Perspectives on the Need for Improved (Pediatric) Formulations

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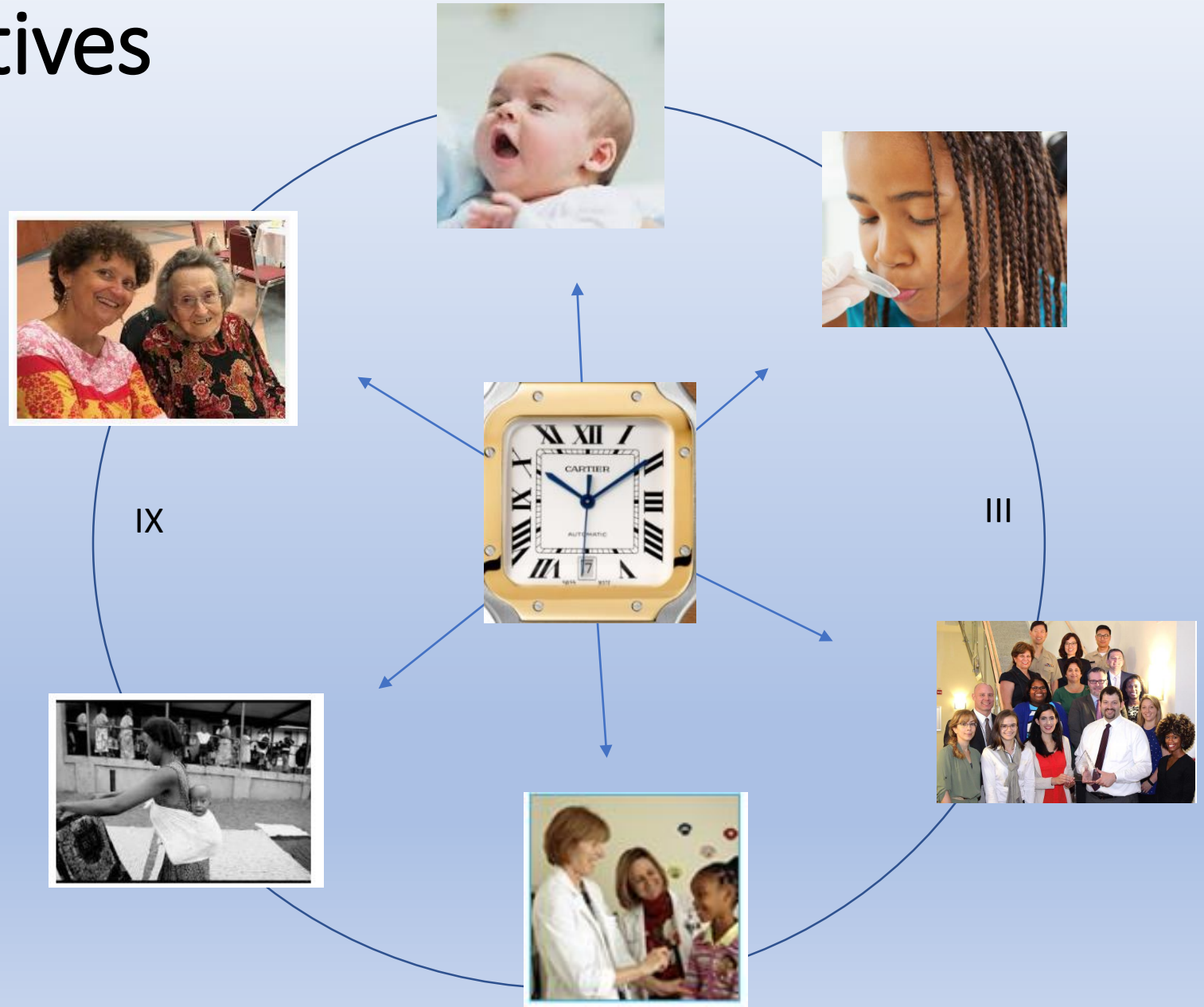
Perspectives



