TIM

RE-IMAGINING ORAL FORMULATION TESTING

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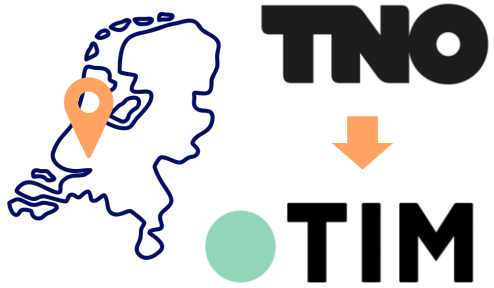
About The TIM Company

Predicting formulation performance

The TIM Technology was developed since >30 years

Most advanced *in vitro* GI model

High predictability for **in** vivo performance



The TIM Company is an independent **CRO** since 2020

TIM Studies complementing PK data & dissolution data

Accelerating drug development and reducing animal studies

TIM

Agenda

The TIM Systems explained

(Minekus *et al*., 1997; Bellmann *et al*., 2016)

Case Study 1: TIM predicts drug solubility with ARA co-administration

(Liu *et al*., 2021)

Case Study 2: TIMagc and Computational Fluid Dynamics

(Hopgood *et al., 2018)*

Case Study 3: Paracetamol Ring Study

(Manuscript in Preparation)

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The TIM Systems explained

Mimicking the GI tract for physiological relevant dissolution

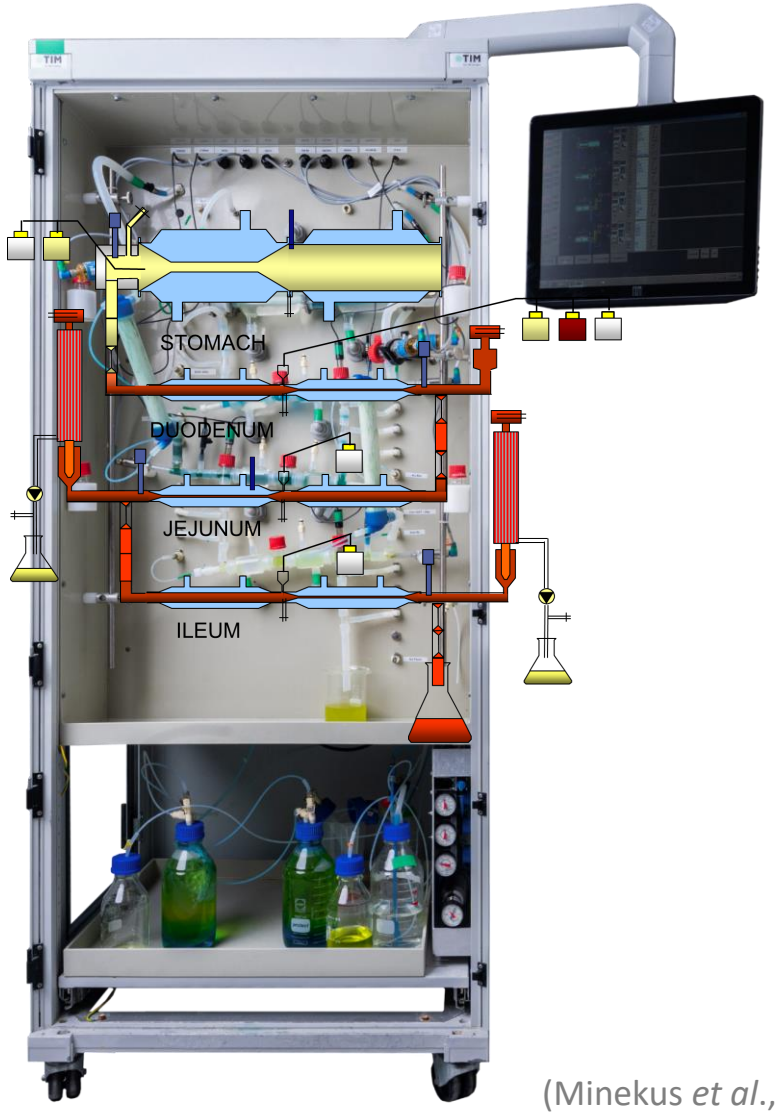
- TIM Systems are computer controlled **dynamic *in vitro* models**
- They **simulate** luminal conditions of the **gastrointestinal (GI) tract**
- Used for predicting **oral drug behavior**
- Applied in **preclinical candidate selection** of the high potential formulation &
- In vitro evaluation of (unexpected) findings in **clinical studies**

- Consist of serial glass vessels representing stomach, small intestine (and large intestine), i.e. TIM-1 / tiny-TIMsg (and TIM-2)

TIM - TNO Intestinal Models

Computer-controlled *in vitro* models simulating the upper GI tract

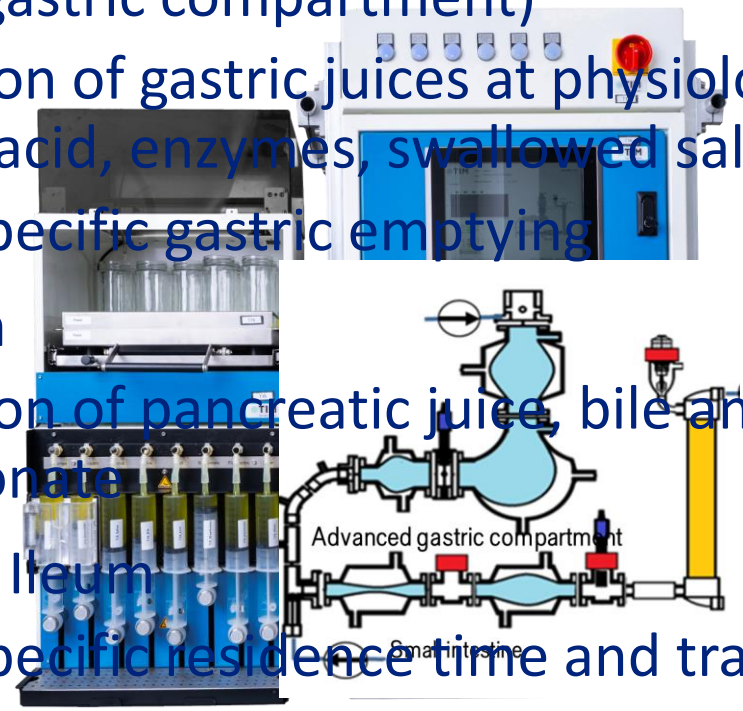
TIM-1



(Minekus *et al.*, 1997)

