SUN PHARMA
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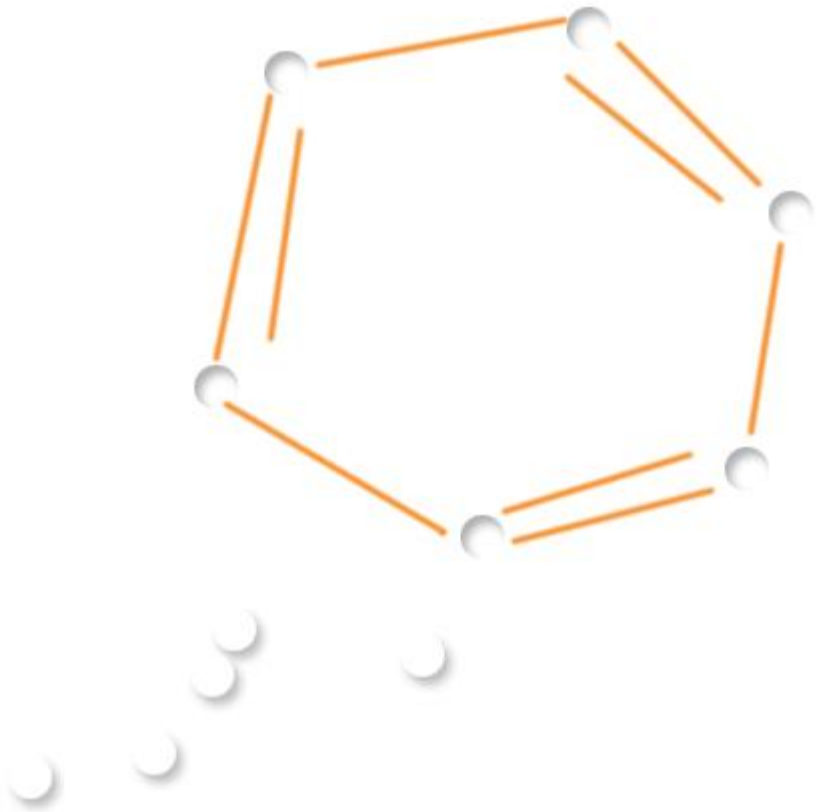
COMPANY LTD.

M S Global Health Conference

14th September 2011



Connecting the dots

BSE:532872 | NSE: SPARC | Bloomberg: SPADV@IN | Reuters: SPRC.BO

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About us

SUN PHARMA ADVANCED RESEARCH COMPANY LTD.

- In 2007 , Sun Pharmaceutical Industries Ltd, spun off its innovative business into an independent , listed company, viz; Sun Pharma Advanced Research Company Ltd.(SPARC)
- SPARC is focussing on new drug discovery and novel drug delivery systems based programs.
- 2 state of the art research facilities.
    - 160 labs spread over 120,000 sq ft floor space.
- Scientific manpower 237

SPARC – *Innovating, with measured risk.*

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- A disciplined and systematic innovation process
- Focus on niche indications with predictable and sustainable market
- Develop products/technologies which solve unresolved problems and add meaningful value
- Early confirmation of the proof of concept
- Balanced resource allocation to projects of short and long gestation period

SPARC – *Innovating, with measured risk.*

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Key approaches to research at SPARC

NDDS Approach

- Improve patient compliance
- Enhance safety
- Reduced regulatory hurdles
- Expand product indications

NCE Approach

- Work on validated targets and biology
- Address limitations of current products
- Improve therapeutic index and product PK characteristics