Meropenem 500 mg Vial

Dose for premature neonate:

10 mg/kg x 0.5 kg = 5 mg

Hydroxyurea 500 mg capsule

Dose for 9-month old with Sickle Cell

Anemia: 20 mg/kg QD x 8 kg = 160 mg

Isotretinoin 10 mg capsule

Dose for 2-year old with neuroblastoma:

80 mg/m^2 PO BID x 0.5 m^2 = 40 mg PO BID

Pediatric formulations 2019

Some Drugs in Need of Reformulation

- **Baclofen**
- **Hydroxyurea**
- **Prednisone (taste)**
- ~~**6-mercaptopurine**~~, ~~**methotrexate**~~
- ~~**Liquid-stable L-thyroxine**~~
- ~~**Albendazole**~~
- **Isotretinoin**
- ~~**Isoniazid**~~

Albendazole

DOSAGE AND ADMINISTRATION
Patients weighing 60 kg or greater, 400 mg twice daily; less than 60 kg, 15 mg/kg/day in divided doses twice daily (maximum total daily dose 800 mg). ALBENZA tablets should be taken with food.

Albendazole 200mg Tablet

This medicine is a white, round tablet imprinted with "C237". and is manufactured by Cipla USA, Inc

Current Methods of Making Pediatric Formulations

- **Tablet splitting**
- **Tablet crushing, adding to liquids/soft foods**

Tablet Splitting of a Narrow Therapeutic Index Drug: A case with levothyroxine sodium

Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ, Khan MA. AAPS Pharm Sci Tech 2010; 11(3):1359-1367.

Fig. 2. Marketed levothyroxine tablets (L-3) cut with hand and tablet splitter. Tablet splitter produced more fragments for all the tablets (only figure for L-3 is shown here)

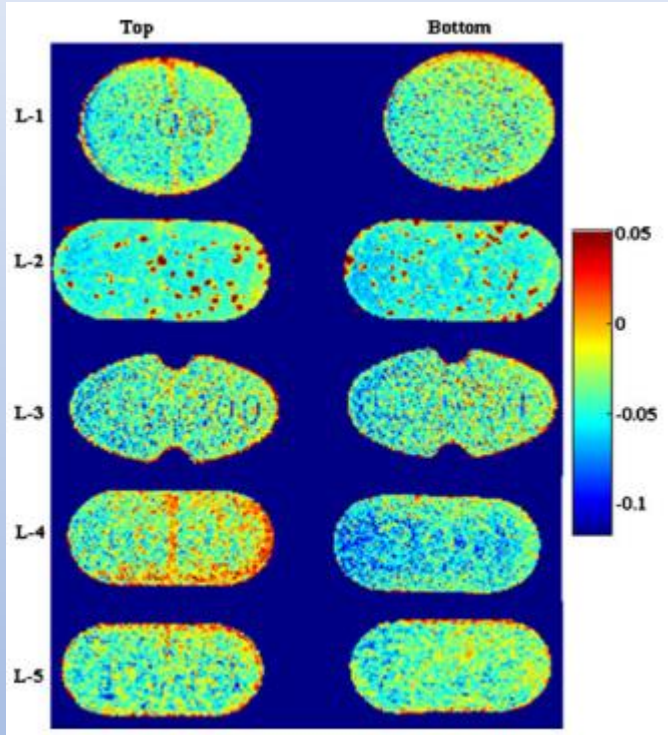


Fig. 4. NIR chemical images of marketed levothyroxine sodium tablets (L-1 to L-5) with factor index of levothyroxine sodium

DOI: 10.1208/s12249-010-9515-8

Ideal Oral Pediatric Dosage Form

- **Tasteless/taste-masked**
- **With minimal excipients**
- **In flexible dosage increments**
- **Orally dissolvable, or easy to swallow or dissolve in small amount of liquid**
- **Heat, humidity and light stable**

Industrial Pharmacy
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Improving the Palatability of Minitablets for Feline Medication

by

Jaana Hautala

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Pharmacy of the University of Helsinki, for public examination in Auditorium 2041 at Biocenter 2 (Viikinkaari 5E, Helsinki) on March 31st 2017, at 12.00 noon.

