Key Points to Keep in Mind

- It is ***very easy*** to know what the blood plasma profile for a once-a-day bupropion product would look like.
- It is ***very difficult*** to create a dosage form that achieves the once-a-day blood plasma profile.
- Andrx attempts at making a once-a-day product ***solely used pellets.***
- ***GSK's product doesn't use pellets.***

Variability in Blood Plasma Parameters Results from:

- ***THE DRUG*** used in testing
- ***THE DOSAGE FORM***
- ***DIFFERENCES BETWEEN*** different individuals tested
- ***DIFFERENCES WITHIN*** the same individual studied at different times
- ***DIFFERENCES*** in how the study is designed and carried out
- ***DIFFERENCES*** in testing conditions
- ***DIFFERENCES*** in measurement techniques for blood drug levels

Drug Delivery

Multiple Drug Administration:

Repeated administration of immediate release dosage form is needed to maintain therapeutic blood plasma levels

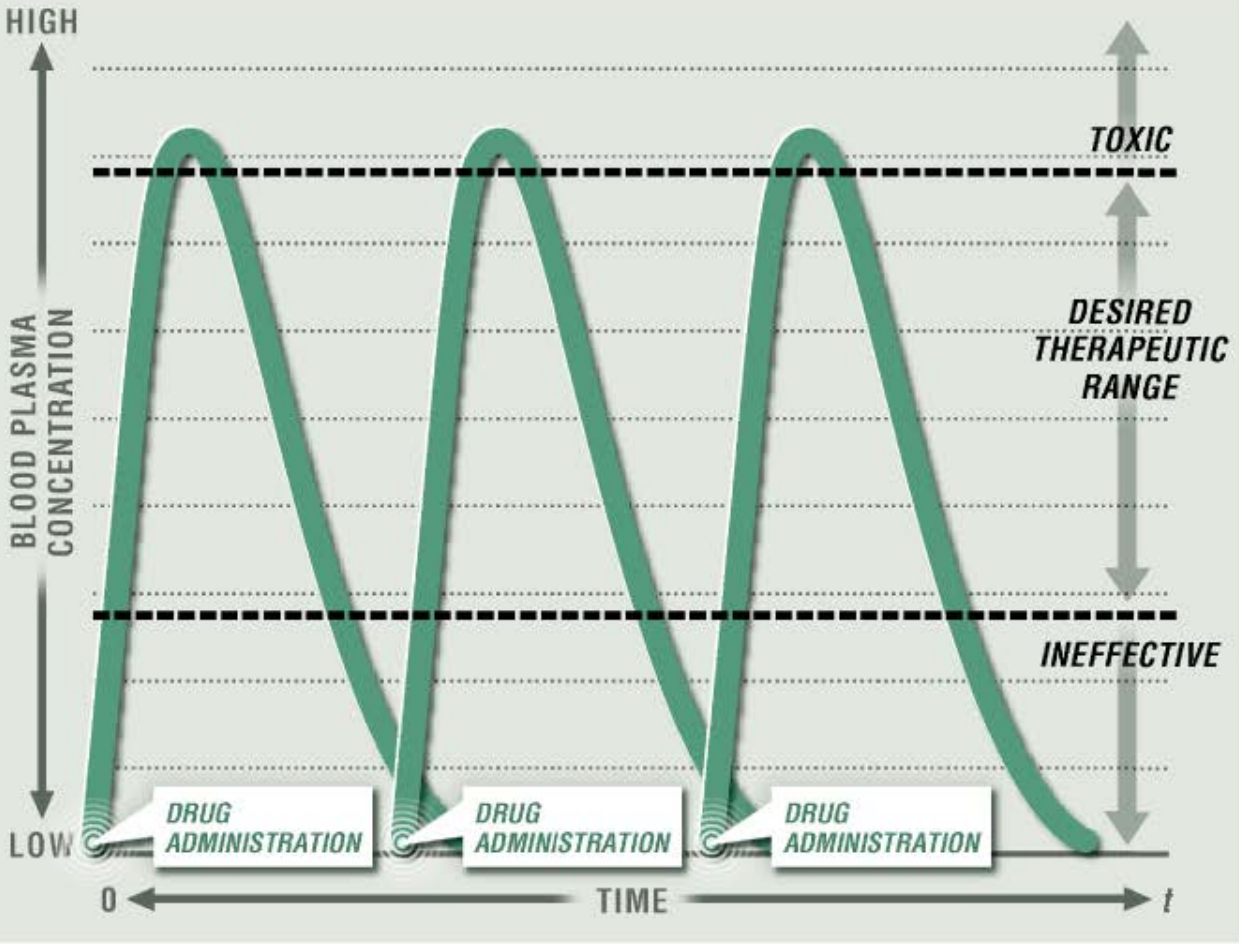


Exhibit ADH

Drug Delivery

Single Drug Administration:

Maintain desired drug level for specified time periods

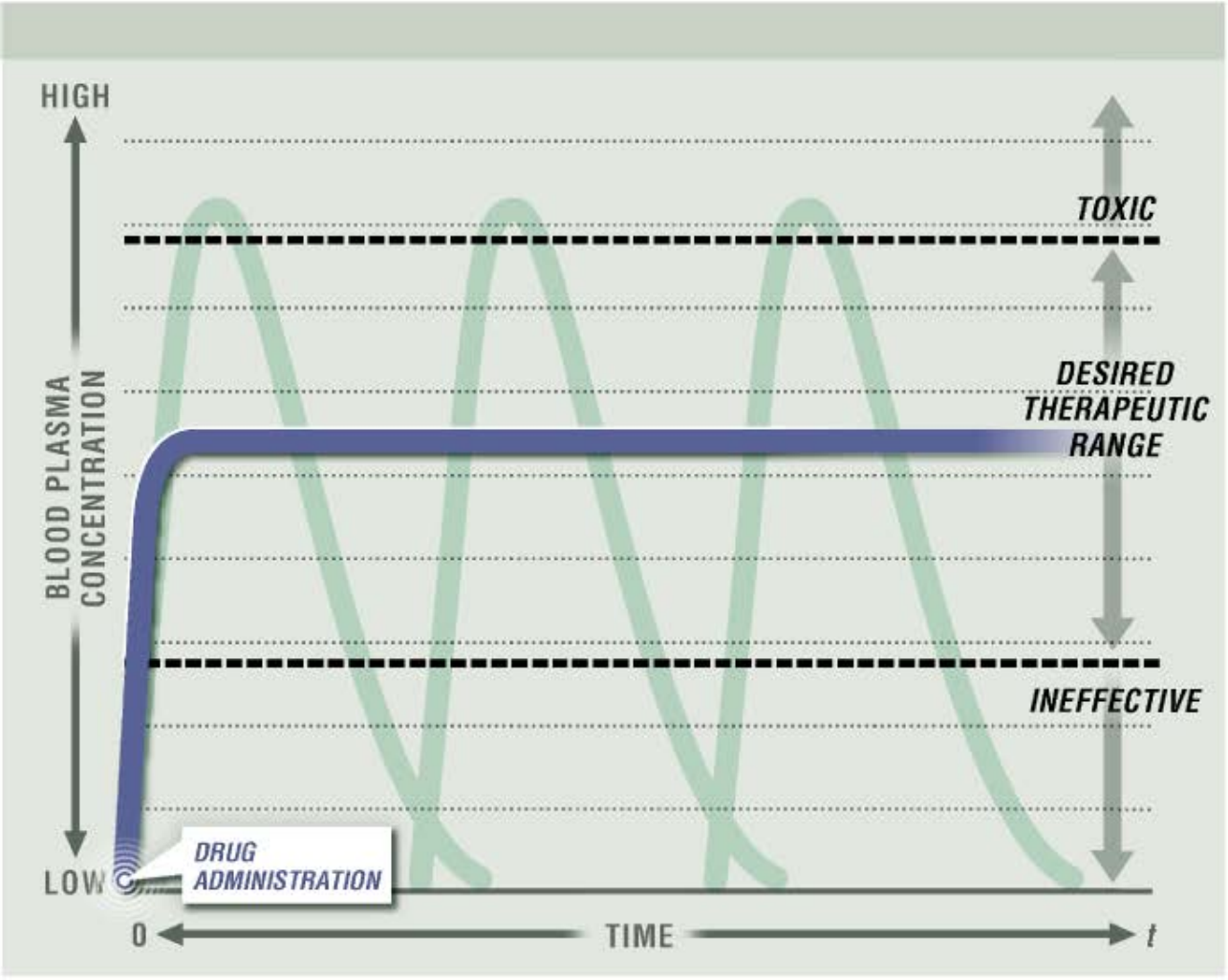


Exhibit ADI

Route of Administration of Drugs

- Oral
- Injection
- Intravenous
- Transdermal
- Inhaled
- Suppository
- Topical

Many Factors Influence the Route of Administration Chosen for a Particular Drug

- The chemical and physical properties of the drug itself
  - solubility
  - permeability
  - stability
- Location of the target organs or tissues
- Ability to manufacture dosage form
- Ability to control release
- Patient convenience

Exhibit ADQ

In General, Oral Administration Is Preferred for Patient Convenience

TYPES OF ORAL DOSAGE FORMS:

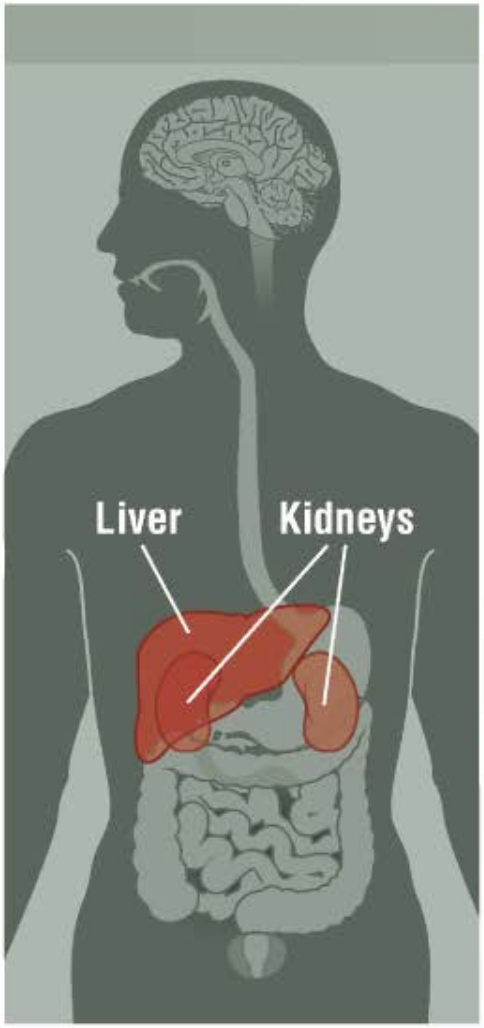
- Tablet
- Capsule
- Gel capsule
- Pellets
- Syrup or solution
- Powder
- Liquid suspension
- Film coated tablet
- Hybrid tablet

Exhibit ADR

In Order for a Drug That Is Given Orally to Work, the Active Ingredient:

- ***MUST*** be released from the formulation
- ***MUST*** dissolve in the GI tract
- ***MUST*** be absorbed into the bloodstream
- ***MUST*** distribute itself to the target organs or tissues

