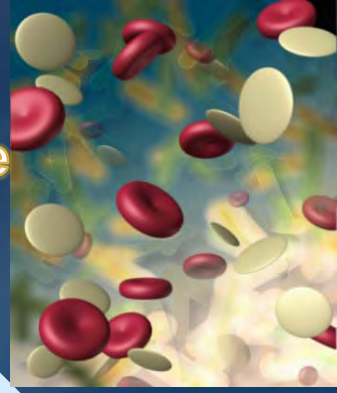
Workshop B: Product Enhancement and Product Life Cycle Management through Strategic Pharmaceutical Journey using Science, Technology, and Innovation

The Hub CityView, Philadelphia, PA, September 14, 2009



- Product Enhancement Life Cycle Management
- Strategic Pharmaceutical Development
- Science, Technology, and Innovation
- Strategic Regulatory Pathway

Strategic Journey

Raj Devalapalli, President & CEO, RiconPharma LLC (Workshop Leader)
Mukteeshwar Gande, CSO, RiconPharma LLC
Dr. Satya Valiveti, VP, Pre-formulations/Analytical R & D, RiconPharma LLC

Workshop Schedule

1.	Introductions, Workshop Overview and Business Overview	11 am-11:50 am
1.	Break	11:50 am-12:00 pm
2.	Approaches and Regulatory Strategies	12:00 pm -12:30 pm
3.	Case Study	12:30 pm-1:00 pm
4.	Break	1:00 pm – 1:10 pm
5.	Examples	1:10 pm – 1:30 pm

Presentation Outline

1. Introductions
2. Workshop Overview
3. Product Enhancement Strategic Journey
   - ✓ Business Overview
   - ✓ Strategic Product Development Approaches
   - ✓ Strategic Technology Development Approaches
   - ✓ Regulatory Strategy Pathway -505 (b) (2)
4. Case Study "A journey through Strategic Product Enhancement and Implementation Plan"

Speaker Introduction

Raj Devalapalli, President & CEO – Co-Founder at RiconPharma LLC

MS in Industrial Pharmacy, Registered Pharmacist in NJ, and an MBA in Pharmaceutical Business with 20 years of proven experience in Pharmaceutical Product and Process Technologies, Scale-ups, Technology Transfers, and Manufacturing Support.

Held key responsibility as Head of the Pilot Plant Group and Global Product/Process Technical Lead for a major product in Pfizer. Led several Technology Initiatives involving Continuous Processing and PAT at Pfizer.

Raj held key positions in companies such as Warner Lambert, Becton Dickinson, and Penwest Pharmaceuticals (TIMERx Technologies)

Speaker Introduction

Mukti Gande, CSO – Co-Founder at RiconPharma LLC

Mukti has an MS in Pharmaceutical Sciences with16 + years of proven experience in Pharmaceutical Formulation R & D, Sourcing, and Regulatory Submissions.

Mukti started his career industry career in Invamed in the formulation R & D. He was instrumental in the development and approval of several ANDA's at Invamed (Sandoz).

Mukti Co-founded CorePharma, a generic pharmaceutical company in 1998, which was acquired by a private equity firm in 2005. He was again instrumental in developing and commercializing several ANDA's at CorePharma.

Mukti is also co-founded Apicore, a custom synthesis API company, with development facilities in the US and manufacturing facilities in India. He also Co-founded Synerex, a specialty pharmaceutical company in New Jersey, which develops specialty products.

Speaker Introduction

Dr. Satya Valiveti, VP, Preformulation and Analytical R & D, RiconPharma LLC

Satya has a Ph.D in Pharmaceutical Sciences and Registered Pharmacist with 10 years of proven hands on experience in discovery, pre-clinical formulations, pre-formulations, and formulation development of Topicals and Transdermal Patches

Satya worked in companies such as Pfizer and Boehringer Ingelheim in the discovery and Pharmaceutical R & D groups. He was recognized as a good Scientist at both companies.

He was also a Post-Doctoral Research Fellow at University of Kentucky doing research on Transdermal and Topical drug delivery systems. He published over 90 publications and presentations in various peer reviewed journals and conferences.

He is a reviewer for several journals

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Strategic Product Enhancement Overview

1. Strategic overview on product enhancement strategies
2. Paradigm shift
3. Understanding business needs and drivers
4. Examining Opportunities and challenges
5. Building innovation model
6. Strategic product development and technology approaches
7. Developing appropriate strategies through both development pathway and regulatory pathway

Strategic Product Enhancement Journey

Case Study "A journey through Strategic Product Enhancement and Implementation Plan"

1. Opportunity evaluation and product selection
2. Molecular modification to enhance the bio-availability and reduce side effects
3. Reduce dosage strength
4. Reduce dosage frequency
5. Creative pre-formulation and formulation approaches
6. Creating regulatory pathway
7. Implementation plan
8. Discuss other examples

Strategic Learning Benefits

1. Obtaining an in-depth understanding of the business needs for product enhancement strategies Understanding the opportunities and challenges
2. Building up development and regulatory pathway from step to step
3. Learning to implement product ideas through a creative and strategic journey
4. Going through the comprehensive life-cycle management journey to ensure maximum takeaway

Spot Quiz

1. An NCE product filing should use _____ filing strategy ?
2. A copy of the existing product use _____ filing strategy?
3. Product Enhancement and _____ are closely associated
4. Would you enhance a product before patent expiration or after patent expiration?
5. Would lowering a dose considered as enhancement or degradation?
6. An existing product enhancement should use _____ filing strategy?

Spot Quiz

1. An NCE product filing should use 505 (b) (1) filing strategy ?
2. A copy of the existing product use ANDA filing strategy?
3. Product Enhancement and Life Cycle Management are closely associated
4. Would you enhance a product before patent expiration or after patent expiration?
5. Would lowering a dose considered as enhancement or degradation?
6. An existing product enhancement should use 505 (b) (2) filing strategy?

