

International Perspectives: Appropriate Pharmaceutical Design of Oral Medicines in Pediatric and Geriatric populations

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Intro / 'Disclaimer'

Similarities and differences between **Pediatric** and **Geriatric** centric oral drug product design

Target Product Profile

Regulatory guideline/guidance

'Candy-like' (non) prescription drug products

international...EU...UK

USA: FDA vs EU: 'F' and 'DA' often 2 entities

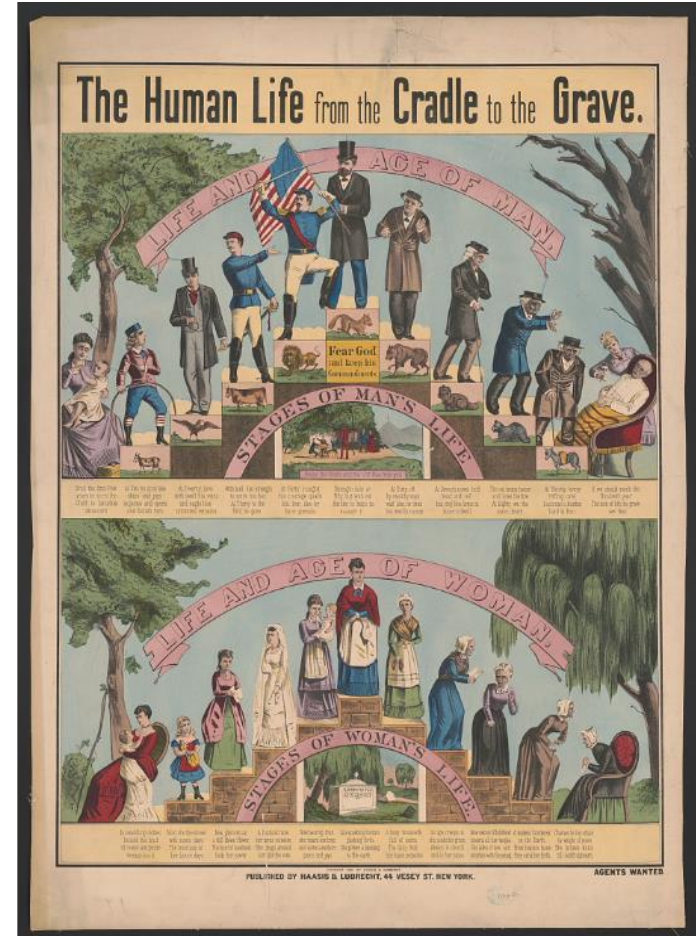
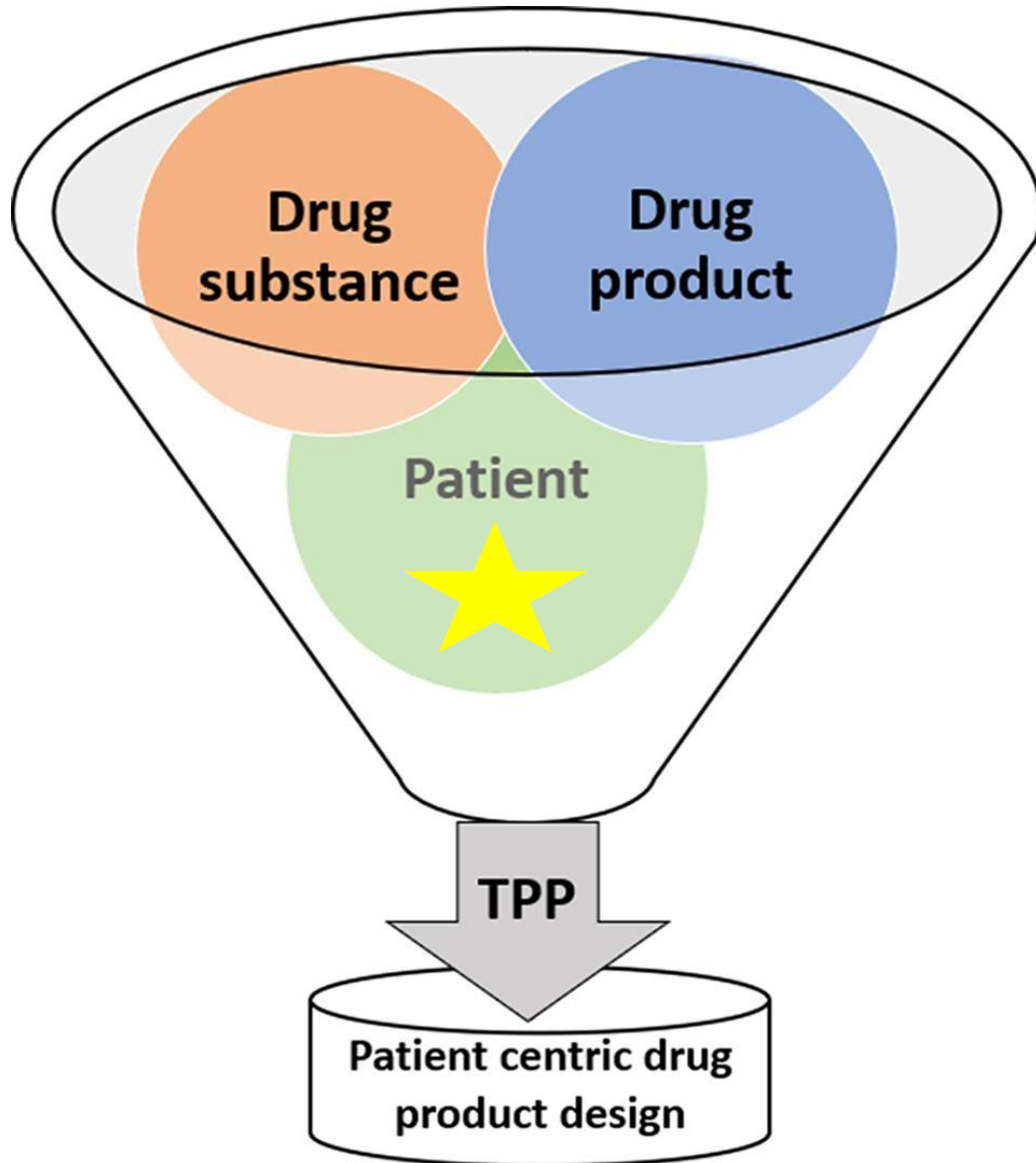
Personal reflection



