Treat	No	No	No	No	no	no	No
Gruppi	No	No	No	No	no	no	No
Criteri di inclusione	No	No	Paziente pediatrico affetto da ALPS trattato senza successo con altre terapie	Pazienti pediatrici con ALPS refrattaria ad altri trattamenti (corticosteroidi e MMF)	paziente con ALPS	studi che approfondiscono l'eziogenesi, la diagnosi ed i possibili trattamenti della ALPS	Pazienti affetti da citopenie autoimmuni di età > 12 anni < 40 anni
Numerosità	No	No	1 bambina	6 bambini	1 pz	no	30 bambini

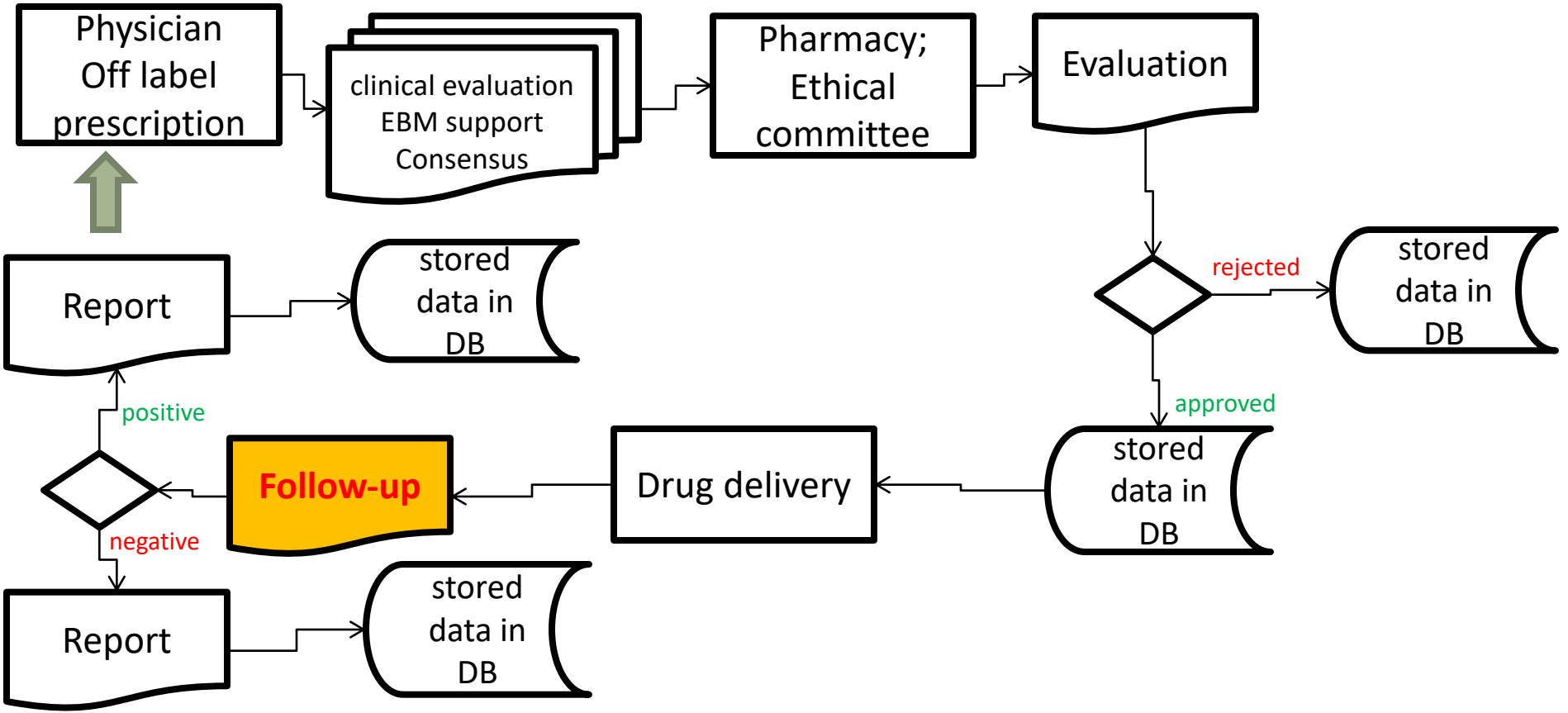
approved/rejected

Follow-up

number of patients

. . .

