New Scientific Directions in Oral Bioequivalence(BE):

[Implications for Product Development and QC Standards (QbD, PAT,BE)]

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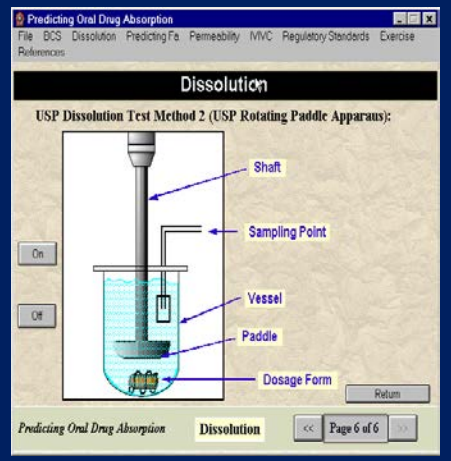
2010

1950

1970

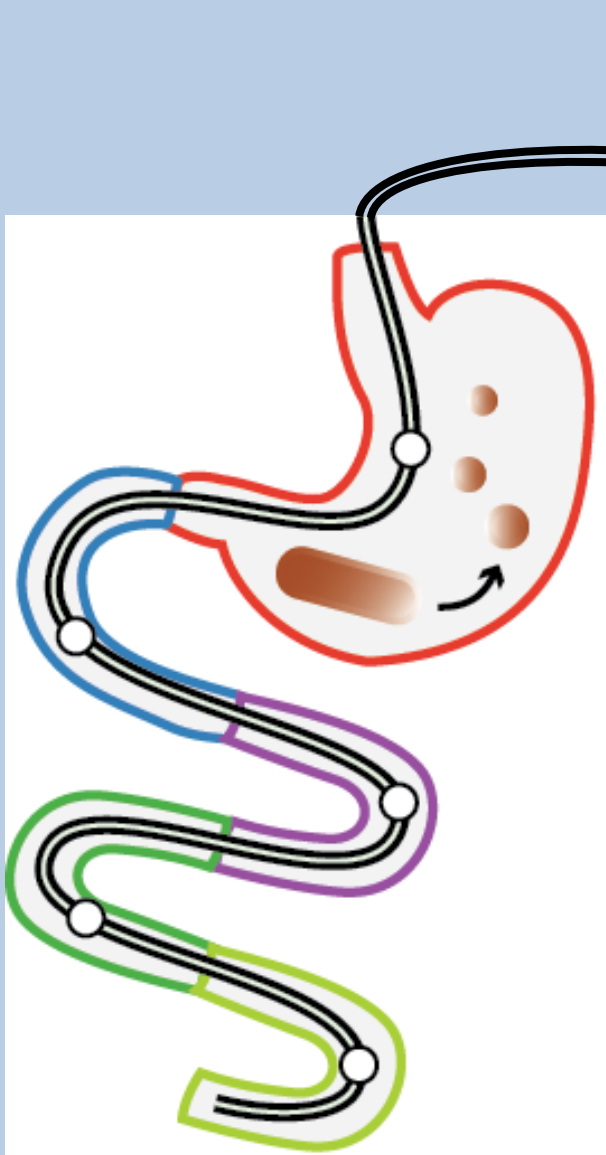


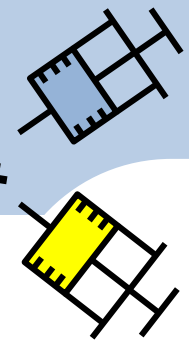
Regulatory Science Initiative, Oral: FDA 5-3-17

