External Design Review

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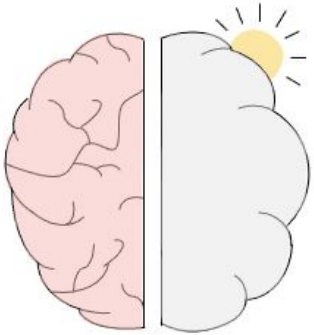
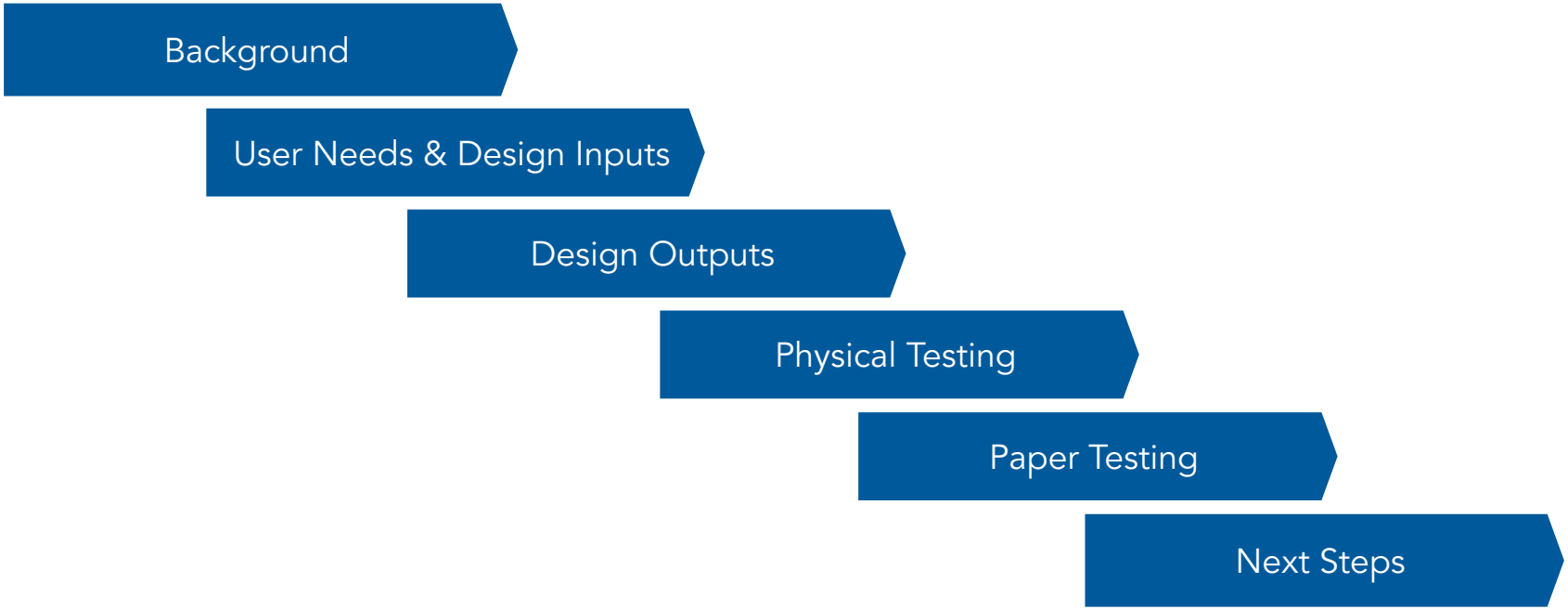