Step 2: how to use it



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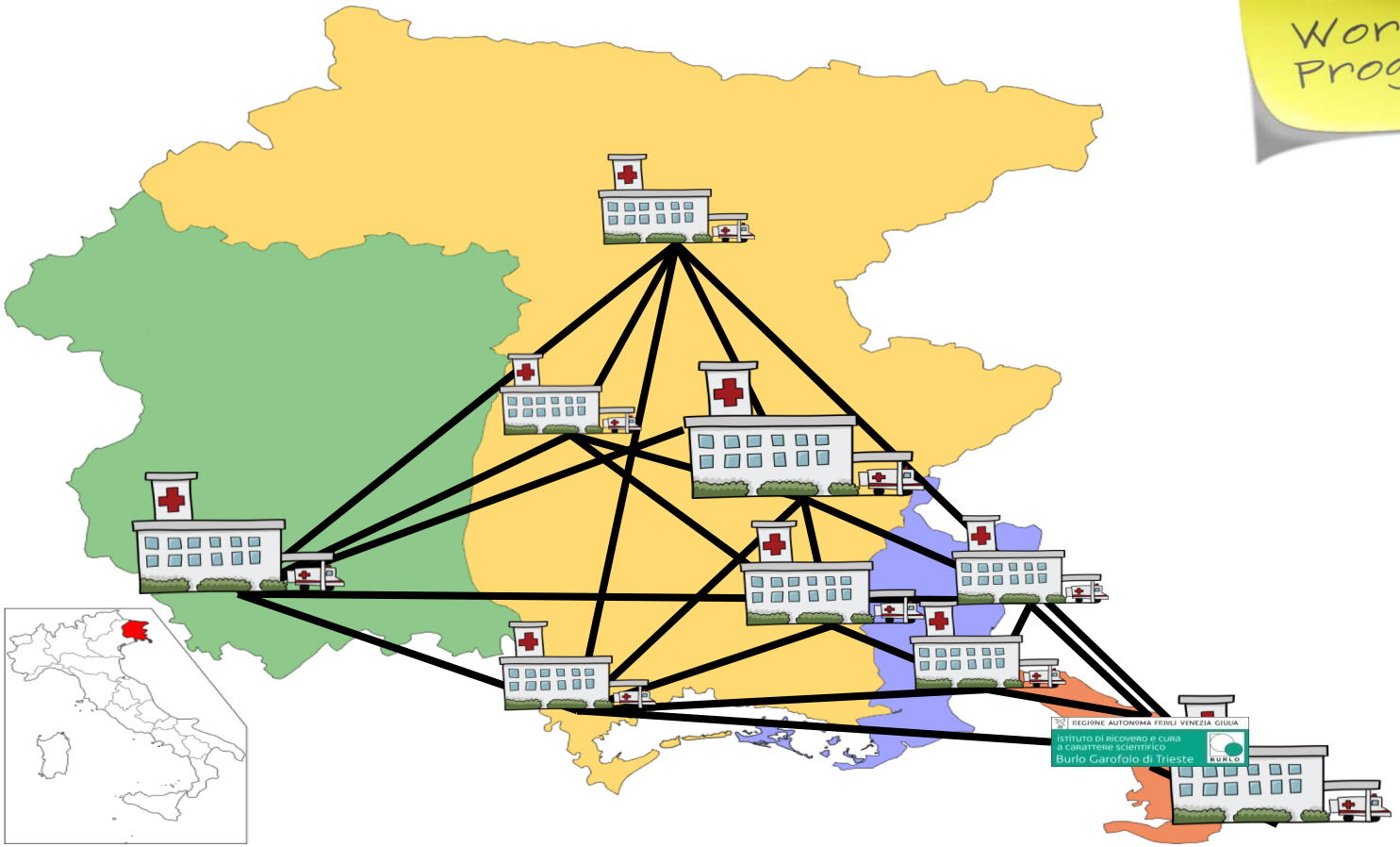
Step 3: share it!

LABEL USE LICENCED USE quality safety efficacy

OFF-LABEL USE UNLICENCED-USE quality safety efficacy

extemporaneous DRUGS COMPOUNDING quality safety efficacy

Work in Progress



Take Home Message

When an off label drug is administered (to a child), if a **follow-up** is not carried out, nobody will never know whether that treatment was necessary or not.

