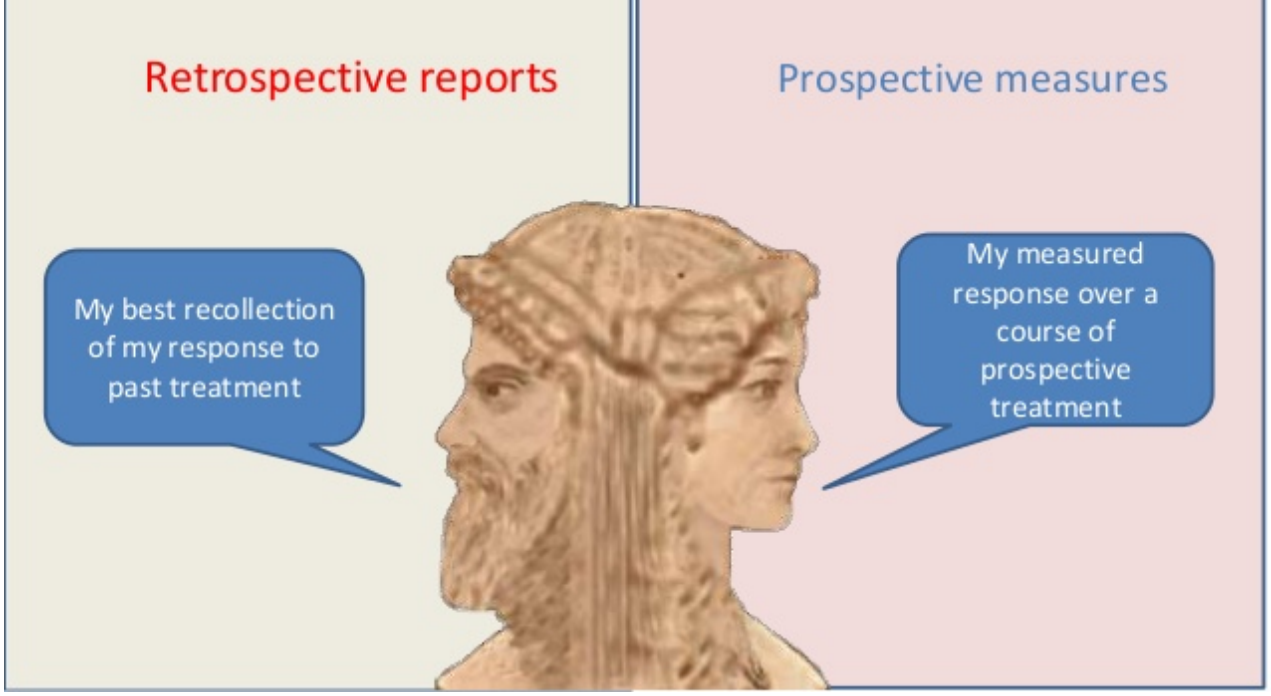
When do clinicians usually extrapolate in their practice?



Clinical approach

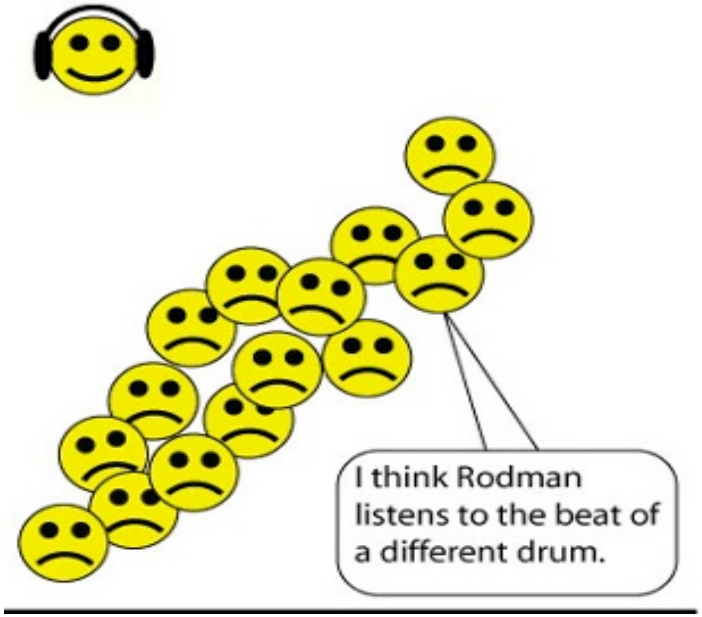
« Extrapolation refers to the use of an empirical rule outside its field of validation »