ACUI-CARE

December 7th, 2021

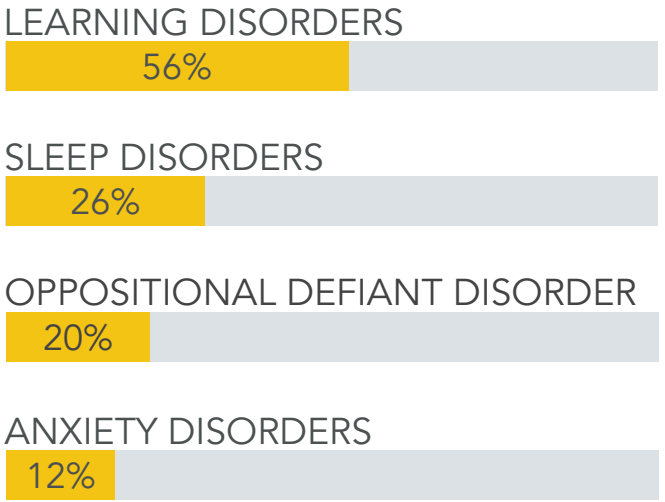
Presentation Overview



Background

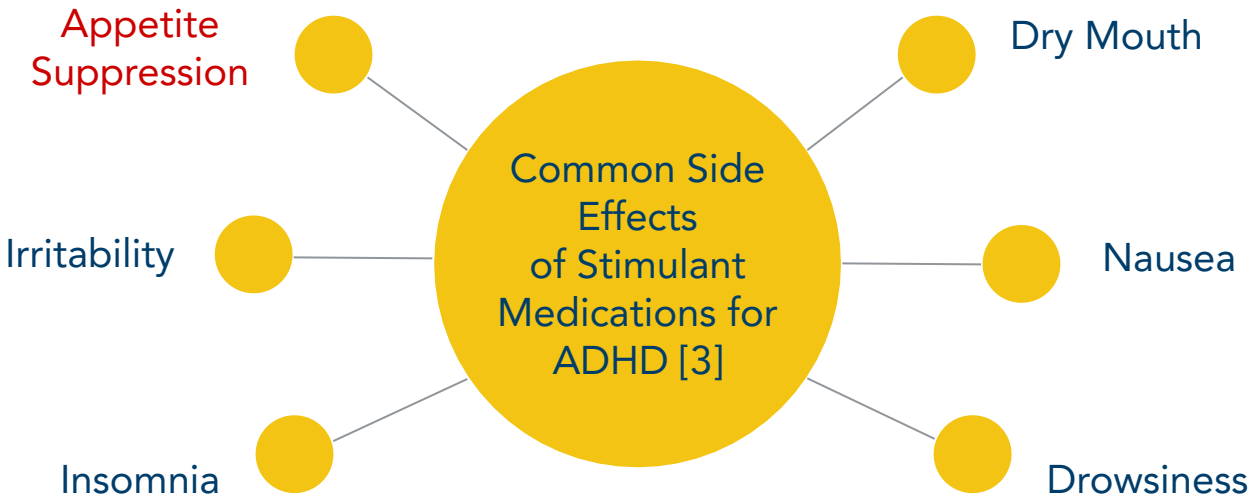
Attention-Deficit/Hyperactivity Disorder is a neurodevelopmental disorder commonly associated with comorbid psychiatric conditions [1]

Inattentive type [2]	Hyperactive type [2]
Difficulty focusing	Restlessness
Difficulty listening	Impatience
Forgetfulness	Difficulty being quiet