Drug Absorption and Elimination



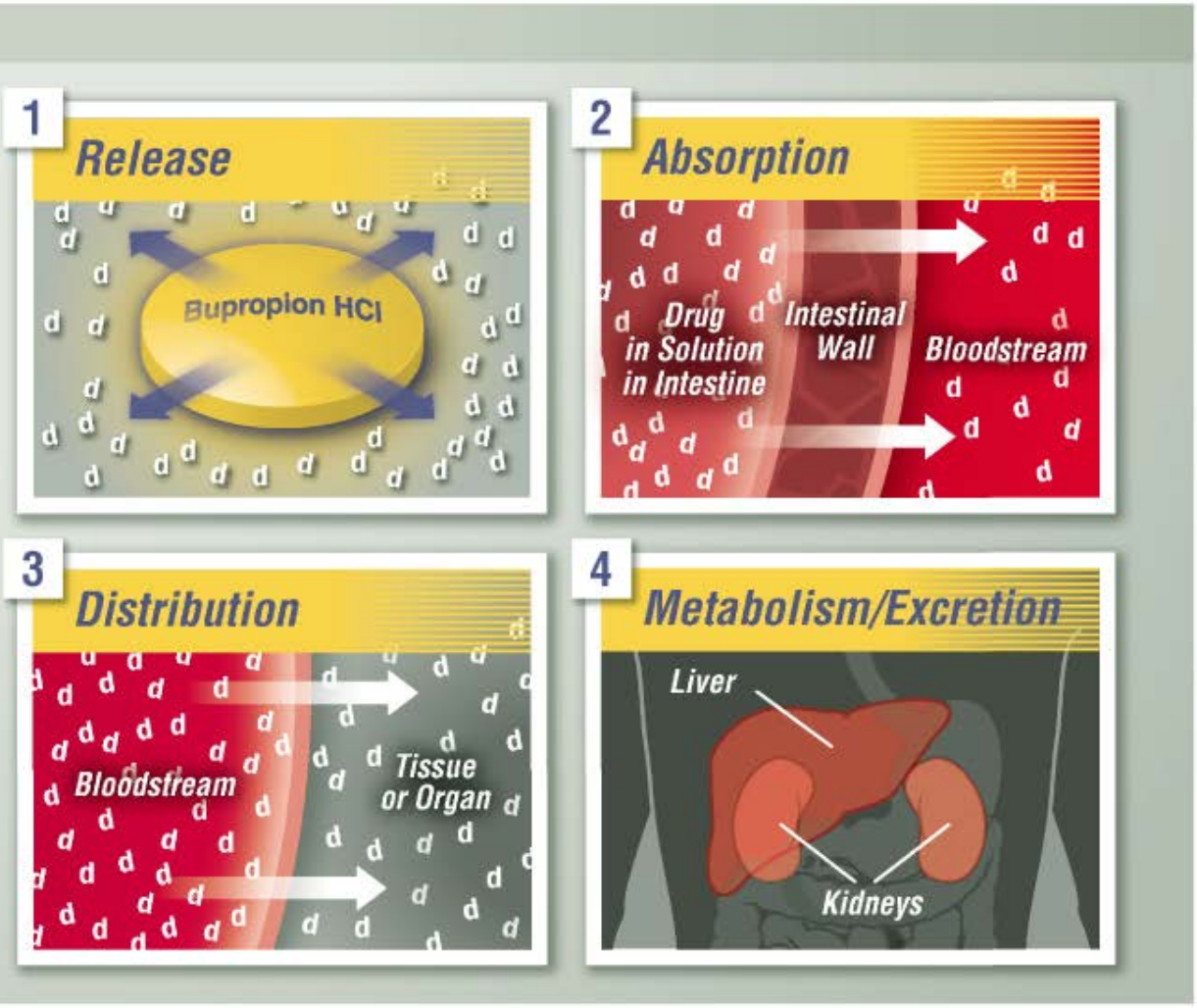


Exhibit ADU

Blood Plasma Profiles Are Used to Measure the Effectiveness of a Drug

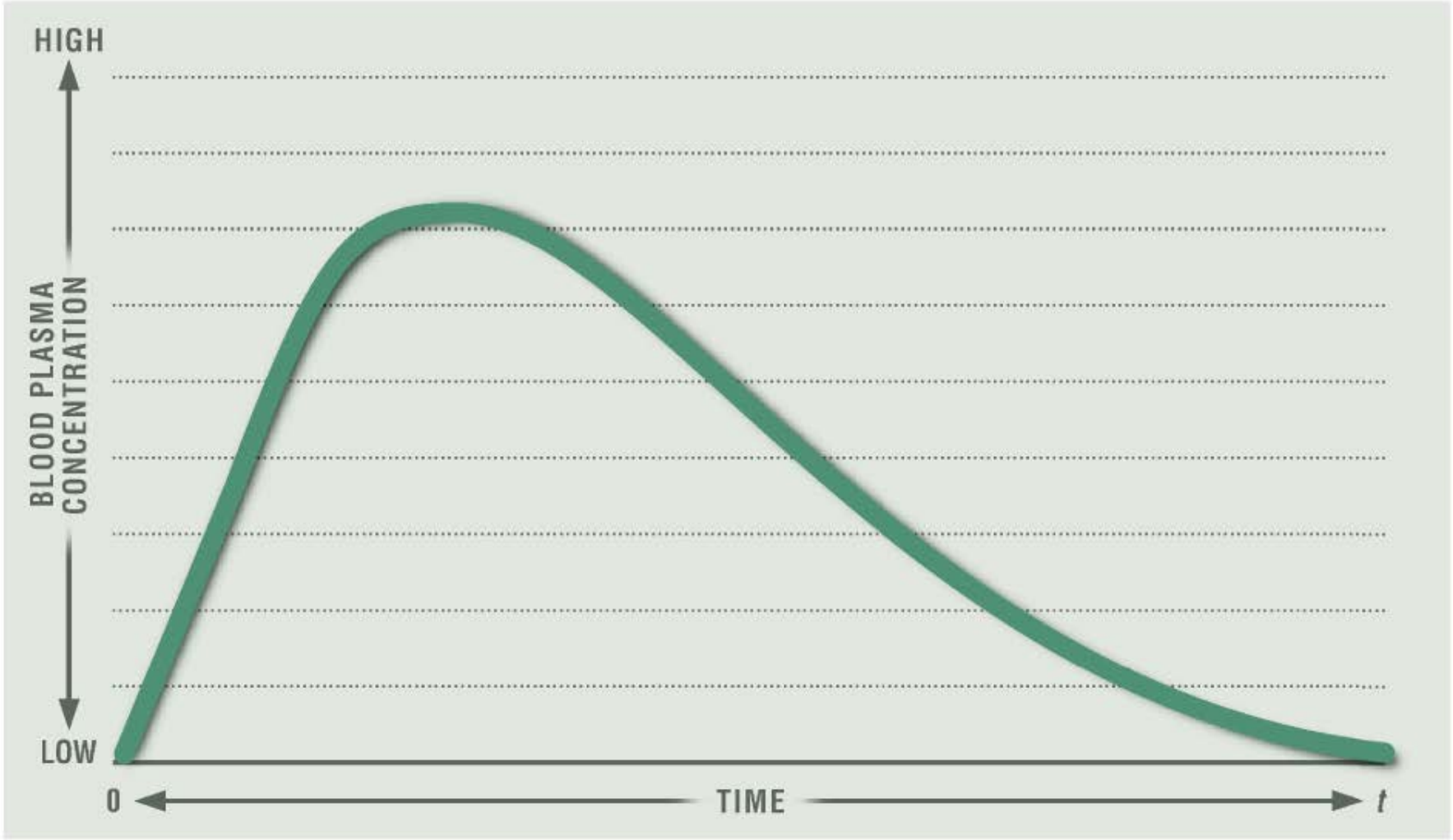


Exhibit ADD

Definitions of Pharmacokinetic (PK) Parameters

C_{max}

Represents the maximum concentration of drug found in the blood plasma of a patient to whom the dosage form has been administered.

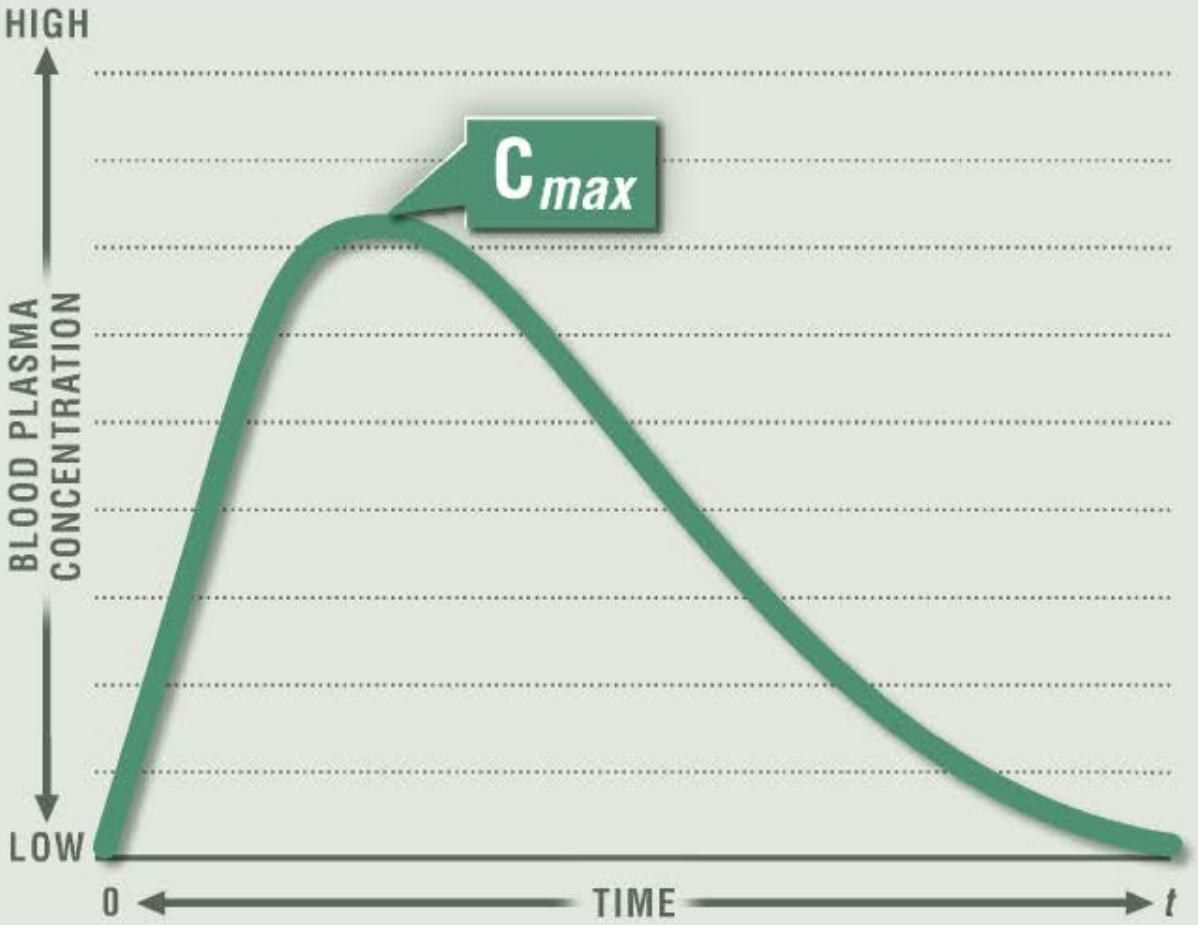


Exhibit ADE

Definitions of Pharmacokinetic (PK) Parameters

T_{max}

The time from administration at which the plasma concentration achieves C_{max}.