Frequent Extrapolation approaches in Clinical setting

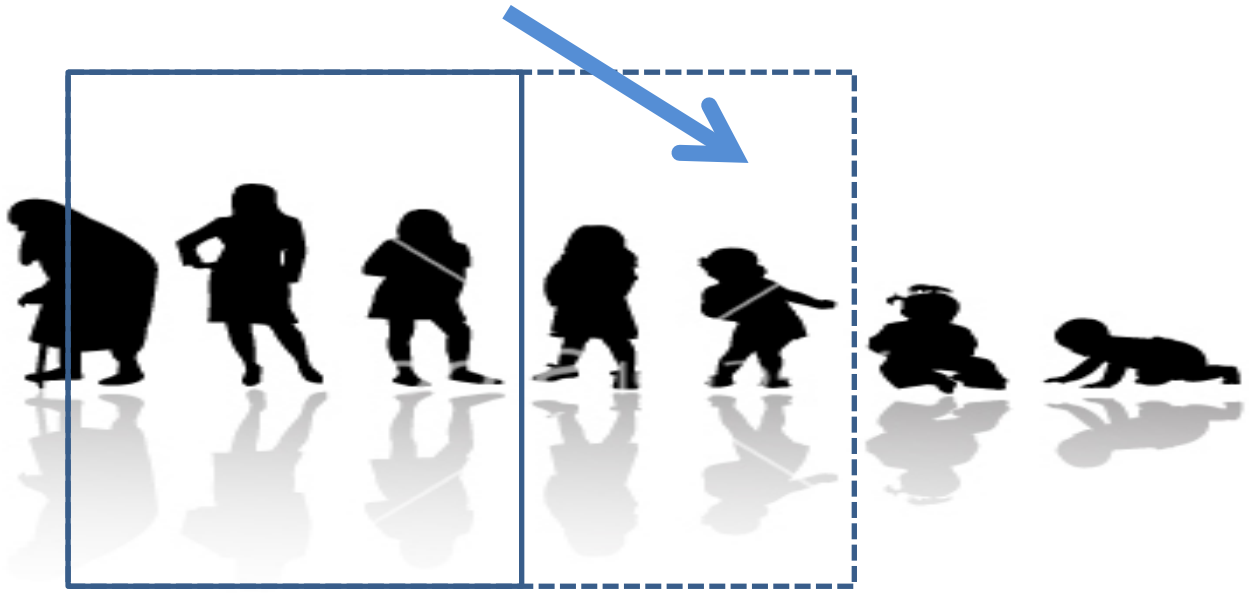
1 / ‘down / up’ the age class

2 / between medicines belonging to a class

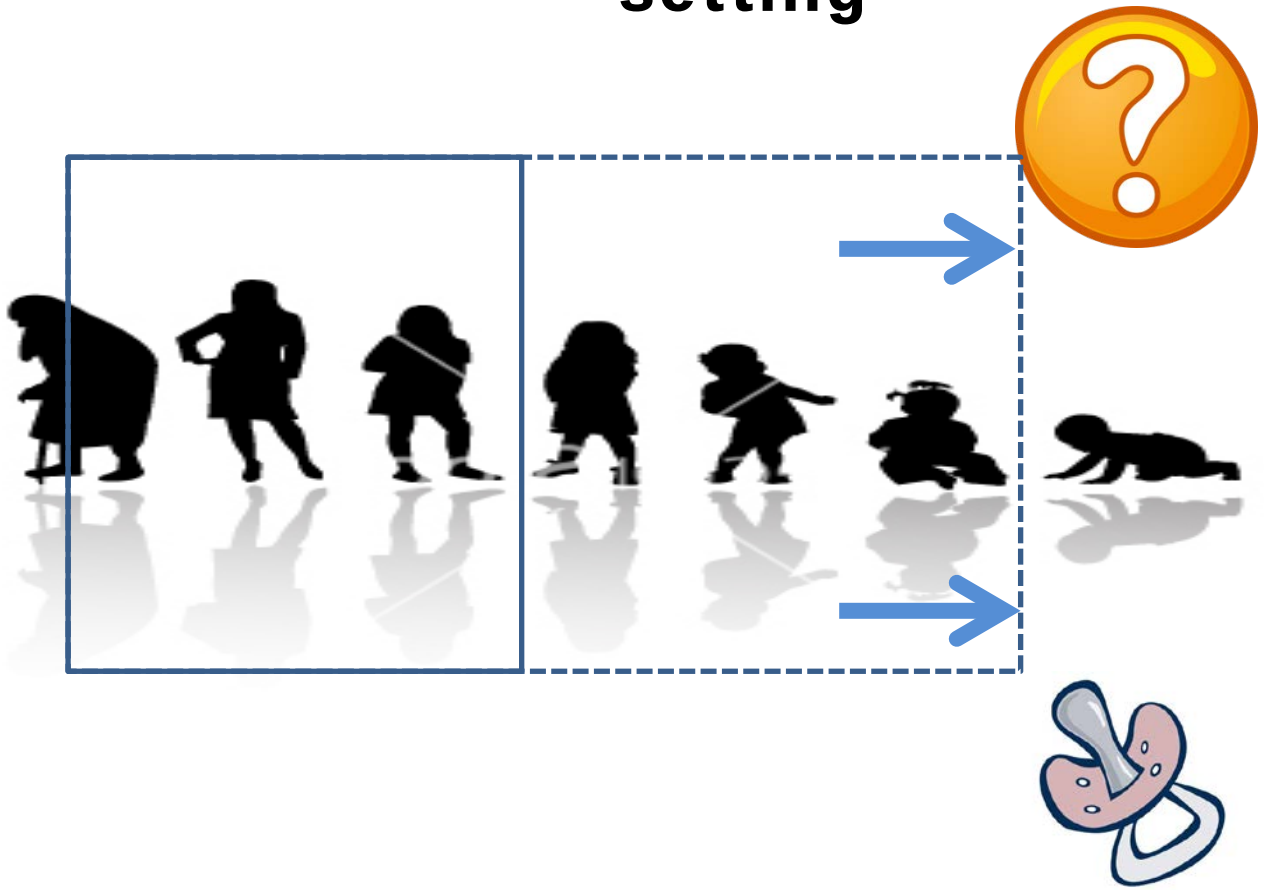
3 / from one disease to another,
from one stage / line to another