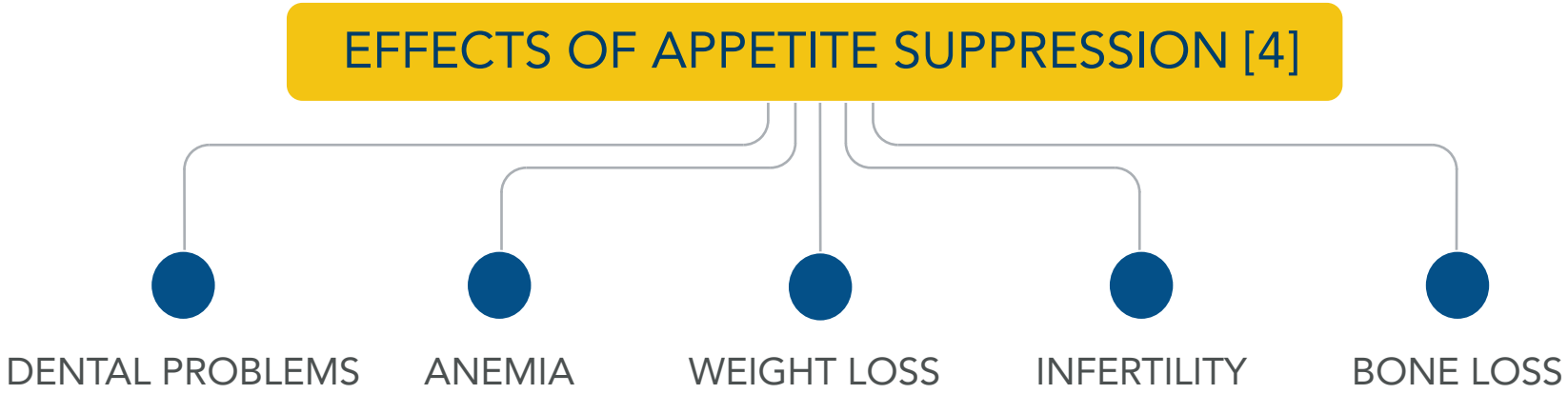


User Needs & Design Inputs

Effective current treatments pose a number of adverse effects

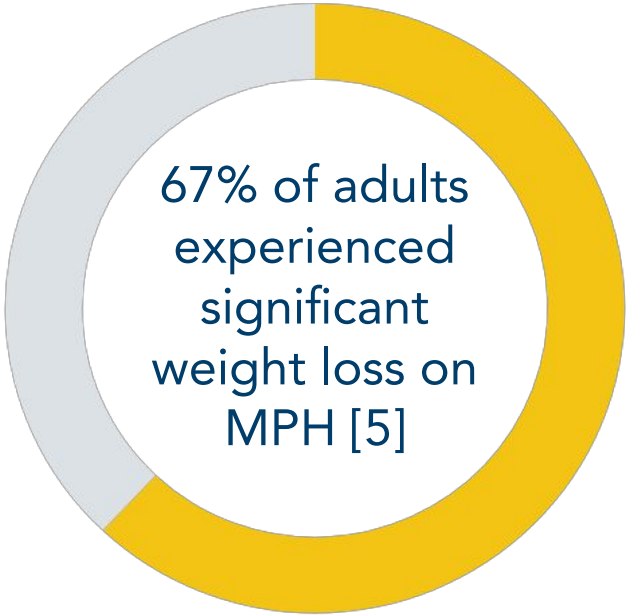


Appetite suppression can have many long term health impacts

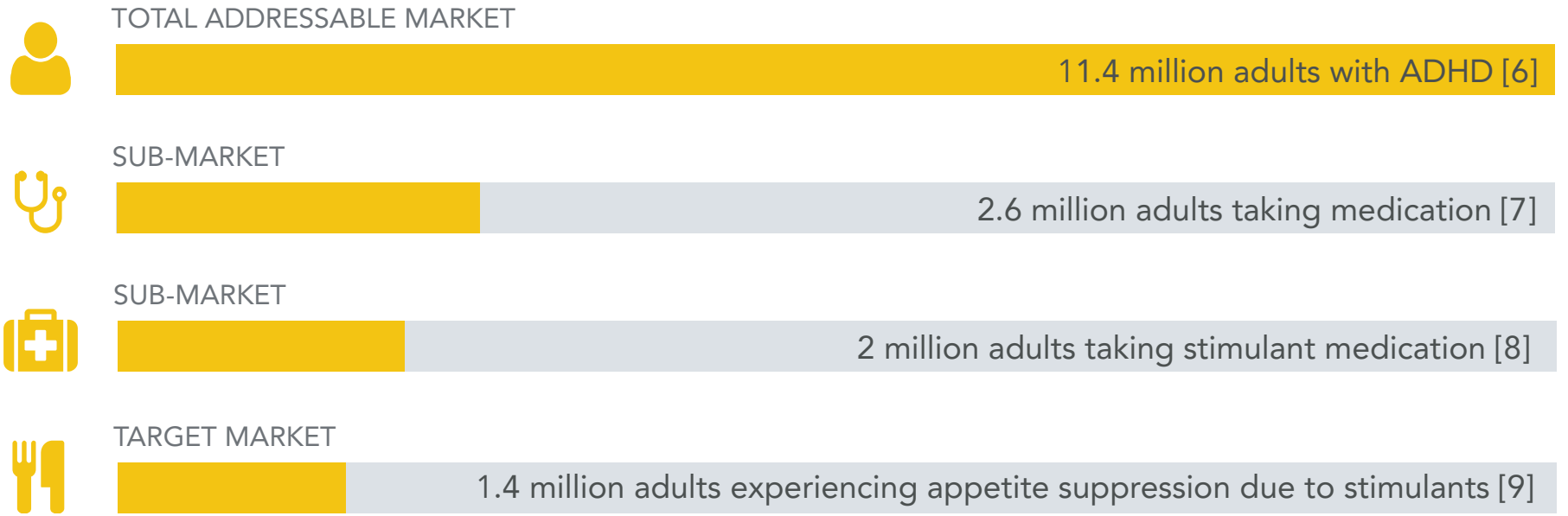


Adult stimulant medication users most require a solution to appetite suppression

Eating routines are well-maintained for children in school and by guardians; adults frequently do not have any external reminders to eat.



The target market comprises approximately 12 percent of the total addressable market



Need Statement

There is a need to reduce the impact of appetite suppression in adult ADHD patients prescribed stimulant medications to ultimately improve patient wellbeing and tolerance of their otherwise effective medication regimen.

A wide array of short-term patient needs were synthesized into a set of critical design inputs

Safety

The solution must be safe alone and in combination with other psychiatric medications

Accessibility

The solution must be usable by most of the target market and not significantly increase the burden of treatment

Effectiveness

The solution must be effective for ADHD treatment and appetite suppression

Long-term goals reflect our patient-centered approach

Tolerability

Solution improves patient tolerability of adverse side effects, specifically appetite suppression

Functionality

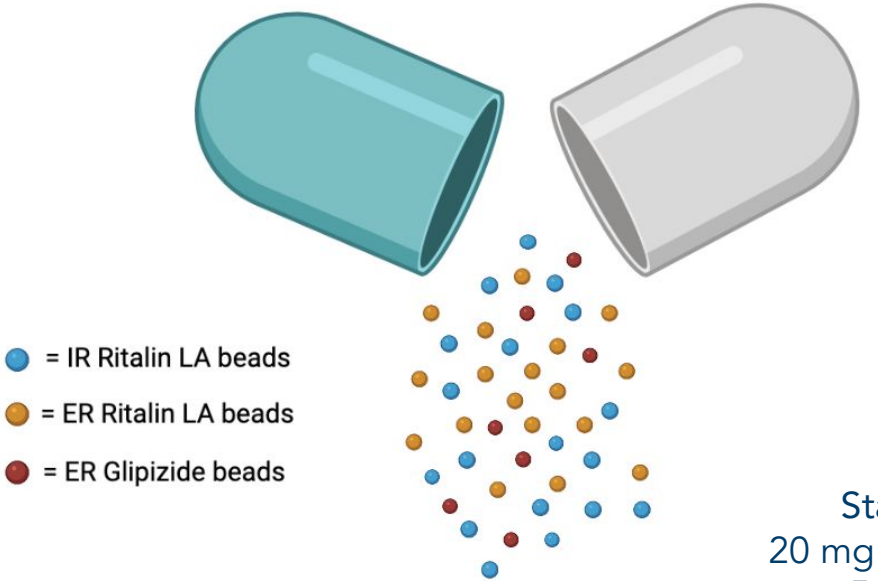
Solution improves patient functionality in everyday life