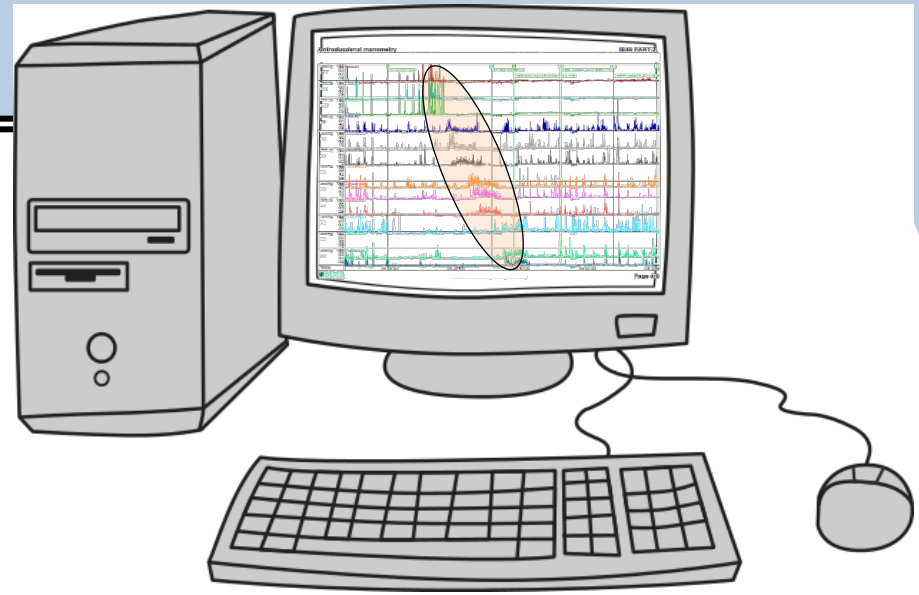
Our Goal as Pharmaceutical Scientists

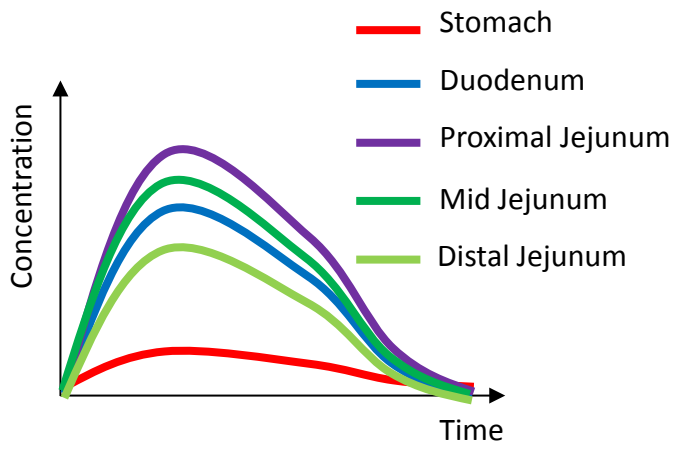
1) Gastrointestinal Concentrations

2) Motility Contractions