Something about compounding

3. Added value of pharmacy preparations and responsibilities of health care professionals

Pharmacy preparations are of **added value** if, due to medical, pharmaceutical or personal reasons, they are needed by a specific patient or by specific population groups with particular needs.

Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients

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Childhood Vs Adulthood What change?

LABEL USE LICENCED USE quality safety efficacy
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extemporaneous DRUGS COMPOUNDING quality safety efficacy

ABSORPTION

- Gastric pH less acidic; by 3 year, acid per kg of body weight similar to adults
- Gastric emptying is slowed; reaches adult levels in 6-8 months

EXCRETION

- Kidney immaturity affects glomerular filtration rate and tubular secretion
- Decreased perfusion rate of the kidneys
- Renal clearance reaches adult values after 2 years

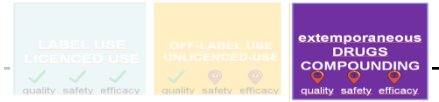
METABOLISM

- Liver immature; does not produce enough microsomal enzymes
- Older children may have increased metabolism, requiring higher dosing

DISTRIBUTION

- Total body water 70%to80% in full-term infants, 85% in premature newborns, 64%in children 1 to 12 years, similar to adults
- Decreases level of protein binding
- Immature blood-brain barrier

Immature functions



Overview of developmental features that can affect pharmacokinetics

Developmental feature	Relevant age period	TK implications
Chemical absorption		
Increased oral absorption of certain agents (e.g., metals)	birth through weaning	potential for greater chemical uptake
Greater dermal absorption	primarily in premature neonates	potential for greater chemical uptake
Greater inhalation rate per respiratory surface area	birth through several years	potential for greater local dose in respiratory tract
Body composition	birth through 3 months	less partitioning and retention of lipid soluble chemicals; larger volume of distribution (V_d) for water-soluble chemicals
Lower lipid content		
Greater water content		
Larger liver weight/body weight	birth–6 years but largest factor in first 2 years	greater opportunity for hepatic extraction and metabolic clearance; however, also greater potential for activation to toxic metabolites
Immature enzyme function	birth–1 year but largest factor in first 2 months	slower metabolic clearance of many drugs and environmental chemicals; less metabolic activation but also less removal of activated metabolites
Phase I reactions		
Phase II reactions		
Larger brain weight/body weight; greater blood flow to CNS; higher BBB permeability	birth–6 years but largest factor in first 2 years	greater CNS exposure, particularly for water-soluble chemicals which are normally impeded by BBB; larger V_d
Immature renal function	birth–2 months	slower elimination of renally cleared chemicals and metabolites
Limited serum protein binding capacity	birth–3 months	potential for greater amount of free toxicant and more extensive distribution

Pediatric Pharmacokinetic Data: Implications for Environmental RiskAssessment for Children.Gary Ginsberg, Dale Hattis, Richard Miller, and Babasaheb Sonawane, PEDIATRICS Vol. 113 No. 4 April 2004

Only one example: Metabolism

Different half-lives (hours) between neonates, infants, children and adults.

Isoenzyme	Drug	Neonate	Infant	Children	Adult
CYP1A2	Caffeine	95	7	3	4
	Theophylline	24-36			3-9
CYP 2C9	Phenytoin	30-60	2-7	2-20	20-30
CYP2C19	Phenobarbital	70-500	20-70	20-80	60-160
	Diazepam	22-46	10-12	15-21	24-48
CYP3A	Carbamazepine	8-28	–	14-19	16-36
	Lidocaine	2,9-3,3	–	1-5	1-2,2