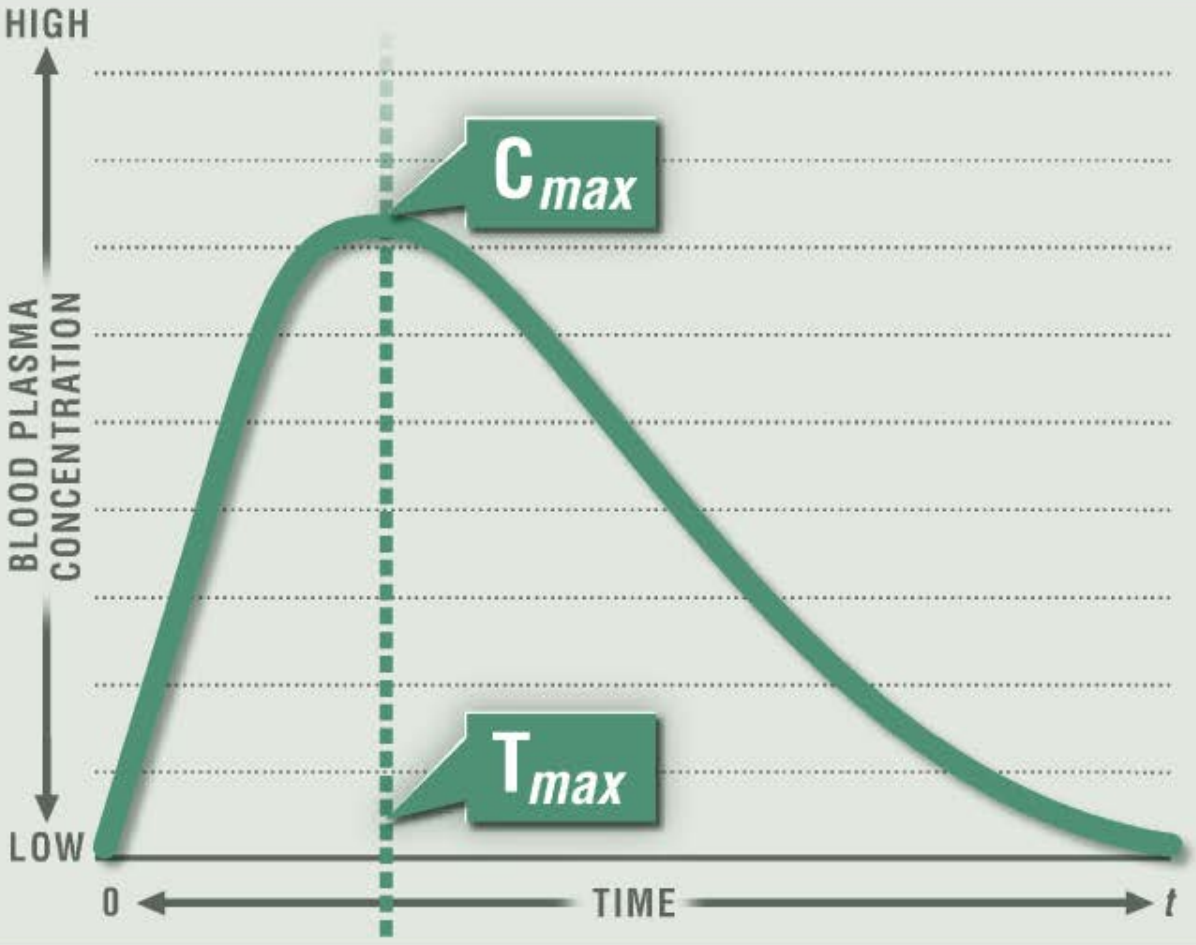


Exhibit ADF

Definitions of Pharmacokinetic (PK) Parameters

AUC

AREA UNDER THE CURVE

The total amount of drug available over time in the blood to achieve the desired therapeutic effect.

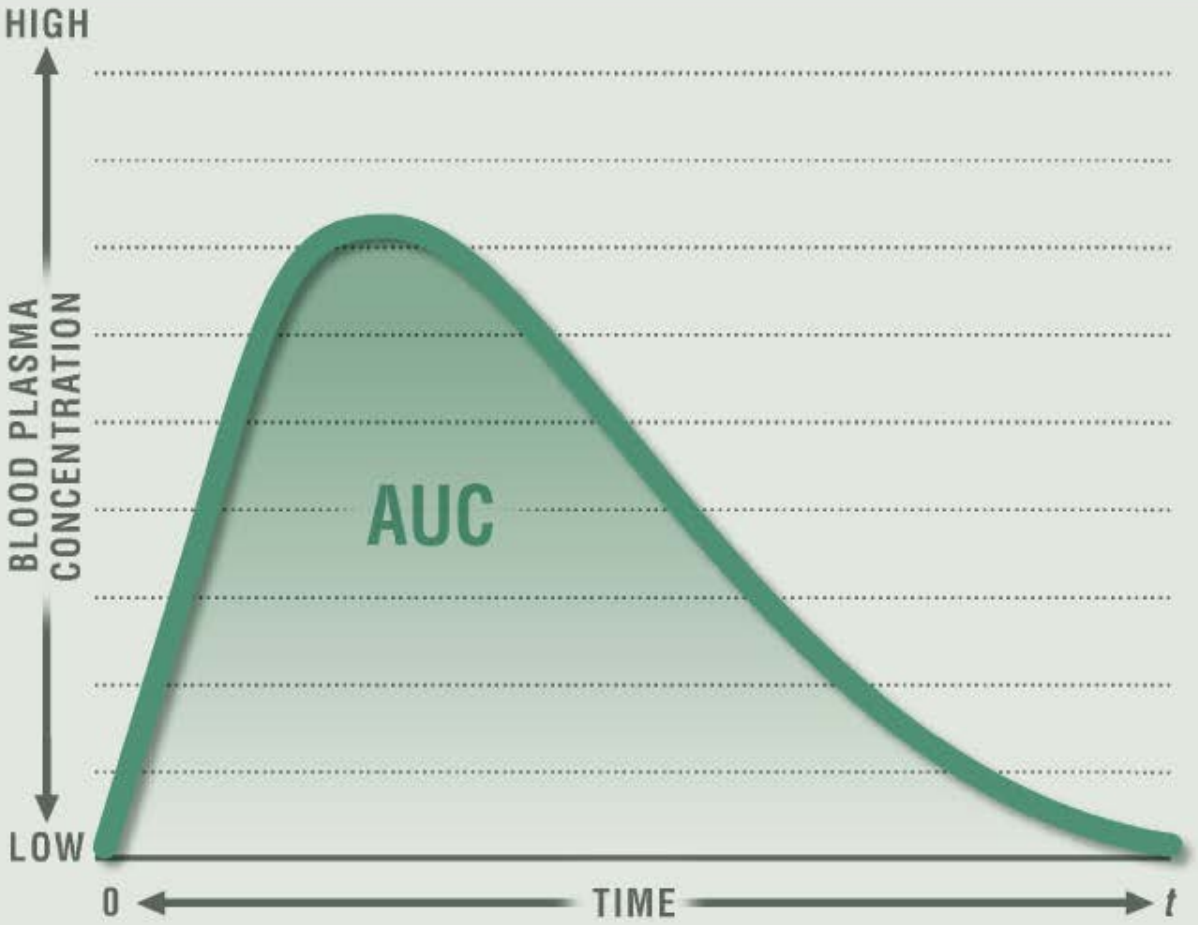


Exhibit ADG

Bioavailability

AUC

AREA UNDER THE CURVE

*A measure of the **bioavailability** of the active drug from the dosage form.*

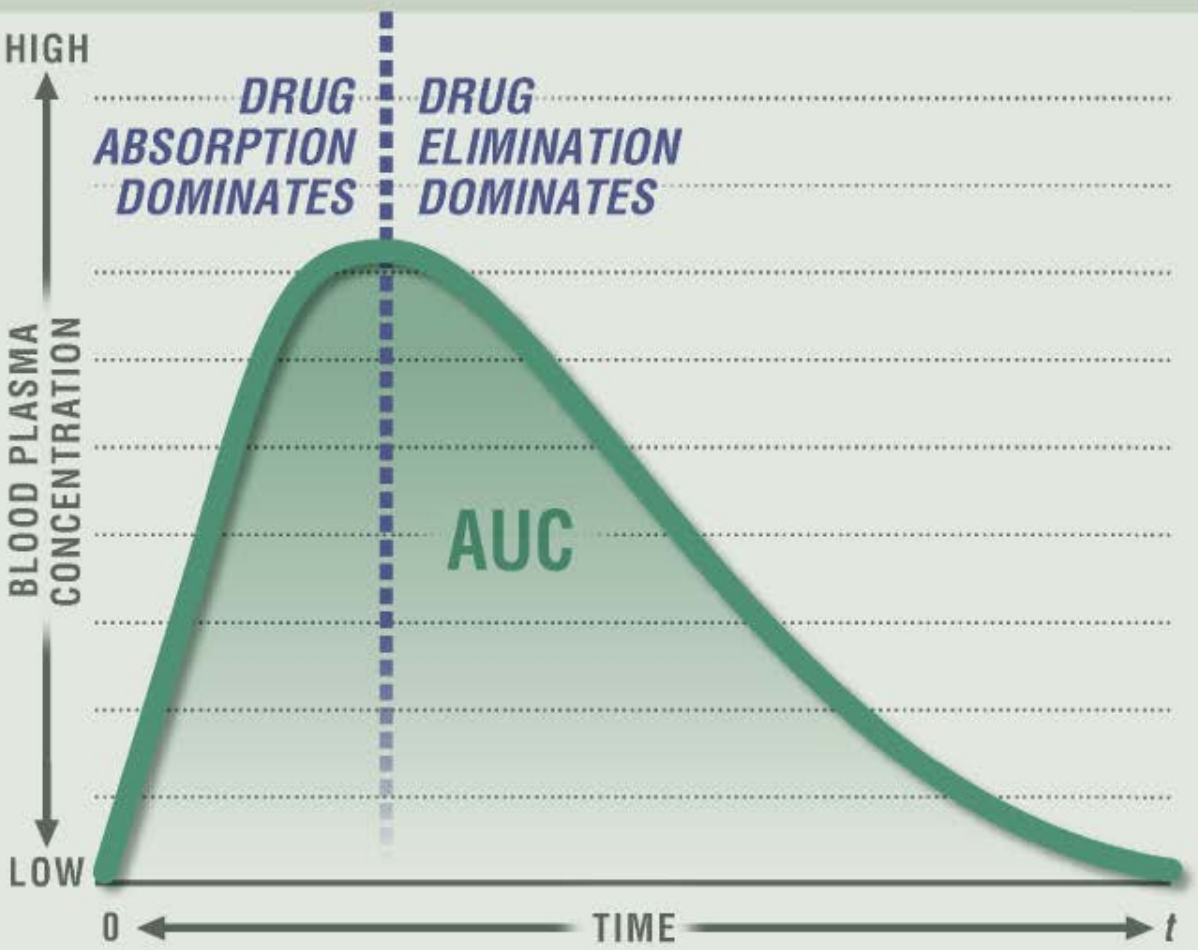


Exhibit ADV

pH in the Digestive (GI) Tract

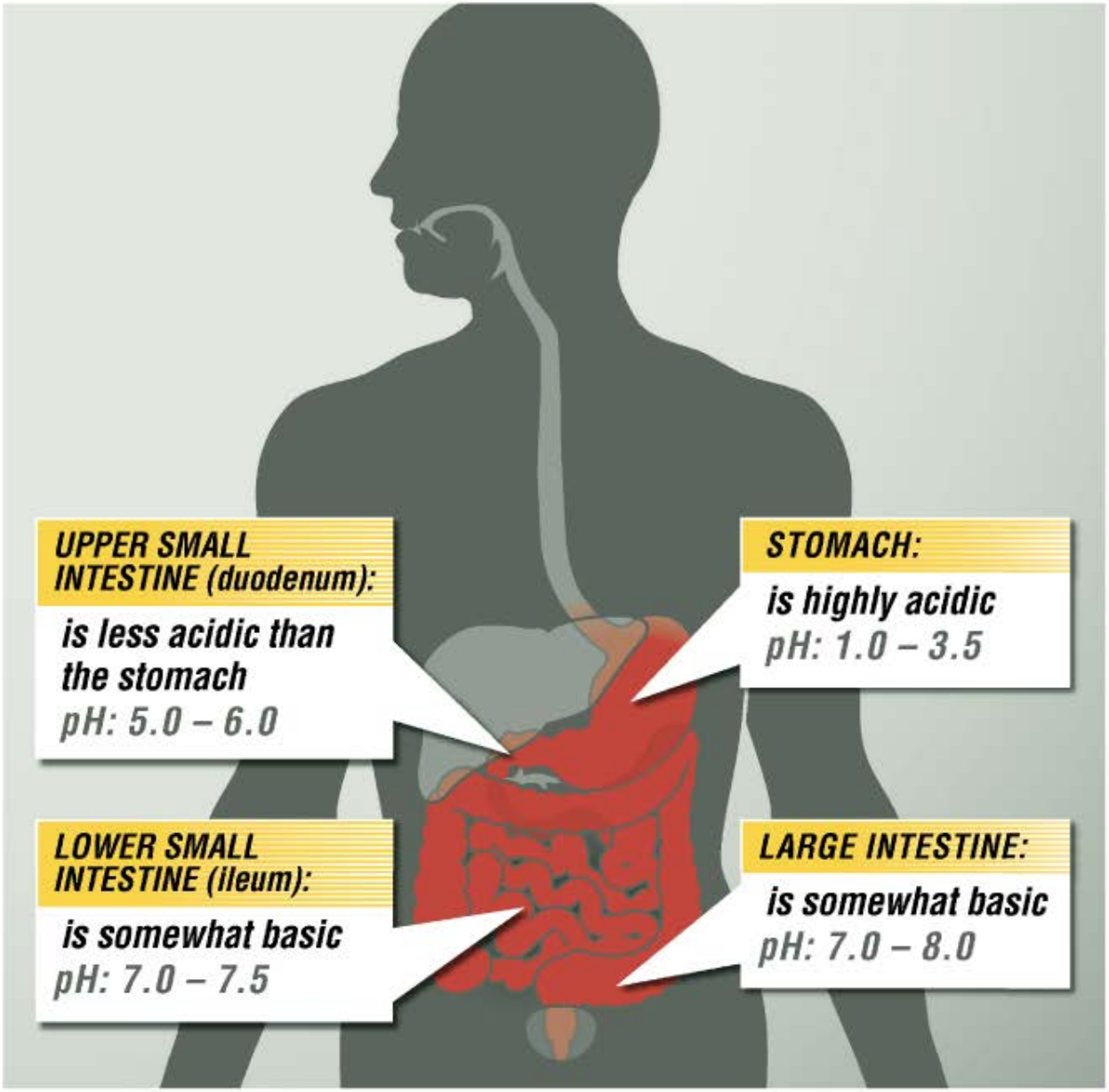


Exhibit AEA

What Is pH?