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Product Life Cycle

Discovery → Pre-clinical → Phase I Healthy → Phase II Patients 100-300 → Phase III Patients 3-10,000 → Market

Patents/IP

Patents/IP

Paradigm Shift

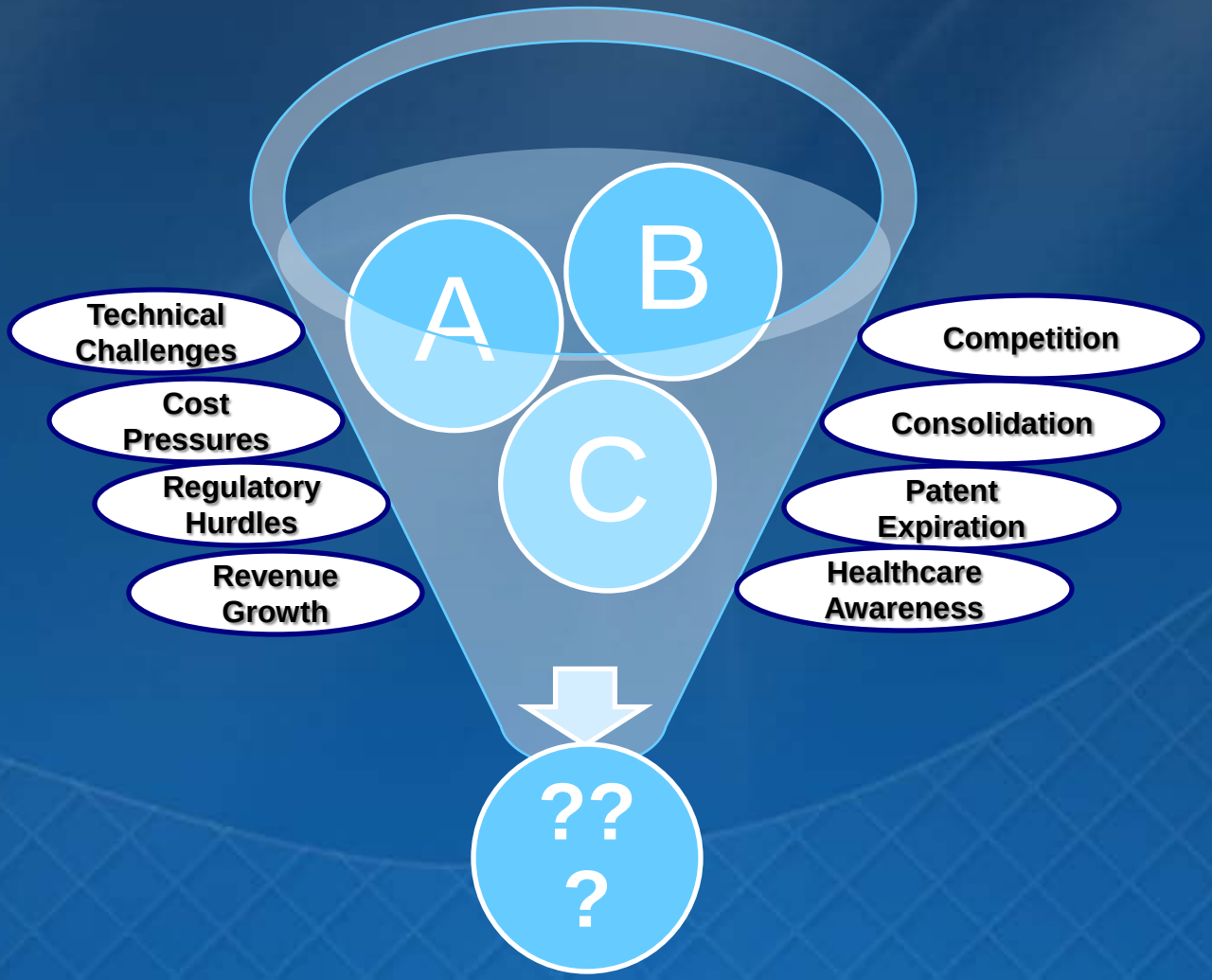
Classic Product Enhancement Example

Science, Innovation, and Technology

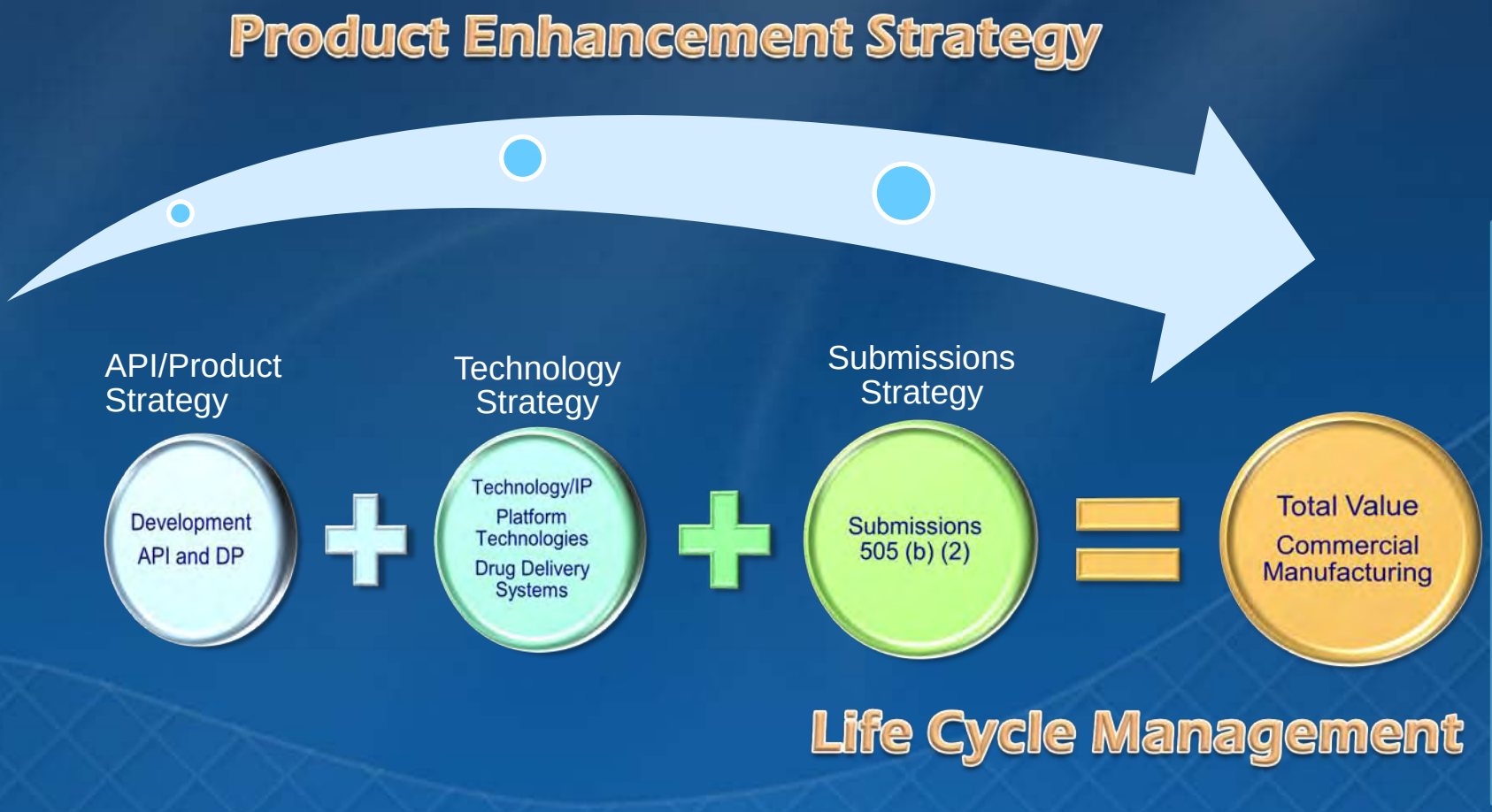
Features	Iphone 3 G	Iphone 3G S
Price	$99	$199 - $299
Storage	8 GB	16 GB – 32 GB
New Features	NA NA NA NA	Improved Performance Built-in Video Camera Voice Control Compass
Color	Black	Black & Silver
Battery Life	Internet Use 6 hours	Internet Use 9 hours
Camera	2 megapixels	3 megapixels Auto focus Video recording