Isoenzyme	Pediatric population activity	Drug class	Examples
CYP1A2	↓ until 2 years	Antidepressant Bronchodilator Diuretic	Duloxetine Theophylline Triamterene
CYP2C9	↓ until 1-2 years	Anticoagulant Antidepressant Nonesteroidal antiinflammatory	Warfarin Phenytoin Diclofenac,ibuprofen, naproxen, tolbutamide
CYP2C19	↓ until 10 years	Antidepressant Benzodiazepine Proton pump inhibitor	Citalopram, sertraline Diazepam Lansoprazole, omeprazole, pantoprazole
CYP2D6	↓ until 12 years	Analgesic Antidepressant Antihistamine Antipsychotic ß-Blocker	Codeine, tramadol amitriptyline, desipramine, doxepin, imipramine, fluoxetine, nortriptyline, paroxetine, venlafaxine Diphenhydramine Risperidone Labetalol, metoprolol
CYP3A4	↓ until 2 years	Analgesic Antiepileptic Antifungal Antihistamine Antiretroviral Benzodiazepine	Alfentanil, fentanyl Carbamazepine Itraconazole, ketoconazole loratadine Indinavir, lopinavir ritonavir, saquinavir Alprazolam, midazolam
MAO A	↑ until 2 years		
MAO B	≈		
N-Methyltransferases	≈		
UGTs	↓ until 7-10 years	Analgesic Antiepileptic Benzodiazepine	Morphine Lamotrigine Clonazepam, lorazepam
NAT2	↓ until 1-4 years	Antihypertensive Antiinfectious	Hydralazine Isoniazid

Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults.Eva Fernandez, Raul Perezz, Alfredo Hernandez, Pilar Tejada, Marta Arteta, and Jose T. Ramos. Pharmaceutics. 2011 Mar; 3(1): 53–72.

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Before risk assessment

Risks associated with Extemp dispensing

- Unstandardised formulations
- Calculation errors
- Formulation failure (OD or UD)
- Uniformity of dose
- Binding of drug to excipients
- Micro contamination
- Staff issues
- Organoleptic issues
- Measurement & labelling errors
- Use of concentrated raw materials e.g. concentrated chloroform water
- Toxicity & contamination of raw materials
- Bioavailability issues
- Safety & efficacy untested
- QA/GMP issues

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When compounding

1. Know your patient
2. Talk about him with his physician
3. Assess the risk of compounding
4. Compound the best formulation for best compliance but never let affected drug stability
5. Make drug use safe at home

4. Preparation process

All pharmacy-prepared medicinal products should be prepared using an appropriate quality assurance system. Before preparation, a risk assessment should always be carried out in order to define the level of the quality assurance system which should be applied to the preparation of the medicinal product.

Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients

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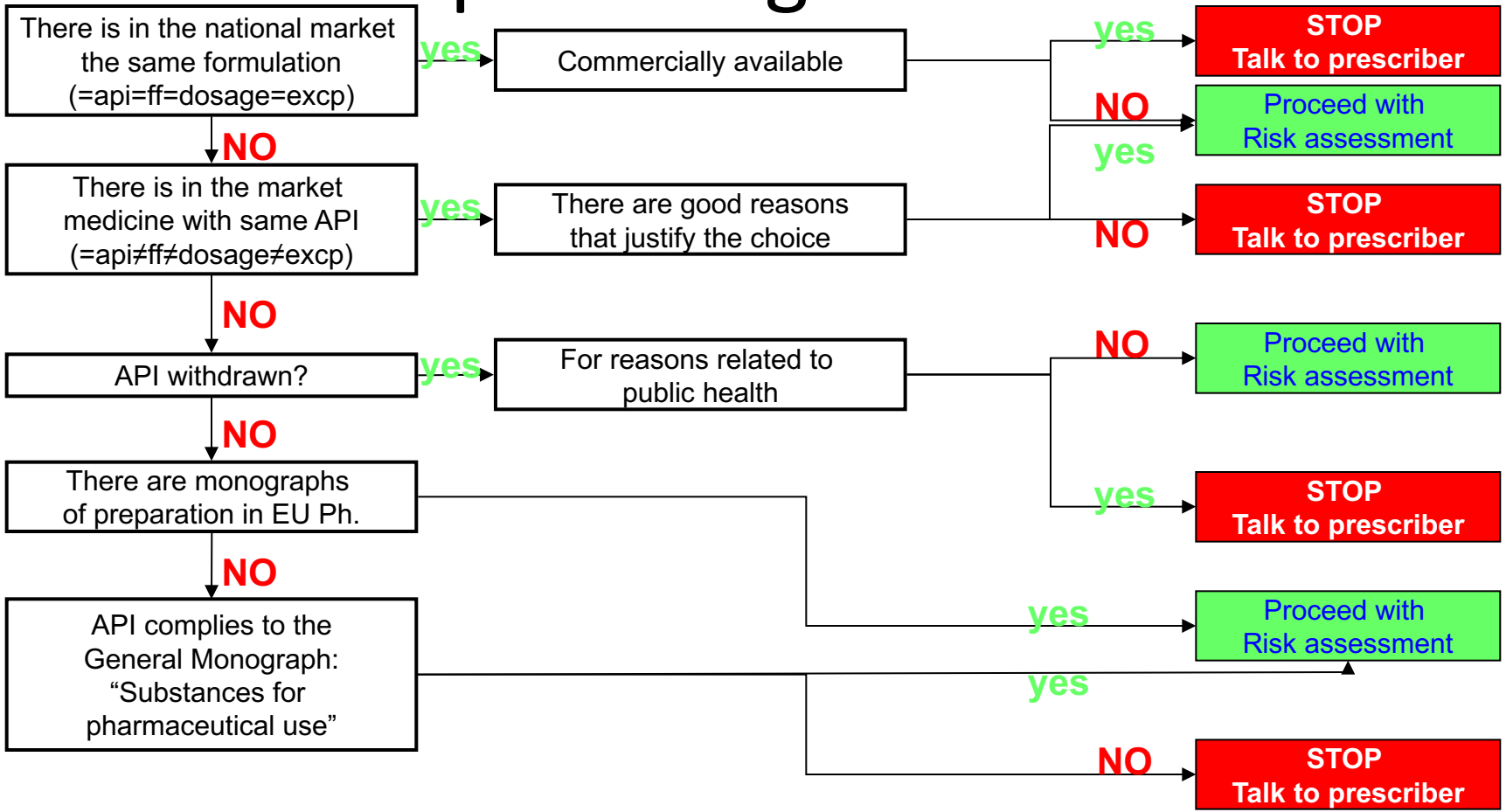
Compounding & risk assessment