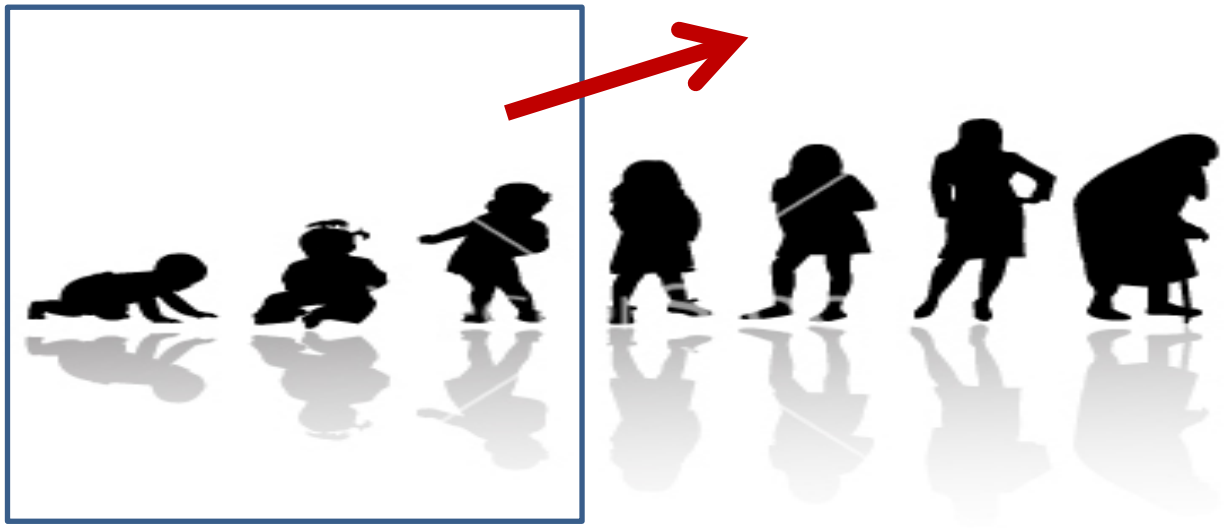
Frequent Extrapolation approaches in Clinical setting



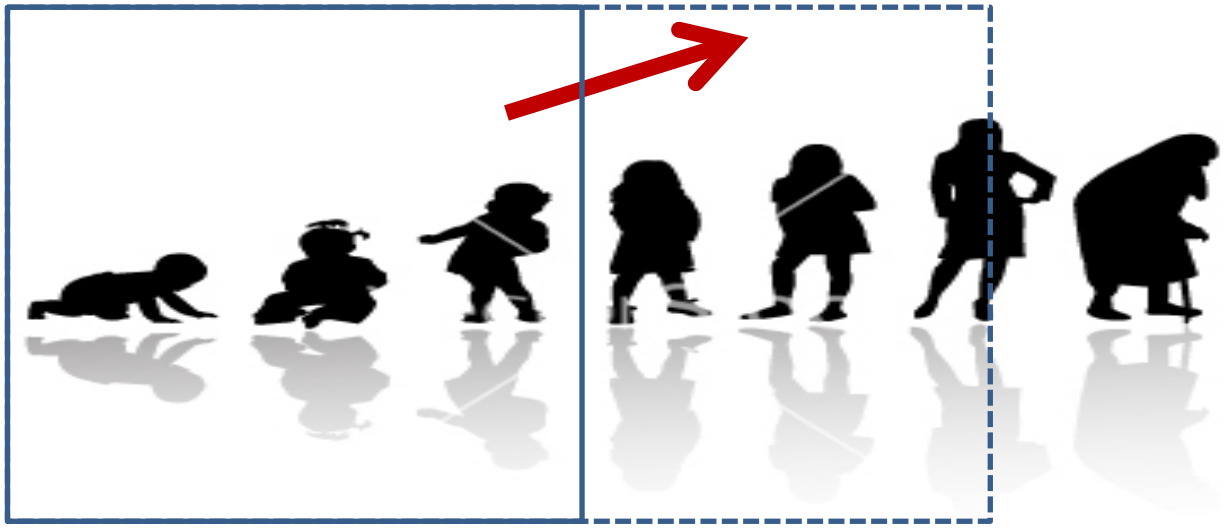
Frequent Extrapolation approaches in Clinical setting