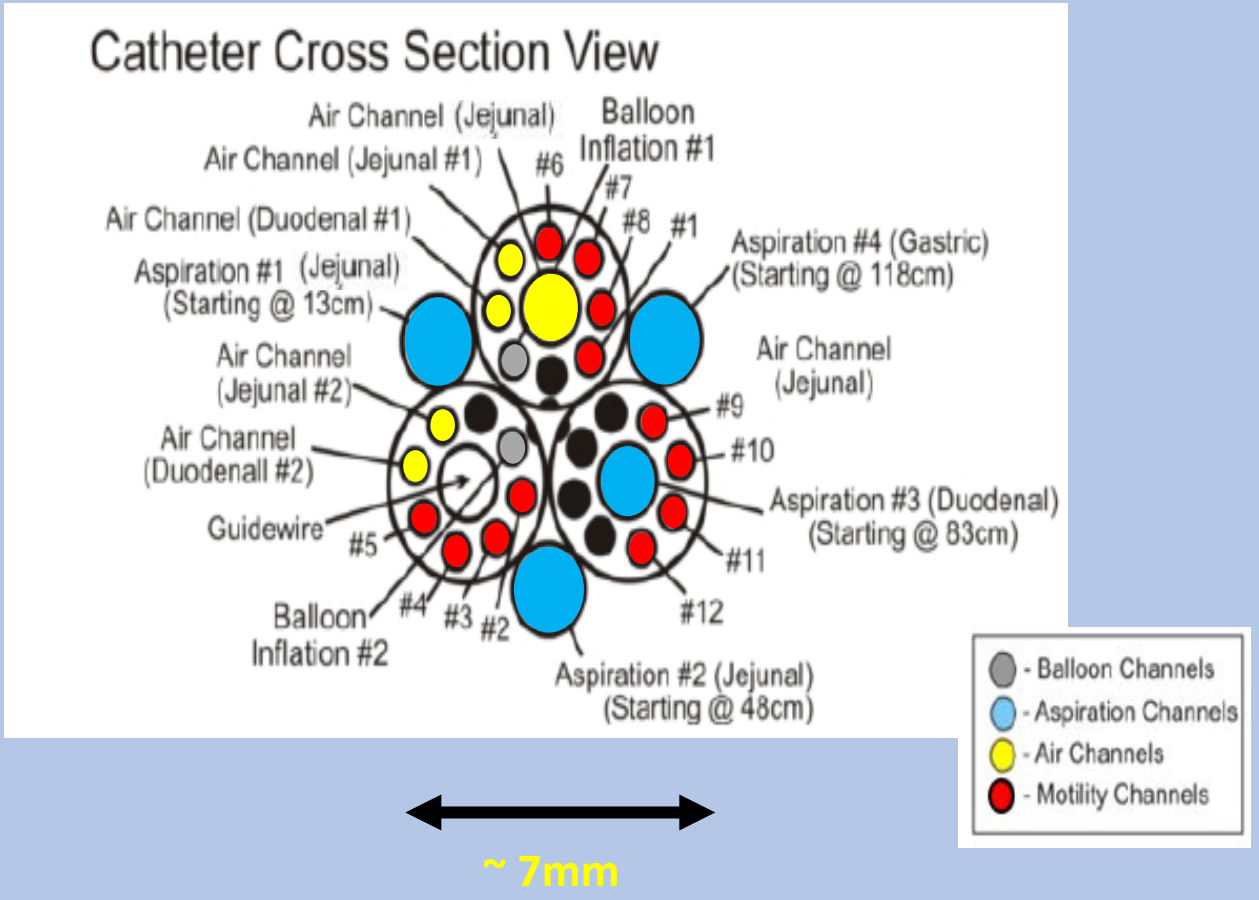




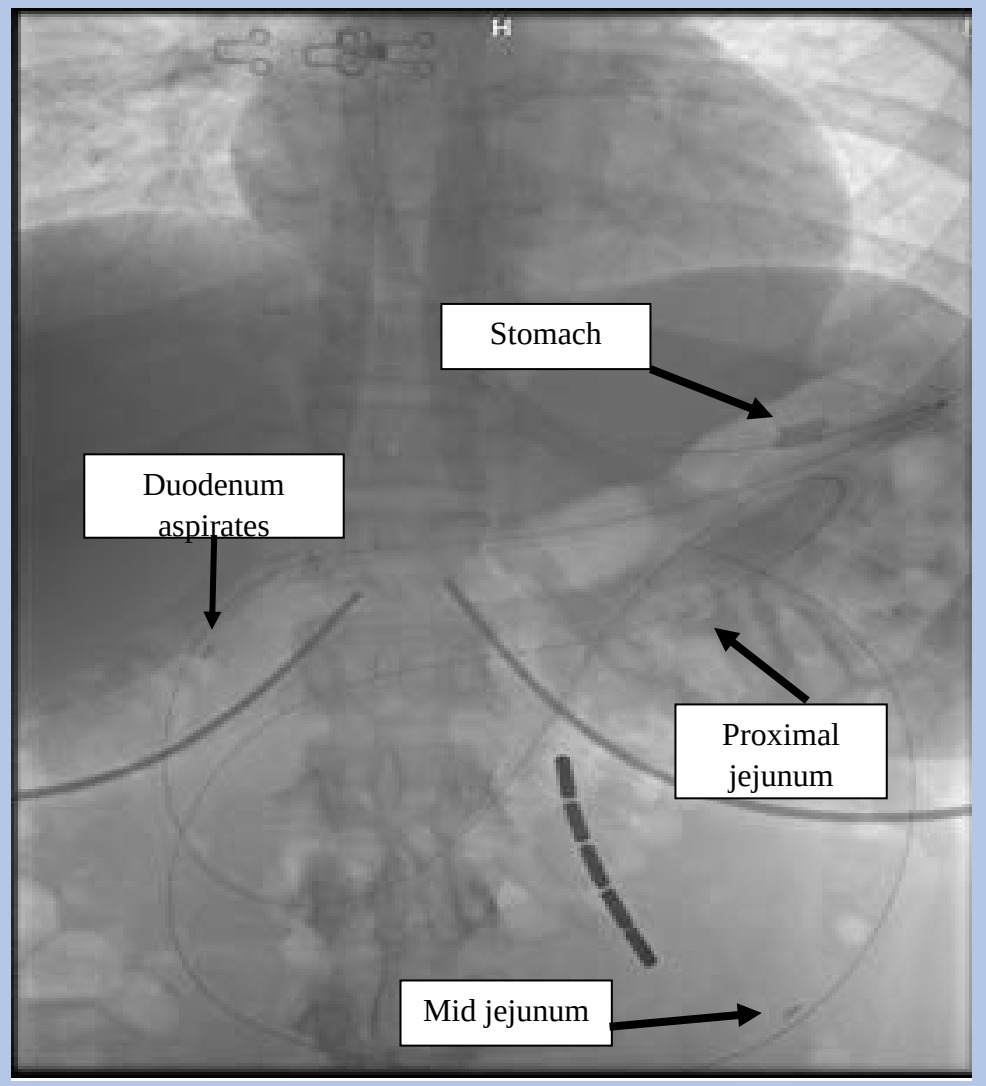


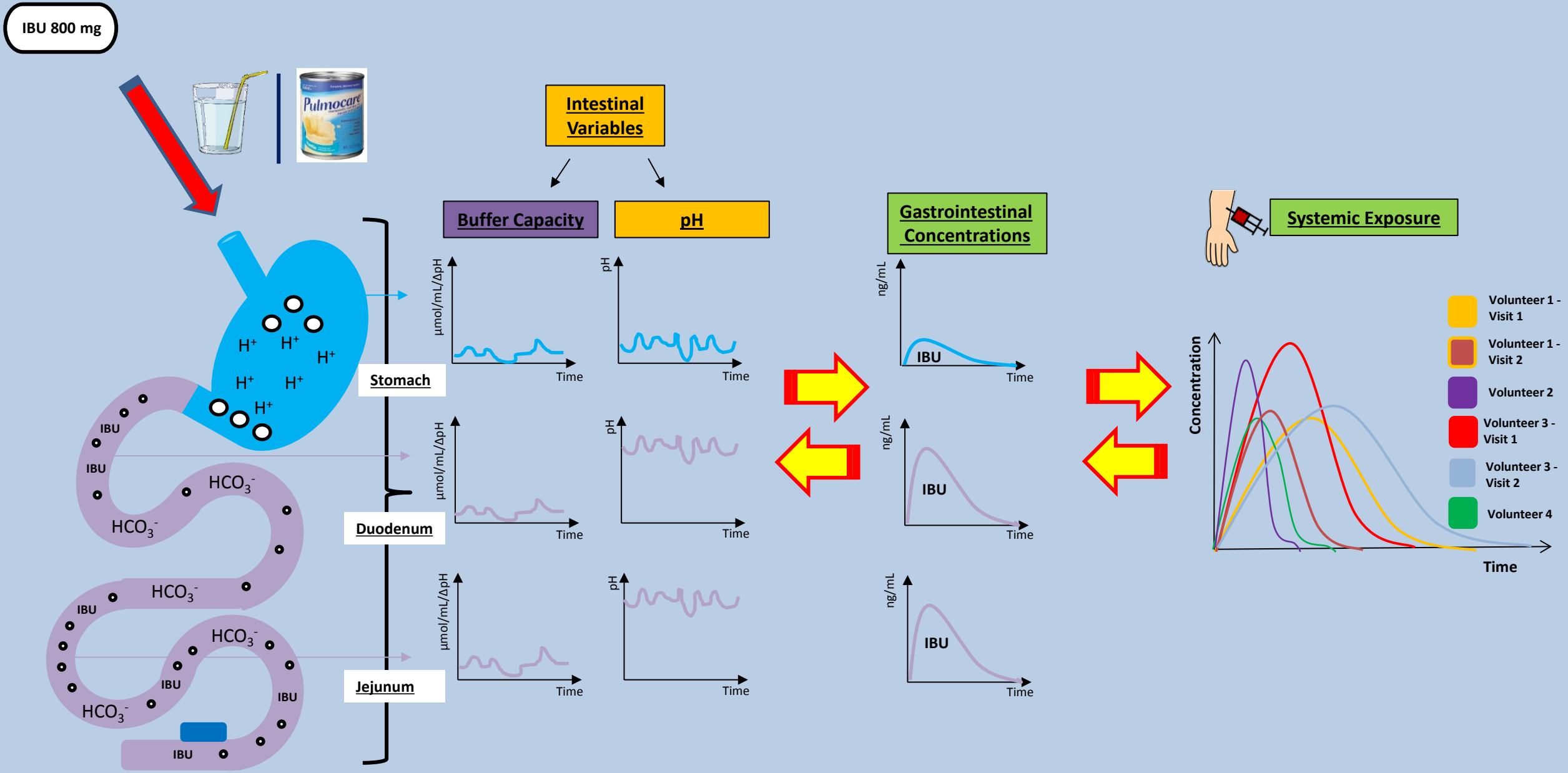
Measuring GI Variables

Tube Placement



Fluoroscopy

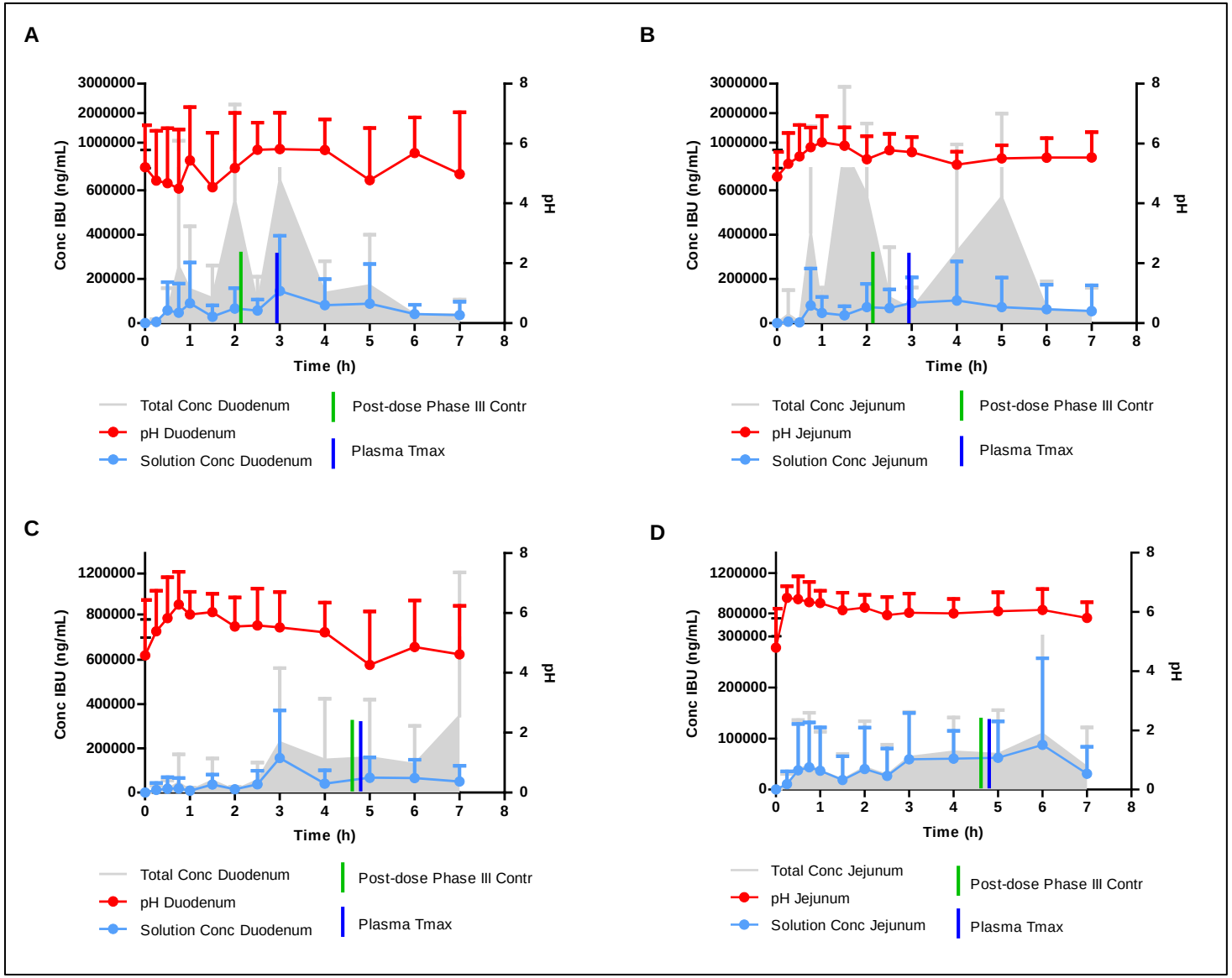