Position Paper SIFO-SIFAP - https://www.sifap.org/

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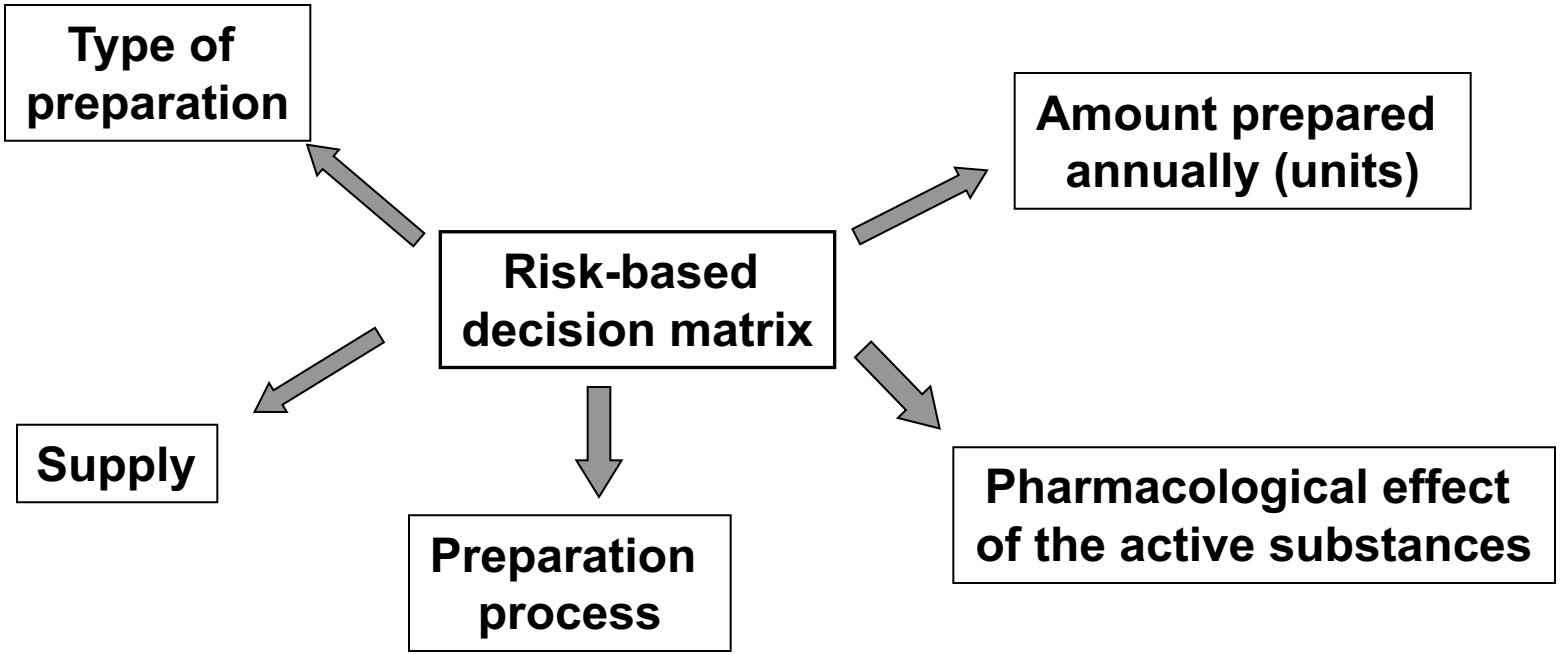
Risk assessment