Improved Performance with Additional Features for Consumer Benefit

Product Enhancement and Life Cycle Management
Key Business Drivers

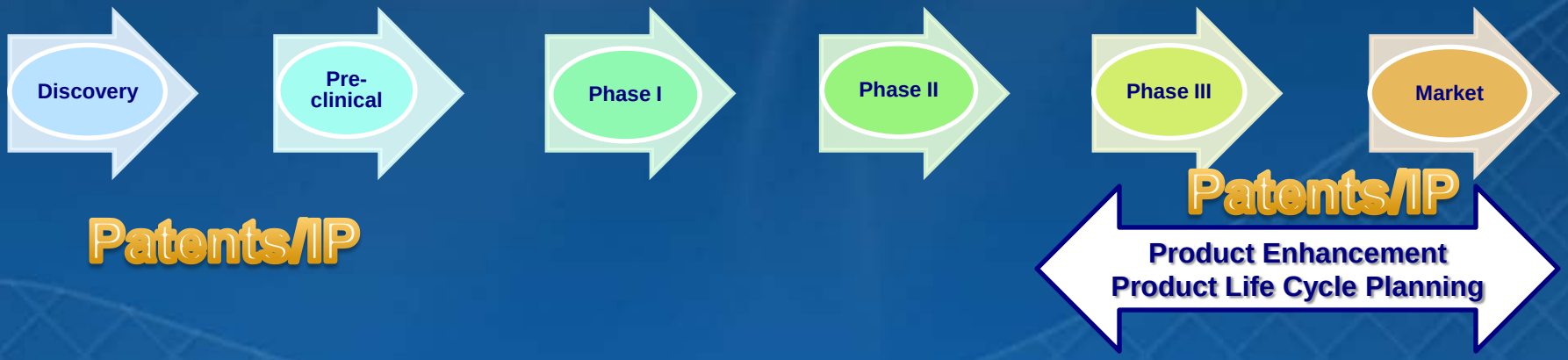


Product Enhancement Value Chain



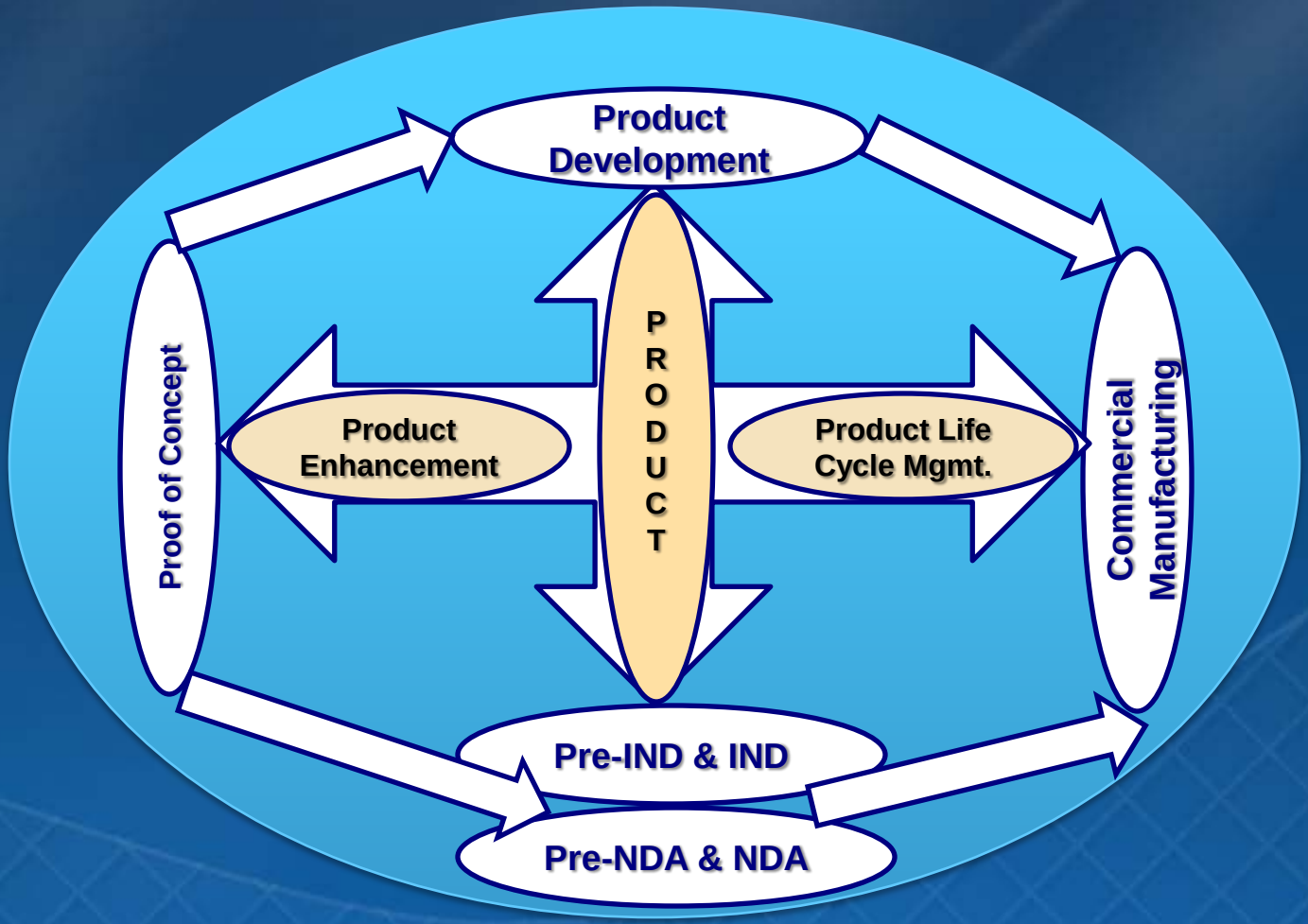
Product Life Cycle Management

Leading PE/PLM Through Science, Technology, and Innovation



Product Enhancement

Product Life Cycle Management



Innovation Model and Why now?