<https://www.conveniencestore.co.uk/products-in-depth/six-things-to-know-about-otc-medicines-and-winter-remedies/672462.a>



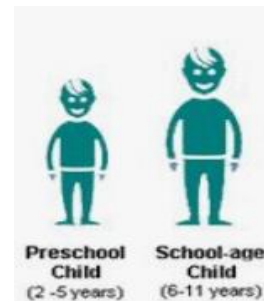
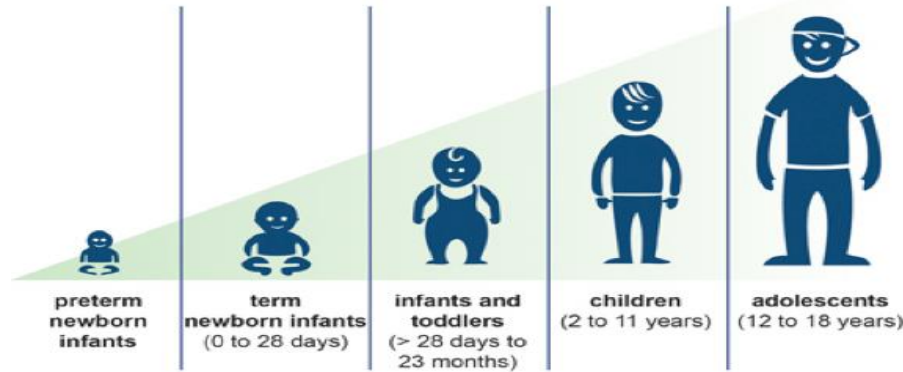
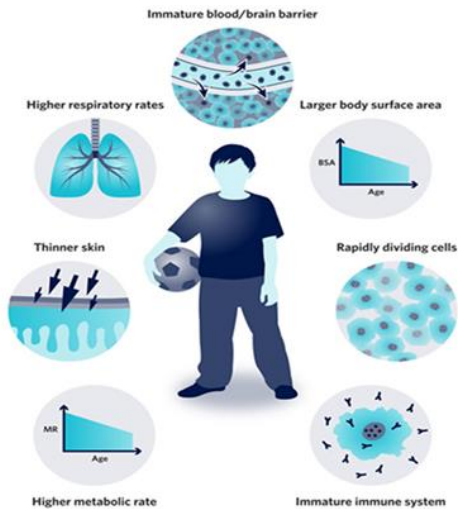
doi.org/10.1016/j.ejpb.2022.06.006



Developing children centric dosage forms: not a child's play!

ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population

Developmental age



Physical and behavioural age

Considerations:

- Route of administration
- Dosage form (incl. **EXCIPIENTS**)
- Dosing
- Acceptability
- Administration aid (from food-beverages to devices)



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

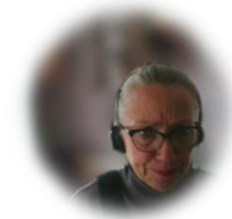
Keywords	<i>child, pharmaceutical development, quality</i>
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Guideline on pharmaceutical development of medicines for paediatric use

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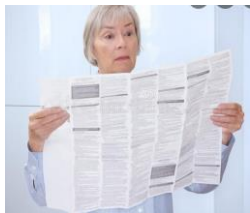
age specificity, condition of patient, duration of therapy, dosing regimen etc.



EU Paediatric Regulation; EC No. 1901/2006

Acceptability is:

-Overall **ability and willingness** of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)



Swallowability (size and shape, volume...)

Palatability (smell, taste, mouth-feel, after-taste)

Appearance (e.g. colour, shape, embossing, etc)

Required dose (e.g. dosing volume, number of tablets, break marks, precision of dose etc.)

Required dosing frequency and duration of treatment

Complexity of modification prior to administration (if required)
Administration device if any

Primary and secondary container closure system

Actual mode of administration (ease, practicality, pain or discomfort)

Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf

WHO guideline development of paediatric medicines: points to consider in pharmaceutical development, 2012

https://www.who.int/medicines/areas/quality_safety/quality_assurance/Rev3-PaediatricMedicinesDevelopment_QAS08-257Rev3_17082011.pdf

- a **Key Binding element** in PIPs



Geriatric population

- Age subgroups proposed
 - early old (age 65-74)
 - middle old (age 75 - 84)
 - late old (age ≥ 85)
- *Ref: ICH Topic E 7 Studies in Support of Special Populations: Geriatrics Q&A*
- **!!! HOWEVER !!!** age subgroups do not often properly reflect biologic age which may considerably vary within each subgroup
- A further physiological approach uses the classification of ‘fit’ and ‘frail’
- More complex to study than younger due to **comorbidities**, sensory deficits, cognitive impairment or physical frailty