A measure of whether something is acidic or basic

What Is pH?

A measure of whether something is acidic or basic

What Is pH?

A measure of whether something is acidic or basic

What Is pH?

A measure of whether something is acidic or basic

GI Tract Transit Time

GENERALLY TAKES 24 HOURS

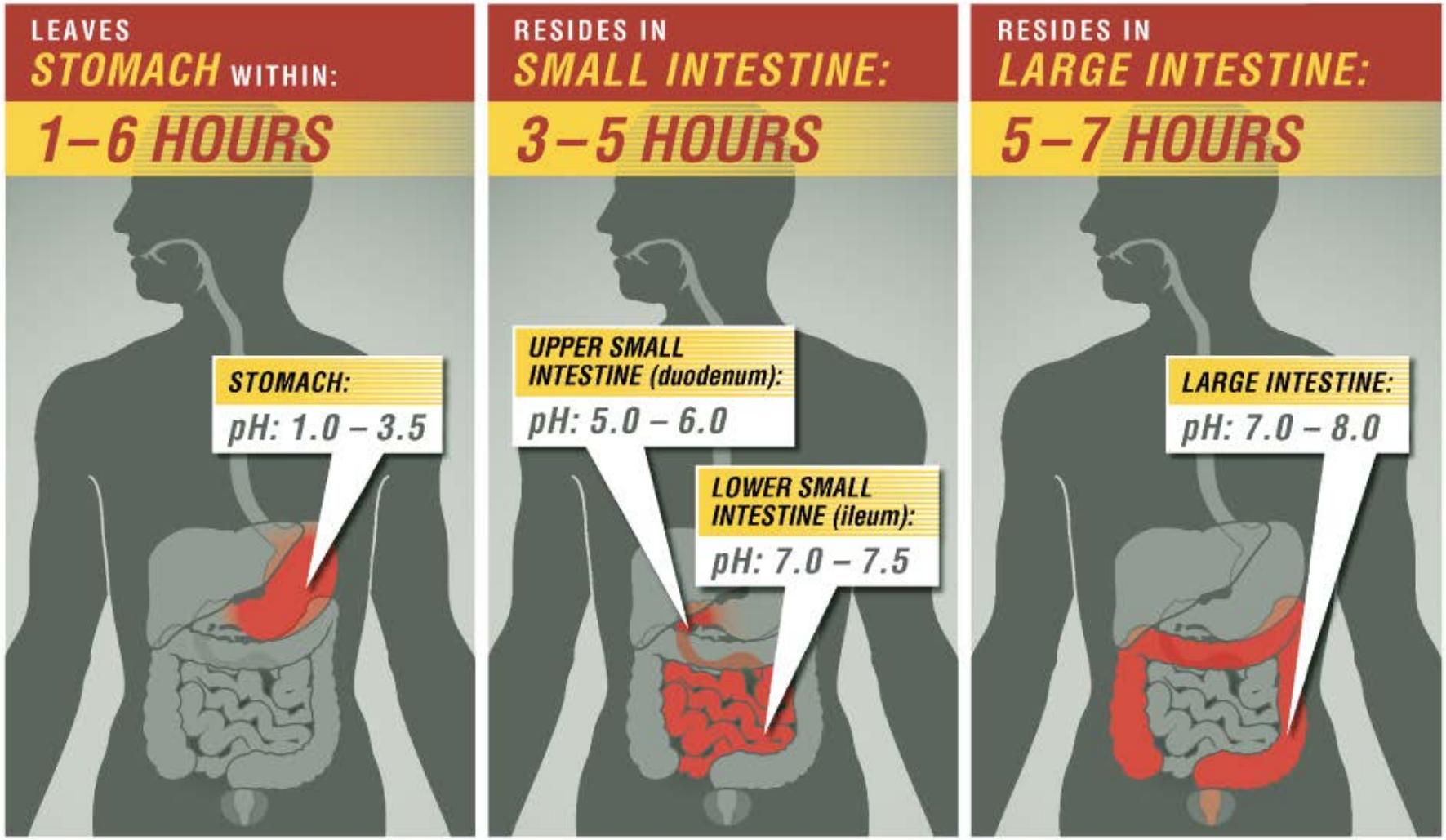


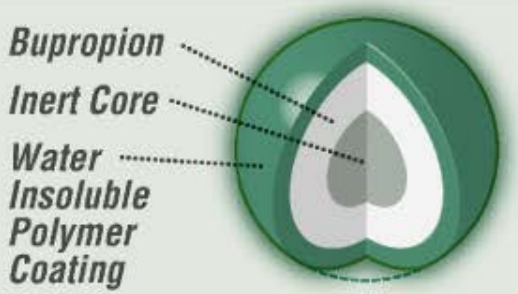
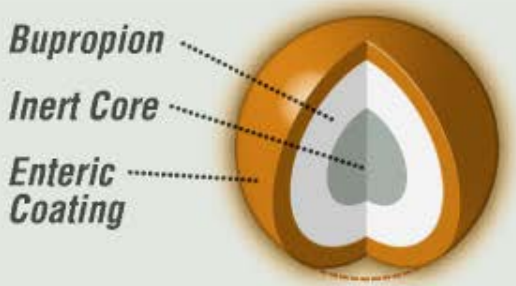
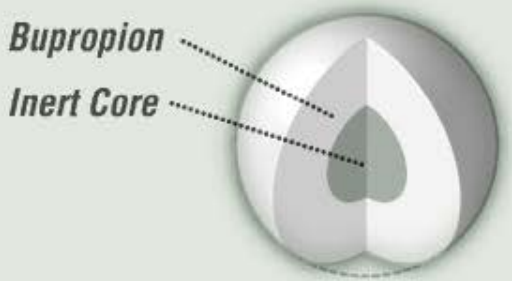
Exhibit AEB

Dosage Form Disclosed in the Andrx '708 Patent

ANDRX '708 PATENT

A multi-pellet dosage form comprised of two or three types of pellets designed to be released into a different region of the digestive tract at a different time as a function of pH.

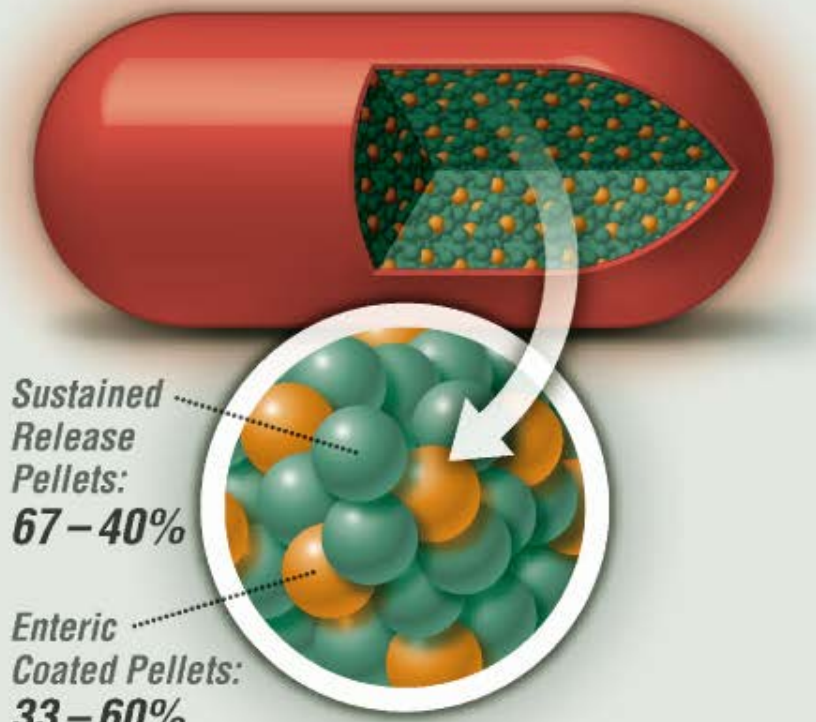
See '708 Patent Col. 6: 37 – 49

Sustained Release Pellets		***Drug released at pH of about 4.8 and lower***
Enteric Coated Pellets		***Drug released at pH of about 7.0 and above***
Instant Release Pellets		***No coating — Drug released immediately***