tiny-TIM*sg*

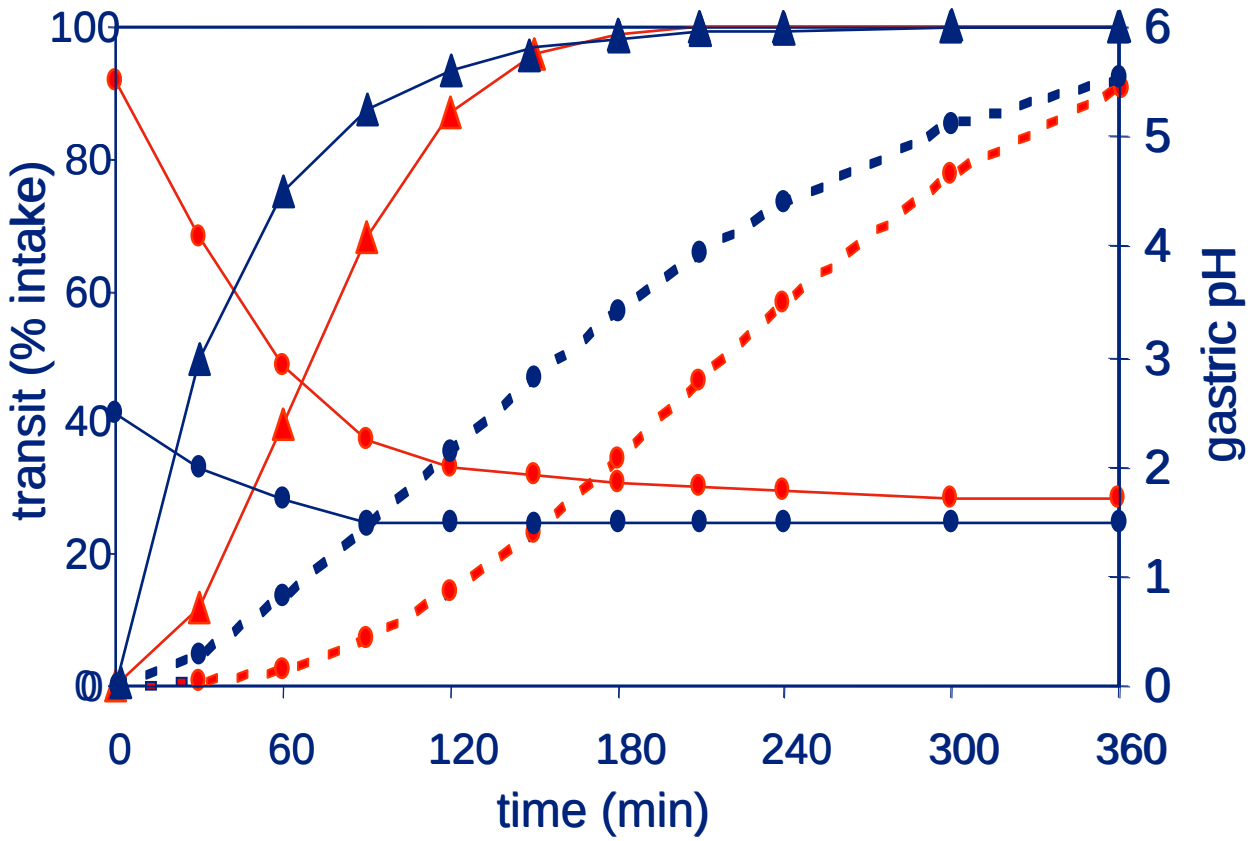
- Stomach (gastric compartment)
  - Secretion of gastric juices at physiological levels (acid, enzymes, swallowed saliva)
  - Food specific gastric emptying
- Duodenum
  - Secretion of pancreatic juice, bile and bicarbonate
- Jejunum & Ileum
  - Food specific residence time and transit
  - Absorption of dissolved compounds and water



(Bellmann *et al.*, 2016)

Dynamic Parameters simulated in TIM

Fasted versus Fed state conditions



- Controlled parameters include
  - meal specific gastric pH
  - gastric emptying
  - Small intestinal transit times
  - Adapted secretion levels