EMA geriatric medicines strategy 2011

15 October 2020
 EMA/CHMP/QWP/292439/2017
 Committee for Medicinal Products for Human Use (CHMP)

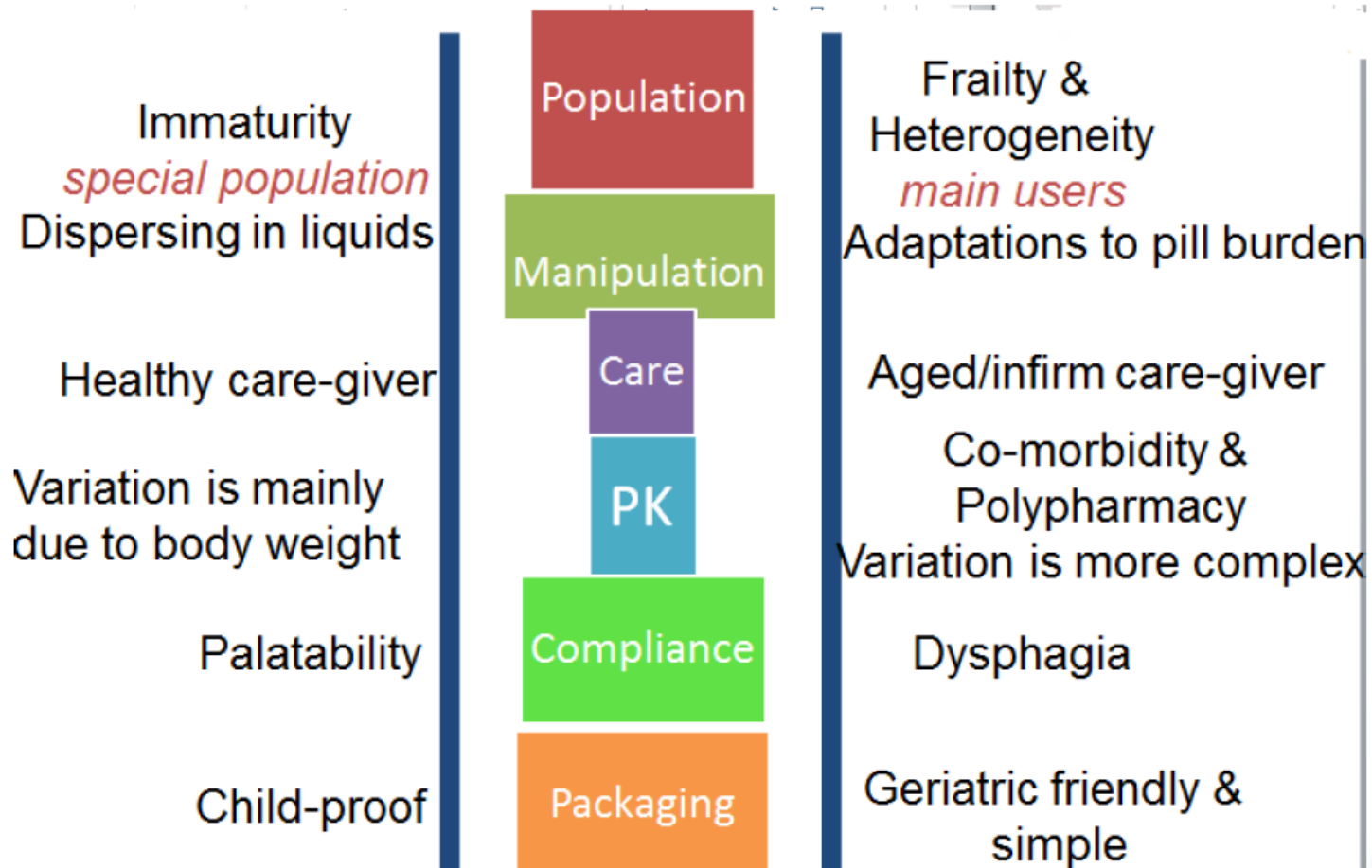
Reflection paper on the pharmaceutical development of medicines for use in the older population

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Points to consider are similar BUT Ways to consider are different



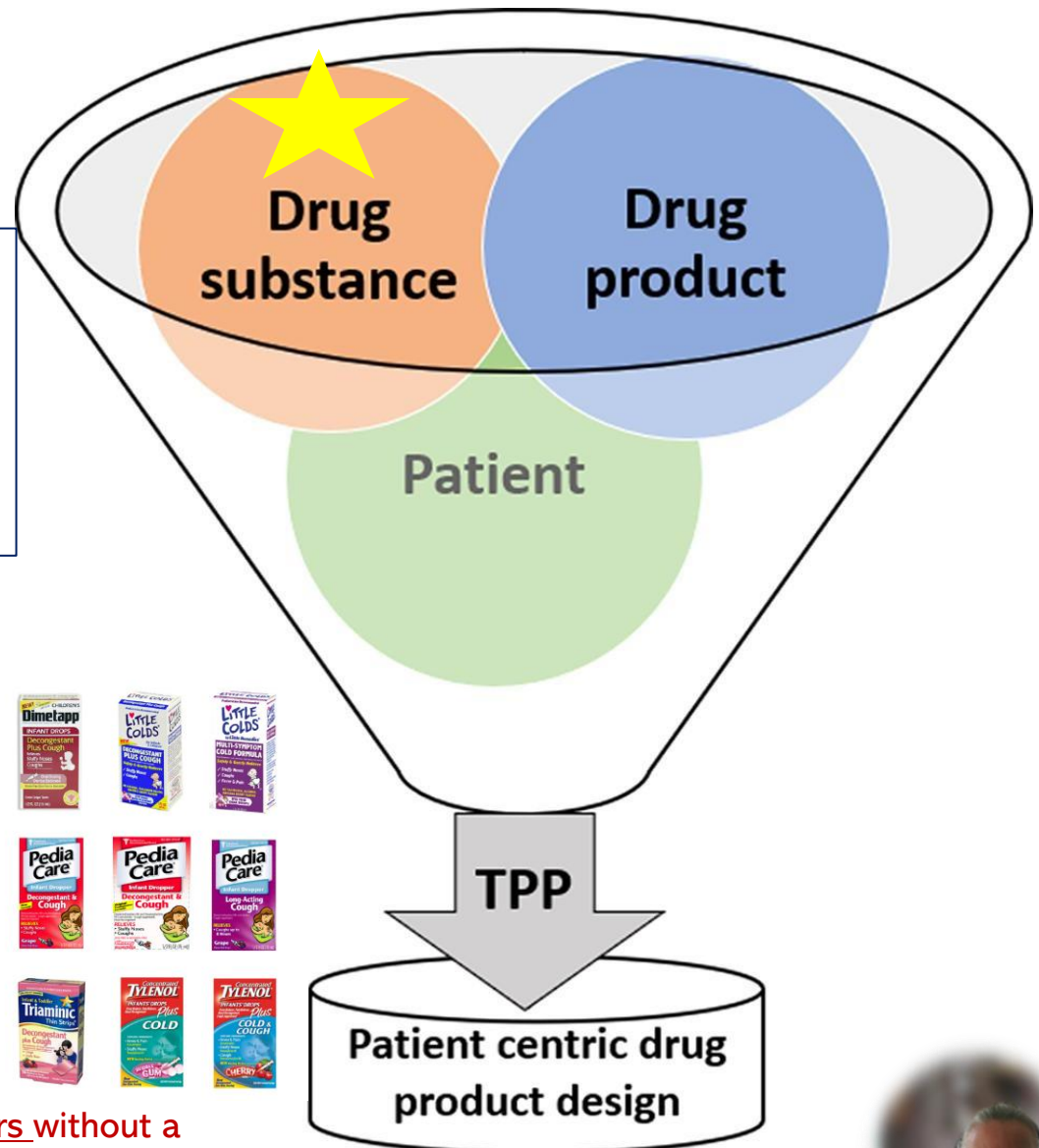
- criticality of the Dose
- API Therapeutic index
- Q API & pack size