Dosage Form Claimed in the Andrx '708 Patent

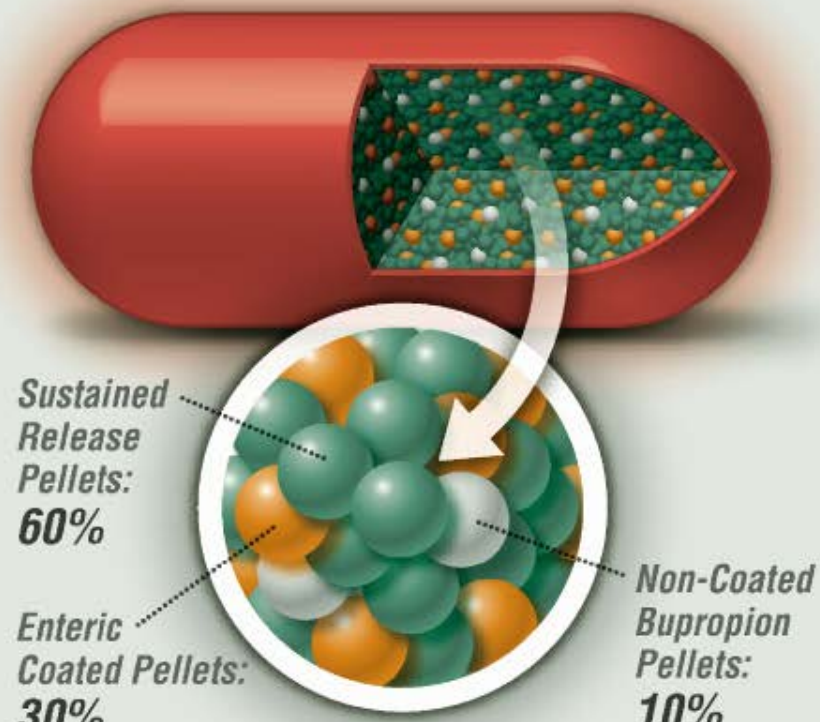
ANDRX '708 PATENT

Preferred Embodiment

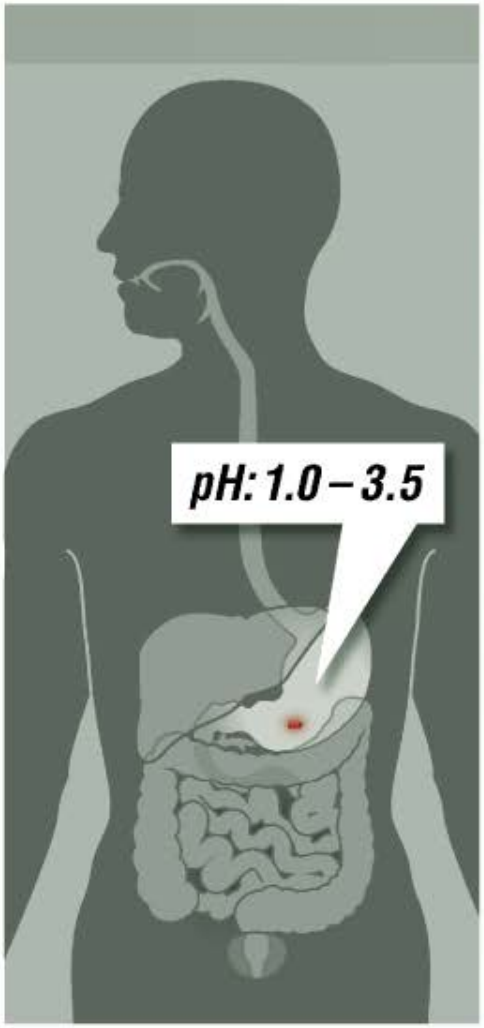


ANDRX '708 PATENT

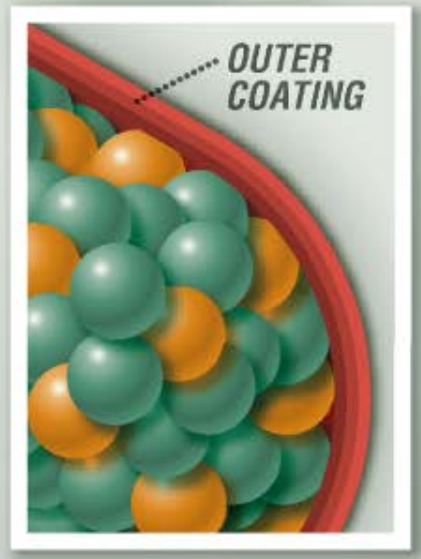
Alternate Embodiment



Dosage Form Claimed in the Andrx '708 Patent



OUTER COATING
of capsule dissolves in the stomach



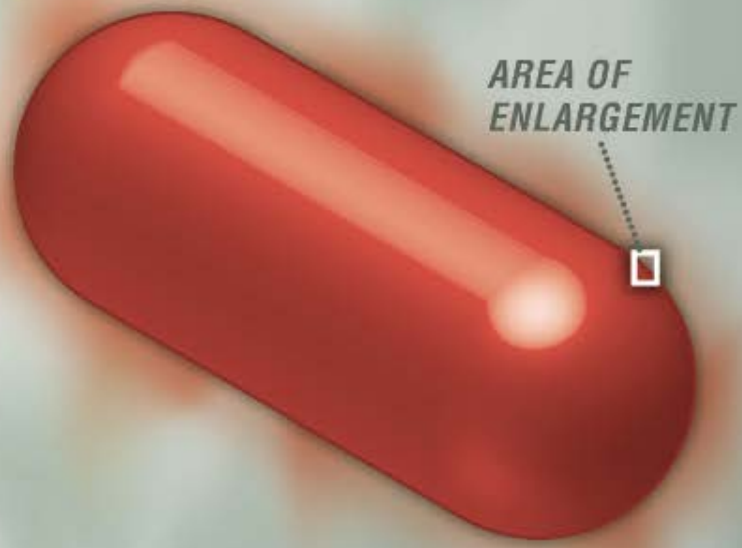
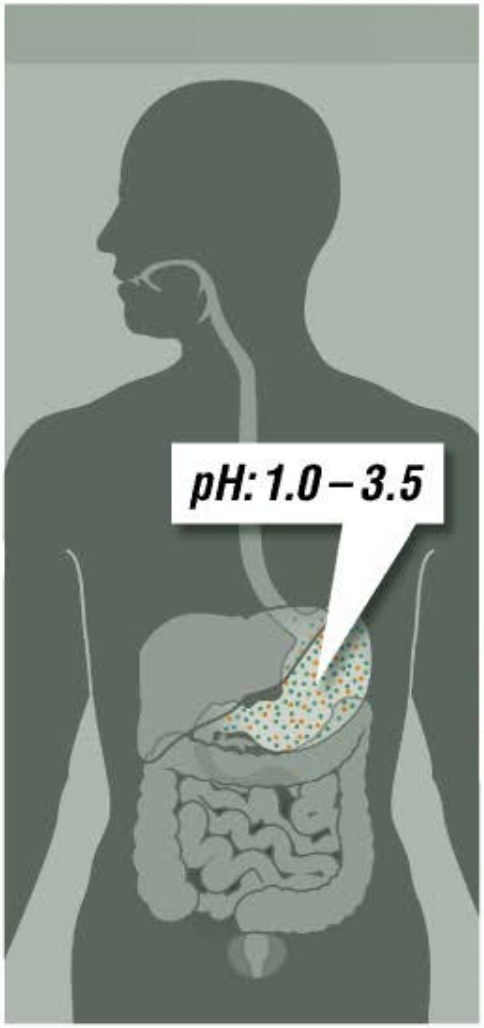


Exhibit AEE

Dosage Form Claimed in the Andrx '708 Patent



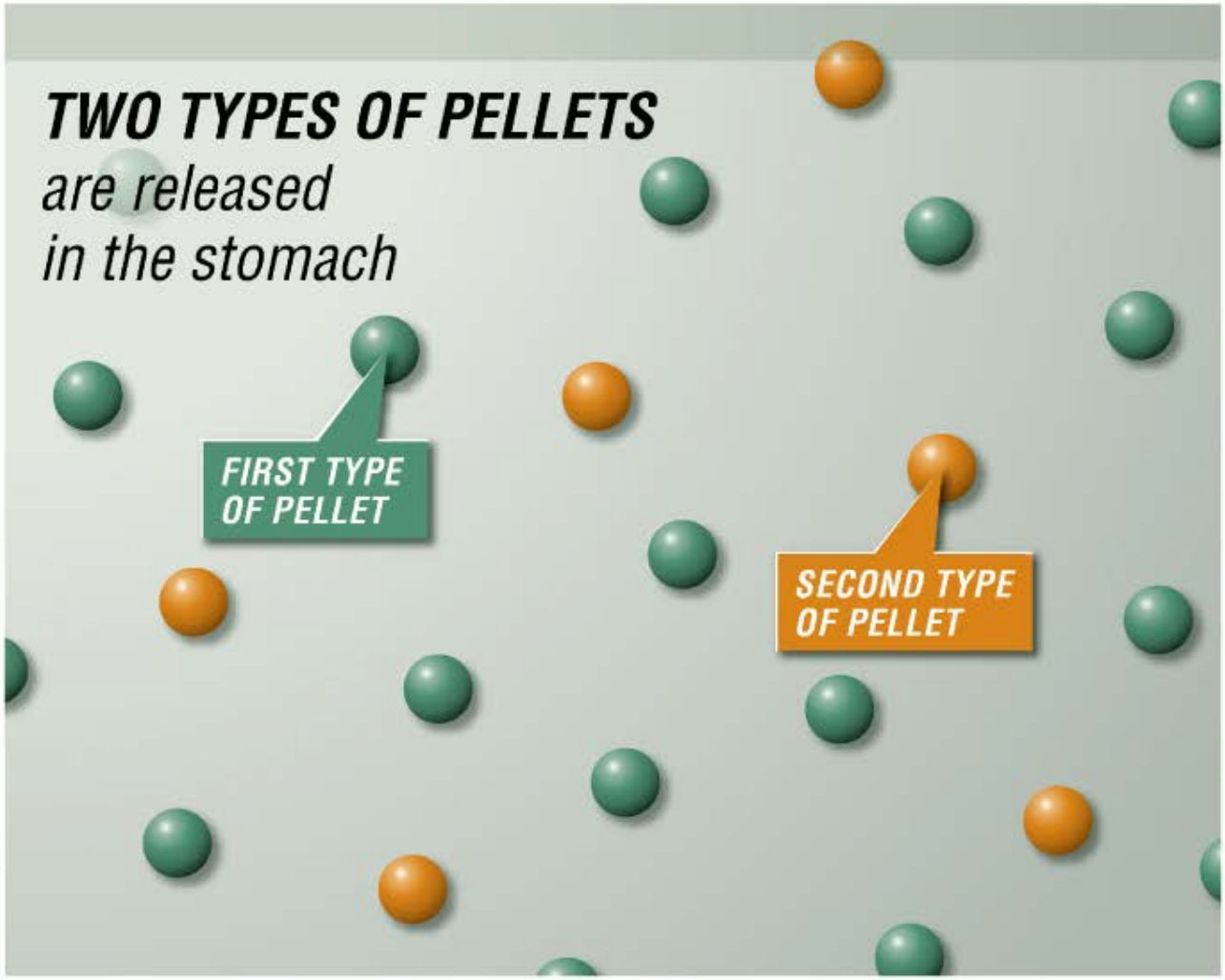
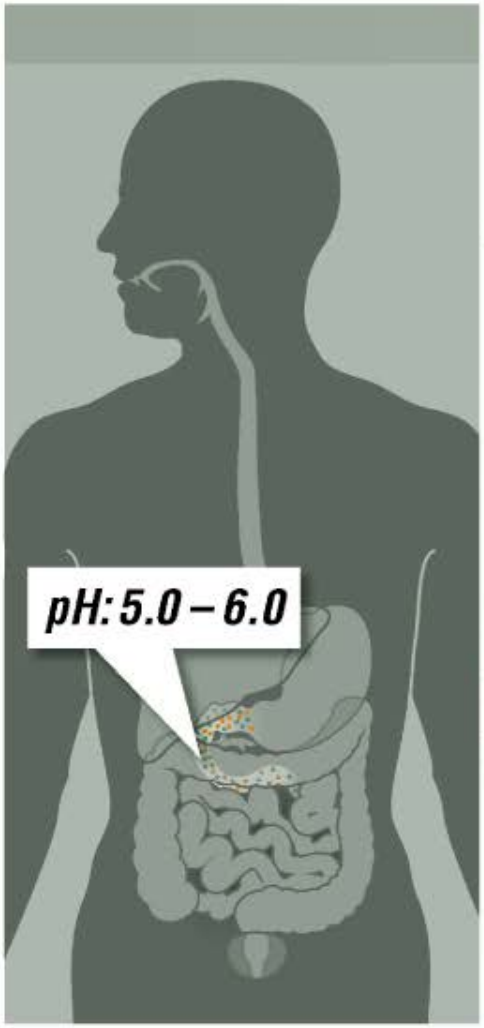