pH

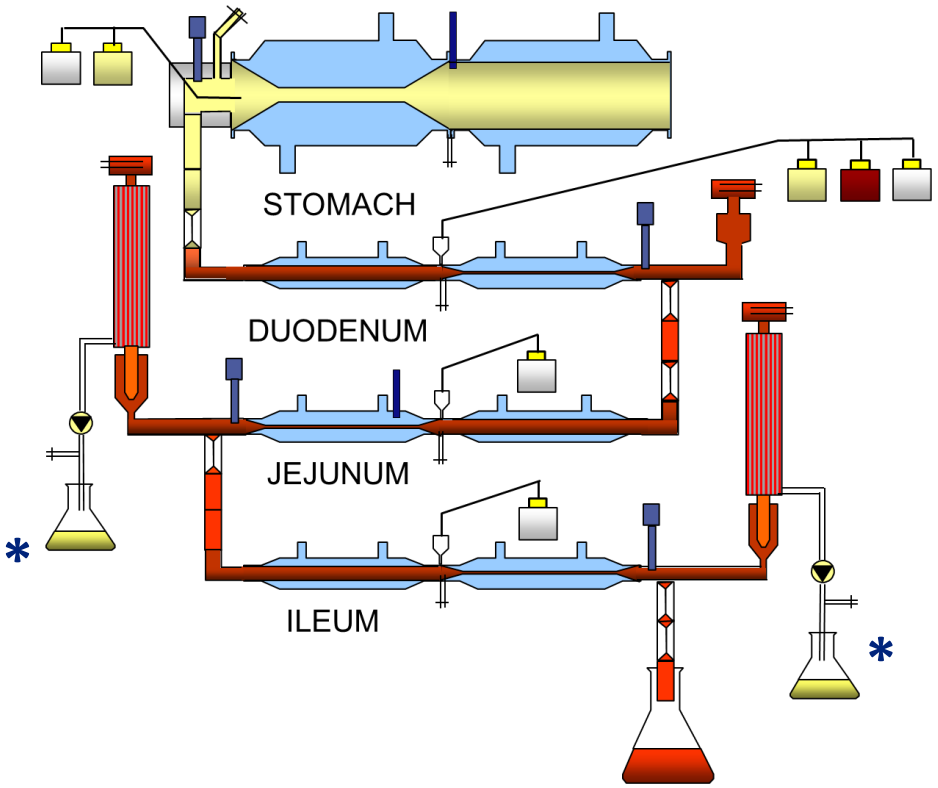
Fasted state
10-20% secretion
- gastric emptying
- Ileum effluent
- gastric pH

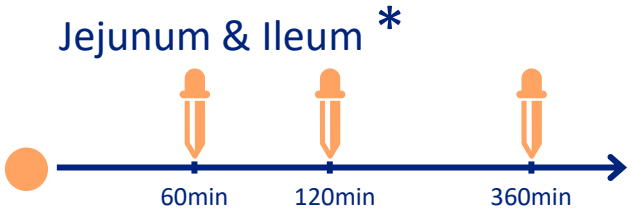
Fed state
100% secretion
- gastric emptying
- Ileum effluent
- gastric pH

(Elashoff *et al.*, 1982, Dresman *et al.*, 1990)

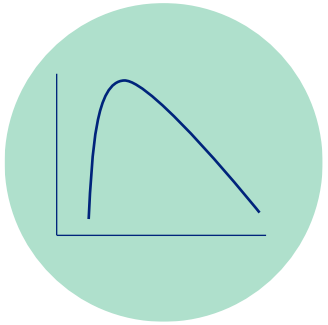
Sampling

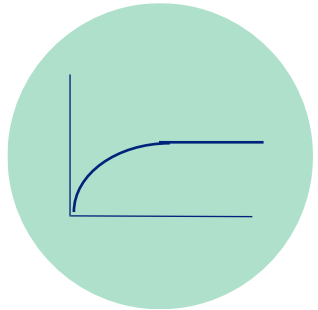
Measuring the fraction available for absorption - Bioaccessible fraction





- Removal / filtration of bioaccessible fraction over time
- Measuring API concentration
- Obtain the release profile of API





Predicting formulation performance

Services to support along the drug development pipeline

Bioavailability of drug substance e.g. API in liquid / capsule

Bridging Studies Bioequiavalnce (BE)

Preclinical Development	Phase I	Phase II	Phase III	Phase IV	Life cycle management