Rare
Extrapolation approaches in Clinical setting

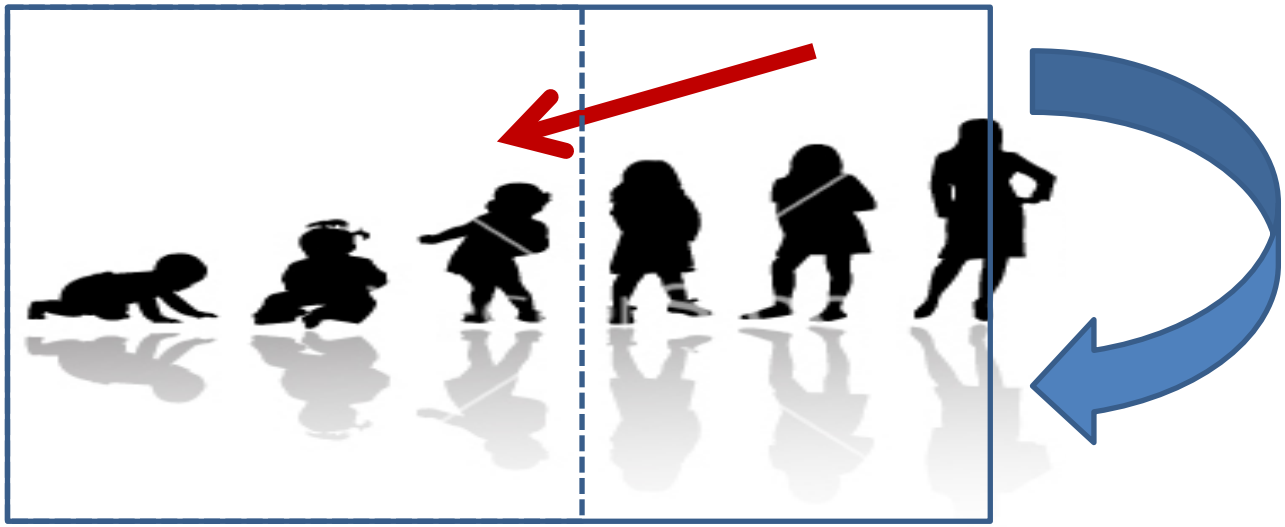


Rare
Extrapolation approaches in Clinical setting



Cystic fibrosis
Congenital disorders
(orphan conditions)
…

Rare
Extrapolation approaches in Clinical setting

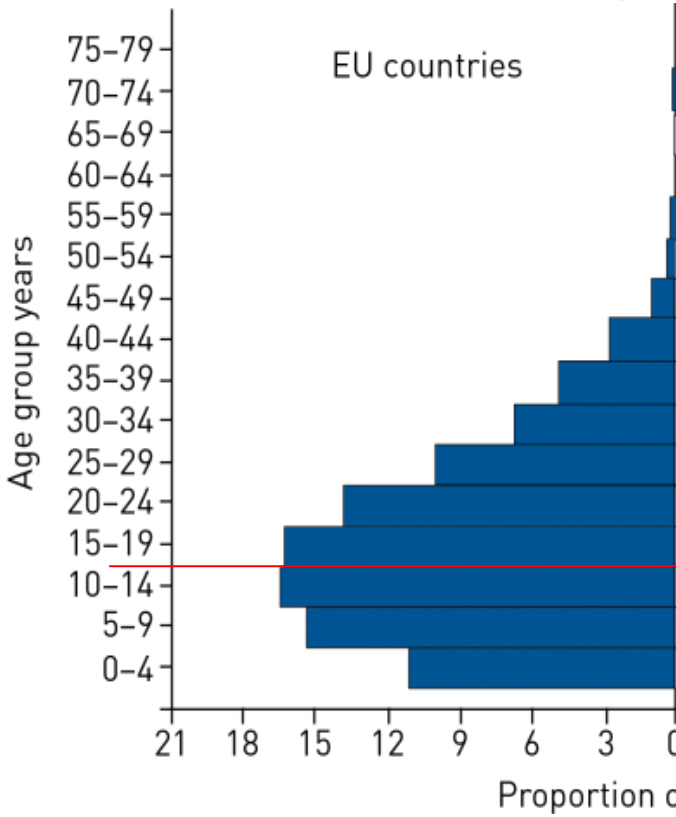


Cystic fibrosis
Congenital disorders
(orphan conditions)
…

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

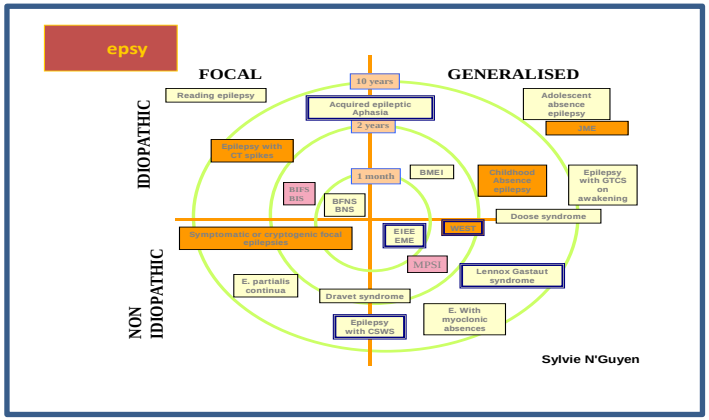
(CHMP)

GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF CYSTIC FIBROSIS



1/ same medicine ‘down/up’ the age classes

- **Facing same disease ?**



&

- **Bio-availability is similar**
- **PK is linear**
- **Dose response is similar (PD)**

or…

Report published on the uses of medicines for children in the European Union

YES

Off-label use

blished on the uses of medicines for children in the Union

1 - A report on the survey of all uses of medicines for children in published today. The report is a key deliverable of the Euro egulation (EC) No 1901/2006 which aims to improve the e European Union.

results show that the prescription of off-label their marketing authorisation) and unauth ildren pread in Europe.

The therapeutic classes that are used most fr without a marketing authorisation are:

- anti-arrhythmics;
- antihypertensives (renin-angiotensin inhibitors and beta-blockers);
- proton-pump inhibitors and H2-receptor antagonists;
- anti-asthmatics;
- antidepressants (mainly selective serotonin re-uptake inhibitors, serotonin-norepinephrine re-uptake inhibitors and tricyclic antidepressants);
- contraceptives (in adolescents);
- antibiotics (in very young children).

The results of the survey will support the work of the Paediatric Committee (PDCO) when it develops its next inventory of paediatric needs. This is a list which describes the different therapeutic areas where research into and development of medicines for children is especially needed. This applies to both old (off-patent) or new medicines (including authorised medicines and those under development).

Related ion

- rvey of all f medicinal urope: Executive (20/01/2011)
- ort on the survey of all paediatric uses of medicinal products in Europe: Questions and answers (20/01/2011)
- Report on the survey of all paediatric uses of medicinal products in Europe (20/01/2011)

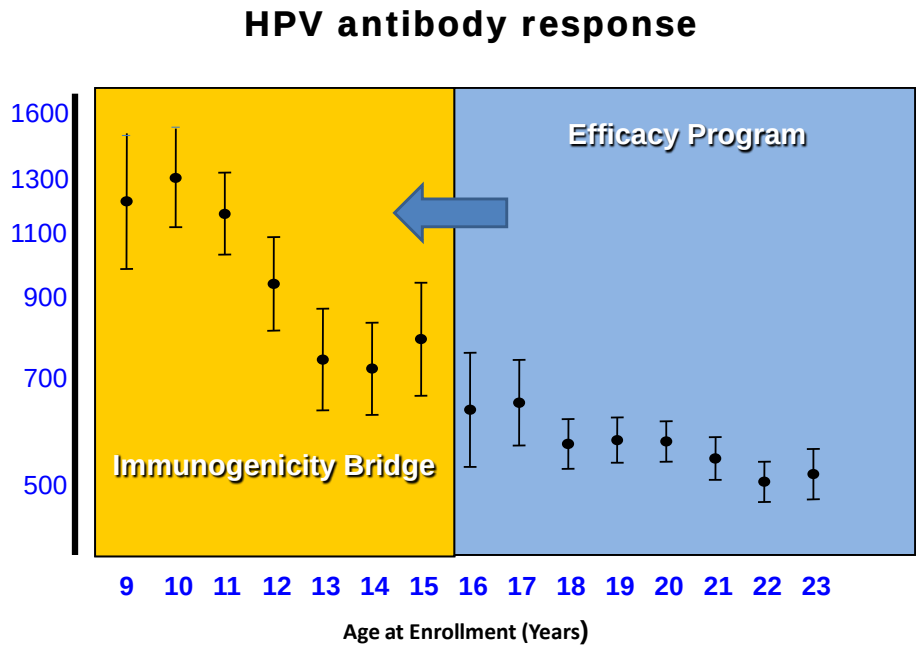
Contact point:

inventory@ema.europa.eu

1 / same medicine down / up the age class

more robust
at hand of a surrogate marker of efficacy
(not necessarily safety)