Exhibit AEF

Dosage Form Claimed in the Andrx '708 Patent



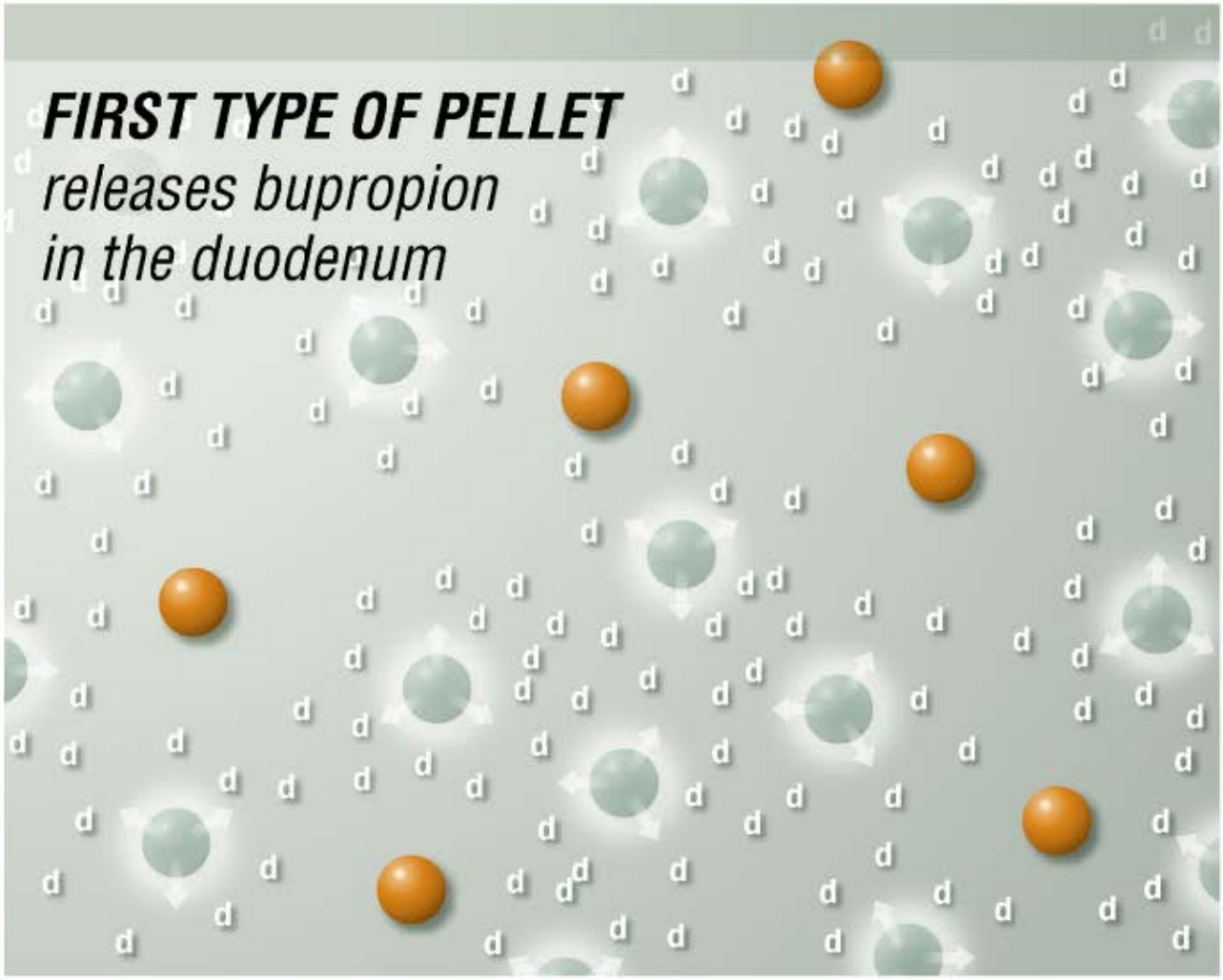
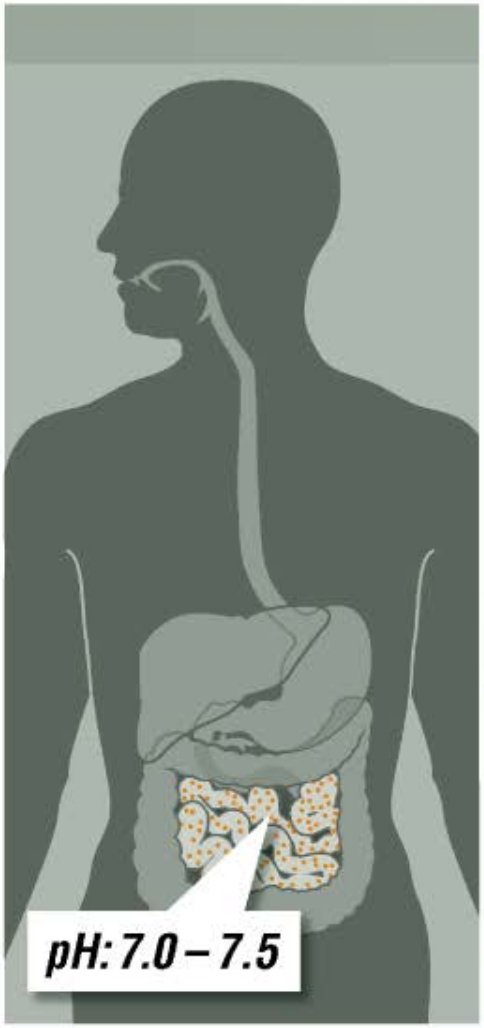


Exhibit AEG

Dosage Form Claimed in the Andrx '708 Patent



SECOND TYPE OF PELLET
releases bupropion in the ileum

Exhibit AEH

The Andrx '708 Patent *IS OBVIOUS*

ANDRX '708 PATENT	
CLAIM 1	**OBVIOUS OVER PRIOR ART?**
A once daily dosage form comprising 150 mg of an [sic] bupropion or salt of bupropion,	?
said dosage form providing an in vivo plasma profile selected from: (a) Mean T_{max} of about 5 or more hours	?
(b) Mean C_{max} of less than about 90 ng/ml, and	?
(c) Mean $AUC_{0\text{-}120h}$ of more than about 350 (ng-h)ml.	?

The Andrx '708 Patent *IS OBVIOUS*

ANDRX '708 PATENT		
CLAIM 1	**OBVIOUS OVER PRIOR ART?**	
A **once daily dosage form** comprising 150 mg of an [sic] bupropion or salt of bupropion,	**YES**	**GSK's '798 Patent:** **"With the tablets of this invention it is now possible to *dose one…times per day*…."** *Col 1: 60 – 62*
said dosage form providing an in vivo plasma profile selected from: (a) Mean T_{max} of about 5 or more hours	?	
(b) Mean C_{max} of less than about 90 ng/ml, and	?	
(c) Mean $AUC_{0\text{-}120h}$ of more than about 350 (ng-h)ml.	?	

The Andrx '708 Patent *IS OBVIOUS*

ANDRX '708 PATENT		
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A **once daily dosage form** comprising 150 mg of an [sic] bupropion or salt of bupropion,	**YES**	**GSK's '798 Patent:** "With the tablets of this invention it is now possible to *dose one…times per day*…." *Col 1: 60 – 62*
said dosage form providing an in vivo plasma profile selected from: (a) Mean T_{max} of **about 5 or more hours**	**YES**	**It was obvious to one skilled in the art to increase T_{max} from the 2.5 hours claimed in GSK's '798 patent to achieve a one-a-day dosage form.** *See Cheng Dep. Tr. at 141: 8 – 21*
(b) Mean C_{max} of less than about 90 ng/ml, and	?	
(c) Mean $AUC_{0\text{-}120h}$ of more than about 350 (ng-h)ml.	?	

The Andrx '708 Patent *IS OBVIOUS*

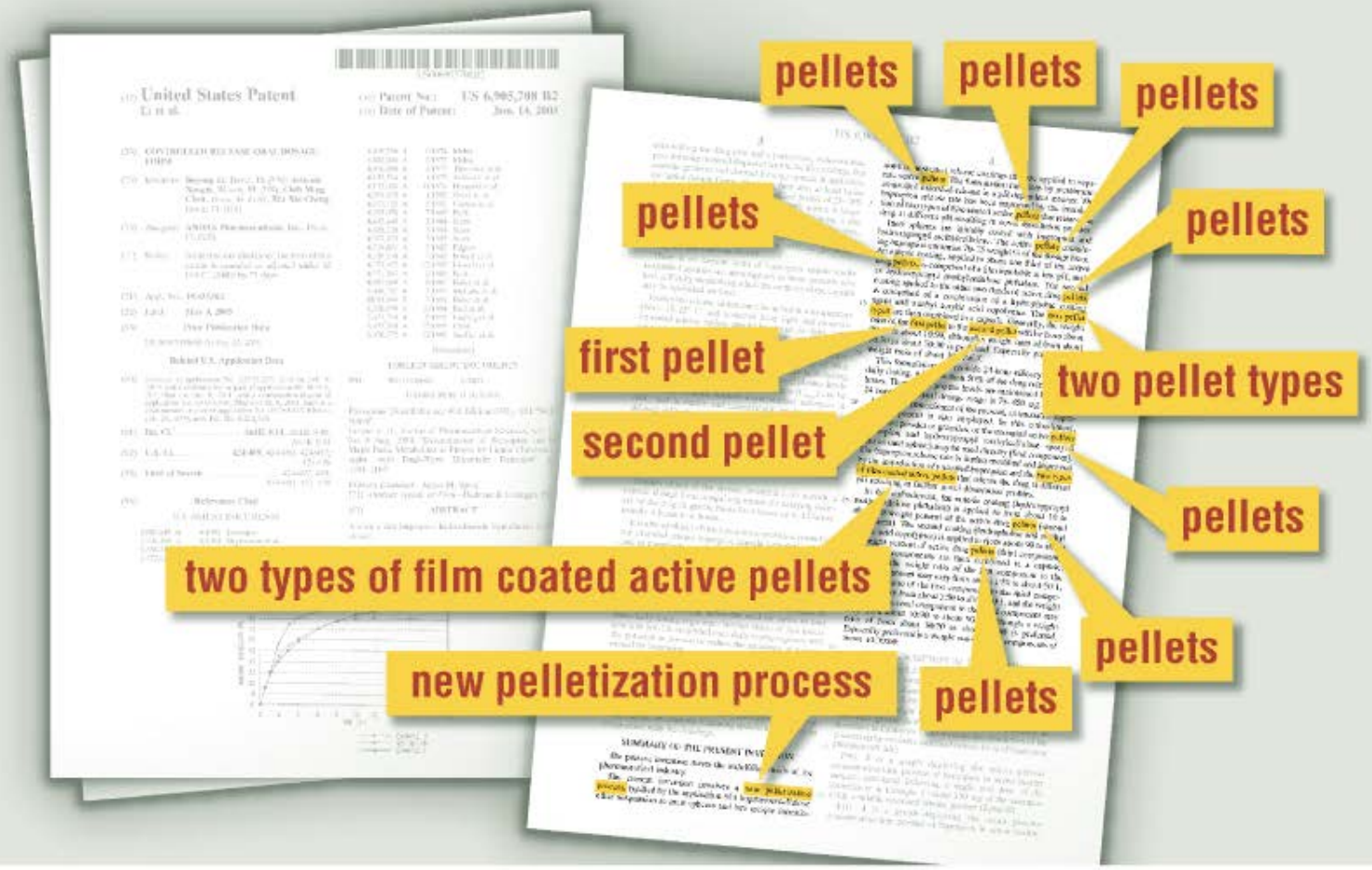
ANDRX '708 PATENT		
CLAIM 1	**OBVIOUS OVER PRIOR ART?**	
A **once daily dosage form** comprising 150 mg of an [sic] bupropion or salt of bupropion,	**YES**	**GSK's '798 Patent:** "With the tablets of this invention it is now possible to *dose one…times per day*…." *Col 1: 60 – 62*
said dosage form providing an in vivo plasma profile selected from: (a) Mean T_{max} of **about 5 or more hours**	**YES**	**It was obvious to one skilled in the art to increase T_{max} from the 2.5 hours claimed in GSK's '798 patent to achieve a one-a-day dosage form.** *See Cheng Dep. Tr. at 141: 8 – 21*
(b) Mean C_{max} of **less than about 90 ng/ml,** and	**YES**	**Figure 6 of GSK's '798 patent discloses a mean C_{max} of about *85 ng/ml.***
(c) Mean $AUC_{0\text{-}120h}$ of more than about 350 (ng-h)ml.	?	

The Andrx '708 Patent *IS OBVIOUS*

ANDRX '708 PATENT CLAIM 1	OBVIOUS OVER PRIOR ART?	
A **once daily dosage form** comprising 150 mg of an [sic] bupropion or salt of bupropion,	**YES**	GSK's '798 Patent: "With the tablets of this invention it is now possible to *dose one…times per day*…." *Col 1: 60 – 62*
said dosage form providing an in vivo plasma profile selected from: (a) Mean T_{max} of **about 5 or more hours**	**YES**	It was obvious to one skilled in the art to **increase T_{max}** from the 2.5 hours claimed in GSK's '798 patent to achieve a one-a-day dosage form. *See Cheng Dep. Tr. at 141: 8 – 21*
(b) Mean C_{max} of **less than about 90 ng/ml,** and	**YES**	Figure 6 of GSK's '798 patent discloses a mean C_{max} of about *85 ng/ml.*
(c) Mean $AUC_{0\text{-}120h}$ of **more than about 350 (ng-h)ml.**	**YES**	Figure 6 of GSK's '798 patent discloses a mean AUC_{0-120h} of about *560 (ng-h)ml.*