Over the next 3 years due to patent loss the Brand Companies will lose $60 Billions in sales

About 28% revenues will be lost in during 2010 and 2011 by Big Pharma

Product Enhancement Key Focus Elements

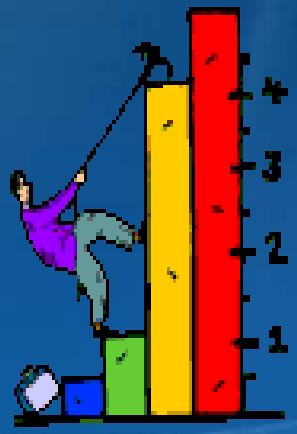
API Development	Product Development	Manufacturing Development	Regulatory Development
•Molecular Modifications • Co-Crystals • Nano-Crystals • Polymorphic Changes •Salt Changes • Co-precipitation • Co-Processing •Co - Micronization	• Polymorphic Screening • Polymorph Stabilization • Salt Screening • RM compatibility Studies • Material Characterization • Solid State Characterization • Formulation Feasibilities • Proof of Concept • Stability Studies	• Process Development • Scale-ups • Technology Transfer • Continuous Process • Alternate Processing • Technology Platforms	• Pre-IND • IND • Pre-NDA • NDA • BA/BE/Clinical Studies • Bridging Studies • NDA 505 (b) (2)

Product Enhancement Opportunities (NDA 505 (b) (2) filing)

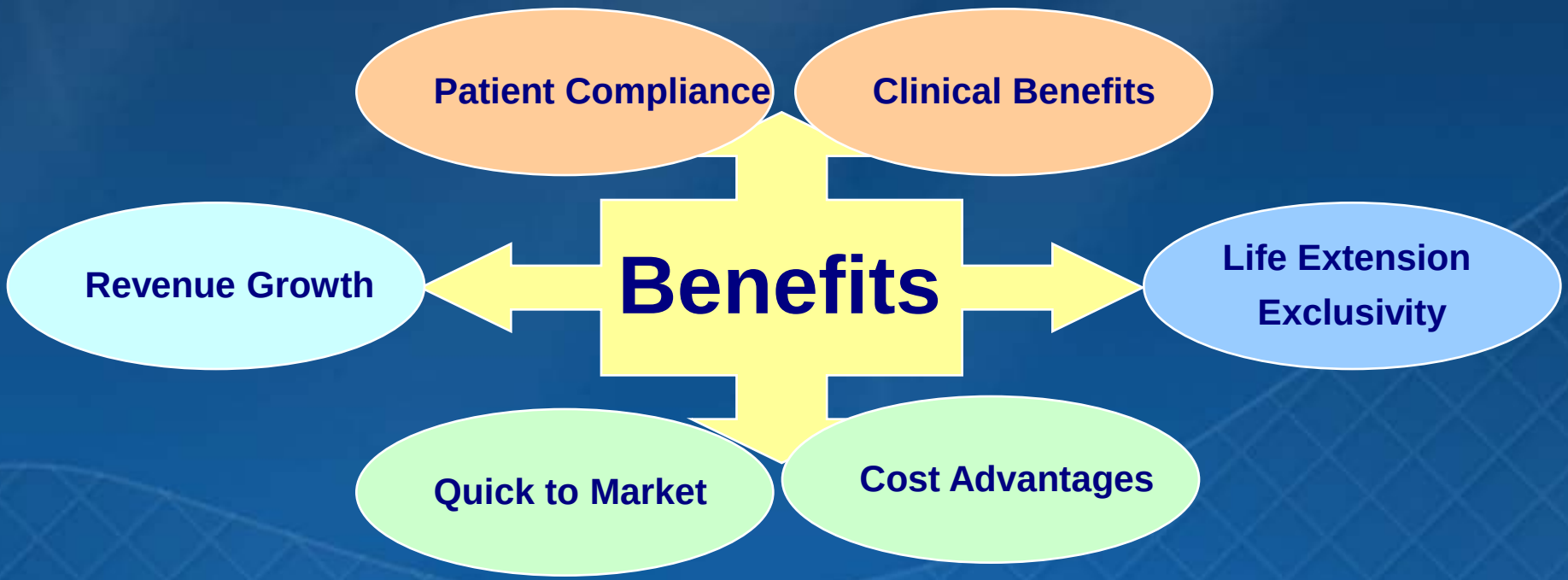
- **Dosage Form Variations**
  - ✓Immediate Release to Modified Release, Orally Disintegrating, and Buccal Tablets
  - ✓Combination Therapy (Single active to two actives or substitution of an active in a combination product)
  - ✓Tablets to Transdermals
  - ✓Creams to Gels to Foams
- **Bio-availability Enhancements, Clinical Variations and Therapeutic Changes**
  - ✓Dosage Strength Reductions
  - ✓Side Effects Reductions
- **Bio-availability Slow-down**
  - ✓Dosage Frequency Reductions (Multiple dosing to Once a day dosing)
  - ✓Delayed Release and Targeted Release
- **Route of administration**
  - ✓IV to intrathecal
- **New Indications**
- **Substitution of and active ingredient in a combination product**

Product Enhancement Challenges

1. Product and Process Understanding
2. Science and Technology Challenges
3. Safety and Efficacy Challenges (Bridging Clinical and Bio-Studies)
4. Regulatory Challenges (Rationale and Justification for FDA buy in)
5. Barrier to entry (Patents and IP)
6. Cost of Development and Manufacturing
7. Patents and IP Challenges
8. Competition
9. Marketing and Detailing
10. Time to market



Product Enhancement and Life Cycle Management Benefits



API Expertise

- Need close associations with several API companies for custom synthesis and developing novel API technologies for product enhancements and stabilization by:
  - Polymorphs
  - Co-crystallization
  - Co-precipitation
  - Nano-crystals
  - Co-micronization
  - Dilution/Combination

Pre-formulation Expertise

Pre-formulation studies:

- Polymorphic Screening
- Salt Screening/Selection
- Solid State Characterization of API
- Intrinsic Dissolution
- Excipient Compatibility Studies