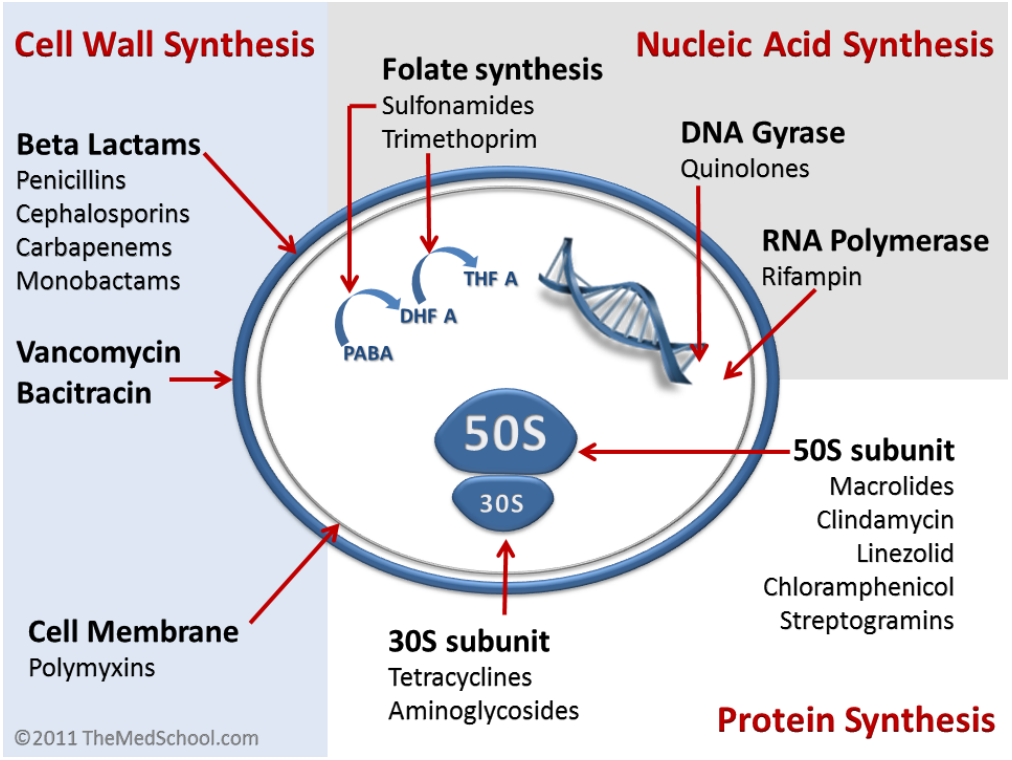
Vaccine



1 / same medicine 'down / up' the age class

or targeting an 'external' pathogen

Antibiotics in...
CAP
ICU
ResistP

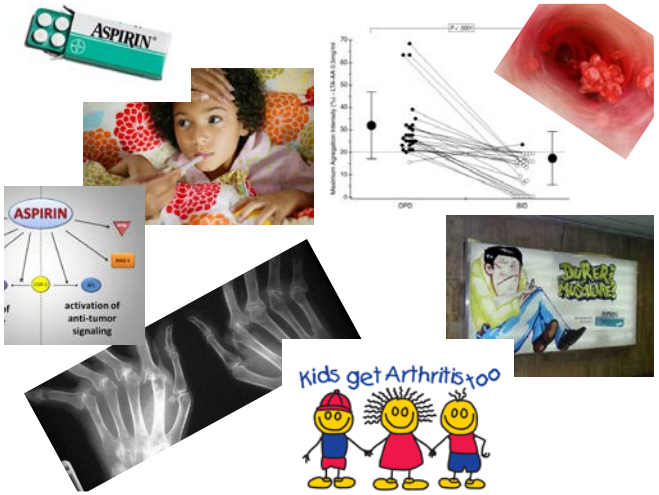


2 / between different medicines belonging to a same class used for a specific disease

- **Drug / pro-drug**
  ([des] loratadine…)
- **Bio-equivalence**
  (Release formulation, conversion factor)
- **Therapeutic equivalence**
  (anti-TNF in MS, Blood factor substitution, ERT)
  (vaccines, based on sero-conversion factors)
  (one statine to another, monitored by LDL-Chol))
- **Me-too, is not equi-potency**
  (for E [long term effect statines] & / or S…)

3 / same medicine from one disease / symptom to a similar, from one stage to another

- pain / fever
- leukaemia / lymphoma
- arthritis…
- HTA [primary,secondary] / heart failure
- Allergy / exercise induced asthma
- Heart failure stage I,II,III,IV
- Cancer stage, relapse…