IBU 800 mg
Pulmocare
Intestinal Variables
Buffer Capacity
pH
Gastrointestinal Concentrations
Systemic Exposure
Stomach
Duodenum
Jejunum
H+
IBU
HCO3-
µmol/mL/ΔpH
pH
ng/mL
Time
Concentration
Volunteer 1 - Visit 1
Volunteer 1 - Visit 2
Volunteer 2
Volunteer 3 - Visit 1
Volunteer 3 - Visit 2
Volunteer 4

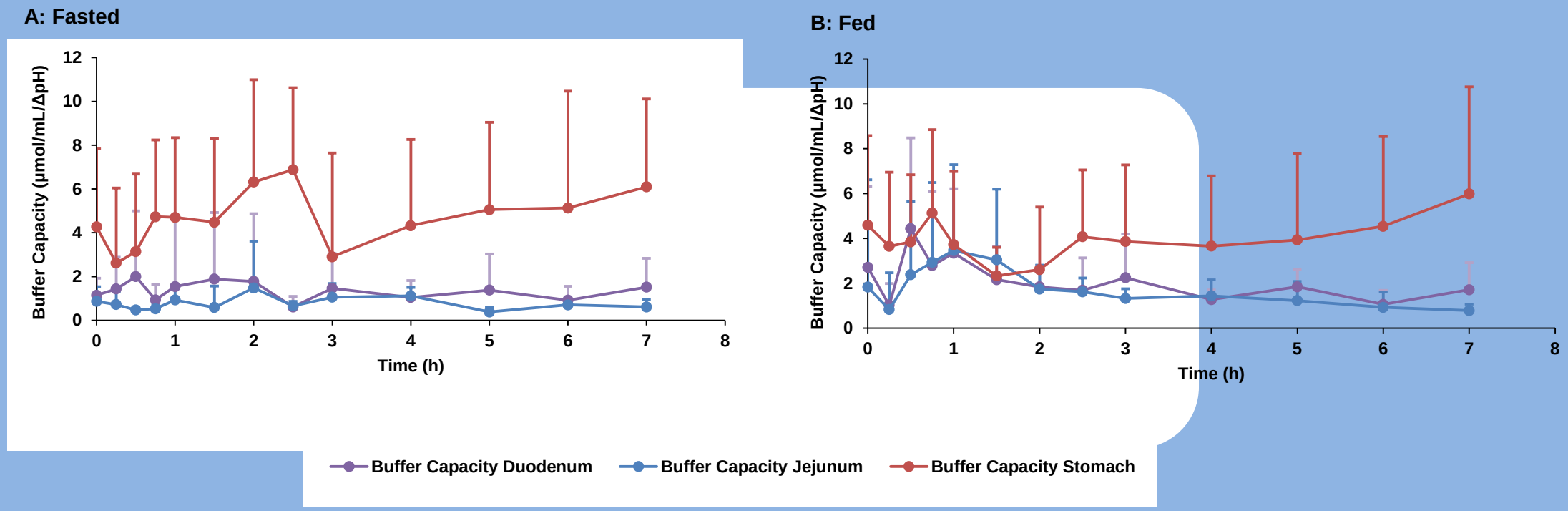
Gastrointestinal pH & Ibuprofen Levels

Fasted (A,B)

Fed(C,D)