Technology Platforms

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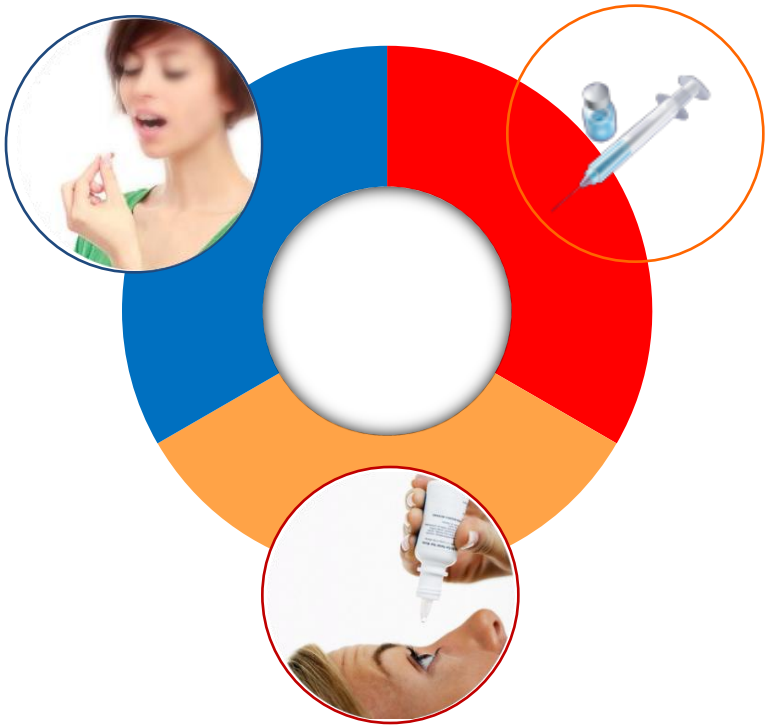
Oral

- Gastro Retentive Innovative Device (GRID)
- Wrap Matrix System



Injectables

- Nano particulate formulations
- Biodegradable Depot Injections.

Topical

- Dry Powder Inhaler(DPI)
- Extended Release (ER) Microspheres for Topical Applications
- GFR Technology for Once a Day Ophthalmic formulations
- SMM Technology for Ophthalmic Formulations

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NDDS – DPI Platform

Salmeterol and Fluticasone DPI Market Opportunity

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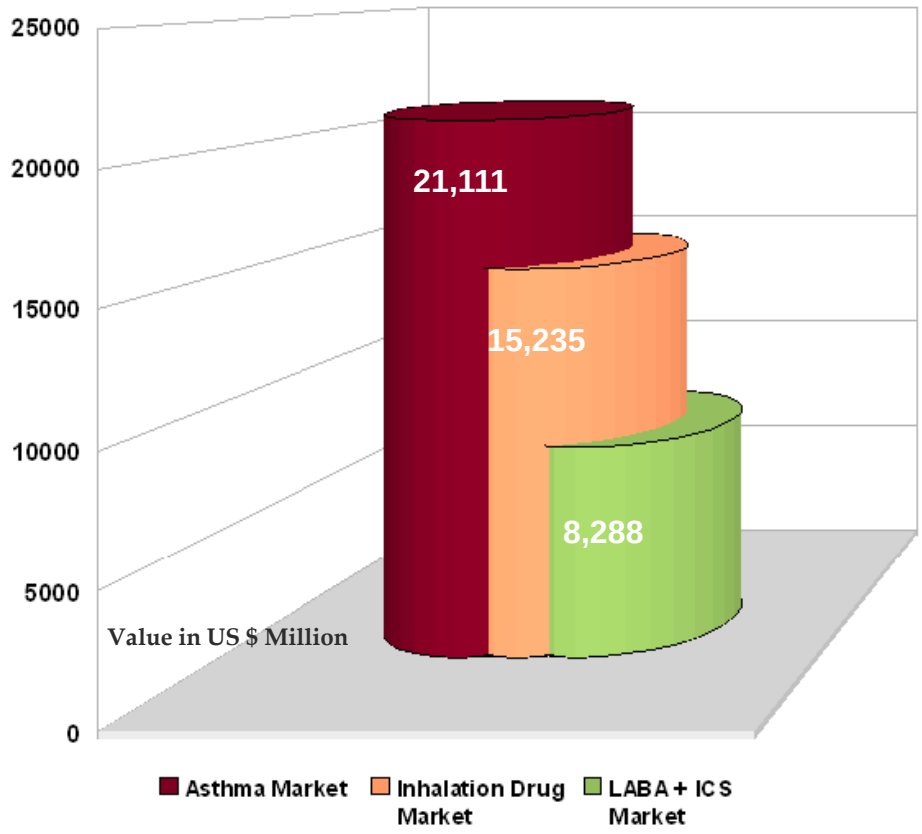
- 300 million Asthma patients worldwide (WHO).
- Asthma market in developed countries (US, Europe and Japan) was valued at $21 billion in 2008.*
- Inhalation drugs contribute 70% of this market.
- Total market of inhaled beta agonists and corticosteroids in the developed markets was valued at $15.2 billion in 2008.*
- DPIs containing long-acting beta agonists and inhaled corticosteroids constitute largest drug class with sales of US$ 8.3 billion* and market share of 54%.