Lead formulation testing

Co-dosing Re-formulation

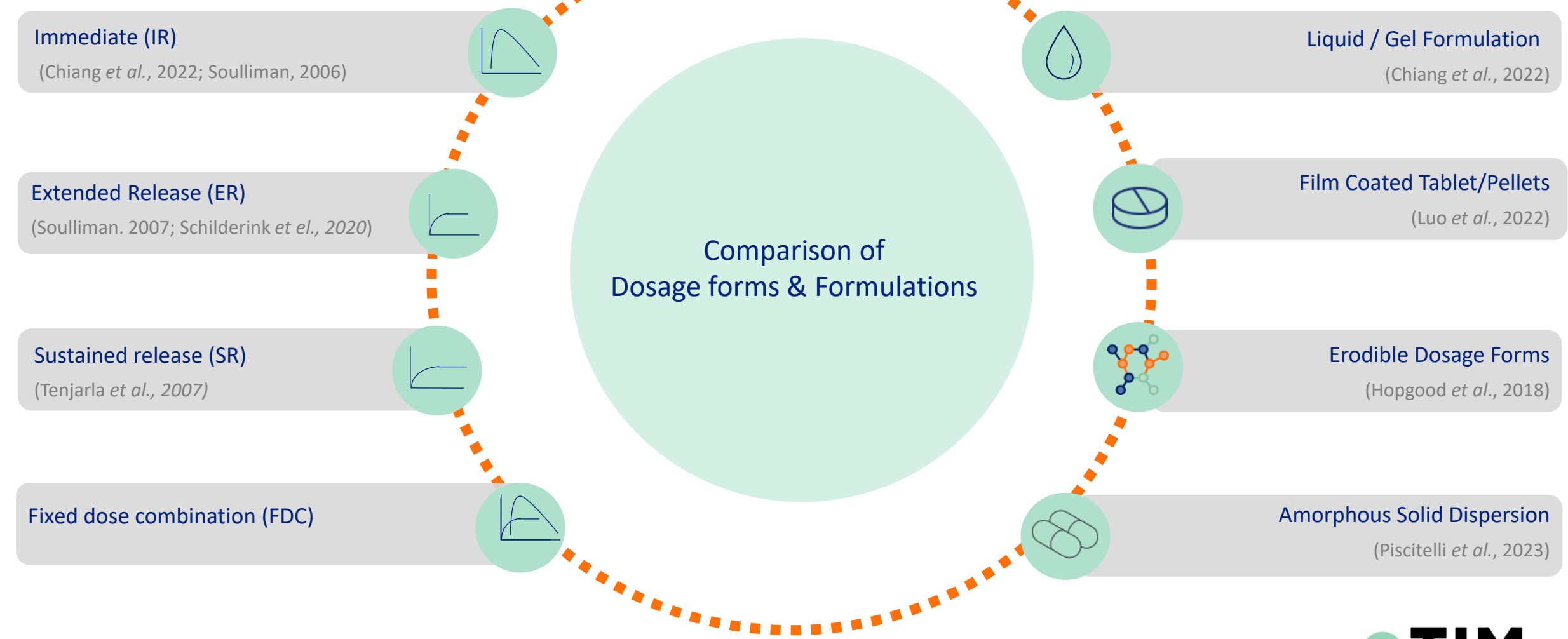
TIM Studies support

Compound selection between different drug substance modifications (different salts, dosage forms, and/or formulations and excipients) in **pre-clinical and clinical stage.**

Risk assessments related to **bridging** between formulations/compounds in **clinical stage or commercial manufacturing and life cycle management.**

FORMULATION COMPARISON

Drug Substance Modifications (salts/solid forms)



- Immediate (IR)
  (Chiang *et al.*, 2022; Soulliman, 2006)
- Extended Release (ER)
  (Soulliman. 2007; Schilderink *et el., 2020*)
- Sustained release (SR)
  (Tenjarla *et al., 2007)*
- Fixed dose combination (FDC)
- Liquid / Gel Formulation
  (Chiang *et al.*, 2022)
- Film Coated Tablet/Pellets
  (Luo *et al.*, 2022)
- Erodible Dosage Forms
  (Hopgood *et al.*, 2018)
- Amorphous Solid Dispersion
  (Piscitelli *et al.*, 2023)

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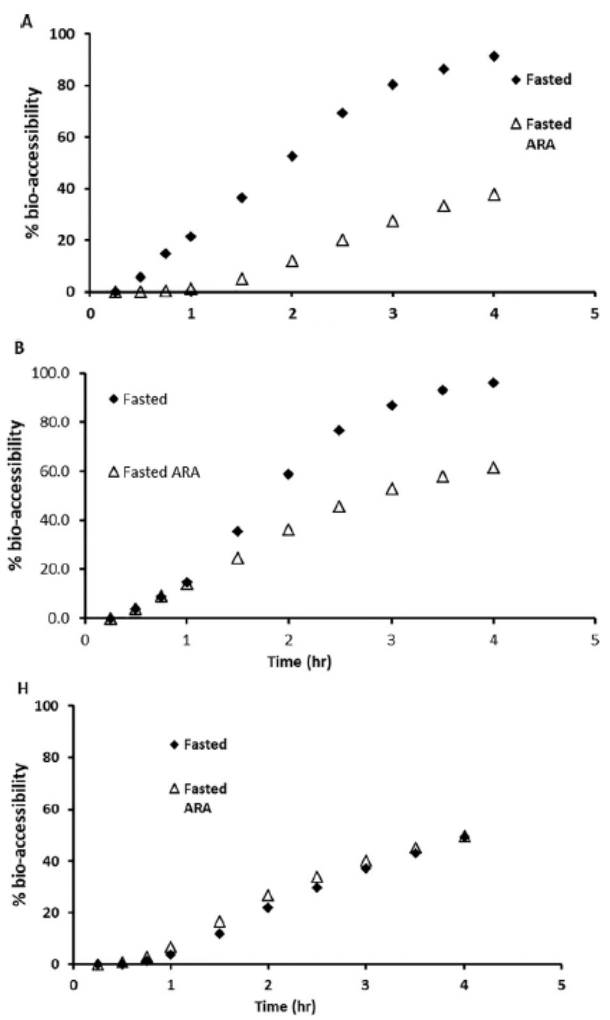
Effects on ARA* co-administration on oral drug absorption

tiny-TIM*sg* prediction matched clinical findings for all drugs tested

- Gastric pH elevation can affect drug solubility
- FDA: Necessity to predict effect of co-administration of drugs with acid-reducing agents, early in development, to prevent formulation delays and increased costs
- 12 model- & approved compounds were tested in tiny-TIMsg during simulation of fasted and fasted ARA conditions



ratio fasted : fasted ARA

Dasatinib
0.4 in TIM vs 0.4 in vivo
(Sugano et al, 2012)

Dipyridamole
0.6 in TIM vs 0.63 in vivo
(Sugano et al, 2012)

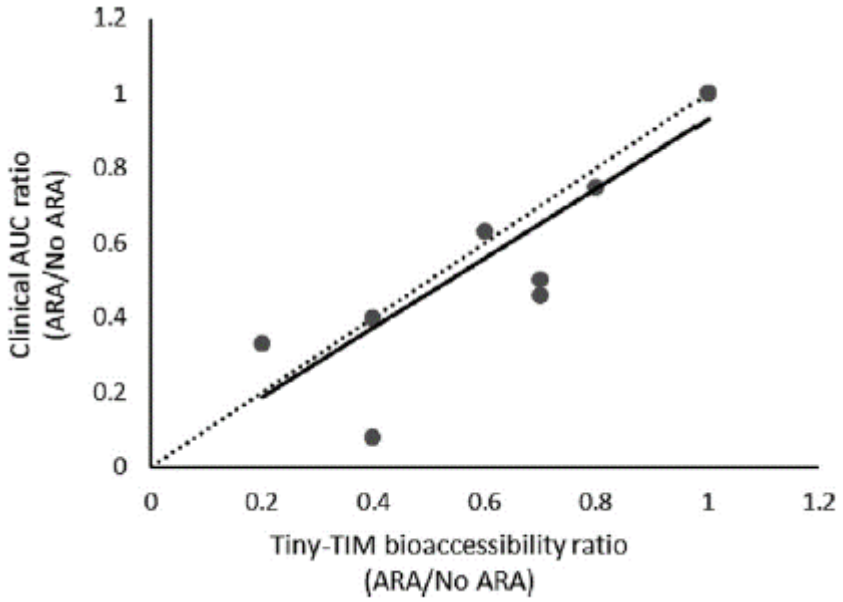
Alectinib
1 in TIM vs 1 in vivo
(Morcos et al, 2017)