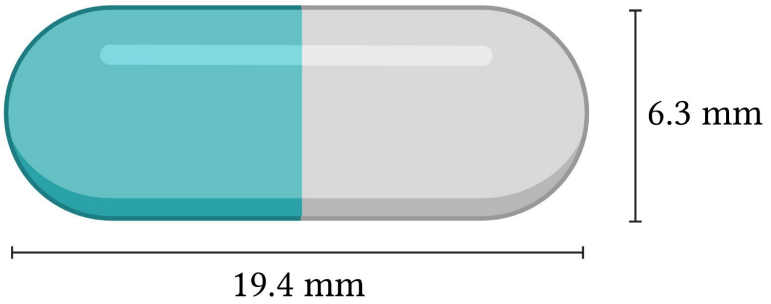
Compliance

Solution improves long-term compliance rates due to decreased adverse effects

Design Outputs

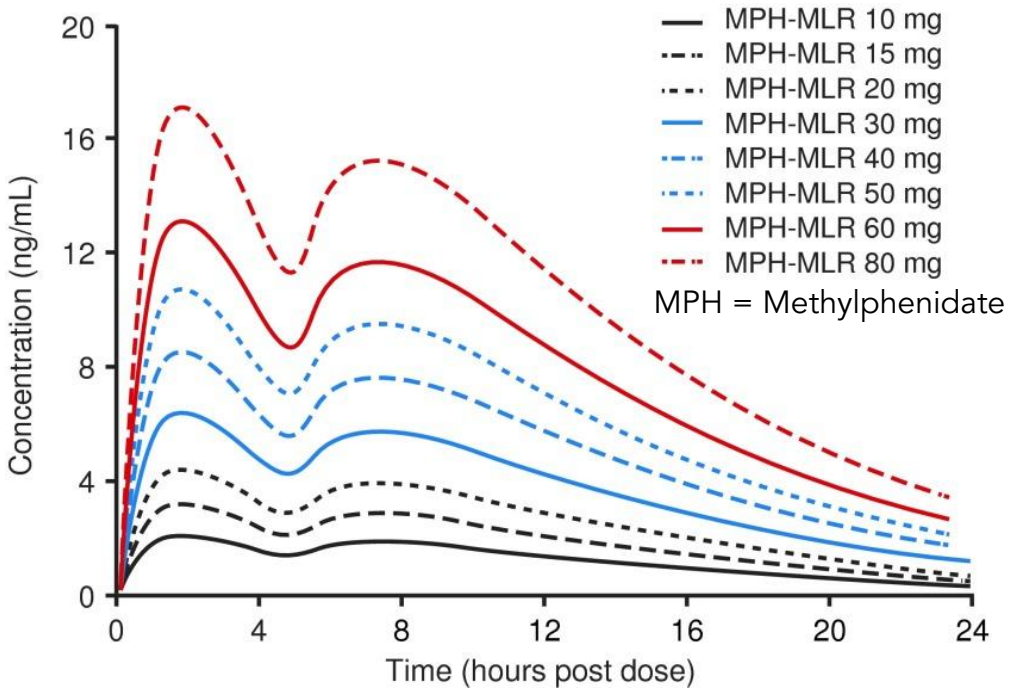
Our final proposed design is a delayed-release appetite stimulant embedded in an ADHD stimulant





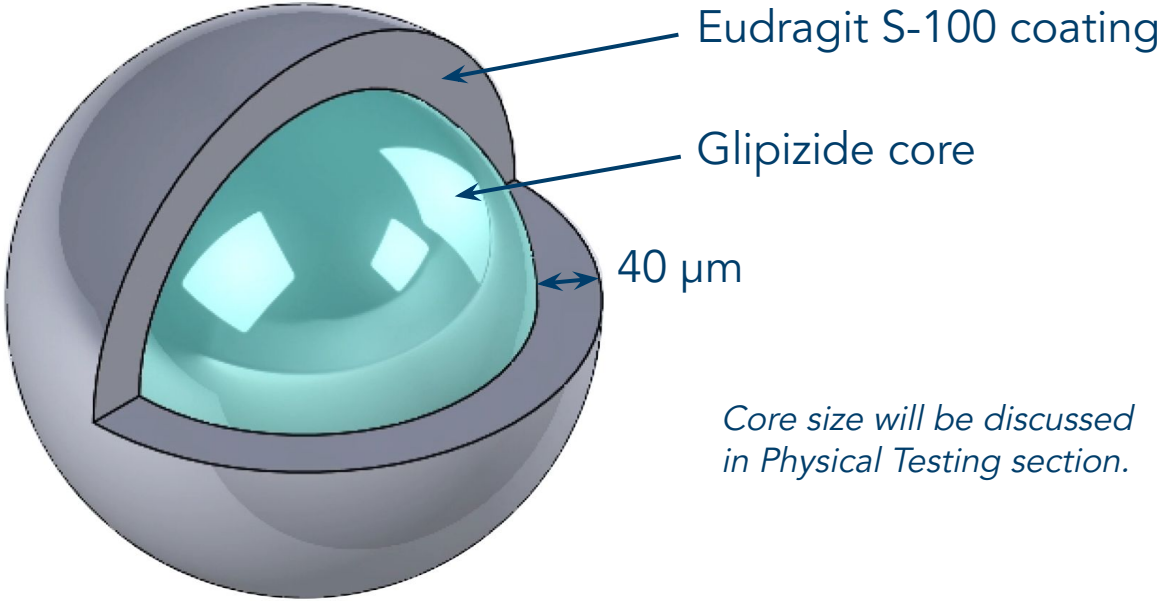
Starting Dosages:
20 mg of methylphenidate
5 mg of glipizide

Ritalin LA uses SODAS technology and has a distinctly bimodal plasma concentration curve



www.ncbi.nlm.nih.gov

Our microspheres will include a glipizide core and enteric polymer coating to delay drug release