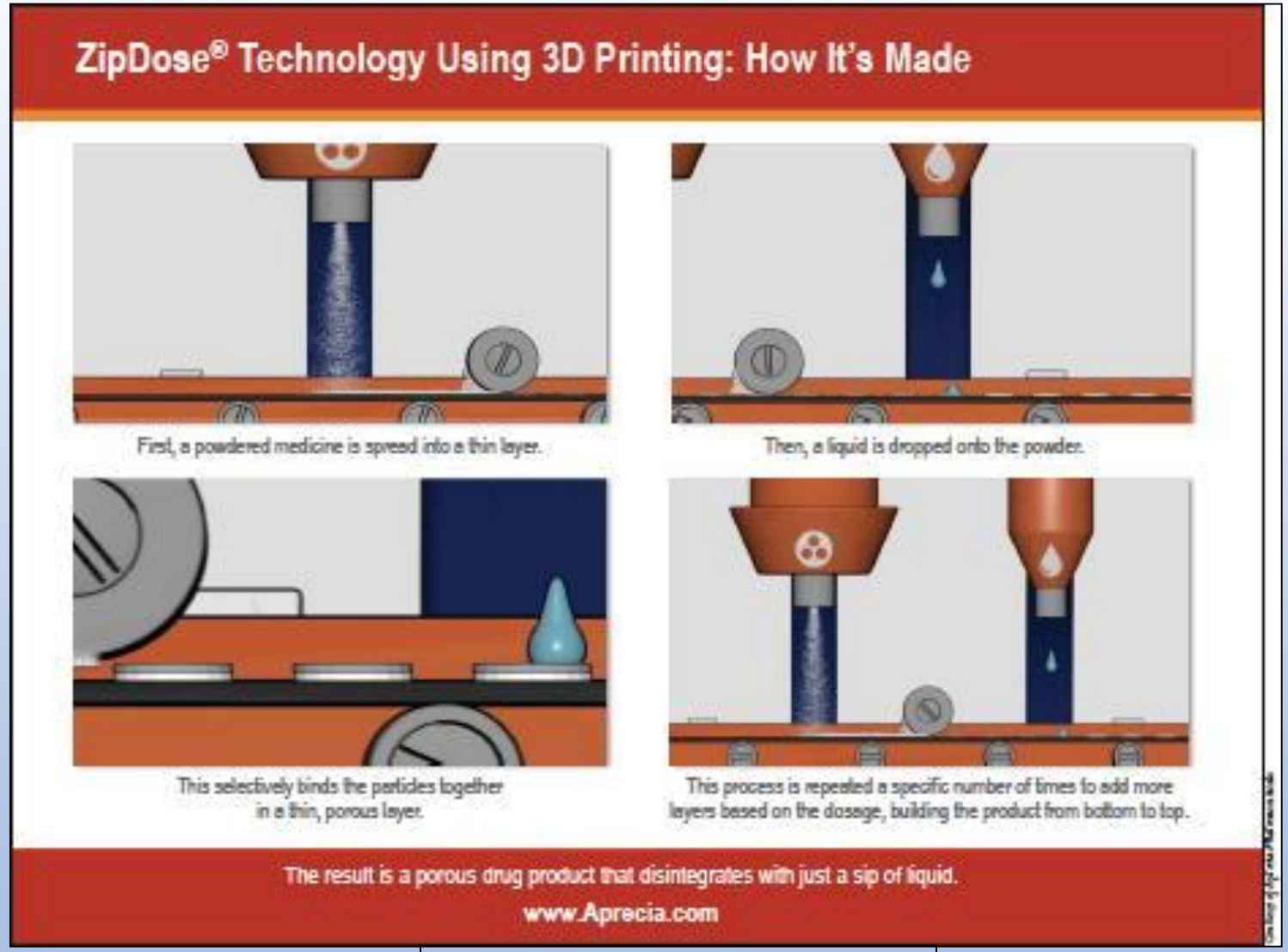
Helsinki 2017

https://pdfs.semanticscholar.org/3ba8/a081f8fd90f526d60b4c07a23aa2b13050f3.pdf

NIH-FDA Inter-Agency Agreement: Pediatric Formulations Platform

https://www.nichd.nih.gov/research/supported/bpca/research-initiatives-collaborations

- Perform an **assessment of all commercially available products** to determine which have pediatric formulations.
- Determine what **technologies are publicly available**, how these technologies have been used, and for what types of products.
- Use **prototypical drug products and computational methods** to distinguish their molecular structure through characteristics such as solubility, permeability, light sensitivity, pH instability, heat instability, hygroscopic properties, and bitterness.
- Determine the **best formulations technology** for specific drug categories based on information from tasks 1–3.
- Produce **prototype batches** of selected drug products.



FDA Approves First 3D-Printed Epilepsy Drug Experts Assess the Benefits and Caveats.
Fitzgerald, Susan

Neurology Today. 15(18):26-27, September 17, 2015.
DOI: 10.1097/01.NT.0000472137.66046.b5

3D printing

EPILEPSY FOUNDATION

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The First FDA Approved Drug Made by a 3D printer is Levetiracetam

Back

LISTEN: INTERVIEW WITH APRECIA CEO DON WETHERHOLD

Epilepsy.com Editor-In-Chief Dr. Joseph Sirven interviews Aprecia CEO Don Wetherhold about Spritam, the first 3D printed drug.

RELATED LINKS:

- Seizure and Epilepsy Medicines

CONTENT HIGHLIGHTS

UPDATE: March 22, 2016

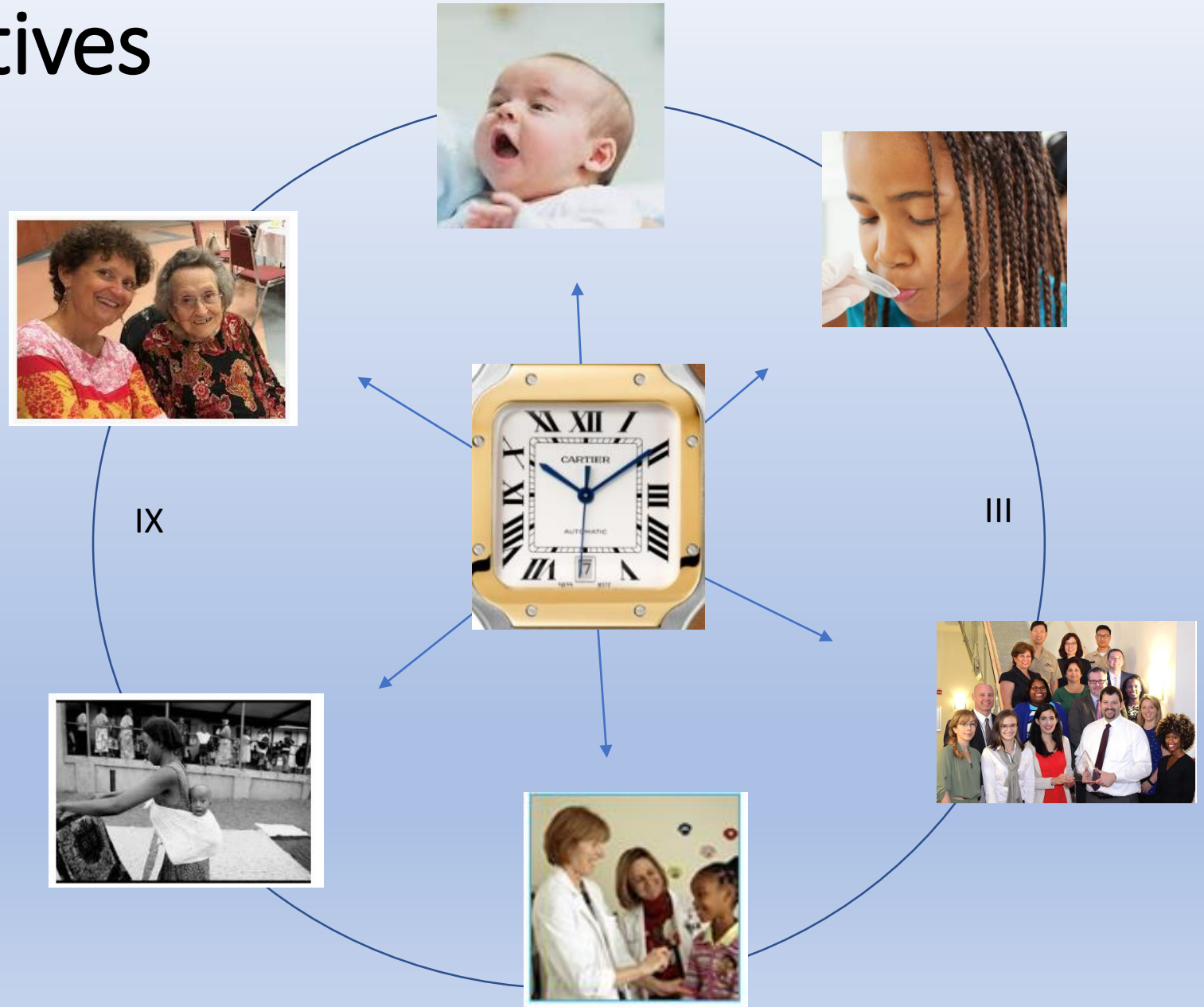
SPRITAM® (levetiracetam) tablets are now available. Read Aprecia Pharmaceuticals' annoucemnent.

Thermal Stabilization of Viral Vaccines in Low-Cost Sugar Films

Leung V, Mapletoft J, Zhang A, Lee A, Vahedi F, Chew M, Szewczyk A, Jahanshahi-Anbuhi S, Ang J, Cowbrough B, Miller MS, Ashkar A, Filipe CD> Nature Scientific Reports 2019; 9(7631)

https://www.nature.com/articles/s41598-019-44020-w

Perspectives



Child

- **Medication refusal due to taste,**
- **Inability to swallow tablets/capsules**
- **Disease relapse**

Pharmacist

- **Reformulation of solid oral dosage forms into liquids/suspensions**
- **Problem: Lack of stability data**

Pediatrician

- **Constraints in prescribing due to palatability, especially antibiotics**
- **Home drug reformulation by parents**
- **Disease relapse due to poor medication adherence (prednisone, antibiotics)**

Mother

- **Specific prescribing requests based on palatability: antibiotics**
- **Home drug reformulation**
- **Child's disease relapse due to poor medication adherence, need for more medical attention, missed work, school, sleep**

Daughter

- **Choking due to dental extractions**
- **Addition of medications to soft foods**
- **Compliance problems with liquids (taste) and solids (swallowing)**
- **Tablet crushing**

Summary

- **Technology has improved the capability to produce palatable and swallowable formulations**
- **Technology has not translated into much daily improvement in formulations, especially generics/off-patent drug products**
- **Availability of mini-tablets and oral dissolvable products, taste-masking, and new just-in-time technologies like 3D printing for small batches, would be a real improvement for children, adults, the elderly, physicians, and pets**

Thank you

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