*ARA = acid-reducing-agents

(Liu *et al.*, , 2021)

Effects on PPI co-administration on oral drug absorption

tiny-TIM*sg* prediction matched clinical findings for all drugs tested



- tiny-TIMsg predictions matched clinical findings of ARA effects for all 12 compounds, for free bases and even salts at low doses
- With 8 of 12 compounds having a high* predictivity and 4 out of 12 compounds with moderate** predictivity

*experimental ratio is < 0.2
** experimental ratio is > 0.2

Ratios of bioaccessibility from tiny-TIMsg and in vivo (AUC_{0-24}) result in a linear regression, indicating high predictivity

(Liu *et al.*, , 2021)

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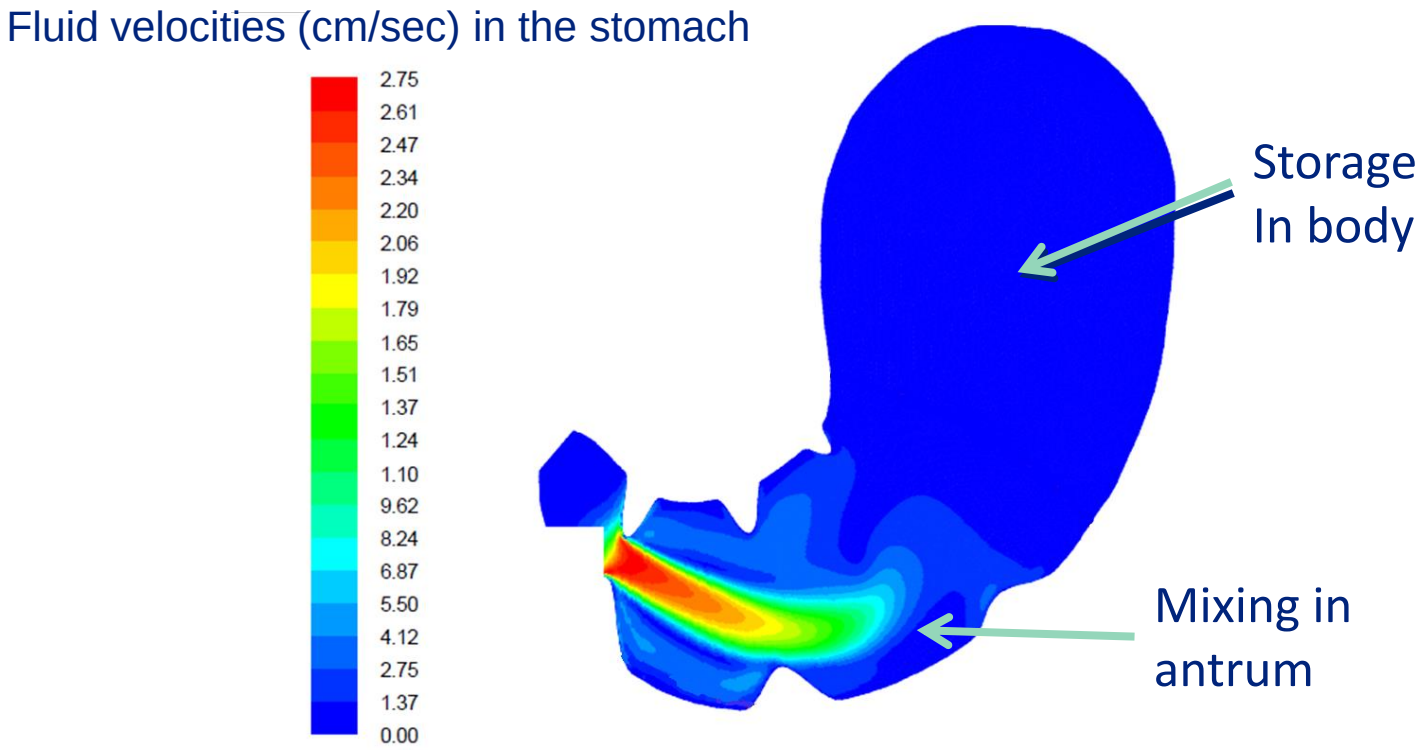
Why an advanced gastric compartment

Gastric content is not homogeneous in vivo

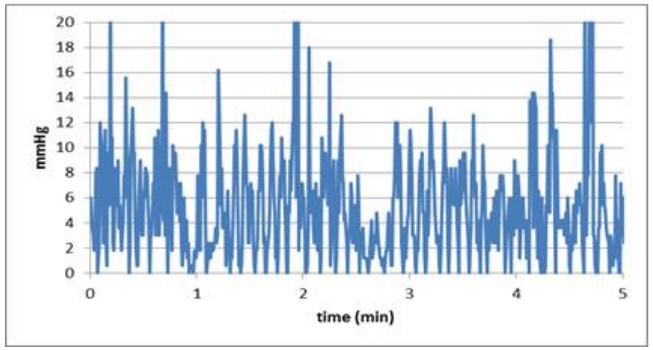
Regional mixing, liquid flows and pressure forces