Physicochemical Characterization of Drug Substance

- Purity (HPLC)
- Polymorph stability in aqueous slurry (1 day to 7 days)
- Solution stability studies (under stress conditions at physiological pH)
- Equilibrium and apparent solubility: pH solubility, FaSSIF and FeSSIF
- Solid state characterization
  - DSC, TGA, XRPD, Dynamic vapor sorption (DVS for hygroscopicity information) and Microscopy
- Solid state physical state stability (DSC and XRPD)
- Solid state chemical stability (HPLC)

Physicochemical Characterization of Drug Substance

- Simulated wet granulation studies (DSC and XRPD)
- Corrosive studies for salts (stainless steel)
- Photostability studies
- Mechanical and Stress stability studies
- Density and flow properties
- Intrinsic dissolution

Formulation Expertise

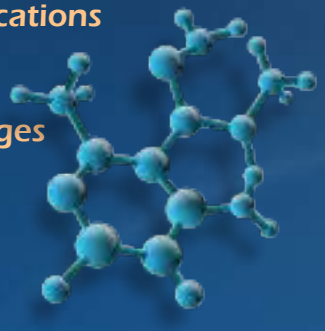
- Need experience in various Formulation Techniques:
  - Compressed/Film Coated Tablets
  - Delayed Release and Extended Release Tablets
  - Chewable and Orally Disintegrating Tablets
  - Capsules (Hard/Soft Gelatin and Powder/Beads filled)
  - Oral Liquids and Suspensions
  - Transdermal Patches (Matrix and Hydrogels)
  - Topicals (Ointments, Creams, Gels, and Foams)
  - Parenterals (Solutions, Suspensions, Emulsions, Lyophilizations)

Technology Platforms

- Abuse Deterrents Technology
- Follicle Target Drug Delivery systems
- Colon Target Drug Delivery systems
- Orally Disintegrating Tablets
- Buccal Delivery Systems
- Modified Release Dosage Forms

Product Enhancement Approaches

- API modifications
  - ✓Molecular Modifications
  - ✓Salt Changes
  - ✓Polymorph Changes
  - ✓Co-Crystals
  - ✓Nano-Crystals
  - ✓Co-Precipitations
  - ✓Co-Processing
  - ✓Co-Micronization



- Drug Product Changes
  - ✓Combination Drugs
  - ✓Dosage Form Changes
  - ✓Formulation Changes
  - ✓Excipient Changes

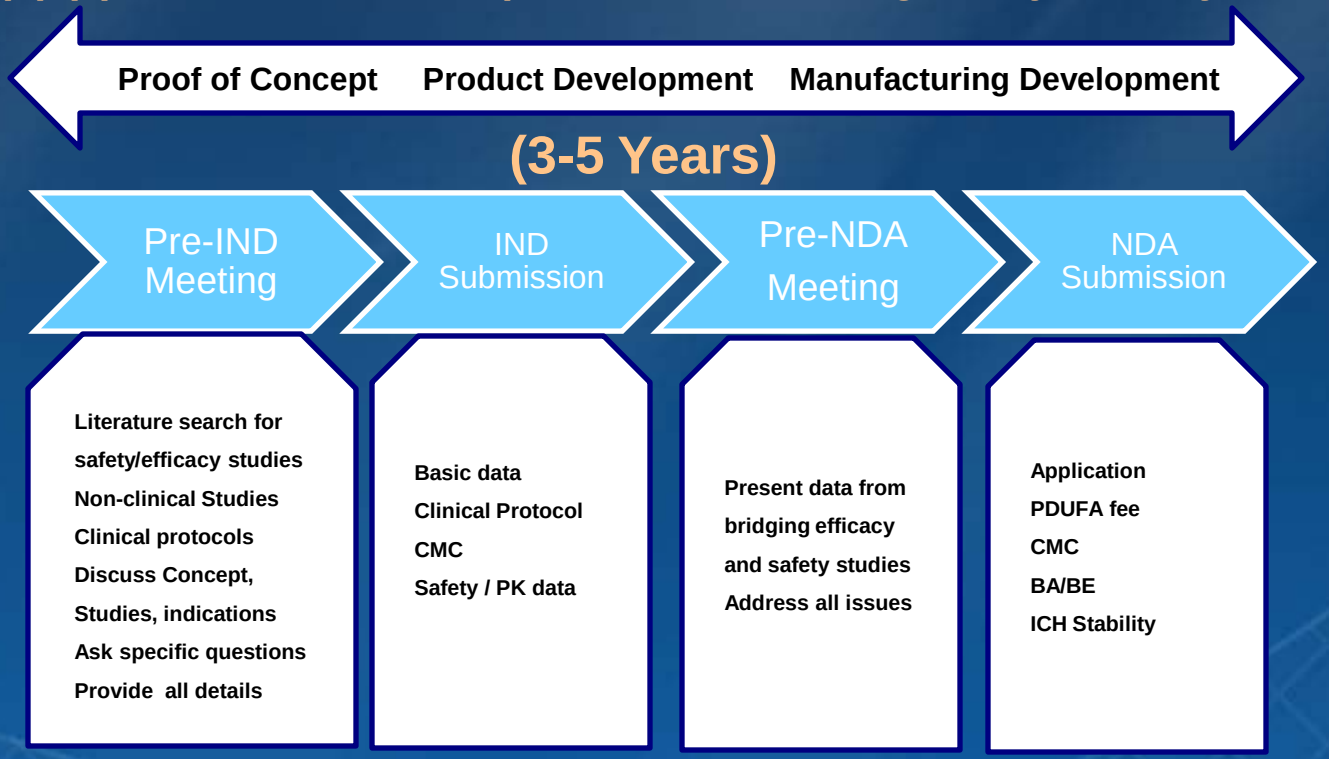
Product Enhancement Approaches

- Technology Platforms
  - ✓Modified Release Technologies
  - ✓Targeted Release Technologies
  - ✓Nano-Technologies
  - ✓Spray Dispersion Technologies
  - ✓Melt Extrusion Technologies
  - ✓Abuse Deterrent Technologies