11.2. Container size EMA/CHMP/QWP/805880/2012 Rev. 2

General considerations

The full contents of a container should be justified in terms of:

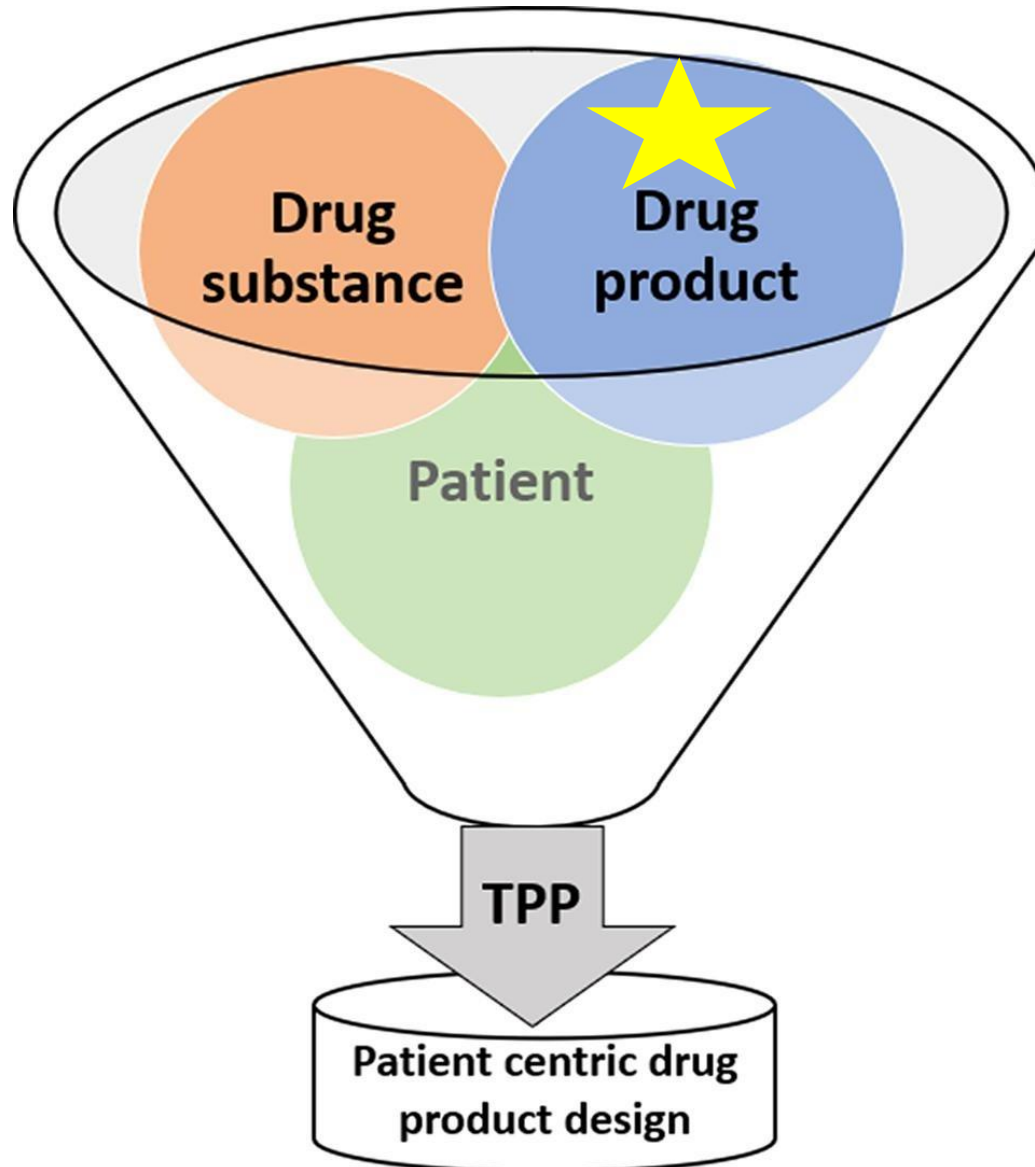
- 1) dosing recommendations and dosing duration in the SmPC and PIL for each of the target age group(s);
- 2) accidental dosing errors, specially the risk of 10-fold overdosing;
- 3) accidental ingestion of the full contents;
- 4) patient acceptability.



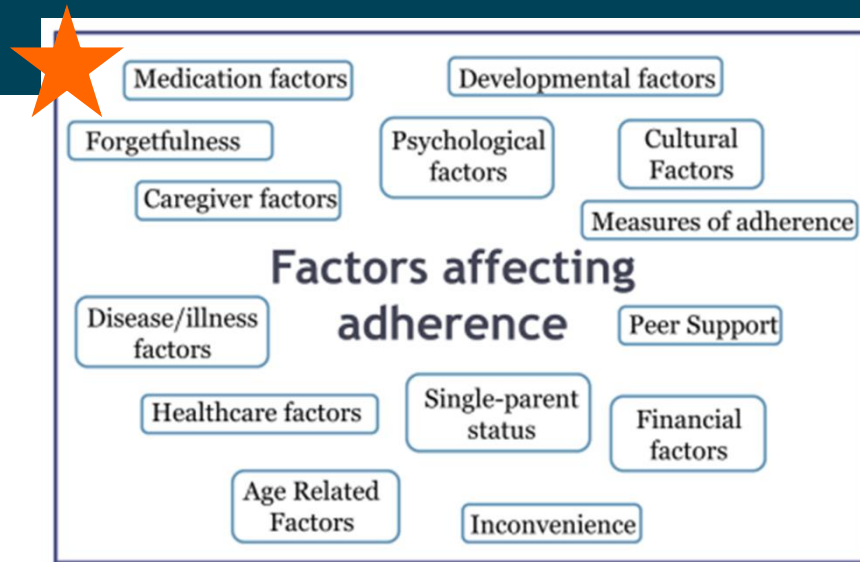
• Rx

- OTCs are products that can be bought by consumers without a prescription, at a pharmacy or another retail outlet. These products are intended for the treatment of minor ailments.