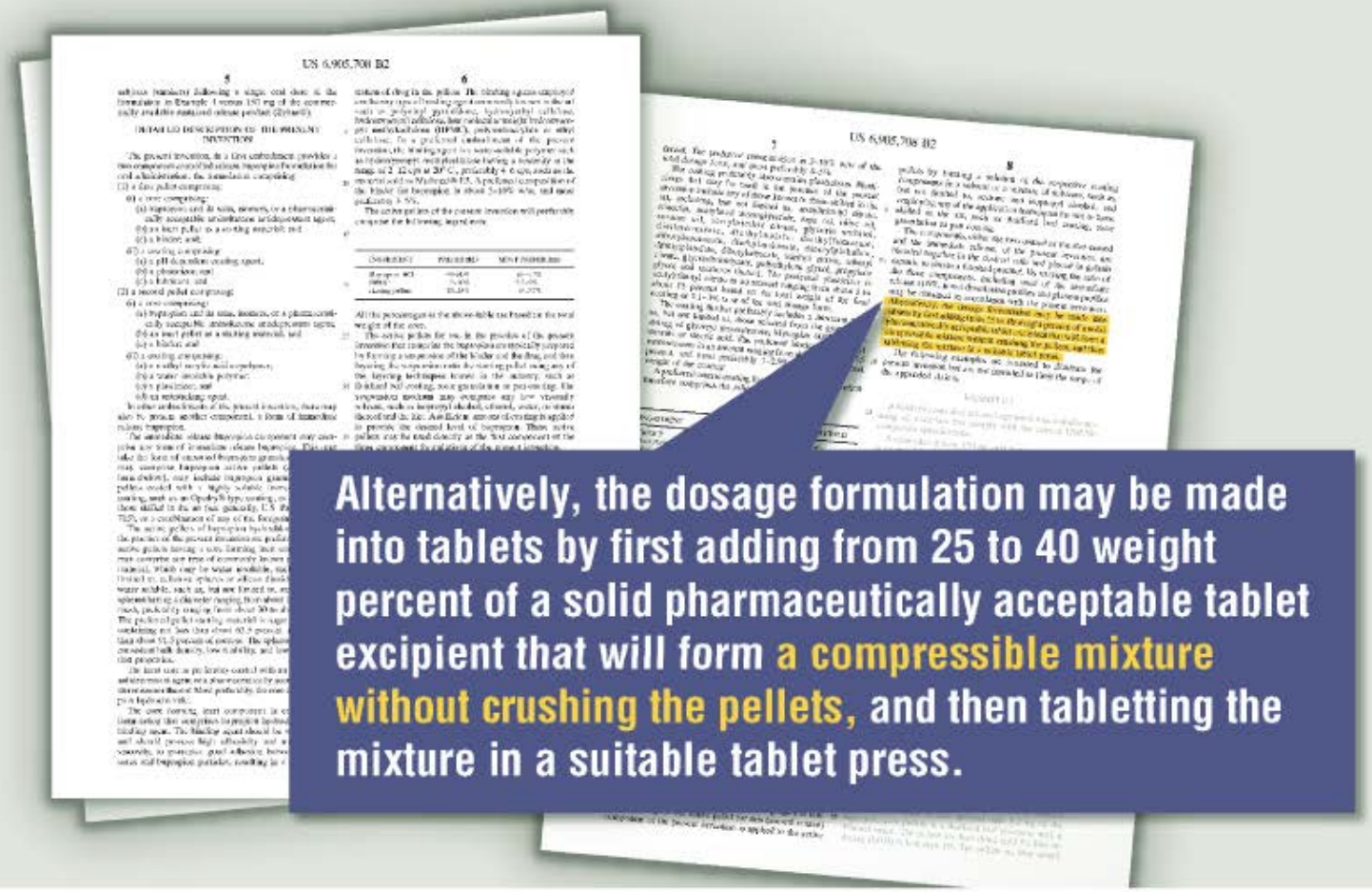
The Andrx '708 Patent Specification Limits the Dosage Form Structure to Pellets

SUMMARY OF THE PRESENT INVENTION



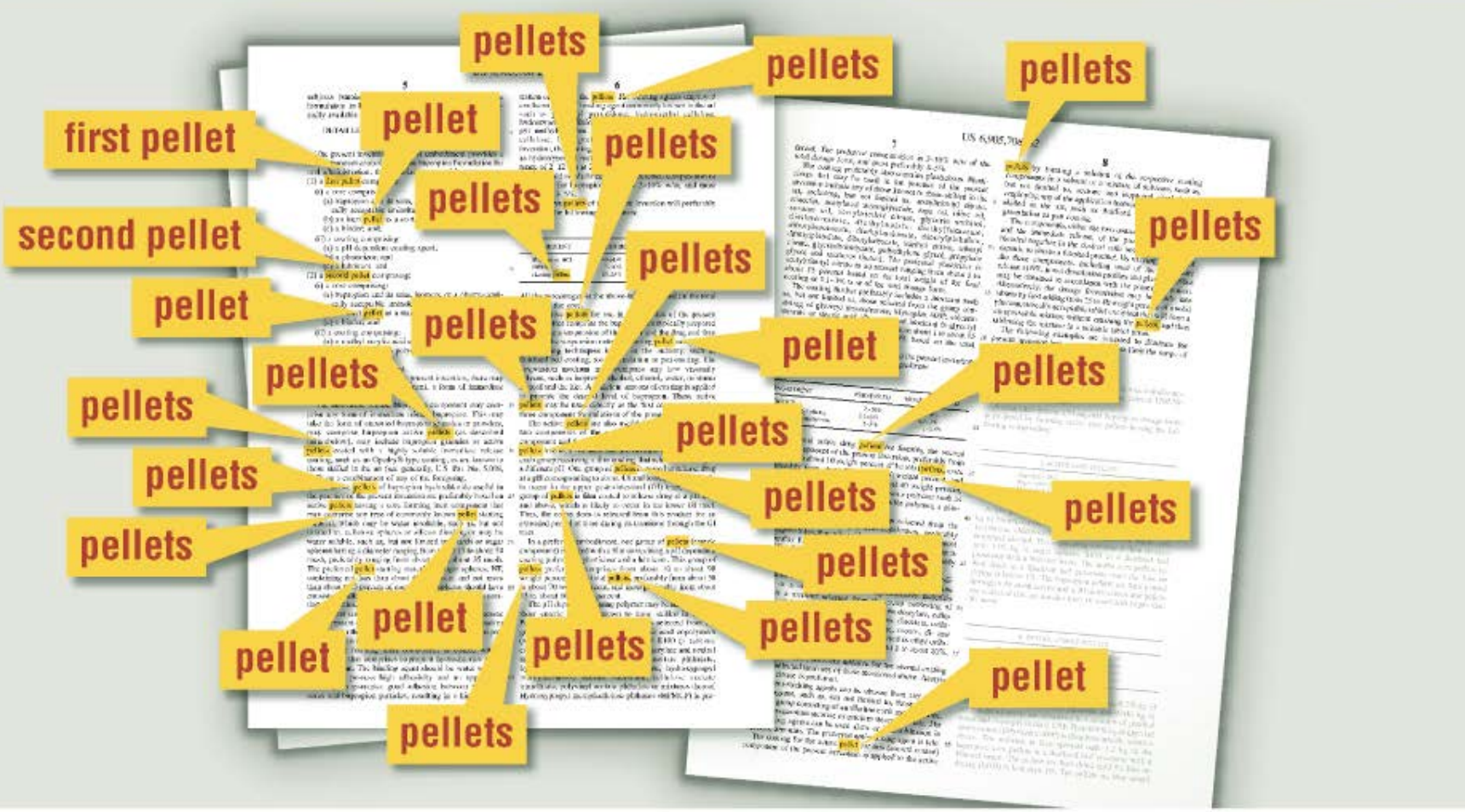
The Andrx '708 Patent Specification Limits the Dosage Form Structure to Pellets

DETAILED DESCRIPTION OF THE PRESENT INVENTION



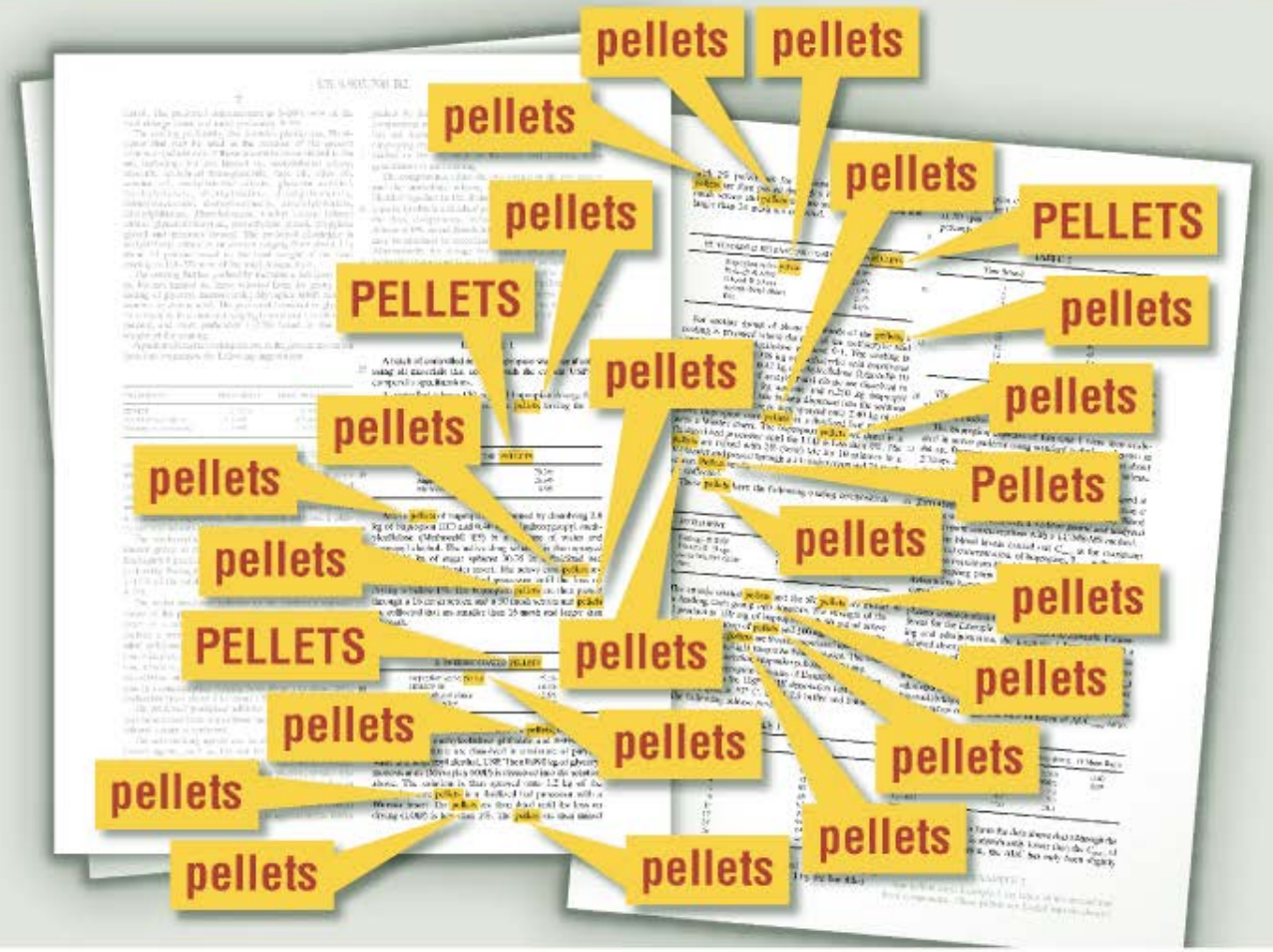
The Andrx '708 Patent Specification Limits the Dosage Form Structure to Pellets