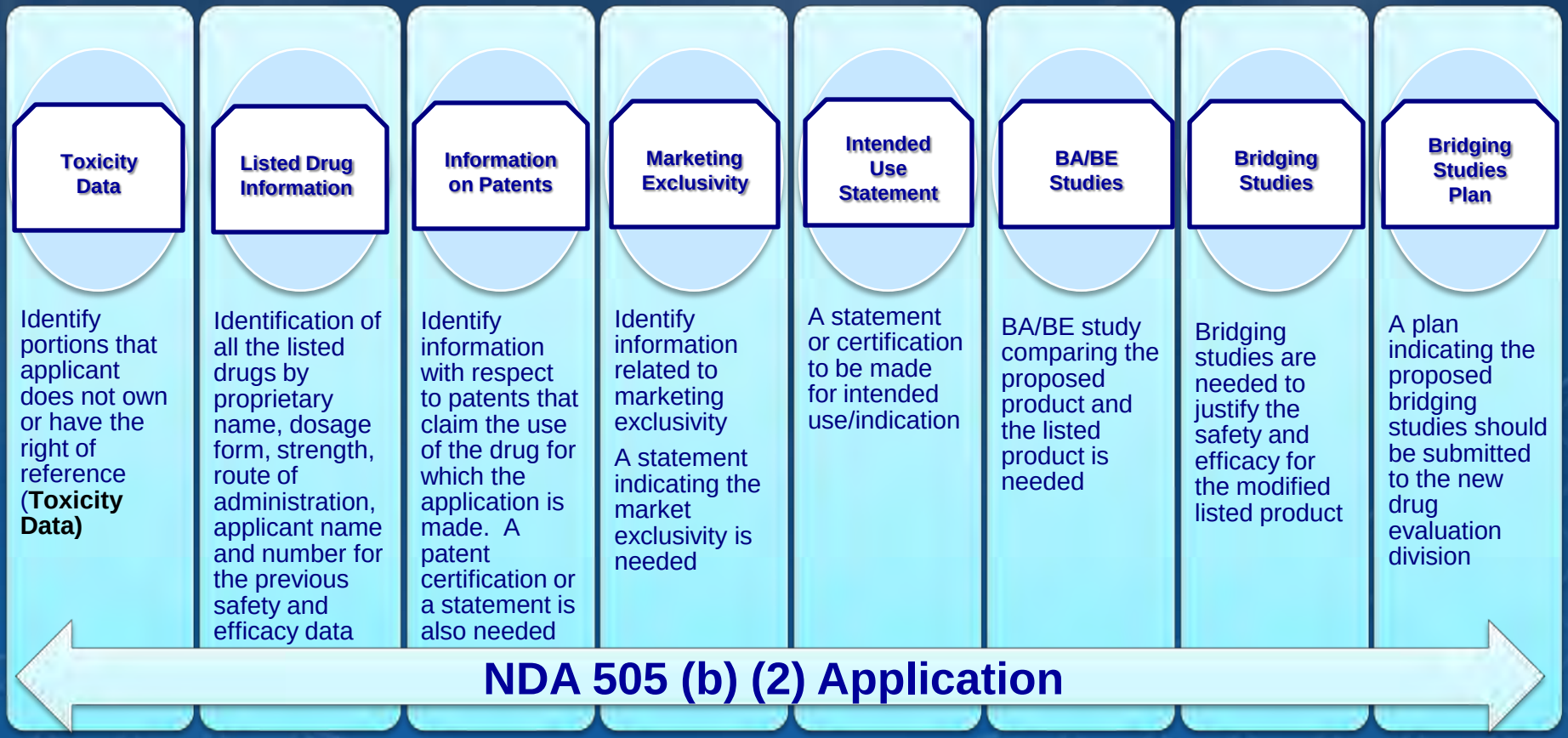
- Other Approaches for enhancing the profits and sustain the markets
  - ✓Process Enhancements such as alternate processes, continuous processes, process analytical technologies
  - ✓Sourcing Strategies
  - ✓Cycle Time reductions and Capacity enhancements
  - ✓Manufacturing site changes (Low Cost Locations)

Regulatory Strategy and Pathway

- NDA 505 (b) (1) if it is a NCE
- NDA 505 (b) (2) if it is a NCE/NME (We can use existing safety/efficacy data from NDA)



Components of NDA 505 (b) (2) Application



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Case Study "A journey through Strategic Product Enhancement and Implementation Plan"

Case Study Problem

EnhanceRx, a pharmaceutical company is faced with a critical challenge due to the pipeline and upcoming revenue issues. The following key points to be noted:

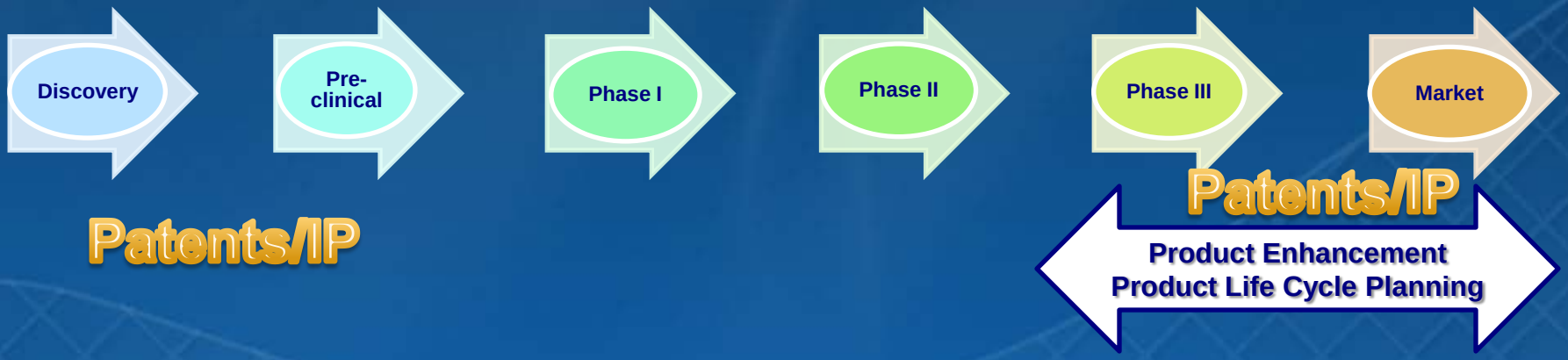
1. It is marketing three brand products with sales of about $2.0 B
2. It has two lead candidates in the development of which one candidate did not get FDA approval due to safety related issues.
4. Three existing products will lose their patent protection in 2014, 2015, and 2016.
5. The current environment, cost pressures, generic competition, and regulatory challenges have put the company's business at risk.
6. How can the company overcome this challenge and still be able to increase the revenues growth by extending the product life cycle.