Medication factors= Major challenges



Kids perspective

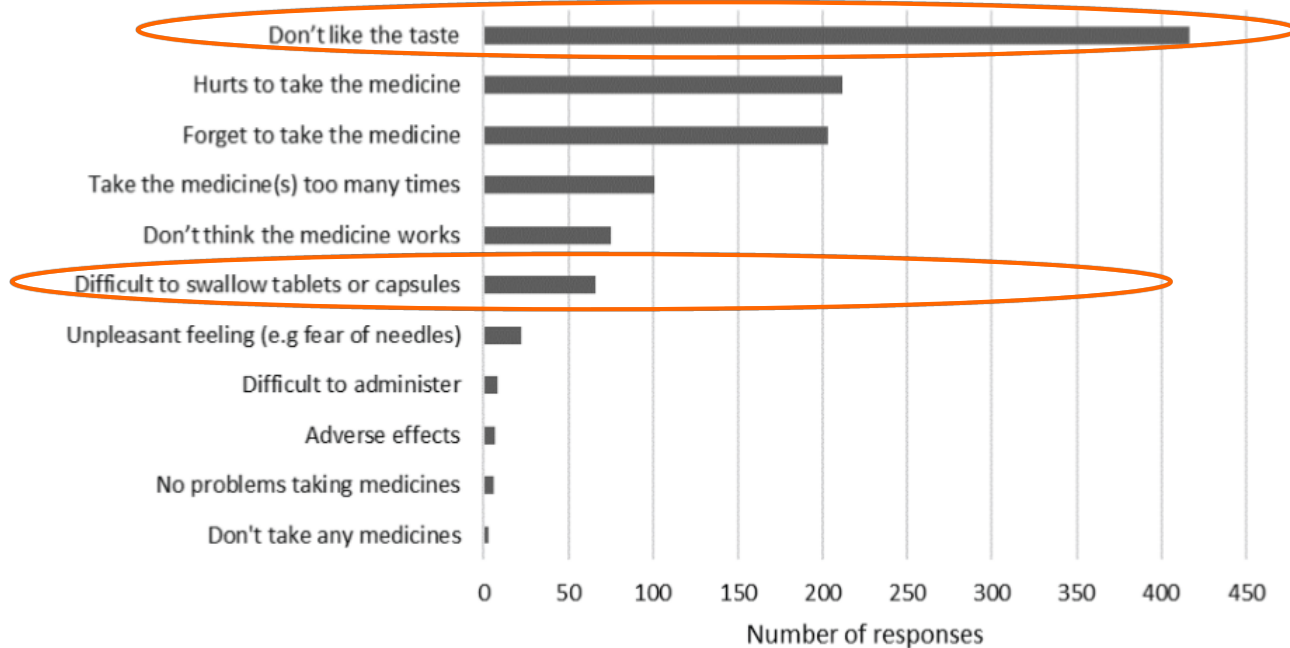


Figure 4 'Why do you find some of the medicines difficult to take?' (multiple-answer question), n=652.



10. Palatability

Examples of measures that can be undertaken to improve the palatability of a paediatric preparation include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), a change in particle size of the active substance or the excipients, a choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent (e.g. cyclodextrines) or for liquid preparations, lowering the amount of the free active ingredient in solution by the choice of a different strength and associated change in volume.

However, paediatric preparations must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning.

- What is the definition of a candylike Rx dosage form?



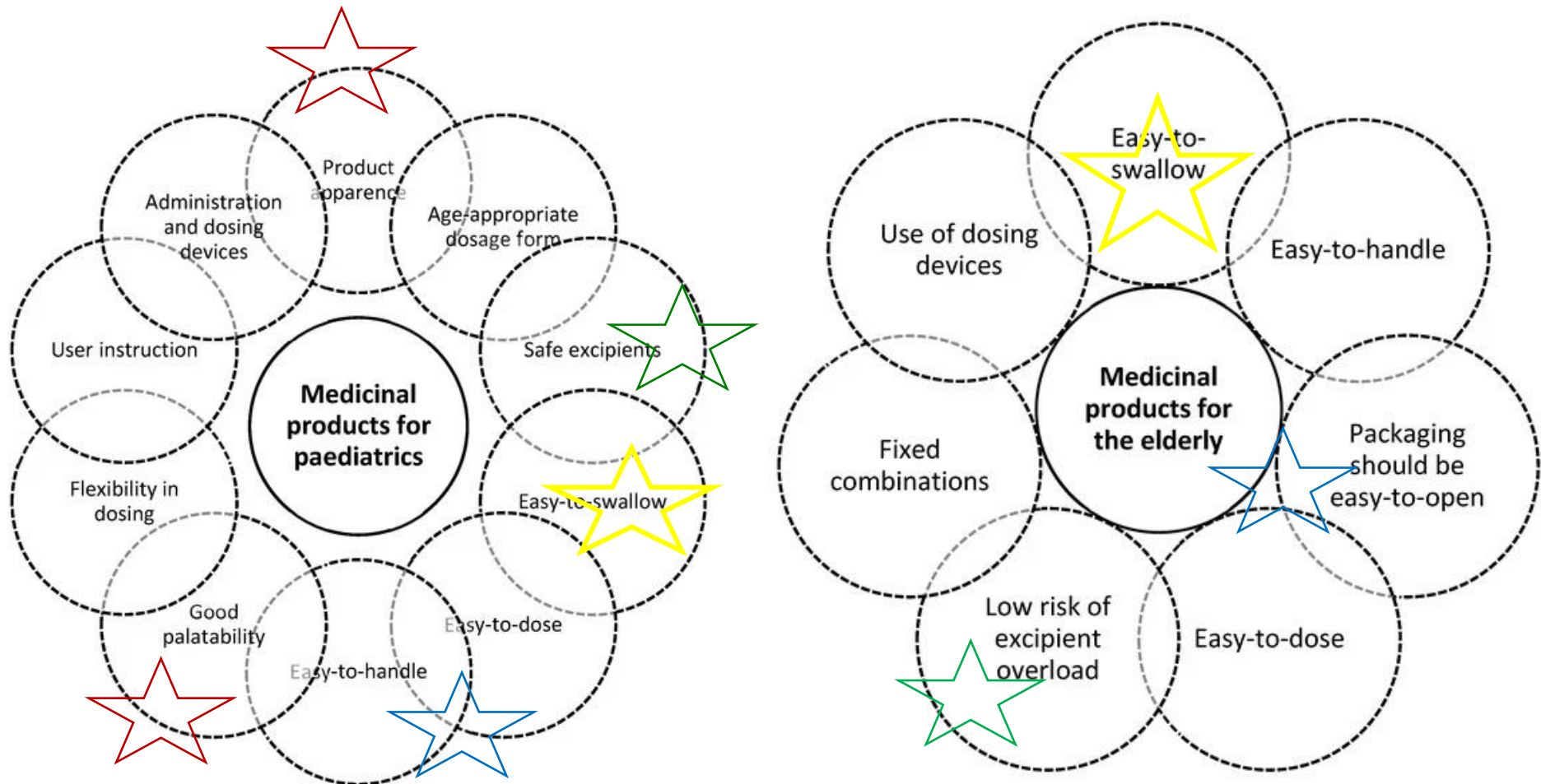
- MORE Desirable
- MORE palatable
- EASIER to handle
- EASIER to dose



