Bringing an Excipient to Market

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Innovation and Excipients

- **Do we need new excipients?**
  - Solubility challenges with new drugs
  - Enable drug delivery
  - New manufacturing techniques
  - Make drug delivery more cost effective
  - New dosage forms
  - Grow business/Make money
- **Or not?**
  - Gene therapy
  - Personalized medicine
  - Existing technology is sufficient

Innovation and Time

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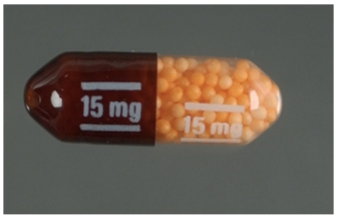
Innovation and Time

Is the pharma industry Innovative?



Regulation slows innovation?

- **Drug delivery innovation has not kept pace with computer innovation**
  - Has drug discovery?
- **Automobile industry vs pharma industry**
  - Lesser regulated vs heavily regulated
- **Governmental oversight**
  - Current model around globe
  - Too slow, not enough funding?
  - Upgrades include PDUFA
    - Roughly halved the average approval time
    - Has been renewed several times so seems to be a good thing

Excipient Allowal Process

- **New excipient is invented**
  - Establish safety
  - GMP and GDP assured
  - Benefits over existing technology promoted
  - Pharma company formulates it into a product
- **Pharma company enters phase 3 human studies**
- **FDA reviews and approves phase 3 studies**
- **Excipient has now passed FDA safety evaluation**
- **FDA approves NDA**
- **Excipient is added to IID at use level in product**
- **Excipient is never approved, it is allowed for human consumption at certain amount**

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Innovation and New Excipients

- **Co-Processed excipient of commonly used materials**
  - No covalent bonds formed
  - Constituent materials are familiar to end user
  - Unique functionality not seen in DC blend of materials
  - Currently favored by excipient manufacturers
- **Novel use of excipient**
  - New route of administration
  - Use beyond current IID level citations
- **New to industry material**
  - Constituent material not familiar to end user
  - Toxicity data exists from other industry
  - No IID citations

Innovation and Excipients

- **Co-Processed excipient with new to industry material**
  - No covalent bonds formed
  - Constituent material(s) are not familiar to end user
  - Unique functionality not seen in DC blend of materials
  - No IID citations, toxicity data exists
- **New Molecular Entity (NME)**
  - No toxicity data
  - No IID citations
  - Unfamiliar to world
- **Multiple pathways, investment & time frame**
  - Let's try to take a look at a few scenarios

NME Toxicity Costs

Regulatory Update: The IPEC Novel Excipient Safety Evaluation Procedure

Table II: Estimated costs of a proposed tiered-testing toxicology program.

Toxicology study	Estimated cost ($)
Tier 1	
In vitro cytotoxicity	1000
In vitro membrane penetration	1000*
Genotoxicity	
Bacterial reverse mutation	8000
In vitro chromosomal aberration	8000
In vivo micronucleus	8000
In vivo chromosomal aberration	8000
QSAR	1000
Tier 2	
90-day toxicity (OECD 422, rat, with micronucleus)	300,000
90-day toxicity (dog)	350,000
Tier 3	
Developmental and reproductive toxicity	See Table I
Safety pharmacology	See Table I
Carcinogenicity	See Table I

*Cost is dependent on tissue system (e.g., dermal, gastrointestinal).

QSAR is quantitative structure activity relationship. OECD is Organization for Economic Cooperation and Development.

Table II: Estimated costs of a proposed tiered-testing toxicology program.

Table I: Estimated costs of a typical toxicology program.

Toxicology study	Estimated cost ($)
90-day repeat dose toxicity (two species)*	250,000-400,000
Developmental and reproductive toxicity	
Fertility/early prenatal development (Seg. I)	150,000
Developmental toxicity (Seg. II)	125,000
Postnatal development (Seg. III)	175,000
Safety pharmacology	
Central nervous system	20,000
Respiratory	25,000
Cardiovascular	60,000
Carcinogenicity (two species)*	900,000-1,500,000
Absorption, distribution, metabolism, excretion (ADME)	250,000

Costs reflect 2009 estimates.
*For repeat dose toxicity studies, the species would be rodent and non-rodent; for carcinogenicity studies, the species would be rat and mouse.