Problem Statement

Identify opportunities to enhance the existing products in order to extend life cycle and also increase the revenues

Product Life Cycle Management

Leading PE/PLM Through Science, Technology, and Innovation



Strengths: What do you do well? What unique resources can you draw on? What do others see as your strengths?	**Weaknesses:** What could you improve? Where do you have fewer resources than others? What are others likely to see as weaknesses?
API/DP Product Understanding Pre-formulation and Formulation Pharmacokinetics/Clinical Understanding New Technologies Development Controlled Release Technologies Knowledge of Patents and IP Technology/Equipment Designing Designing of Experiments/Analysis RFT, Statistical Analysis, Six Sigma, LVM	Lean New Products Pipeline Patent Expirations and Loss of Exclusivity Revenue Growth Potential Need to build novel expertise Need to build IP and Patents base
Opportunities: What good opportunities are open to you? What trends could you take advantage of? How can you turn your strengths into opportunities?	**Threats:** What trends could harm you? What is your competition doing? What threats do your weaknesses expose you to?
Product Enhancement and Product Life Cycle Management API Modifications Clinical and Dosage Form Variations Drug Delivery Systems Continuous Manufacturing PAT/LVM/Adaptive Control Mechanisms Parametric Release Lean and Agile Manufacturing	Patent Infringements and Legal Issues Competition Probability of success Technology Challenges Exclusivity Issues Commitment or availability of funds Regulatory Issues

SWOT Analysis

Opportunity Analysis

A team was formed to assess the problem and identify the opportunities to enhance the existing products. The team has selected the following criteria:

1. Identify opportunities to modify the API characteristics such as molecular modifications, polymorphic changes, salt changes etc.

2. Identify opportunities to modify the clinical efficacy and dosage form by studying the PK/PDM profiles, half lives, first pass, metabolism, absorption, excretion etc.

3. Identify opportunities to enhance the therapy by bio-availability enhancement and dose /side effects reductions

4. Identify technologies to enhance the product performance

Solutions Offered

After thorough brainstorming and analysis the team has come up with the following:

1. Product Enhancement through molecular modification of the API for Product A
    a. Dosage Strength Reduction
    b. Dosing frequency reduction

2. Product Enhancement through dosage form change (IR to MR)

The case study will present the first solution

Case Study – Product A

- Product A is a capsule formulation with $300 MM sales revenue. The patent will expire in 2016.

- This product will be a perfect candidate for enhancement using NDA 505 (b) (2) filing:
  - ✓Dosage strength and side effects reduction
  - ✓Dosing frequency reduction (Multiple dosing to Once a day)

- The literature search to pre-IND through development to NDA submission and approval should take 3-6 years.

- This involves pre-IND, IND, Proof of Concept, Pre-NDA, NDA, and Commercialization

- Life extension, a double opportunity , first low dose followed by once a day delivery .

Rationale

Team have found in almost all the clinical studies the intact Product A was excreted in urine and the lower molecular weight of the API molecules which are much less than the molecular weight distribution as found in Product A, were being absorbed through the GI tract.

Also the potential side effects related to the residence time of the high molecular weight molecules of Product A in the GI tract can be eliminated by customizing the molecular weight distribution much lower than the 4kD range and cleansing the higher molecular weight molecules from the existing approved drug substance. The reason for the low bio-availability could be attributed to the High molecular weight of the API.

The metabolism of this drug is mainly taken up by reticuloendothelial system and returned to circulation in the biologically inactive form, from where it is subsequently depolymerized and excreted by kidney. The biologically available drug near the site of action was eliminated primarily intact and is assumed to be of lower molecular weight.

If administered orally the modified drug will have enhanced absorption and bioavailability, which will eventually open up the possibilities of reducing the dose or even reducing the duration of the dosing in the patients with less side effects.

Collaboration with and API Company

- Based on the information the EnhanceRx has initiated discussions with an API company to develop a low molecular weight API, which can be absorbed quickly and be available for providing the therapeutic efficacy safely.
- The company would also propose exclusive arrangement with the API company for the supply of low molecular weight API.
- This collaboration will help the company in planning for the proof of concept studies and engage discussions with the FDA for pre-IND meeting to obtain guidance for the safety and efficacy bridging studies.
- The API company will perform the preliminary characterization of the modified API and in collaboration with the EnhanceRx conduct preliminary animal studies.

Implementation Pathway
API and Drug Product Characterization and Evaluations

- Design experiments to characterize the API at the molecular level (range studies) to identify the optimum molecular weight suitable for the bio-availability , safety, and efficacy.
- Design animal studies to compare the new API with the RLD for safety and efficacy.
- Assess purity, stability, and degradents for further formulation development.
- Conduct pre-formulation and formulation feasibility studies and compare with the RLD for assay, dissolution, and stability.
- Conduct literature search and prepare a questionnaire for the FDA.

Implementation Pathway
API and Drug Product Characterization and Evaluations

- Engage discussions with FDA through pre-IND meeting in order to justify and obtain guidance from FDA on the requirements.
- Prepare and submit IND submission package.
- Design pilot scale bio-studies for verifying the proof of concept.
- Based on the positive data progress with the full development of the product.
- Design pivotal safety and efficacy bridging studies for the NDA 505 (b) (2) submissions.
- Prepare and submit an NDA 505 (b) (2) submission for market approval.
- Launch planning and commercial manufacturing

Product Enhancement Pathway for Product A

Product Idea and Proof of Concept

- Product Ideation
  Opportunity Analysis
  Literature Search
  Product Planning-API/DP
- Pre-IND Meeting, Product Development Planning and Design
- Pre-formulation, Analytical Methods Development, Formulation Feasibility Studies
- Pilot Scale Clinical Bridging Studies
  (Safety & Efficacy)

Manufacturing Development

- Pre-NDA Meeting
  Process Development and Optimization
- NDA Meeting
  Scale-up, and Technology Transfer
  Clinical Protocols
- Pivotal Clinical Studies
- ICH Stability Studies

Commercial Development

- Regulatory Submissions
  NDA 505 (b) (2)
- Launch Planning
- Validations and PAI
- Commercial Supply
  Continuous Improvement