- Rational of Excipients use (colours/flavours/sweetening agents)
- Different commercial pressure

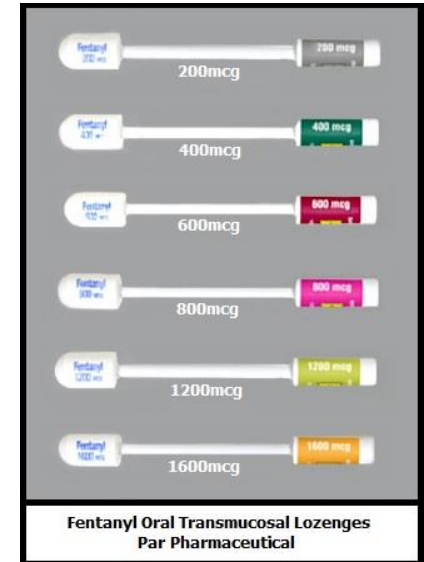
consumer led vs patient centric/Rxer led product design





Medicines that look like Candies have in common easier swallowability

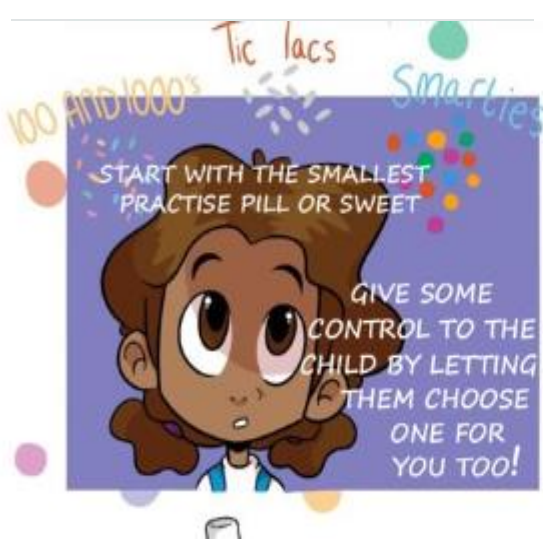
Prescription-Only Medicine (POM) - has to be prescribed by a doctor or other authorised health professional and it has to be dispensed from a pharmacy or from another specifically licensed place



Pharmacy (P) - an intermediate level of control, can be bought only from pharmacies and under a pharmacist's supervision;



General Sales List (GSL) may be bought from retail stores, such as a newsagent, a supermarket or a vending machine in a shop



136/archdischild-2020-319154 Original research

ng children's Pill School within

Andy Fox ^{1,4}, Nanna Christiansen, ²

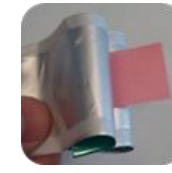


make medicines **child size**

WHO Better Medicines for Children Project 2008

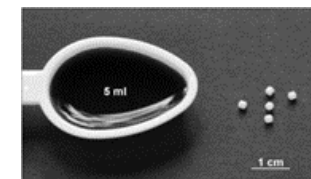
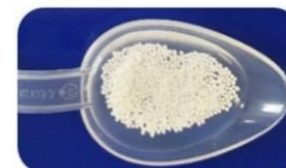
Flexible solid oral dosage forms

- do not have to be swallowed whole, such as dispersible tablets, effervescent tablets, chewable tablets, orodispersible tablets/films and sprinkle capsules