Table I: Estimated costs of a typical toxicology program.

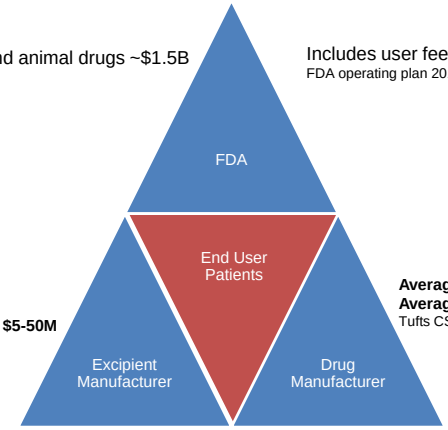
Over 3 million dollars $$$$

Pharmaceutical Technology Volume 33, Issue 11

Stakeholders in New Excipient Technology

FDA budget for Human and animal drugs ~$1.5B
FDA operating plan 2015

Includes user fees of $1.03B
FDA operating plan 2015



Average drug development cost=$2.6B
Average out of pocket=$1.3B
Tufts CSDD 2014

Excipient development cost $5-50M
Educated guess by author

Global pharma market projected to be $1.3T by 2018 IMS Institute 2014
Global dietary supplement market projected to be $0.3T by 2018

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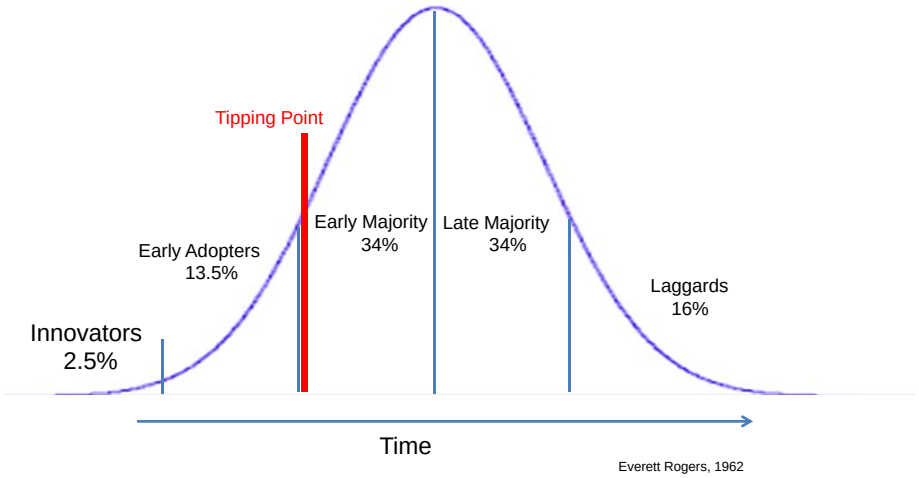
Perspective on development costs

- **Average net income for top 10 pharma companies 9.01B**
- **Average spend per/yr per drug for 10 yr development 0.26B**
- **Expressed as % of net income per/yr spend 2.9%**

- **Fictional net income for top 10 excipient companies 100M**
- **Average spend per/yr @ 20M cost (27M) over 5 years 5.4M**
- **Expressed as % net income per/yr spend 5.4%**
- **Do the math for your company……**