DETAILED DESCRIPTION OF THE PRESENT INVENTION



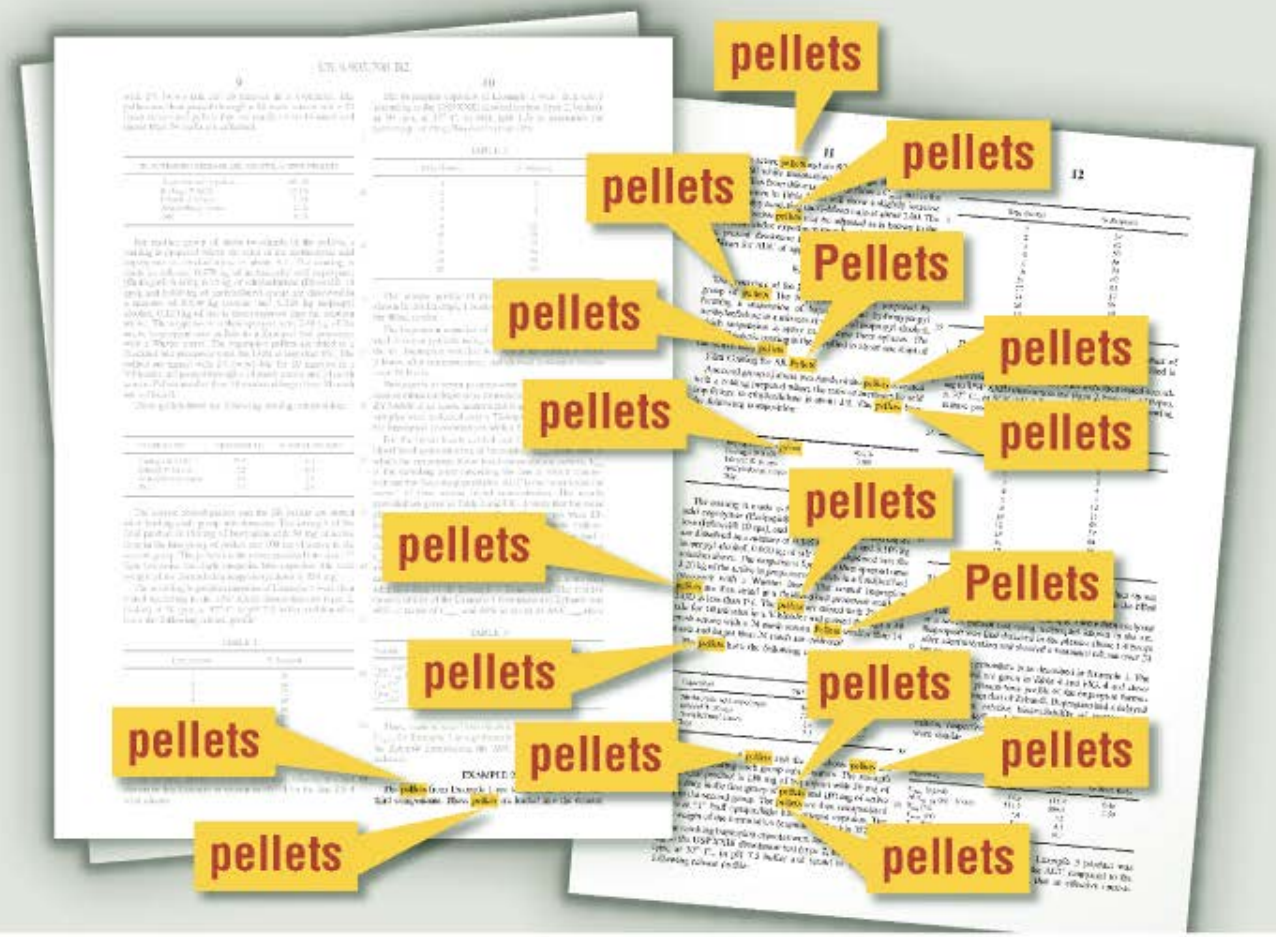
The Andrx '708 Patent Specification Limits the Dosage Form Structure to Pellets

EXAMPLE 1



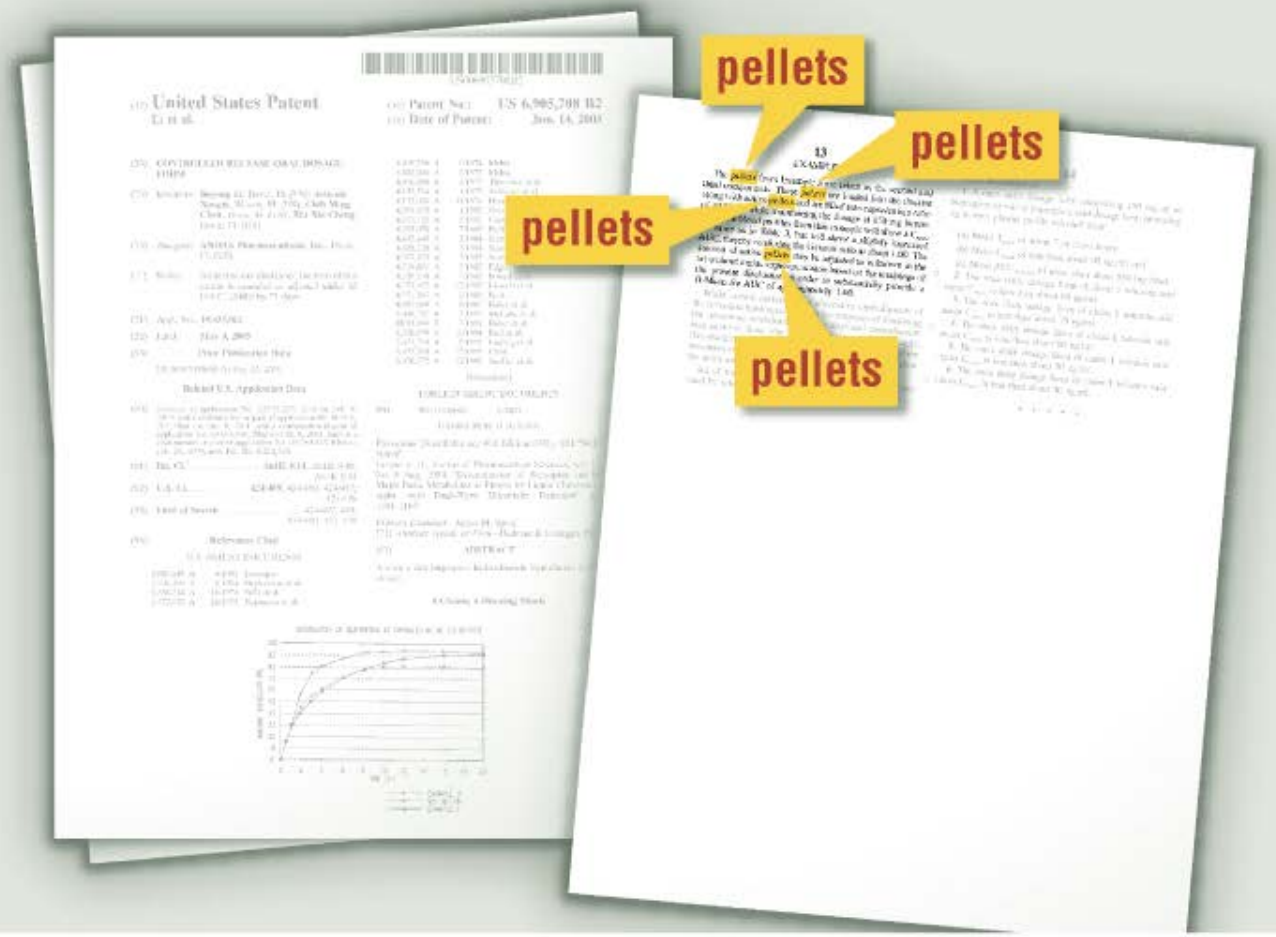
The Andrx '708 Patent Specification Limits the Dosage Form Structure to Pellets

EXAMPLES 2 AND 3



The Andrx '708 Patent Specification Limits the Dosage Form Structure to Pellets

EXAMPLE 4



Georgia-Pacific Factors Analysis
FACTOR #1

FACTOR #1:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Royalty Received by Andrx on '708 Patent	***NO EFFECT***	• Andrx has ***NEVER*** licensed the '708 patent.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #2

FACTOR #2:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Comparable Rates Paid by GSK	***DECREASE*** 	PARTY — AGREEMENT **Biovail:** Agreement includes significant benefits to GSK beyond a naked patent license, thereby limiting its relevance to the determination of a reasonable royalty in a hypothetical negotiation. **Skye Pharma:** Agreement to license a controlled release antidepressant formulation for ***3.0 to 4.0% of net sales*** plus an upfront fee of $2 million and a "Back Payment" of $10 million.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #3

FACTOR #3:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Scope of the License	***NO EFFECT***	• Andrx attempted to make the product itself, which implies a non-exclusive license. • GSK would not want to pay extra for an exclusive license since it already paid Biovail for a de facto exclusive license. • Neither GSK nor Andrx would wish the license to be restricted in any way since it is in both parties' interests to have GSK sell Wellbutrin XL® to as many customers as possible.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #4

FACTOR #4:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Andrx's Established Licensing Policy	***DECREASE*** 	• Andrx 2005 Annual Report clearly states it seeks agreements with third parties to leverage its formulation capabilities and controlled release technologies. • In 2004, Andrx generated almost $50 million in licensing revenues which represents more than 70% of its net income in that year.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #5

FACTOR #5:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Andrx/GSK Relationship	***DECREASE*** 	• Andrx does not sell a product based on a once-a-day bupropion formulation. • Andrx's attempts at producing a once-a-day bupropion product were unsuccessful. • The relationship between GSK and Andrx is one of inventor and promoter.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #6

FACTOR #6:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Wellbutrin XL® Effect on Sales of Related Products	***DECREASE*** 	• No other products are associated with the sale of Wellbutrin XL®. • When Wellbutrin XL® launched in 2003, 50% of its sales came at the expense of Wellbutrin SR®. • In February 2004, 39% of Wellbutrin XL® sales came from Wellbutrin SR®. *GSKAND026903, GSKAND028734*

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #7

FACTOR #7:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Term of the License	***DECREASE*** 	• As of the hypothetical negotiation date, the '708 patent had more than 17 years of patent life remaining. • Long term licenses tend to have lower rates so as not to provide incentives to design around the patented technology.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #8

FACTOR #8:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Commercial Success	***INCREASE*** 	• Wellbutrin XL® allowed GSK to extend the Wellbutrin® brand beyond Wellbutrin SR®. • Wellbutrin XL® has been a commercial success for GSK. • Wellbutrin XL® has been unaffected by Wellbutrin SR® generics due to its superior clinical profile. *GSKAND028594, GSKAND028742*

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTORS #9 and #10

FACTORS #9 and #10:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Utility, Nature, Benefits and Advantages of the '708 Patent	***INCREASE*** 	• Wellbutrin XL® provides an advantage over Wellbutrin SR® and other twice-daily antidepressant formulations – Increases patient compliance – Decreases probability that the medication will interrupt a patient's sleep cycle • Side effects are reduced due to steadier plasma drug level throughout the day *GSKAND012061, GSKAND011672*

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #11

FACTOR #11:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Extent of GSK's Use of the '708 Invention	***INCREASE*** 	• GSK utilized Wellbutrin XL® to extend its Wellbutrin® brand beyond Wellbutrin SR®. • Based on actual and projected GSK sales data, the company anticipates it will have sold more than $1 billion of accused product as of the trial date. • In 2005, Wellbutrin XL® accounted for approximately 4% of GSK's worldwide profits.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #12

FACTOR #12:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Customary Royalty Rates in the Industry	***DECREASE*** 	• Review of 10 licensing agreements involving controlled release pharmaceuticals. – 5 were instances of large pharmaceutical companies licensing a controlled release technology from a smaller development and/or generic pharmaceutical company. – 1 agreement specifically relates to GSK licensing a controlled release antidepressant formulation from Skye Pharma. • Conclusion: A starting point for a hypothetical negotiation would range from 1% to 10% with a strong influence toward a more defined range of 2.8% to 4.6%.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #14

FACTOR #14:	EFFECT ON ROYALTY RATE:	OBSERVATION:
The Opinion of Qualified Experts	***NO EFFECT***	• To date I have considered the expert report of Scott Hampton.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis
FACTOR #15

FACTOR #15:	EFFECT ON ROYALTY RATE:	OBSERVATION:
Willing Buyer/ Willing Seller Hypothetical Negotiation	***DECREASE*** 	• GSK and Andrx are assumed to have an understanding of each other's position. • Hypothetical negotiation presumes the '708 patent is valid and infringed. • Royalty rate must be such that both licensor and licensee are allowed to make reasonable expected economic profits. • Georgia-Pacific analysis suggests a royalty rate at the mid to lower end of the initial range of 0.8% to 8.25%.

Source: Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116 (S.D.N.Y. 1970).

Georgia-Pacific Factors Analysis

	INITIAL RANGE BASED ON QUANTITATIVE FACTORS 0.08% TO 8.25%	
	GEORGIA-PACIFIC FACTOR	EFFECT
Factors Tending to ***DECREASE*** *Royalty Rate:*	Comparable rates paid by GSK	↓
	Andrx's established licensing policy	↓
	GSK/Andrx relationship	↓
	Wellbutrin XL® effect on sales of related products	↓
	Term of the license	↓
	Customary royalty rates in the industry	↓
	Portion of the Wellbutrin XL® profit credited to the '708 patent	↓
	Willing buyer/willing seller hypothetical negotiation	↓
Factors Having ***NO EFFECT*** *on Royalty Rate:*	Royalties received by Andrx on '708 patent	
	Scope of the license	
	Opinion of qualified experts	
Factors Tending to ***INCREASE*** *Royalty Rate:*	Commercial success of Wellbutrin XL®	↑
	Utility and advantages of the '708 patent	↑
	Nature and benefits of the '708 patent	↑
	Extent of GSK's use of the '708 invention	↑
CONCLUSION:	*3.5% OF NET SALES WOULD BE A REASONABLE ROYALTY RATE*	