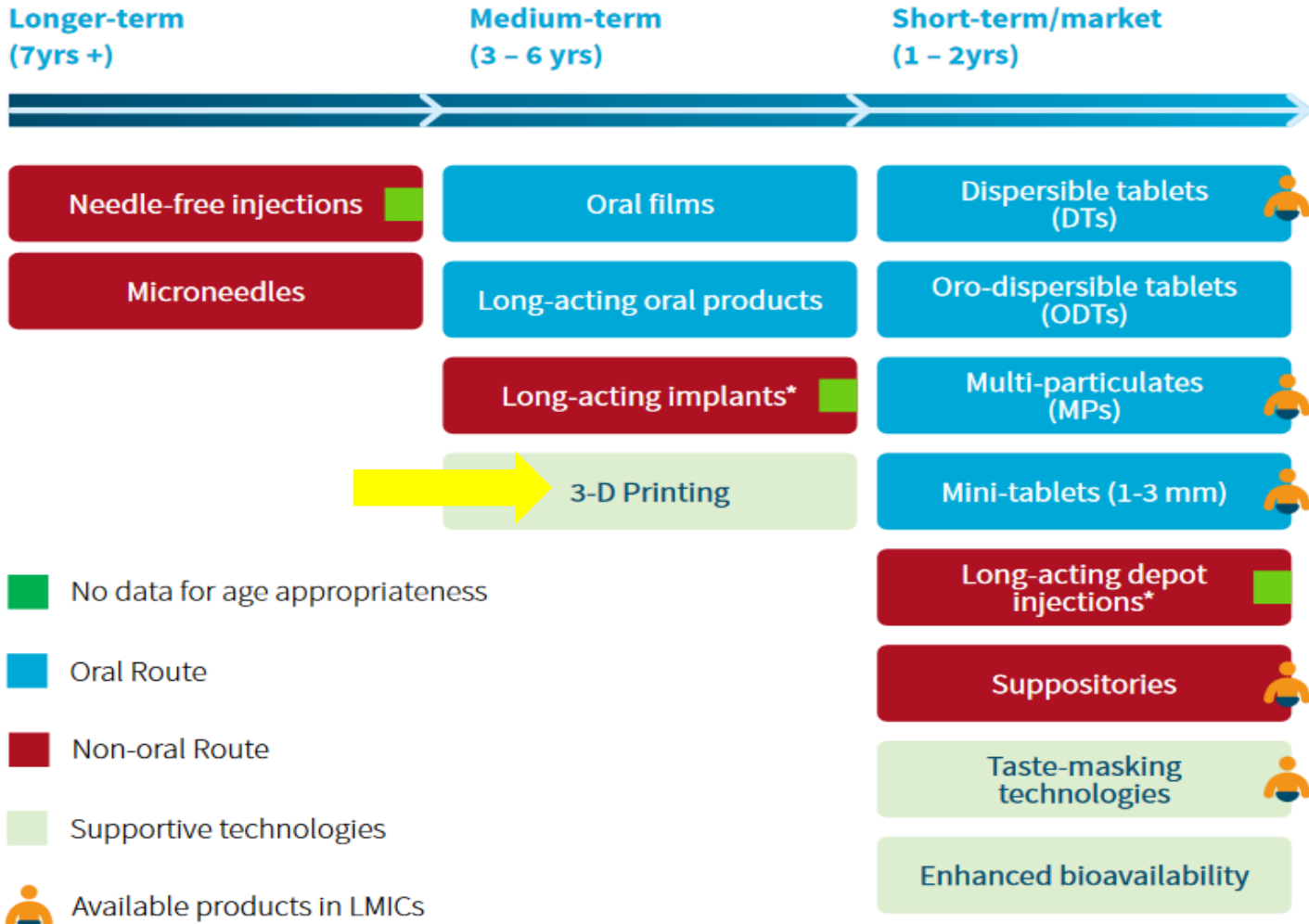
Multiparticulates

- number of discrete units such as granules, pellets or minitables



The future of kids medicines

FIGURE 15. Potential opportunity for application of innovative delivery systems and supportive technologies for children in LMICs



■ No data for age appropriateness

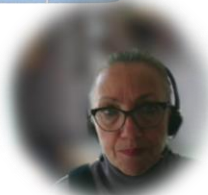
■ Oral Route

■ Non-oral Route

■ Supportive technologies

Available products in LMICs

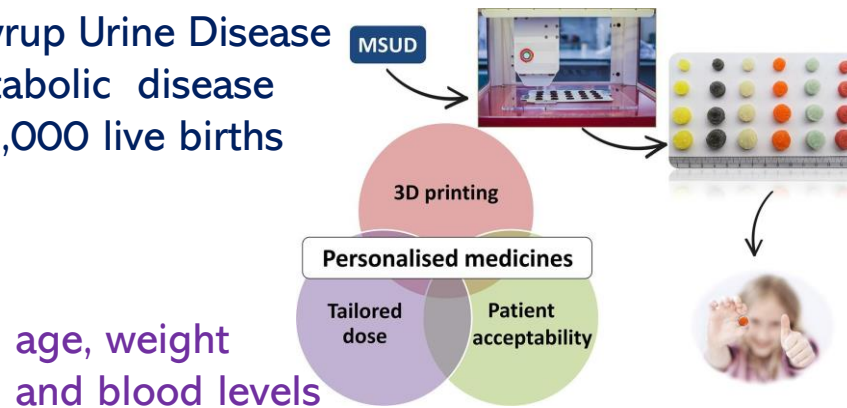
*pipeline contains only application for older ages



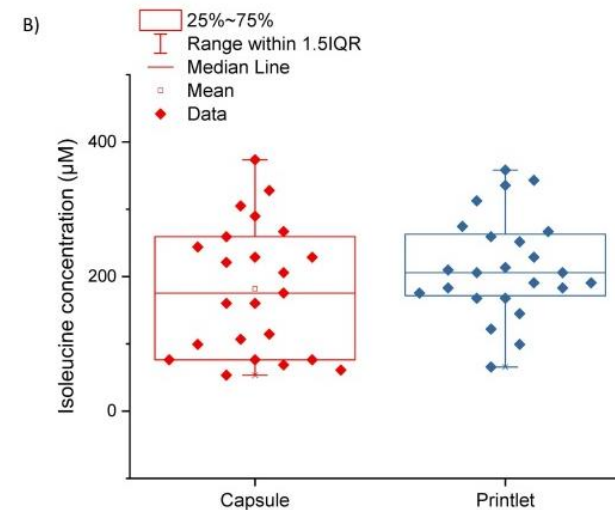
3D printing

- 3DP of personalized formulations is a disruptive technology, bridging the gap toward personalized medicine
- **Opportunities** of adopting 3DP as a 'compounding method' in pharmacies