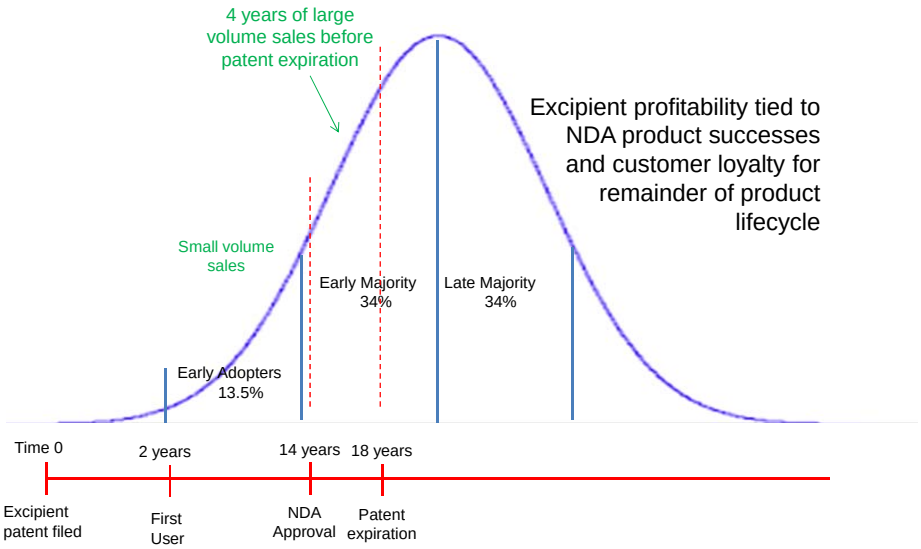
Diffusion of Innovation Theory

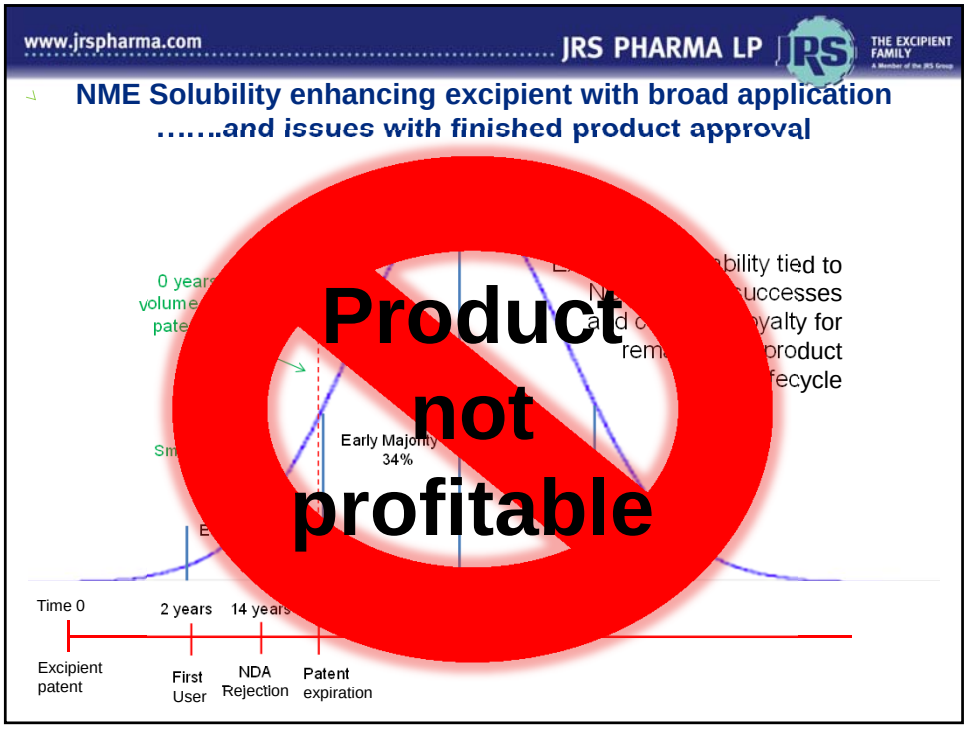
Social system = Healthcare industry



Everett Rogers, 1962

NME Solubility enhancing excipient with broad application

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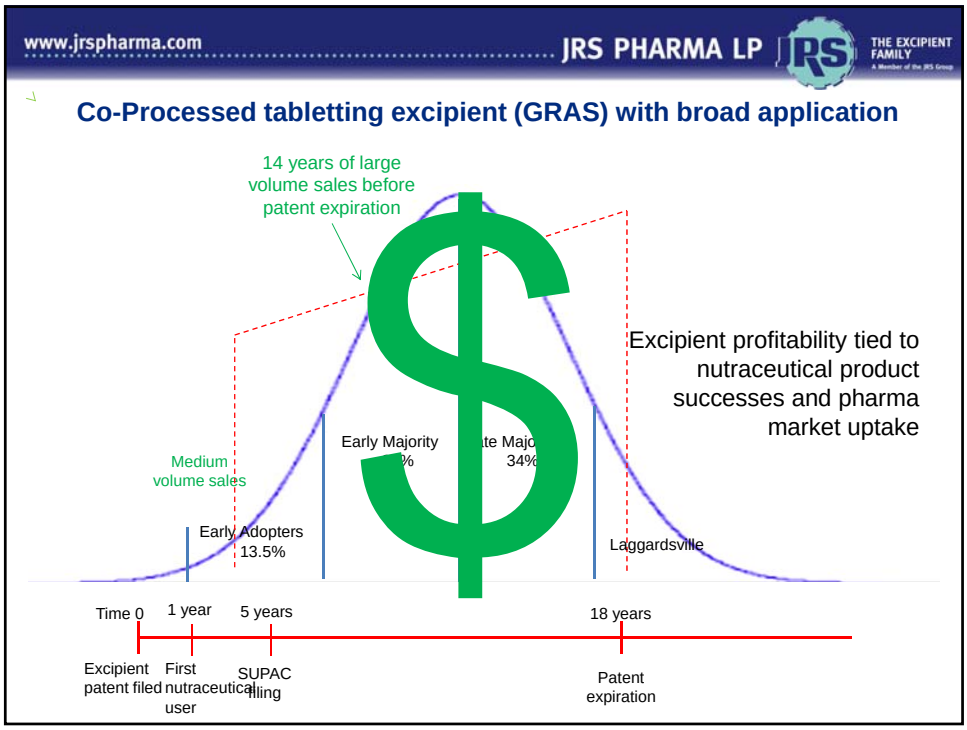
NME Solubility enhancing excipient with broad application
…….and issues with finished product approval
Product not profitable
0 years
volume
pate
bility tied to
uccesses
yalty for
product
fecycle
Early Majority
34%
Time 0
2 years
14 years
Excipient patent
First User
NDA Rejection
Patent expiration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Co-Processed tabletting excipient (GRAS) with broad application
14 years of large volume sales before patent expiration
Excipient profitability tied to nutraceutical product successes and pharma market uptake
Medium volume sales
Early Majority
34%
Early Adopters
13.5%
Laggardsville
Time 0
1 year
5 years
18 years
Excipient patent filed
First nutraceutical user
SUPAC filing
Patent expiration

Food Excipient Allowal Process

- **New excipient is invented**
  - Establish safety with toxicity data, same as drug division
  - GMP and GDP assured
- **Nutritional supplement company decides to use it**
  - Supplement company assumes risk, Other issues with this route
    - Benefits over existing technology must be substantial
    - Cost is king, extremely price sensitive
    - Really need to solve a problem for rapid uptake
    - Clean label
- **GRAS vs. Food Additive**
  - GRAS is pubic assess information regarding safety data