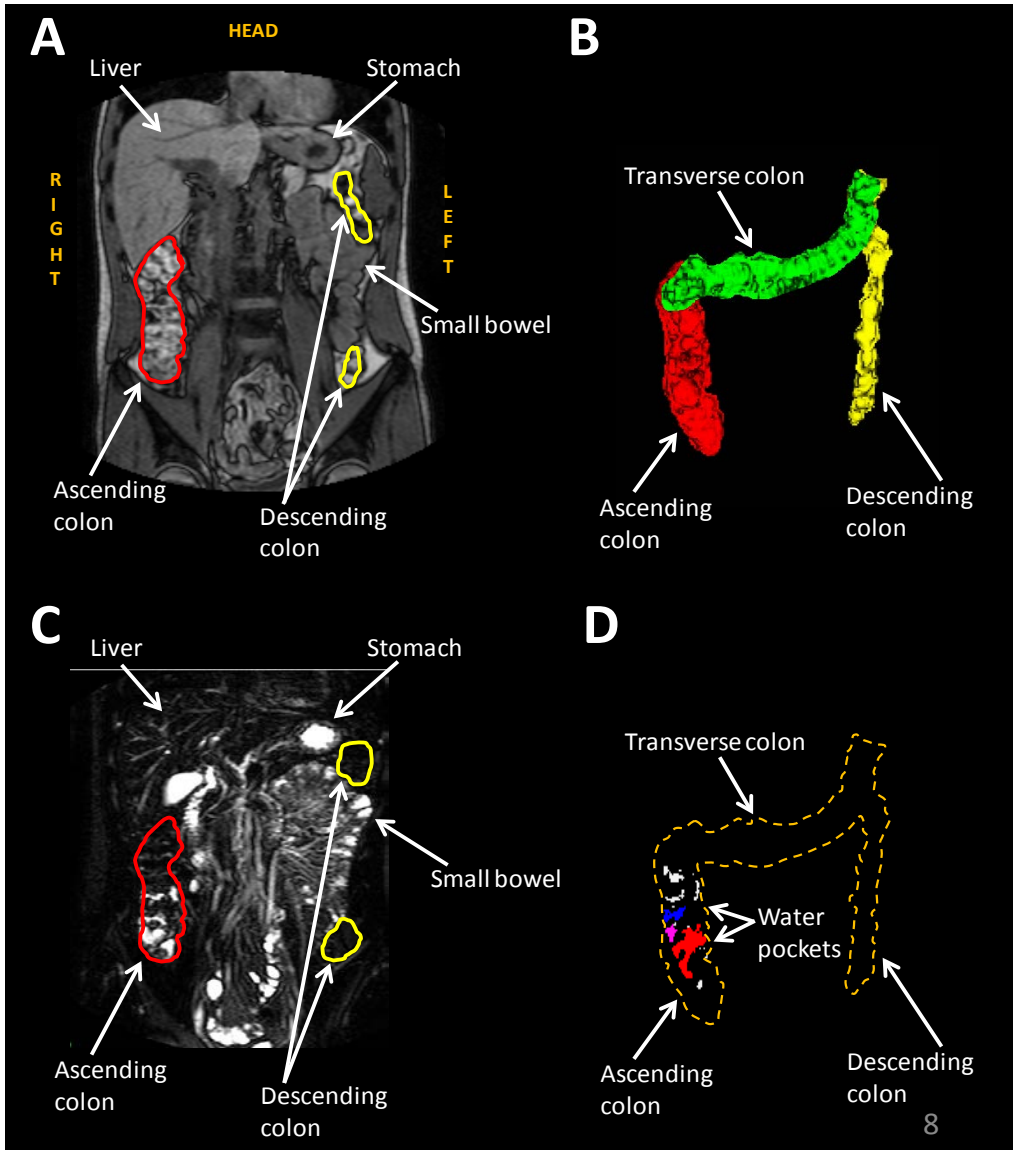


GI Buffer Capacity: Very Low



MRI GI Fluid Study

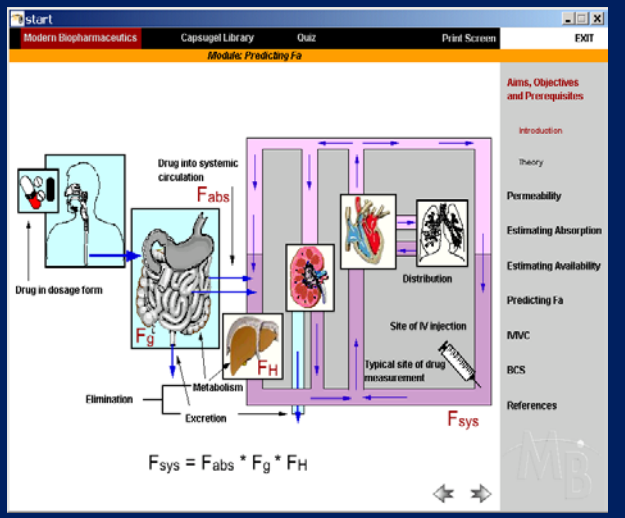
(Where we are Going)



New Scientific Directions in Oral Bioequivalence: Implications for Product Development, QbD, PAT, and QC

- Gastrointestinal (GI) Variables→ Drug Absorption→ Systemic Availability (Bioavailability)
  - What is controlling GI Drug Absorption/Systemic Availability (Cmax, AUC)
- We are performing Direct Simultaneous GI Measurement:
  - GI catheter and Plasma sampling
  - Variables, pH, Buffer, Motility, plasma levels (Fasted/Fed)
- Magnetic Resonance Imaging of GI fluid (MRI of GI water)
  - Validation of Catheter Results with MRI Results
  - Extend to pediatric, patients
- *In Vivo* Predictive Dissolution (iPD) Methodology

BCS: In Vivo->in Vitro



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*Funding: FDA
HHSF223201510157C
HHSF223201310144C