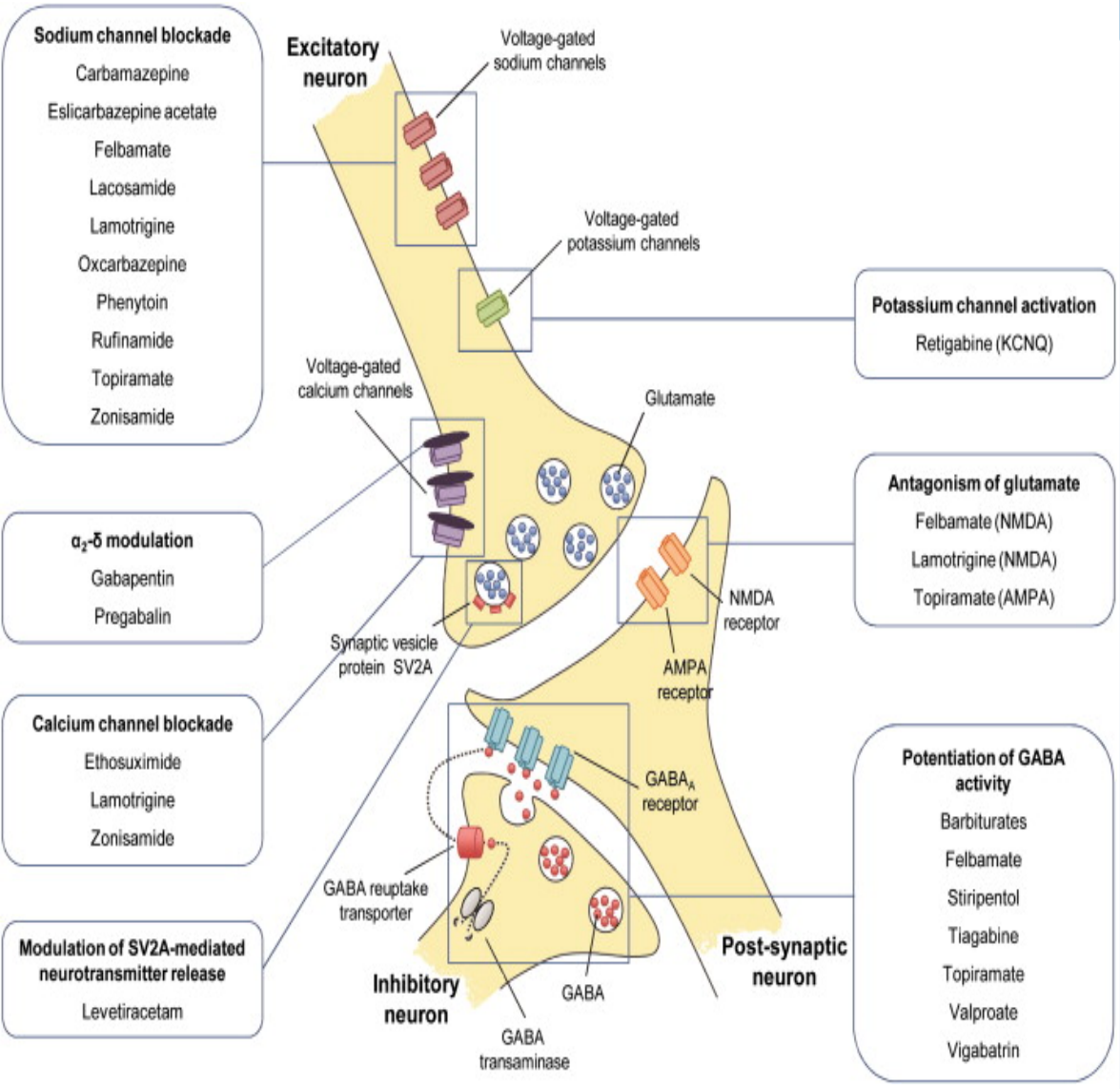


How do Clinicians behave?

Interlinking

- **Mechanism of action of the disease (pathogenesis / pathways)**
- **Mechanism of action of the drug (target, receptors)**
- **Clinical condition / presentation (individual sign & symptoms)**

Within same ‘nosological’ entity



Principal mechanisms of action of anticonvulsant drugs

	Calcium channel block (type)	GABA potentiation
Barbiturate	NK	+ (A)
Benzodiazepine	NA	++ (A)
Carbamazepine	+ (L)	NK
Ethosuximide	++ (T)	NA
Felbamate	+ (L)	+ (A)
Gabapentin	++ (N, P/Q)	NK
Lamotrigine	+ (N, P/Q, R)	+
Levetiracetam	+ (N)	NK
Oxcarbazepine	+ (N, P)	NK
Phenytoin	NK	NA
Pregabalin	++ (N, P/Q)	NA
Tiagabine	NA	++
Topiramate	+ (L)	+ (A)
Valproate	NK	+
Vigabatrin	NA	++
Zonisamide	++ (N, P, T)	NK

GABA, γ-aminobutyric acid; ++, primary action; +, secondary action; NA, no activity; NK, controversial findings; A, GABA potentiation through $GABA_A$ receptors.