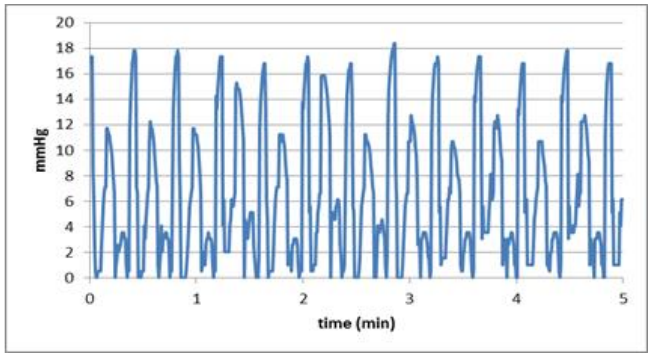


(Ferrua and Singh, 2010)

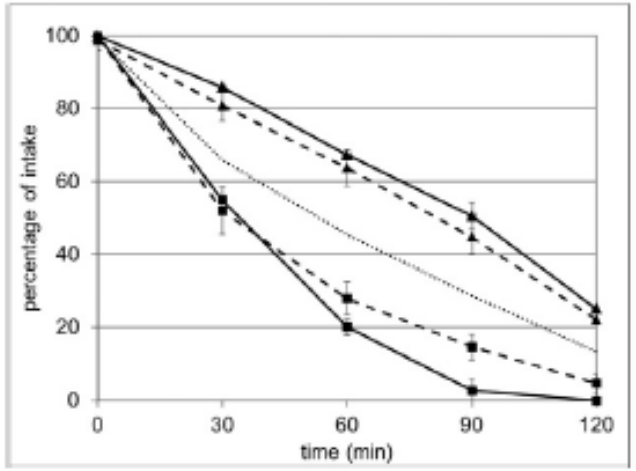
Dynamic Parameters simulated in TIM

Pressure & shear forces





- Pressure profiles obtained from the smartPill® in the human stomach (left) and in TIMagc (right).



(Bellmann *et al.*, , 2016)

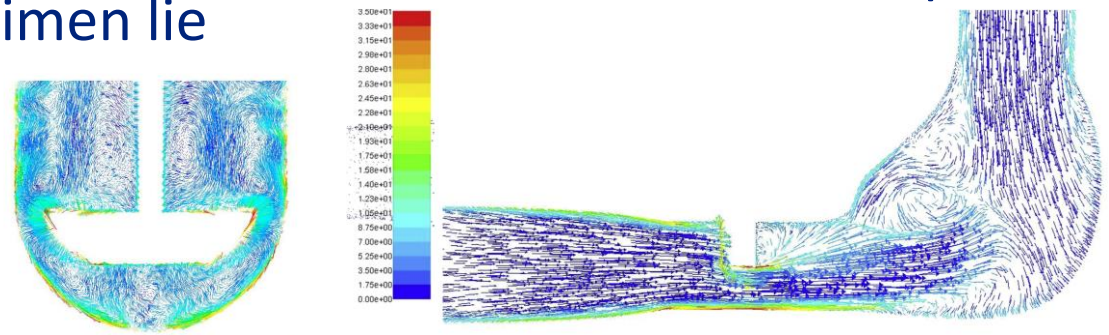
TIMagc and Computational Fluid Dynamics

Erodible dosage forms (AGC vs USP II)

- How does shear rate impact an erosion-based solid oral dosage form ?

- Shear rates are constant for a given paddle speed and increase linearly from 9 to 36s-1 with paddle sped from 25 to 100 rpm
- Strong relationship between tablet shear rate and tablet erosion rate
- Reynold numbers for flow regimen lie above predicted upper bound

- Shear rates in TIMagc are strongly time dependent and fluctuate between 0.0001 and 360 s-1
- Highly variable behavior
- Reynold numbers for flow regimen lie between predicted in vivo bounds



(Hopgood *et al.*, 2018)

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Paracetamol Ring Study

Multisite study shows high reproducibility and repeatability

- Study set up: 500 mg paracetamol dosed:
  - 5 tiny-TIMsg & 4 TIM-1 Systems
  - 2 conditions (fasted & fed)
  - Experimental run time 5 and 6hrs
  - hourly filtrate samples (SI compartment)
  - Samples analyzed at each site
  - 7 sites

	Fasted state	Fed state
Meal	Glass of water	FDA recom. HFM
Gastric emptying t½ [min]	20	80
Gastric pH gradient	3.0 – 1.7	6.5 – 1.7
Small intestinal pH (duo, jej, ile)	6.3 6.5* 7.4	5.9 6.5* 7.4
Small intestinal emptying t½ [min]	140	220

* average small intestinal pH for tiny-TIM*sg*

(Manuscript in preparation, 2022)