It is recommended that the **GMP** Guide be used as a reference for an appropriate quality system for "**high-risk preparations**", and that the **PIC/S GPP** Guide be used for "**low-risk preparations**". The application of other guidelines with an equivalent quality level is possible, depending on national legislation or guidance.

Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients

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After risk assessment

Risks associated with Extemp dispensing

- ✓ Unstandardised formulations
- ✓ Calculation errors
- ✓ Formulation failure (OD or UD)
- ✓ Uniformity of dose
- Binding of drug to excipients
- ✓ Micro contamination
- Staff issues
- Organoleptic issues
- ✓ Measurement & labelling errors
- Use of concentrated raw materials e.g. concentrated chloroform water
- ✓ Toxicity & contamination of raw materials
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- Safety & efficacy untested
- ✓ QA/GMP issues

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Choose the API

Choose the excipients

Are you sure about excipients safety?

Are they certainly inert?

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the choice

- **B. Potential Excipients Intended for Short-Term Use**

- use in products that are limited by labeling to clinical use of 14 or fewer consecutive days per treatment

- **C. Potential Excipients Intended for Intermediate Use**

- more than 2 weeks but less than or equal to 3 months per treatment

- **D. Potential Excipients Intended for Long-Term Use**

- more than 3 months in a given patient (either as a single treatment episode or as a result of multiple courses of therapy to treat a chronic or recurrent condition).

Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients; U.S. Department of Health and Human Services Food and Drug Administration ; Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) May 2005 Pharmacology/Toxicology

Table 3 Excipients known to be harmful and potentially harmful to neonates used in study population, their applications and safety concerns

Excipient	Functional category†	Applications and typical concentration ranges†	Safety concern
Known to be harmful to neonates			
Parabens (methyl- and propyl parahydroxybenzoate)	Antimicrobial	Antimicrobial activity against yeasts and molds. Combination of Methyparaben (0.18%) and propylparaben (0.02%) for parenteral formulations. In combinations with propylene glycol (2-5%)/ imidurea	Hyperbilirubinemia in neonates. Irritant in injections / ophthalmic drugs. Hypersensitivity reactions. [18,19]
Saccharin sodium	Sweetening	0.02-0.5% w/w*	Urticaria with pruritus and photosensitivity reactions. [14]
Sodium benzoate	Antimicrobial, tablet / capsule lubricant	0.02-0.5% in oral medicines; 0.5% in parenteral medicines; 2-5% w/w tablet lubricant	Contact urticaria. [21] Topical irritant. Increased risk of hyperbilirubinaemia in neonates.
Benzyl alcohol	Antimicrobial, solvent	Up to 2% v/v* in parenteral/oral preparations, typically 1% v/v. 5% v/v and up used as solubilisers. 10% v/v local anaesthetic properties (parenterals, ophthalmic solutions, oitments)	Headache, vertigo, nausea, vomiting, diarrhea, metabolic acidosis, seizures, gasping. Hypersensitivity; fatal toxic syndrome in premature infants. Pain on injection, [8,18-20]
Benzalkonium chloride	Antimicrobial, antiseptic, solubilising, wetting	Ophthalmic preparations – preservative, 0.01-0.02% w/v*; In combination with other preservatives	Ototoxic when applied to ear, skin irritation and hypersensitivity Bronchoconstriction in asthmatics. Eye irritation. [18-20]
Propylene glycol	Antimicrobial, humectant, plasticizer, solvent, stabilizing, water-miscible cosolvent	Humectant – topical – approx.15%. Preservative –solutions / semisolids – 15-30%. Solvent or cosolvent: aerosol solutions 10-30%, oral solutions 10-25%, parenterals 10-60%, topical 5-80%	Skin irritation. Central nervous system (CNS) depression. High doses - cardiovascular, hepatic, respiratory adverse events. [18-20]
Polysorbate 80	Dispersing, emulsifying, non-ionic surfactant, solubilising, suspending, wetting	Emulsifying: alone in oil-in-water emulsions 1-15%; in combination 1-10%. To increase water-holding prop of ointments 1-10%. Solubilising: poorly soluble API*s in lipophilic bases 1-5%; insoluble APIs in lipophilic bases 0.1-3%	E-Ferol syndrome - thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, metabolic acidosis. [18]
Ethanol	Solvent	In the USA, the max quantity of alcohol included in over the counter (OTC) medicines 0.5% v/v for products for use by children under 6 years of age. Parenteral products containing up to 50% of alcohol (e 95 or 96% v/v)	CNS depression - muscle incoordination, visual impairment. Negative synergic effects on CNS when associated with dextromethorfan. Chronic toxicity [8,18,20]