Maple Syrup Urine Disease
Rare metabolic disease
1 in 185,000 live births



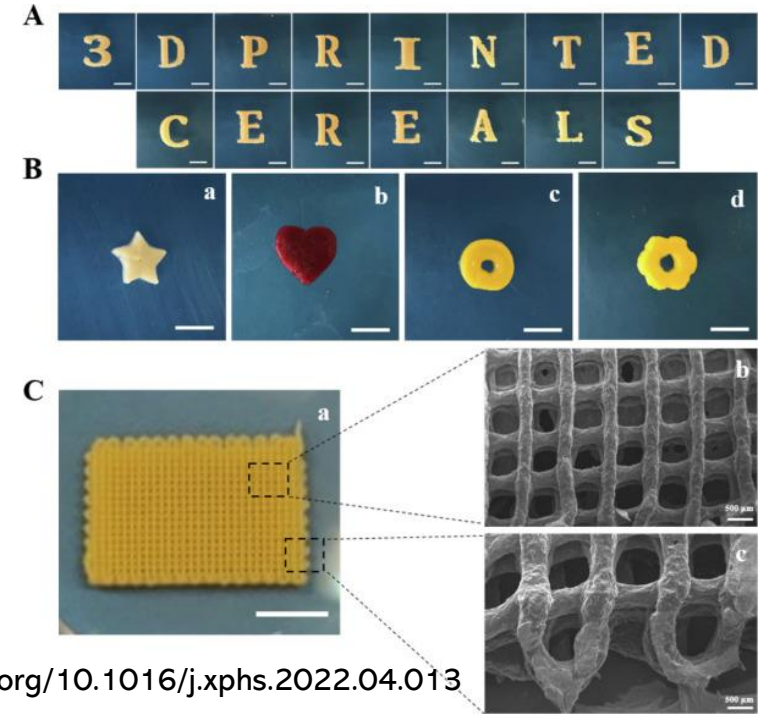
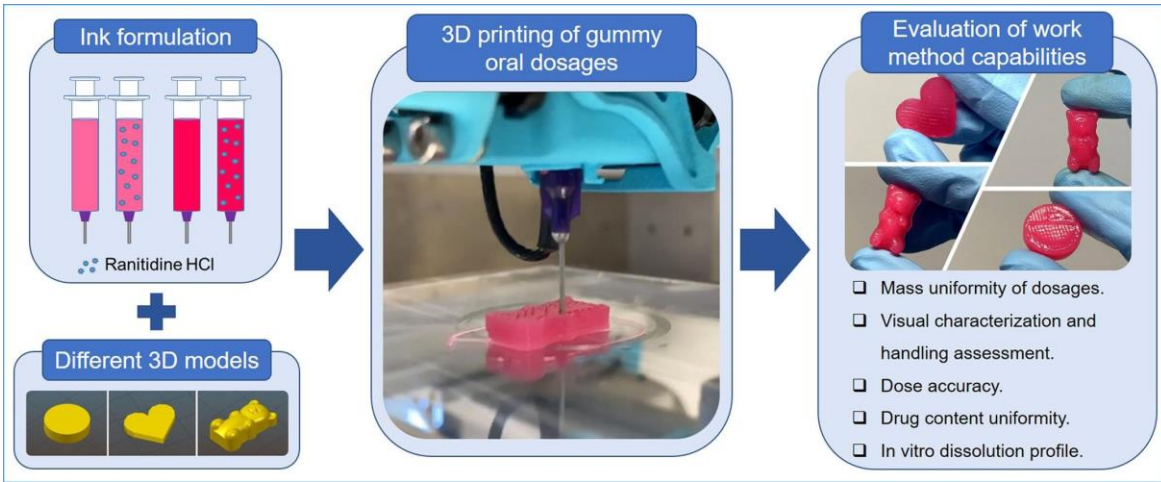
Compounding:
Standard medication (capsules)
Vs. **chewable isoleucine printlets**



N=4
3-16 yo



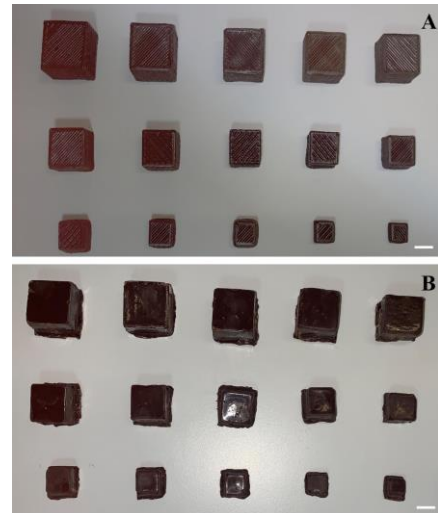
hydrophobic (ibuprofen) or a hydrophilic (paracetamol)



doi.org/10.1016/j.xphs.2022.04.013

doi.org/10.1016/j.ijpharm.2020.119687

A. 3D printed
B. molded
chocolate dosage forms
Scale bar: 1 cm



PARACETAMOL

doi.org/10.1016/j.ijpharm.2022.121991

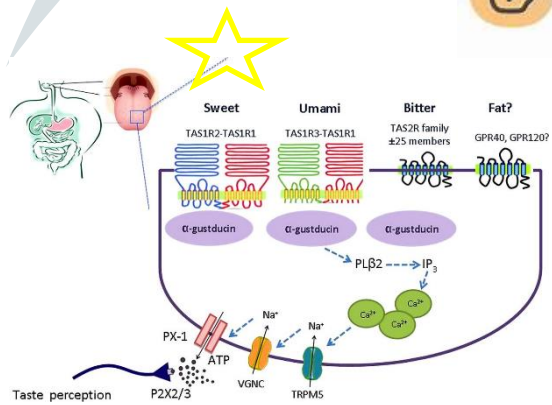
Pleasant/desirable?
recreational
Boosted Compliance

OK/unpleasant
tiresome
compromised safety





Therapeutic success



'I know I should never take any medicine that isn't meant for me'
 'I know medicine can be dangerous if you take the wrong amount. It tells you on the label how much to take'
Always use medicines safely!
 'I only take medicines when a grown up I trust gives them to me'
 'I know it is important to store medicines out of reach of younger children'
 'I know medicines are NOT sweets and that they can be harmful'

The medicines industry supporting science education
 www.alphatech.org.uk

Formulation /Dosage form design factors
Administration factors

Sensory Pharmaceuticals™



Round table