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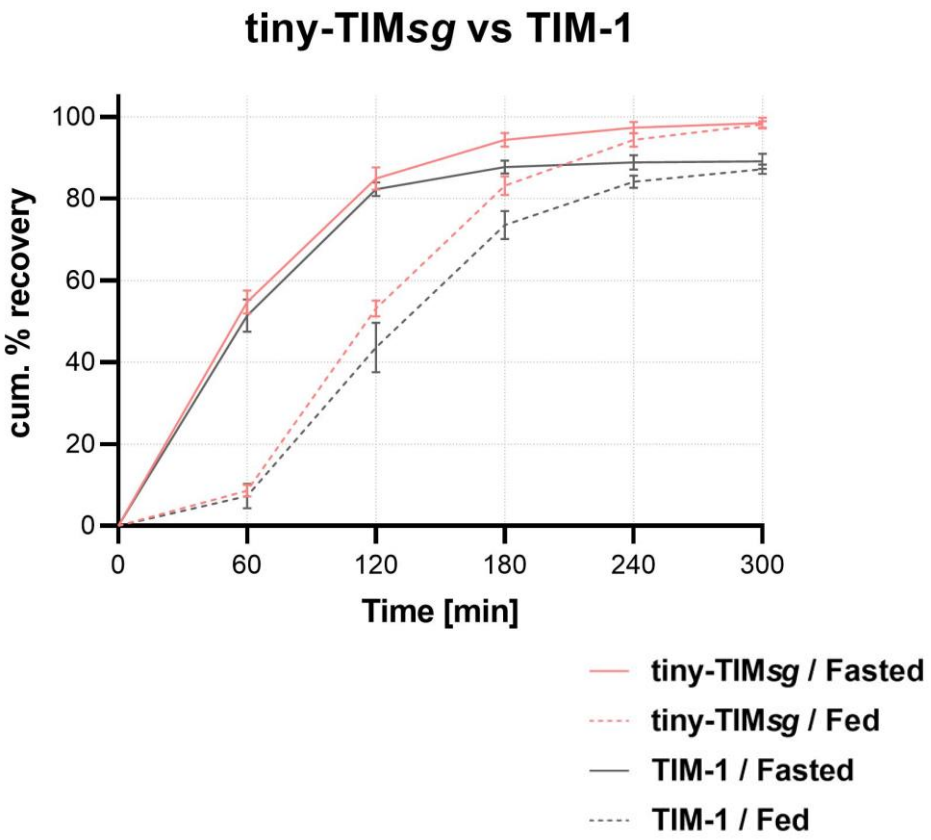
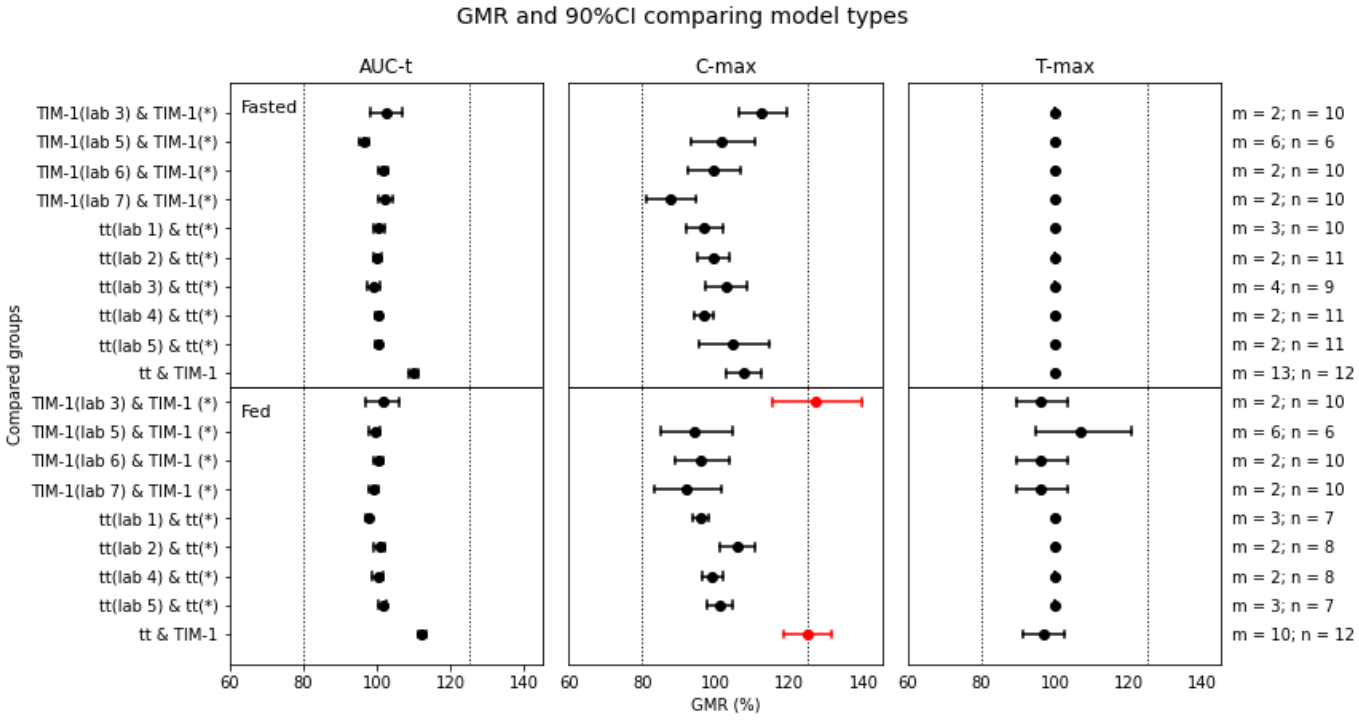
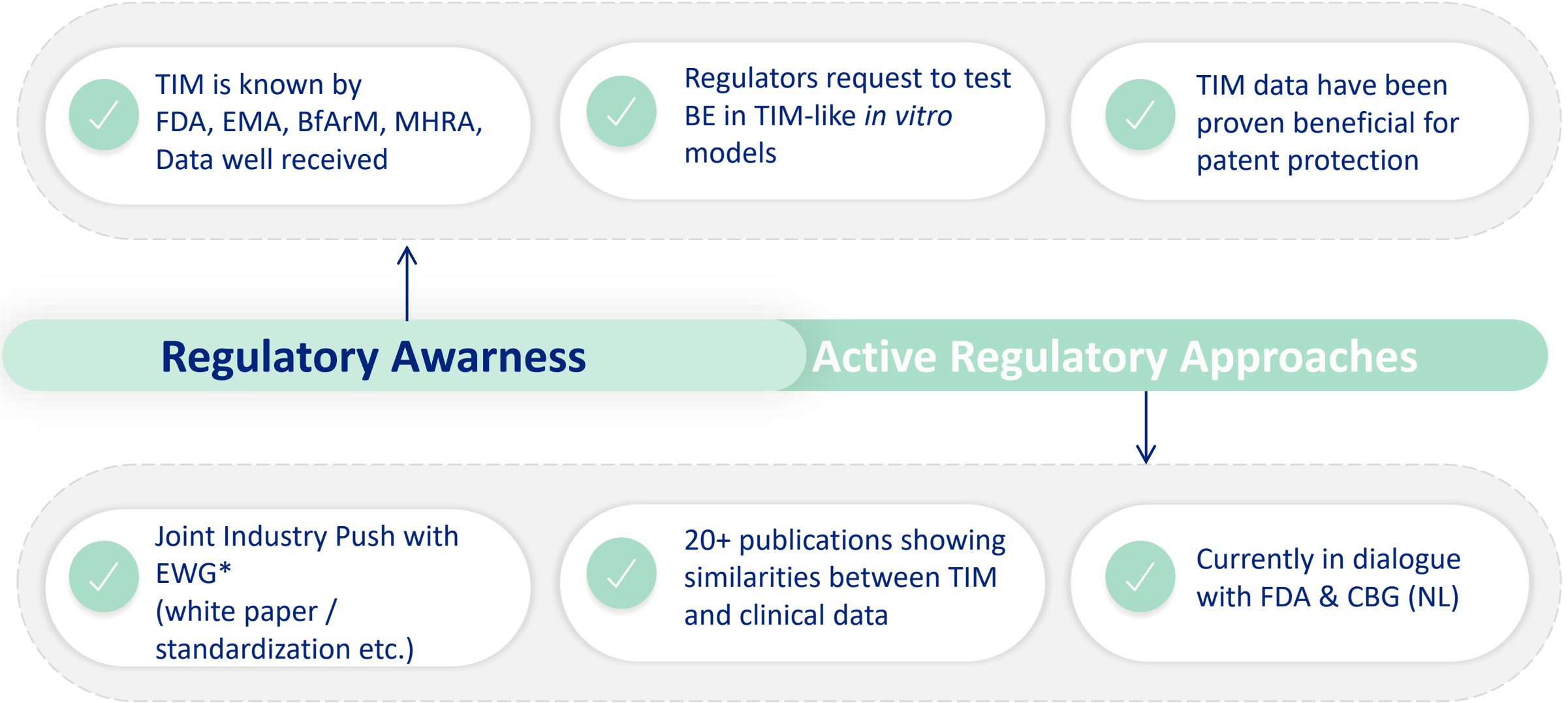
Multisite study shows high reproducibility and repeatability