STRATEGIC JOURNEY

3-6 Years

Regulatory Strategy and Pathway

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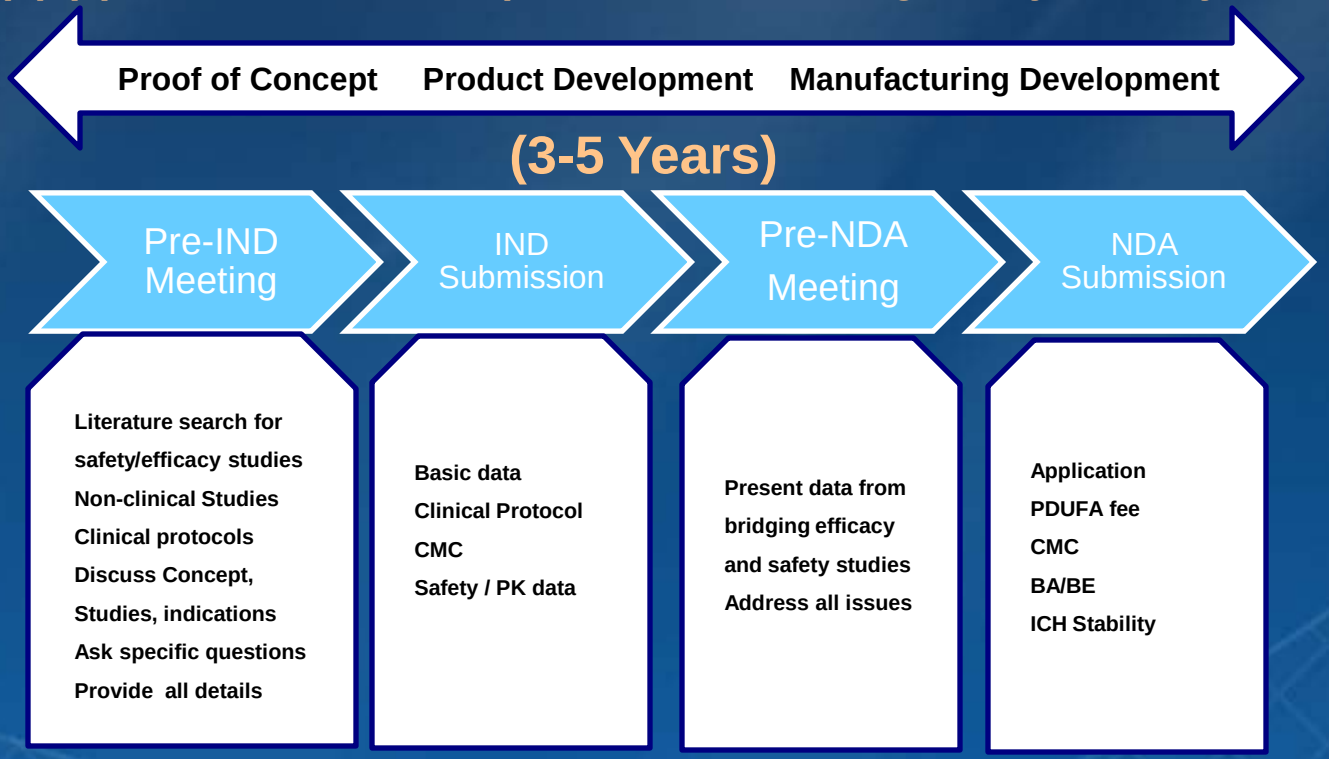

Studies to be Planned

- Plan to use existing and new animal data to define the MW of the fraction of the API that is absorbed, and then fractionate the API to isolate this fraction.

- Three pharmacokinetic studies are proposed in humans:

1. The first study will be a dose-ranging study to determine what dose of the proposed product is likely to be bioequivalent to the listed drug.

2. The second study will be used as a bridging study between the listed drug and the proposed product. This study will be a two-way, randomized, open-label, single-dose crossover study determining the bioequivalence of proposed product to the listed drug, under fasting conditions.

3. The third study will be a study to determine the effect of food on the product. This study will be a two-way, randomized, single-dose crossover study comparing the bioavailability of the proposed drug after a high-fat breakfast to that of the product given under fasting conditions.

Examples of Product Enhancements using NDA 505 (b) (2) filing

- Luxiq Foam (New Delivery)
- Stalevo Tablets (New Formulation)
- Thalomid (New Indication)
- Simcor (Combination Drug)
- Cyclobenzapril ER Tablets (New Dosage Form)
- Tricor 145 mg (Dosage Strength Reduciton)

NDA 505(b) EXAMPLES
New Combination Products

EPIDUO Topical Gel

(Adapalene: Benzoyl Peroxide)

DUAC Topical Gel

(Benzoyl Peroxide: Clindamycin Phosphate)

SOLAGE Topical Solution

(Mequinol: Tretinoin)

ZIANA Topical Gel

(Clindamycin Phosphate: Tretinoin)

NDA 505(b) EXAMPLES: New Dosage Forms

EMSAM Transdermal Patch
(Seligiline)
OXYTRAL Transdermal Patch
(Oxybutynin)
Daytrana Transdermal Patch
(Methylphenidate)
SANCUSO Transdermal Patch
(Granisetron)

NDA 505(b) EXAMPLES: New Delivery Mechanisms

EVOCLIN Topical Foam
(Clindamycin Phosphate)

OLUX Topical Foam
(CLOBETASOL PROPIONATE)

VERDESO Topical Foam
(Desonide)

EXTINA Topical Foam
(Ketoconazole)

CLOBEX Topical Spray and Shampoo
(Clobetasol Propionate)

NDA 505(b) EXAMPLES:
New Form of Active Ingredient

FLECTOR Patch

(Diclofenac Epolamine)

Myfortic Delayed-Release Tablets

(Mycophenolate Sodium)

NDA 505(b) EXAMPLES:
DESI to 505(b)(2)

MUCINEX D Extended Release Tablets

(Guaifenesin: Pseudoephedrine Hydrochloride)

MUCINEX Extended Release Tablets

(Guaifenesin)

MUCINEX DM Extended Release Tablets

(Dextromethorphan Hydrobromide: Guaifenesin)

NDA 505(b) EXAMPLES: Rx-to-OTC Switch

Prevacid^{24HR} Delayed-Release Capsules

(Lansaprozol)

NDA 505(b) EXAMPLES: New Indication

Avodart® Capsules

(dutasteride)

Thalomid® Capsules

(Thalidoamide)

Revatio Tablets

(Sildenafil Citrate)

Final Quiz

1. Can we use existing clinical data for the API modifications?
2. If the FDA determines that after the change the API is a NCE, then what?
3. When should we start the product life cycle planning?
4. Why would it costs less for the 505 (b) (2) approach than the 505 (b) (1) approach?
5. How can you extend the Life Cycle of a product without the mdifications?

Final Quiz

1. Can we use existing clinical data for the API modifications? Yes

2. If the FDA determines that after the change the API is a NCE, then what? 505 (b) (1)

3. When should we start the product life cycle planning? Very early before patent expires

4. Why would it costs less for the 505 (b) (2) approach than the 505 (b) (1) approach?
   Use of existing clinical data and acceptance of bridging safety and efficacy data

5. How can you extend the Life Cycle of a product without the modifications?
   Through patents , use of difficult technologies, creating barriers to entry