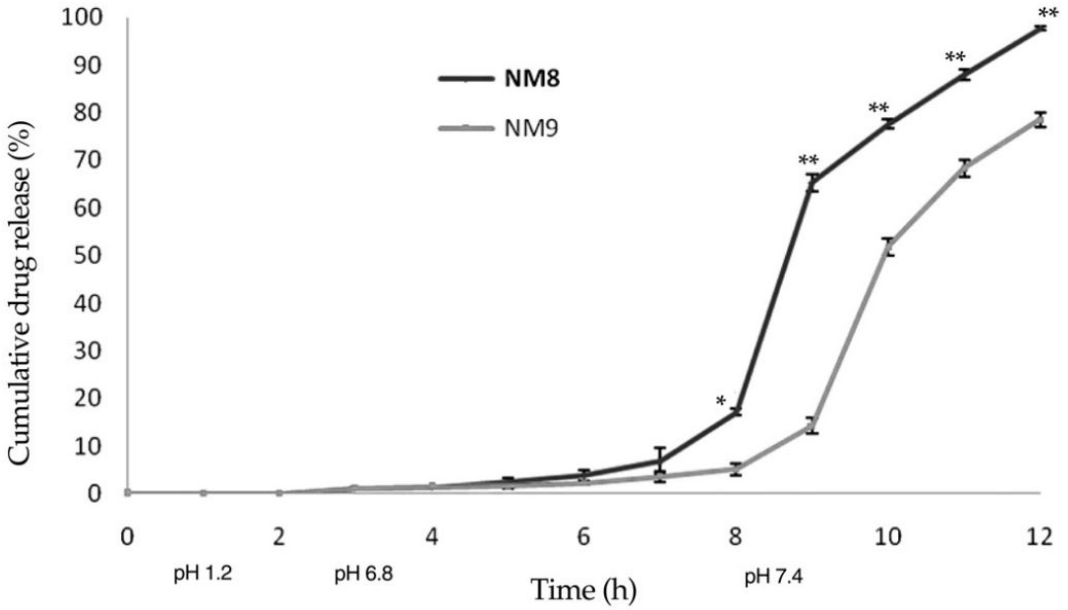
Core size will be discussed in Physical Testing section.

Glipizide release will be delayed until roughly three hours after pill consumption

Compartment	pH	Cumulative Transit Time (hr)
Stomach	1.3	0.25
Duodenum	6.0	0.51
Jejunum 1	6.2	1.46
Jejunum 1	6.4	2.22
Ileum 1	6.6	2.81
Ileum 2	6.9	3.24
Ileum 3	7.4	3.55

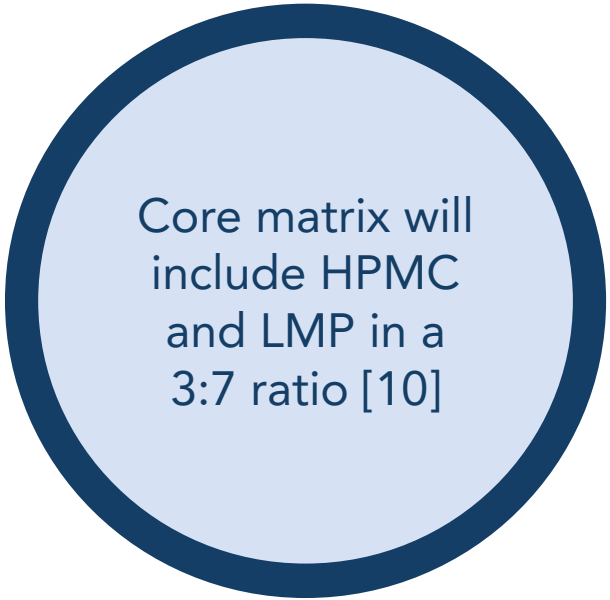
Table adapted from www.ncbi.nlm.nih.gov/pmc/articles/

Eudragit S-100 will delay glipizide release until the pill reaches pH = 7



https://sciendo.com/pdf

Our microbead core coagulants are now hydroxypropylmethylcellulose and low methoxyl pectin



Glipizide concentration will be discussed in Physical Testing section.

Together, each drug's principle of operation functions to achieve the solution's intended use

MPH	Methylphenidate works by diffusing into the blood and blocking dopamine and norepinephrine reuptake by neurons [11]
Glipizide	Glipizide works by diffusing into the blood and stimulating the release of insulin from the pancreas [12]
Our Solution	Solution works by treating ADHD symptoms with MPH and reducing the impact of MPH-caused appetite suppression with glipizide

Verification and Validation

V&V Overview

Verification

Does our design meet the requirements we set for success?

Physical Testing: Modeling drug release in Matlab

Validation

Does our design meet the users' needs?

Paper Testing: Planning a clinical trial for our solution

V&V Overview

Verification

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Paper Testing: Planning a clinical trial for our solution

Physical Testing

We are using the Hopfenberg model to optimize the microbead radius and initial drug concentration

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_{\text{ero},0} t}{C_0 R}\right]^3$$

The Hopfenberg model describes “dissolution, swelling, and polymer chain scission as a final zero-order process” [13].