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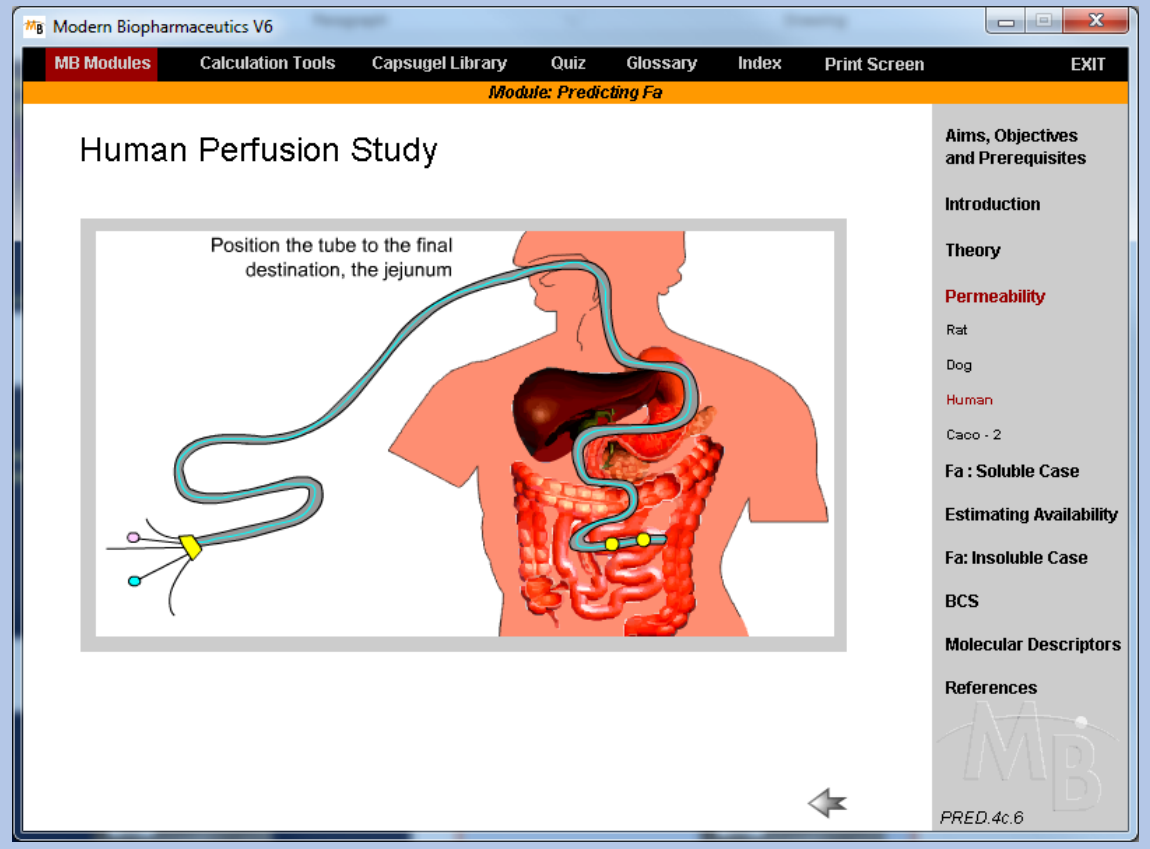

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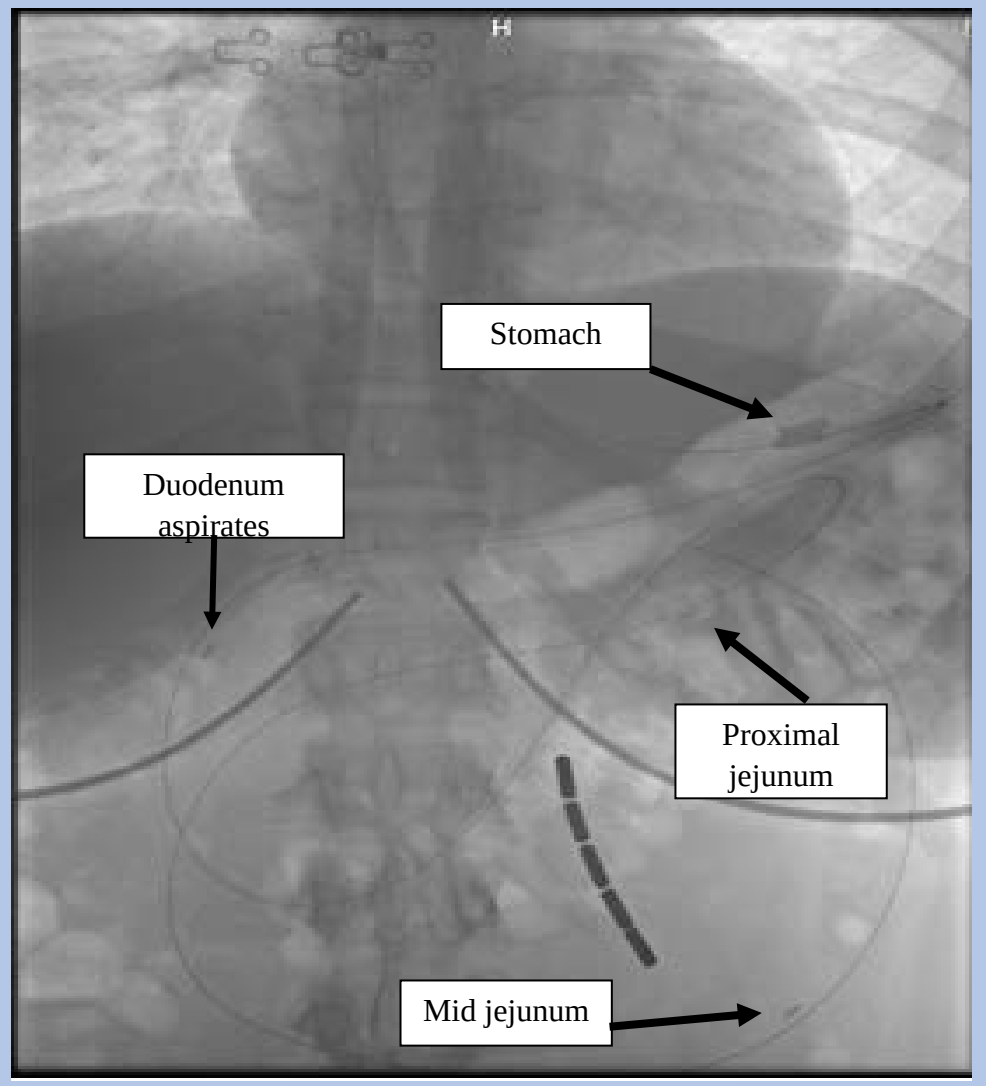