Across same ‘pathological pathways’

Multiple Sclerosis

Psoriasis

Asthma

IBD

Rheumatoid Arthritis

NR3C1

CD86

IL2RA

CD80

IL4

CIITA

H2-EB1

RELA

IL12B

PPARG

CD40LG

NOS2

IL10

TLR2

FAS

CCL2

CD4

TNF

IL23A

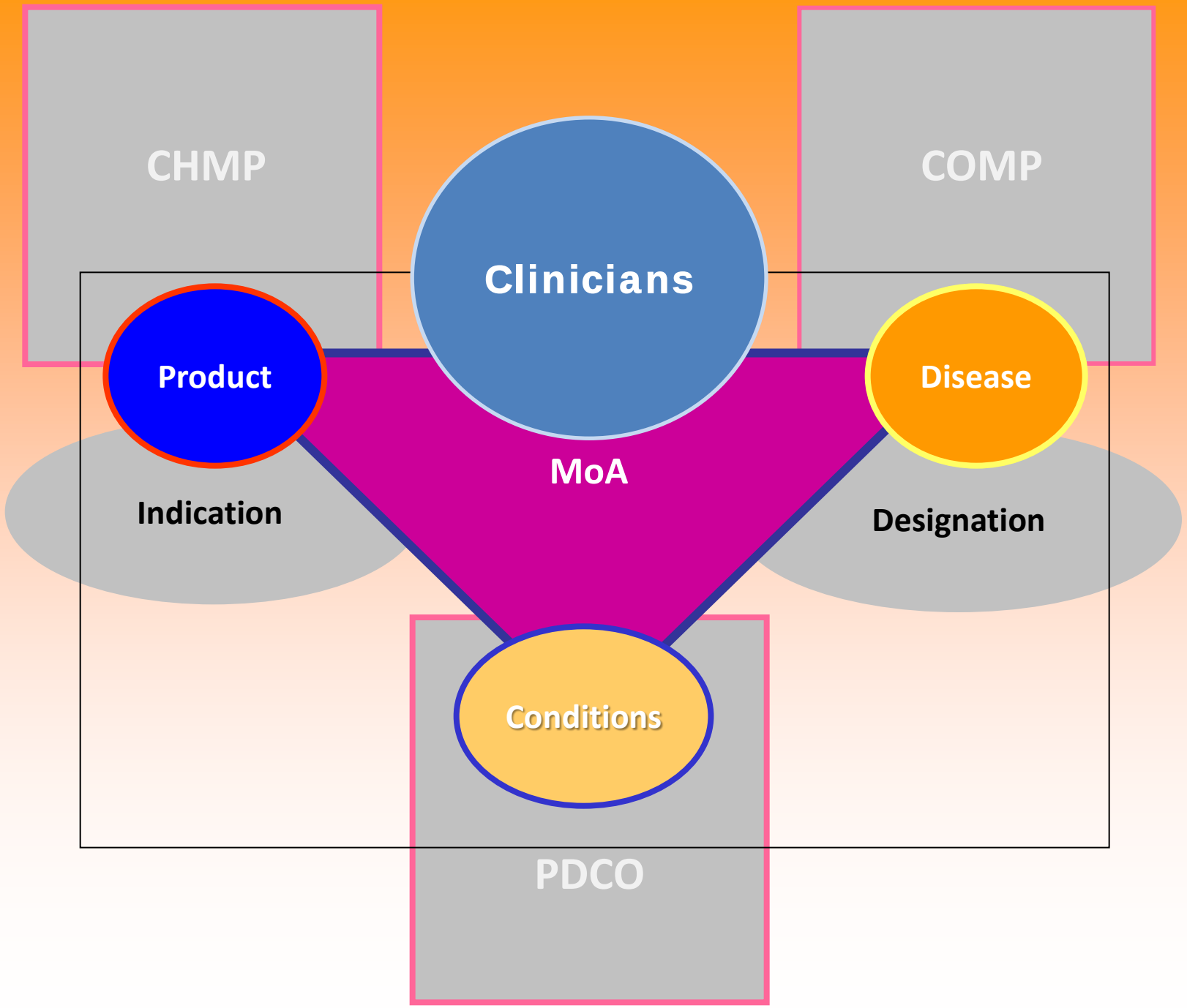
CD40

IL13

IL7

IL1RN

IL6


CHMP
COMP
Clinicians
Product
Disease
MoA
Indication
Designation
Conditions
PDCO

Summary

Extrapolation in use based on Clinical intuition

- **Signs & symptons (presentation)**
- **Knowledge of the disease (pathogenicity)**
- **Mechanism of action drug (target)**
- **Personal experience (off-label)**


outlier.

We are working on it