We used values from literature to calculate K_{ero}

Important Values [10]

Microbead radius — 480.44 μm

Microbead drug content — 15.74%

LMP density — 1.81×10^{-9} mg/μm^3

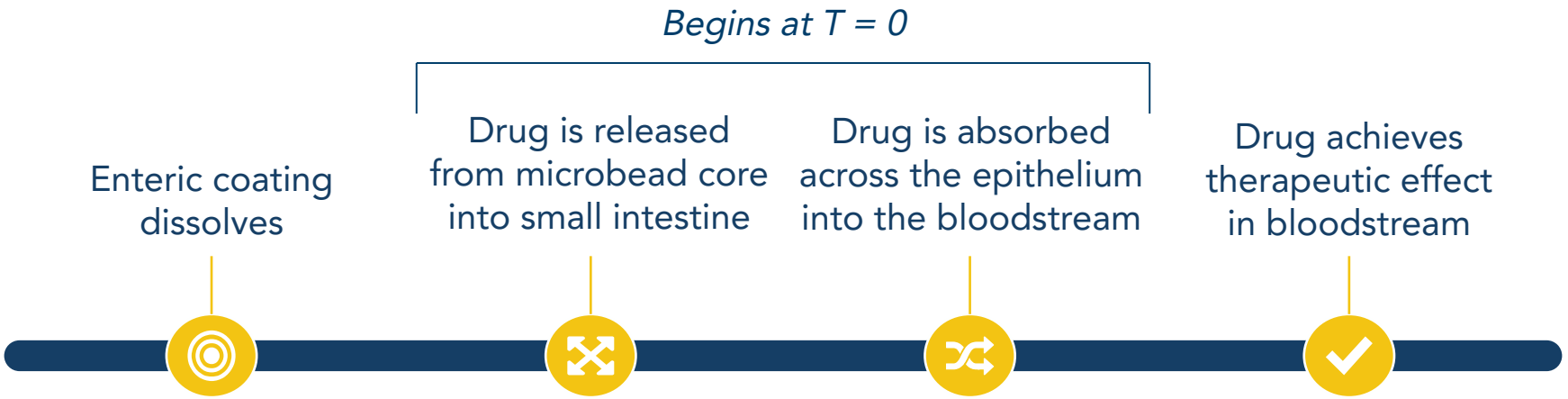
HPMC density — 1.39×10^{-9} mg/μm^3

Glipizide density — 1.3×10^{-9} mg/μm^3

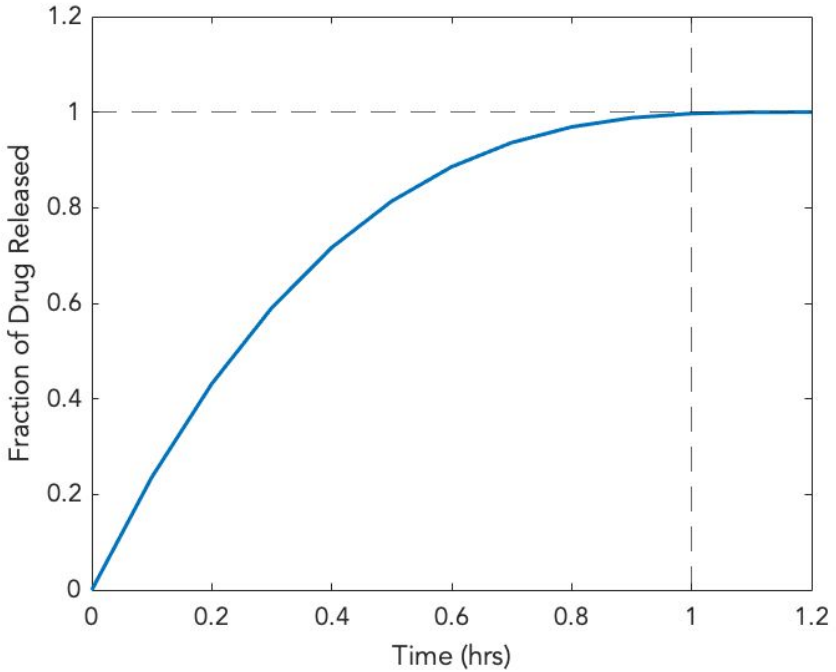
LMP:HPMC ratio — 7:3

1) Calculating microbead core density
2) Calculating microbead mass and number of microbeads
3) Calculating drug content and concentration of one bead
4) Calculating K_{ero} by rearranging Hopfenberg

Our model assumes drug release and drug absorption occur simultaneously



Preliminary results indicate that we can achieve complete drug release in one hour



$R = 100\ \mu m$

$C_0 = 2.55 \times 10^{-10}\ mg/\mu m^3$

Paper Testing

We designed a study to determine solution effectiveness for treatment of appetite suppression and symptom relief over time

Our study will assess a variety of treatment combinations for a diverse population of subjects

Group	Treatment before trial	Treatment during trial
1	No treatment	No treatment
2	No treatment	Ritalin LA
3	No treatment	Acui-Care solution
4	Ritalin LA	Acui-Care solution
5	Ritalin LA	Ritalin LA

Category	Stratification
Age	18-24, 25-30, 31-40, 41-50, 51-60, 60+
Gender	Male-identifying, female-identifying, other
Weight	<100 lbs, 100-140 lbs, 140-180 lbs, 180-220 lbs, 220+ lbs

A power analysis utilizing expected changes in weight informed our choice of study size

Weight is our primary endpoint:

- Expected change can be used to determine required sample size to accurately determine difference

We know:

- Average 1.07 kg drop in weight over two months of using methylphenidate[14]
- Sample has a standard deviation of 11 kg[14]

We want:

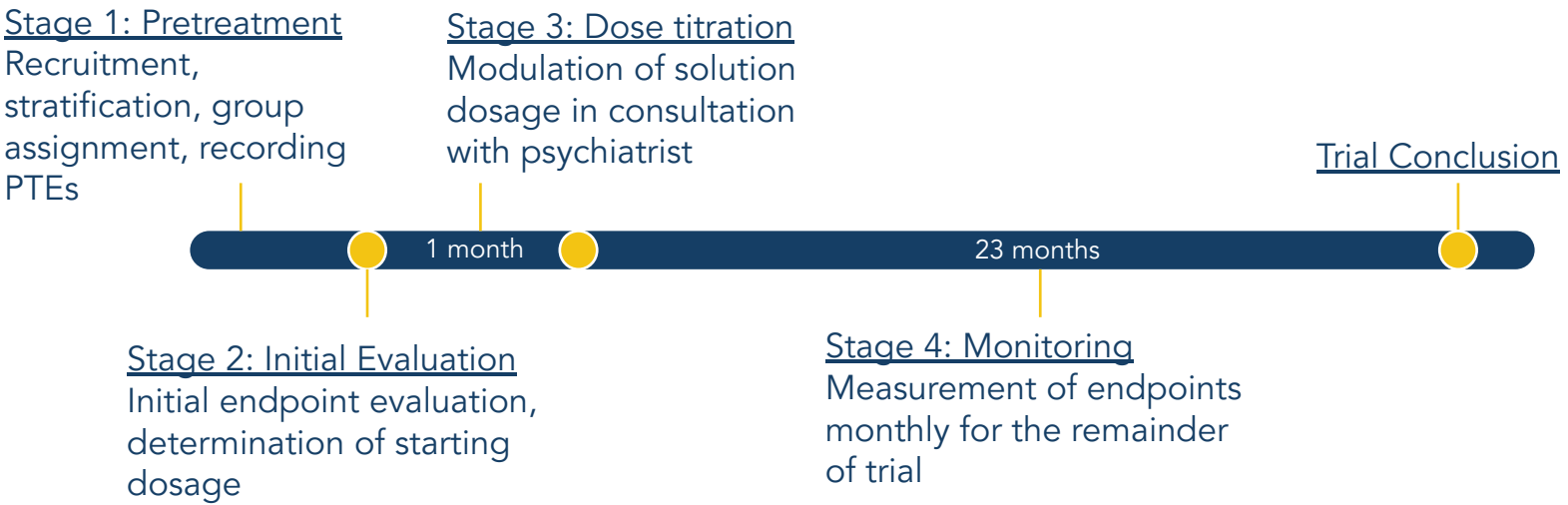
- A false negative rate of less than or equal to 20%
- A false positive rate of less than or equal to 5%

$$n \geq \left(\frac{z^* + z^*_{1-\beta}}{d}\right)^2$$

Where d is the average over the standard deviation, z* and z^*_{1-B} are the z scores of the 95th and 80th percentiles, respectively, of a normal distribution

Yields n ≥ 657 samples per group, or 3285 samples for 5 stratified groups

The Acui-Care trial is comprised of multiple stages over 2 years with 3285 participants



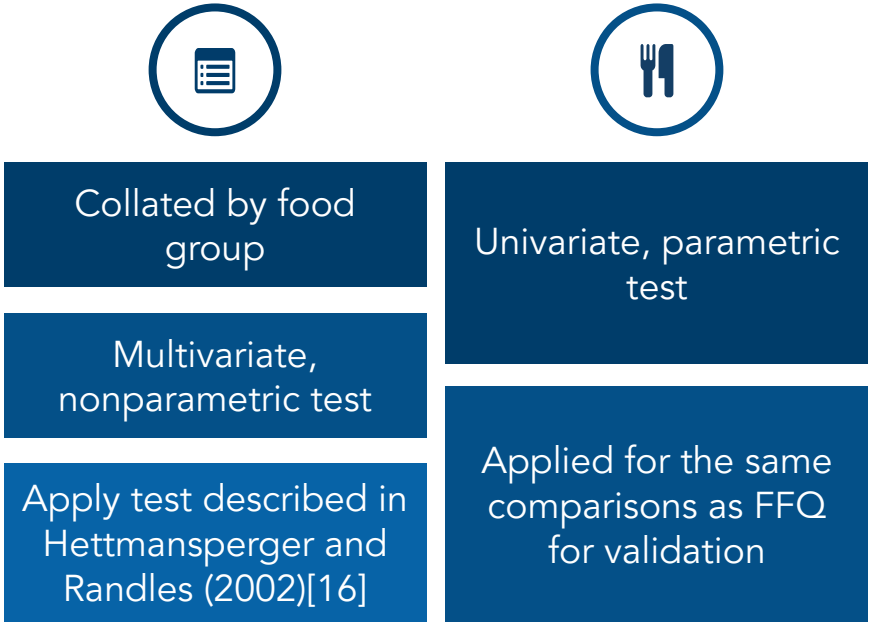
Both weight and FFQ data are used to determine the solution's ability to reduce appetite suppression

FFQ quantifies food intake by item but may not accurately reflect quantity [15]

Weight measures physiological response to food consumption

Both tests combined provide a holistic view on the impact of our solution on appetite and food consumption

Agreement between tests indicates the solution's ability to reduce the impact of appetite suppression