  - Food Additive is privately held safety data (same data as GRAS)
  - Excipients must meet either of the requirement
  - FDA tries to respond to GRAS notifications within 180 days

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Help for New Excipients

- **IPEC**
  - Global leader in excipient issues
- **IPEC novel excipient safety evaluation procedure**
  - Novel Excipient Evaluation Committee an independent expert group of IPEC charged with conducting the safety evaluations of new excipients.
- **IQ Consortium** (International consortium for innovation and quality in pharmaceutical industry)
  - Novel excipients working group
  - IQ and IPEC are currently exploring regulatory pathways to enable the use of novel excipients.

Help for New Excipients

- **Trade Publications**
  - Pharmaceutical Technology, PharmTech.com
  - Tablets and Capsules
- **Dialog**
  - Regulatory bodies
  - Excipient manufacturers and finished dosage manufacturers
    - Should be encouraged for all excipient usage not just new materials or novel use

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What can we do?

- **Partnership with finished dosage manufacturers**
  - Increased communication
  - Vertical integration?
- **Progress relationship with FDA**
  - IID rework
  - FDA guidances regarding excipients
- **Strength in numbers**
  - IPEC, IQ consortium
  - Harmonization, ICH
- **Privatization of governmental responsibility**
  - Good idea or approval for right price?
- **Good science and common sense!**
  - Independent approval up to “X”g/kg based on toxicity data

“You can change the world with a good idea but you can’t do it alone”

Unknown