Lass et al. BMC Pediatrics 2012, 12:136

Table 4 Most commonly prescribed medicines (received by >10 patients) containing known to be harmful or potentially harmful excipients

Rank	Active substance, drug formulation	No of prescriptions	Potentially harmful or known to be harmful excipients
1	Gentamicin, inj solution	200	Parabens, sodium metabisulphite
2	Simeticone, oral suspension	108	Sodium benzoate, saccharin sodium, silicium dioxide, sodium cyclamate, sorbic acid
3	Heparin, inj solution	86	Benzyl alcohol, parabens
4	Laurilsulphate + Sorbitol + Sodium citrate, rectal solution	60	Sorbic acid
5	Salbutamol, nebulisation solution	54	Benzalkonium chloride, propylene glycol
6	Dobutamine, inj solution	45	Sodium metabisulphite
7	Epinephrine, inj solution	36	Sodium metabisulphite
8	Iron, oral solution	32	Parabens, saccharin sodium
9	Budesonide, nebulisation solution	31	Polysorbate 80, disodiumedetate
10	Chloramphenicol, opthalmic solution	29	Benzalkonium chloride, polysorbate 80, borax, boric acid
11	Caffeine, solution	29	Sodium benzoate
12	Phenobarbital, tablet	29	Silicium dioxide, gelatin
13	Paracetamol, suppository	29	Disodium hydrogen phosphate
14	Piperacillin + tazobactam, inj solution	25	Disodium edetate
15	Paracetamol, inj solution	24	Disodium hydrogen phosphate
16	Hydrocortisone, inj solution	23	Benzyl alcohol, disodium hydrogen phosphate
17	Epoetin beta, inj solution	22	Disodium hydrogen phosphate, glycine, calcium chloride dihydrate, leucine,
18	Ibuprofen, inj solution	21	Trometamol
19	Hyoscine butylbromide, tablet	20	Silicium dioxide
20	Spironolactone, tablet	18	Silicium dioxide
21	Zidovudine, oral solution	17	Sodium benzoate, saccharin sodium
22	Fusidic acid, ophthalmic solution	16	Benzalkonium chloride, disodium edetate
23	Morphine, inj solution	14	Sodium metabisulphite
24	Phenobarbital, inj solution	13	Benzyl alcohol, propylene glycol
25	Heparin sodium, topical gel	12	Parabens, ethanol, trietanolamine,
26	Insulin, inj solution	11	Cresol

Inj - injection.

Lass et al. BMC Pediatrics 2012, 12:136

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…Biopharmaceutical Classification System of Excipients

Table 2. Excipients effect in cytochrome P450.