Multiple tests on both endpoints will jointly validate improvement in appetite

Controls

	Sample 1	Sample 2	Expected Result
App.C.1	Group 1 at stage 1	Group 1 at end of stage 4	No difference in medians/means
App.C.2	Group 2 at stage 1	Group 2 at end of stage 4	Difference in medians/means
App.C.3	Groups 1,2,3 at stage 1	Groups 4,5 at stage 1	Difference in medians/means
App.C.3	Groups 2,5, at end of stage 4	Group 1 at end of stage 4	Difference in medians/means

Primary Tests

	Sample 1	Sample 2	Expected Result
App.T.1	Group 3 at stage 1	Group 3 at end of stage 4	No difference in medians/means
App.T.2	Difference between group 3 at stage 1 and end of stage 4	Difference between group 1 at stage 1 and end of stage 4	No difference in medians/means
App.T.3	Group 4 at stage 1	Group 4 at end of stage 4	Difference in medians/means
App.T.4	Group 4 at end of stage 4	Group 5 at end of stage 4	Difference in medians/means

Both the Conners' Scale and Continuous Performance Test are used to assess effectiveness for ADHD treatment

Conners' Scale for ADHD Assessment

Requires intensive interview with patient to holistically determine impact of ADHD on day-to-day life [17]

Conners' Continuous Performance Test

A computerized test of symptoms that treatment with medication should directly address [18]

The Conners' Scale will be measured at the start and end of the trial, while the CPT will be measured monthly

Analyzing the solution's impact on ADHD treatment involves comparing Conners' scale data using paired T-test

Controls

	Sample 1	Sample 2	Expected Result
Eff.C.1	Group 2 at stage 1	Group 2 at end of stage 4	Decrease in mean
Eff.C.2	Group 1 at stage 1	Group 1 at end of stage 4	No change in mean
Eff.C.3	Group 5 at stage 1	Group 5 at end of stage 4	No change in mean

Primary Tests

	Sample 1	Sample 2	Expected Result
Eff.T.1	Group 3 at stage 1	Group 3 at end of stage 4	Decrease in mean
Eff.T.2	Group 4 at stage 1	Group 4 at end of stage 4	No change in mean
Eff.T.3	Group 3 at end of stage 4	Group 4 at end of stage 4	No change in mean
Eff.T.4	Difference between group 4 at stage 1 and end of stage 4	Difference between group 5 at stage 1 and end of stage 4	No change in mean

Further analysis of the solution's impact on ADHD treatment involves tests for Conners' CPT with regression analysis

Controls

	Sample	Expected Result
Eff.C.4	Group 1	Slope not different from 0
Eff.C.5	Group 2	Slope different from 0
Eff.C.6	Group 5	Slope not different from 0

Primary Tests

	Sample	Expected Result
Eff.T.5	Group 3	Slope different from 0
Eff.T.6	Group 4	Slope not different from 0

Statistical tests are applied to endpoints and other trial data to determine if solution meets short-term, critical requirements

	Requirement				
Description	Non-harmful	Does not increase adverse effects experienced by patients	Personalizable dosing	Limits adverse interactions with medications for common comorbid conditions	Does not increase frequency of healthcare visits
Test	One tailed proportion test				Wilcoxon signed rank test
Expected Result	Adverse effects does not exceed 0.5% of number of participants	No more than 5% in Group 4 see an increase in experiencing adverse effects (via FIBSER)	No more than 20% in Groups 3/4 leave due to a lack of individualized dosage options	Proportion of adverse events in patients taking other medication does not exceed 0.5% of proportion of adverse events in patients not taking other medication	The average rate of healthcare visits over months 2-24 should not be greater than once every 30 days

While our specifications do not require continuous data, it could be valuable in modifying our design

Development of tolerance

Both medications used in solution may result in development of tolerance — do patients need more of both as time goes on?

Impact of acclimation vs solution

Do we see patients in group 5 develop better appetites? If so, how much of a positive result is from acclimation to medication?

Impact on diet

Glipizide directly acts by lower blood sugar — might patients shift to a higher sugar diet? Is it sustainable and healthy if they do?

Effectiveness over time

All of these factors may impact the ability of the solution to meet specifications — is there a time of “highest effectiveness” and if so what must change to keep effectiveness high?

Our paper testing will validate requirements and provide ample data for optimizing our design

Trial

3285 participants, stratified, split into 5 groups

Measurements over 2 years

Data

Multiple endpoints for appetite suppression, ADHD treatment effectiveness

Most endpoints measured monthly

Findings

Our solution has similar efficacy for ADHD treatment to Ritalin LA

We expect our solution to preserve appetite

Outcomes

Our solution may meet all specifications and be validated

If not, endpoint data will inform changes to design

Next Steps

Further testing is necessary to verify our final short-term design requirement

Untested short-term critical design requirement: Physically stable
Specification: Product should be able to withstand a 116 centimeter drop when placed at the bottom of a backpack that weighs 20 kilograms.

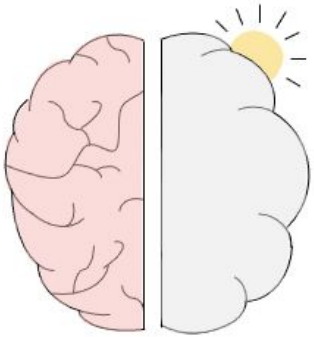
Our design could be modified to be more personalizable

Expand scope from adults to all ages

Offer formulations with other common extended-release ADHD medications

Utilize continuous data to refine changes to regimen over time

Thank you!



ACUI-CARE

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