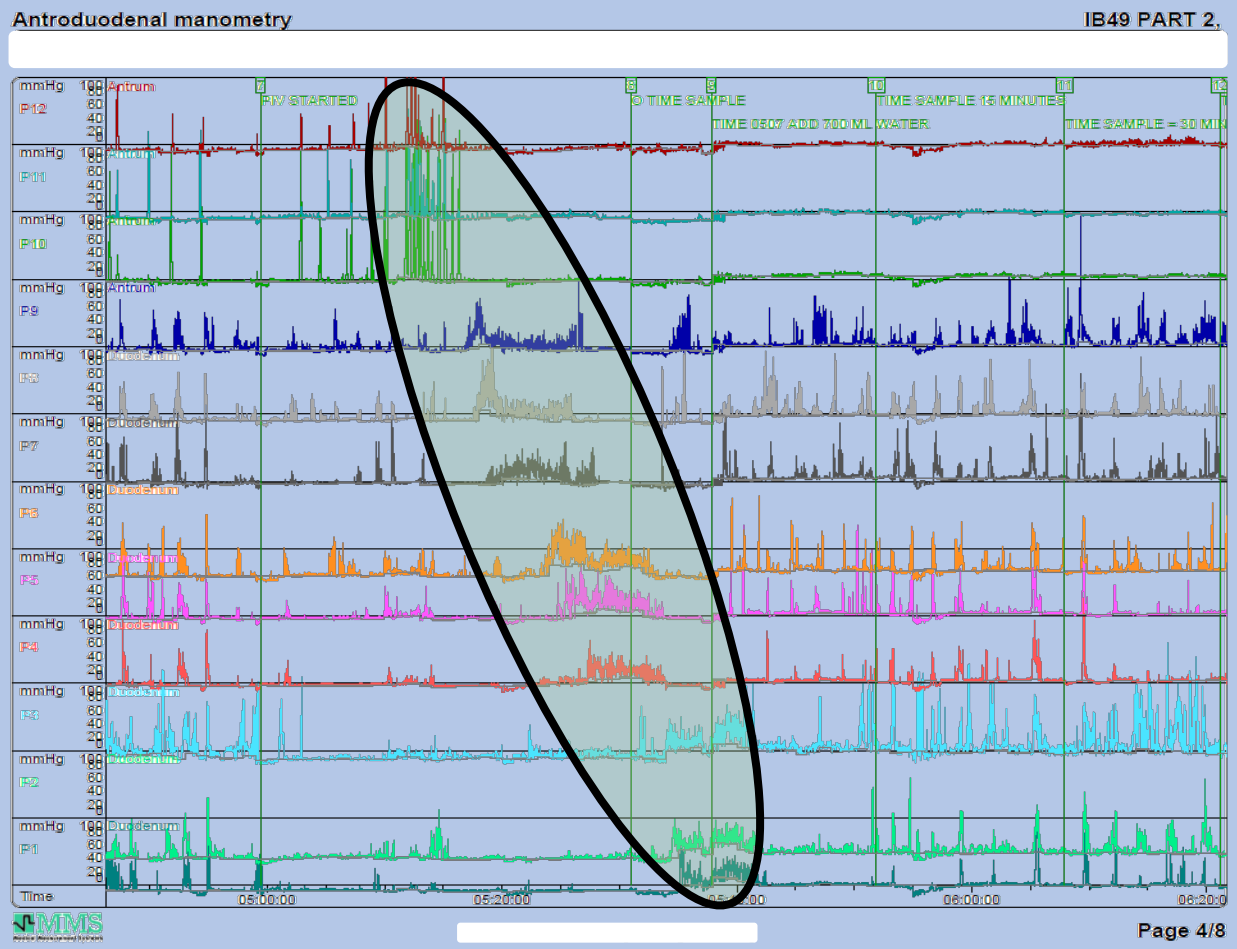
New Era in BE Science: Multidisciplinary

- Gastroenterologists (William Hasler, MD)
  - Catheterization, motility
- Statistical Analysis (Kerby Shedden, PhD)
  - Signal Analysis
- Chemical Engineers (Robert Ziff, PhD)
- Fluid Dynamics (James Brasseur, PhD)
- MRI Fluid (Luca Marciaini, PhD))
- Pharmaceutical Scientists (Gordon Amidon, PhD, Greg Amidon, PhD, Duxin Sun, PhD)

GI Motility (4 sample and pressure ports) at various sites: Fasted

[Phase I, II, III: BE Study Doses Randomly Relative to Phase)

Motility Phase II III I



Stomach

Duodenum

Proximal Jejunum

Distal Jejunum