(Manuscript in preparation, 2022)



* Members of **E**xpert **W**orking **G**roup: Abbvie, AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Janssen, Pfiz

Testimonials

When and How TIM can help

"Due to the **multistage and biorelevant setup** of the TIM-1 model, we were able to evaluate the drug release across the different GI compartments…. During the stage of drug product development, this tool can be extremely useful to provide guidance in the **selection of a lead formulation** for the clinical stage. Multiple candidate formulations can be tested in a (relative) **short period** of time **at a fraction of the cost of a clinical study**."

Publication from Pfizer with TIM: (Piscitelli *et al., 2023)*

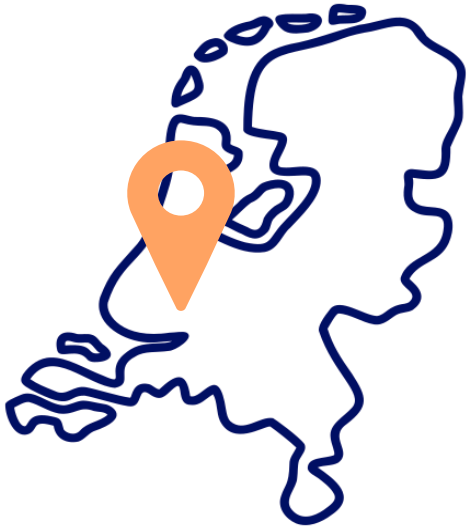
"We believe that the TIM-1 can be used as a **substitute for dog studies** with the purpose of assessing clinically significant differences **between compound modifications and formulations** during product development."

Publication from AstraZeneca with TIM: (Barker *et al*., 2014)

"The predictive model developed using minimal clinical data and the in vitro tiny-TIM data can be used to expedite drug development. **Change in PK profile (if any) induced by change in drug product formulation, drug substance synthesis route, or particle size distribution can be predicted without conducting further animal study or human clinical trial**. …. This can not only **save expensive animal and human experiments but can also expedite the drug development timeline."**

Publication from Boehringer Ingelheim with TIM: (Luo *et el.,* 2022)

Thank you for your attention!



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In Vivo in Vitro correlations (IVIVC)

	High solubility	Low solubility
High permeability	**BCS I** TIM bioaccessibility (BA) vs. in vivo: • **R^2= 0,989 AUC0–∞** (Schilderink *et al., 2020)* • **R^2=0.962 Cmax** (Schilderink *et al*., 2020) **Mean ratio** absorbed found of **1.02** (Soulliman, 2007)	**BCS II** IVIVC level C with correlation coefficients of: • **R^2=0.9689** for TIM amount dissolved vs in vivo **AUC0–∞** (Luo *et al., 2022)* • **R^2=0.982** for TIM BA vs in vivo % drug absorbed, predicts exposure found in vivo. (Chiang *et al., 2022)*
Low permeability	**BCS III** IVIVC level A with correlation coefficients of: • **R^2=0.9128 Fasted state** (Soulliman, 2006) • **R^2=0.9984** in **fed state** (Soulliman, 2006)	**BCS IV** (BCS I-IV) **TIM-1** correctly predicted in vivo rank order in: • **84%** of cases for **AUC** (Barker *et al.,* 2014) • **79%** of cases for **Cmax**. (Barker *et al.* 2014)

TIM