Excipient	CYP3A	CYP3A4	CYP3A5	CYP2C9	Glucuronidation
Kolliphor® HS15	+				+
Kolliphor® EL	+	+		+	+
Kolliphor® RH40		+		+	+
Tween-20®	+		+		+
Tween-80®	+	+	+	+	+
PEG400	+				+
PEG1000			+	+	
PEG3350	+				
Myrj® 52	±	+		+	
Brij® 35		+			
Poloxamer 188	±	+	+	+	
Poloxamer 235	+				
Poloxamer 403	–				
Poloxamer 407	–				
Vitamin E TPGS	–	+			
Thiomers		+			
Modified cyclodextrins		+		↑	
Sucrose laurate		+		+	
HPMC	+				
Croscarmelose sodium	+				
Sodium starch glycolate	+				
Silicon dioxide	+				
Magnesium stearate	+				
Dicalcium phosphate	+				
Crospovidone	+				
Propylene glycol	+				
Acetic acid	+				
Malic Acid	+				
Triacetin	↑				
Phtalates	↑				
Lactose	–				
Cellulose microcrystalline	–				
Povidone	–				
Sodium starch glycolate	–				
Sodium lauryl sulfate	–				
Sucrose	–				
Cetyltrimethylammonium bromide	+				

(+) inhibition; (–) no inhibition; (±) variable information (↑) enzymatic induction.
HPMC: Hydroxypropyl methylcellulose; TPGS: Tocopherol polyethylene glycol succinate.

Table 3. Excipients effect on transporters.

Excipient	P-gp	MRP2	BCRP	OATP
Kolliphor® HS15				+
Kolliphor® EL	+	±	+	+
Kolliphor® RH40	±	+	–	
Tween-20®	+			
Tween-80®	±	+	+	
PEG400	+	+	–	+
PEG300	+			
PEG2000		+		
Myrj® 52	+		–	
Brij® 35	+			
Brij® 30			+	
Span® 20	+		+	
Span® 40	–		–	
Span® 80	–		–	
Poloxamer 181	+			
Poloxamer 188	±	–		
Poloxamer 235	+	+	+	
Poloxamer 333	+	–		
Poloxamer 403	+			
Poloxamer 407	+	±		
Vitamin E TPGS	+	+	–	
Sodium lauryl sulfate		+		
Transcutol®		+		
Sucrose laurate	+	–		
Labrasol®	+	±		
Gelucire® 44/14	+		–	
Stearyl ether	+			
Softigen® 767	+			
8:0 phosphocholine	+			
10:0 phosphocholine	+			
cis-22:6 phosphocholin	+			
Propylene glycol	–		–	
Ethyl oleate	–		–	
Triacetin	–		–	
Inwitor 742®	+			
Miglyol®	+			

(+) inhibition; (–) no inhibition; (±) variable information.
BCRP: Breast cancer resistance protein; MRP2: Multidrug resistance associated protein 2; OATP: Organic anion transporting polypeptide; P-gp: P-glycoprotein.

The biopharmaceutical classification system of excipients,Teófilo Vasconcelos, Sara Marques, Bruno Sarmento,Ther. Deliv. (2017) (2), 65–7

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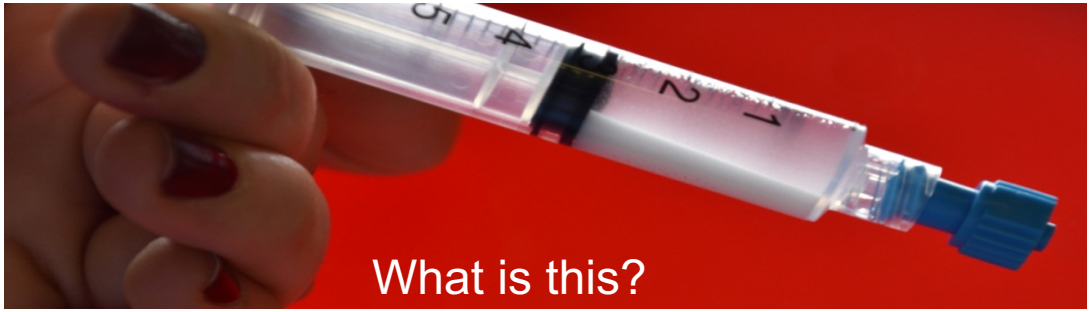
…at home!!!



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Think of the family environment

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Self-assessment questions

1. Risk assessment is possible for Off label use of drugs in children:

a) always b) **not always**

2. Before approaching an extemporaneous preparation, Risk assessment is necessary:

a) True b) False

3. Excipients never involve metabolism:

a) True b) **False**

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Take Home Message

- share your experience
- don’t forget patient follow up
- choose firstly the safer drug form
- choose the most compliant drug form
- for children the best solution is the solution
- think about the family environment of children
- **S h a r e y o u r e x p e r i e n c e**

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Thank you for your patience!