Asthma Market in Developed Countries, 2008*

*Source: IMS

Salmeterol and Fluticasone DPI: Market Opportunity

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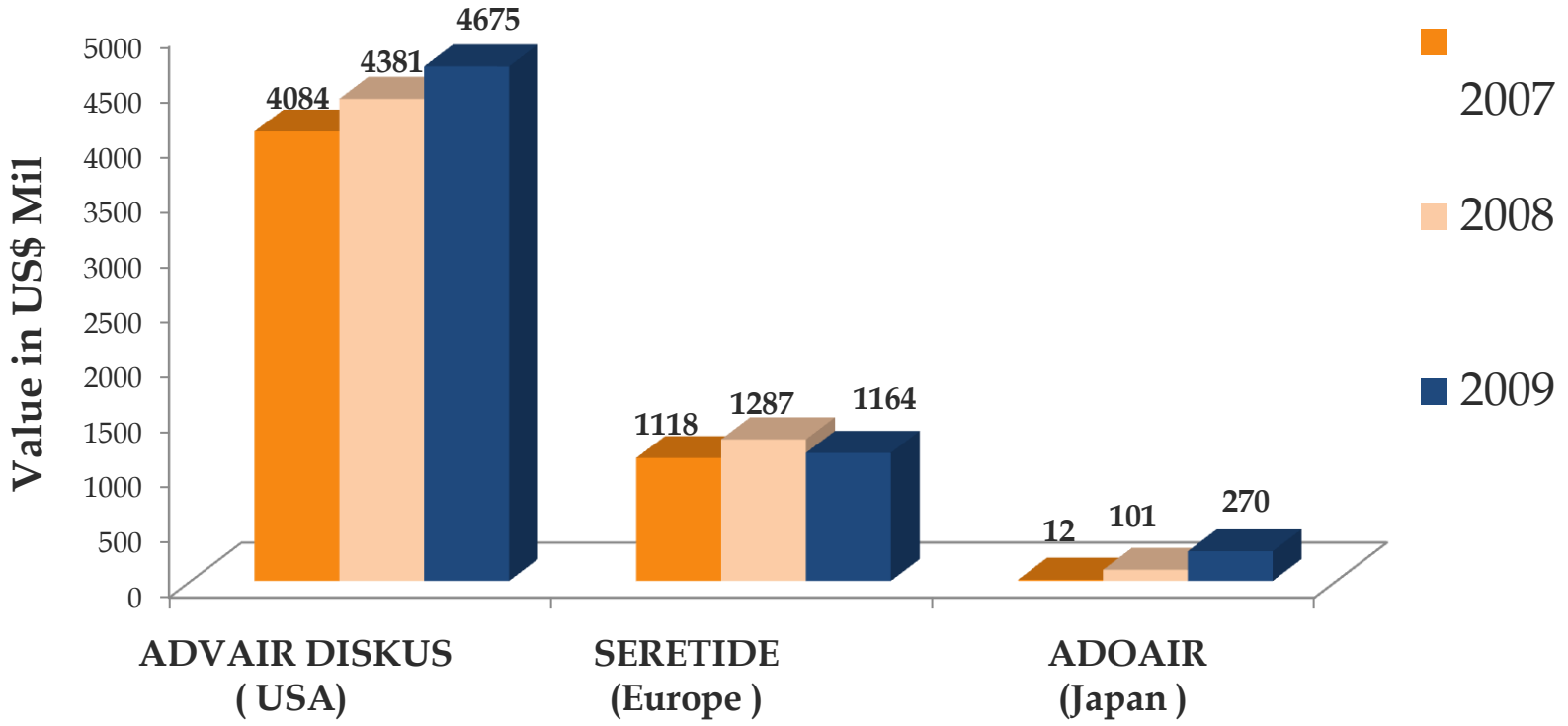
- Salmeterol and Fluticasone DPI is the most successful DPI globally with annual sales of $ 7.7 B. in 2009.



Source: IMS

Dry Powder Inhaler (STARHALER™)

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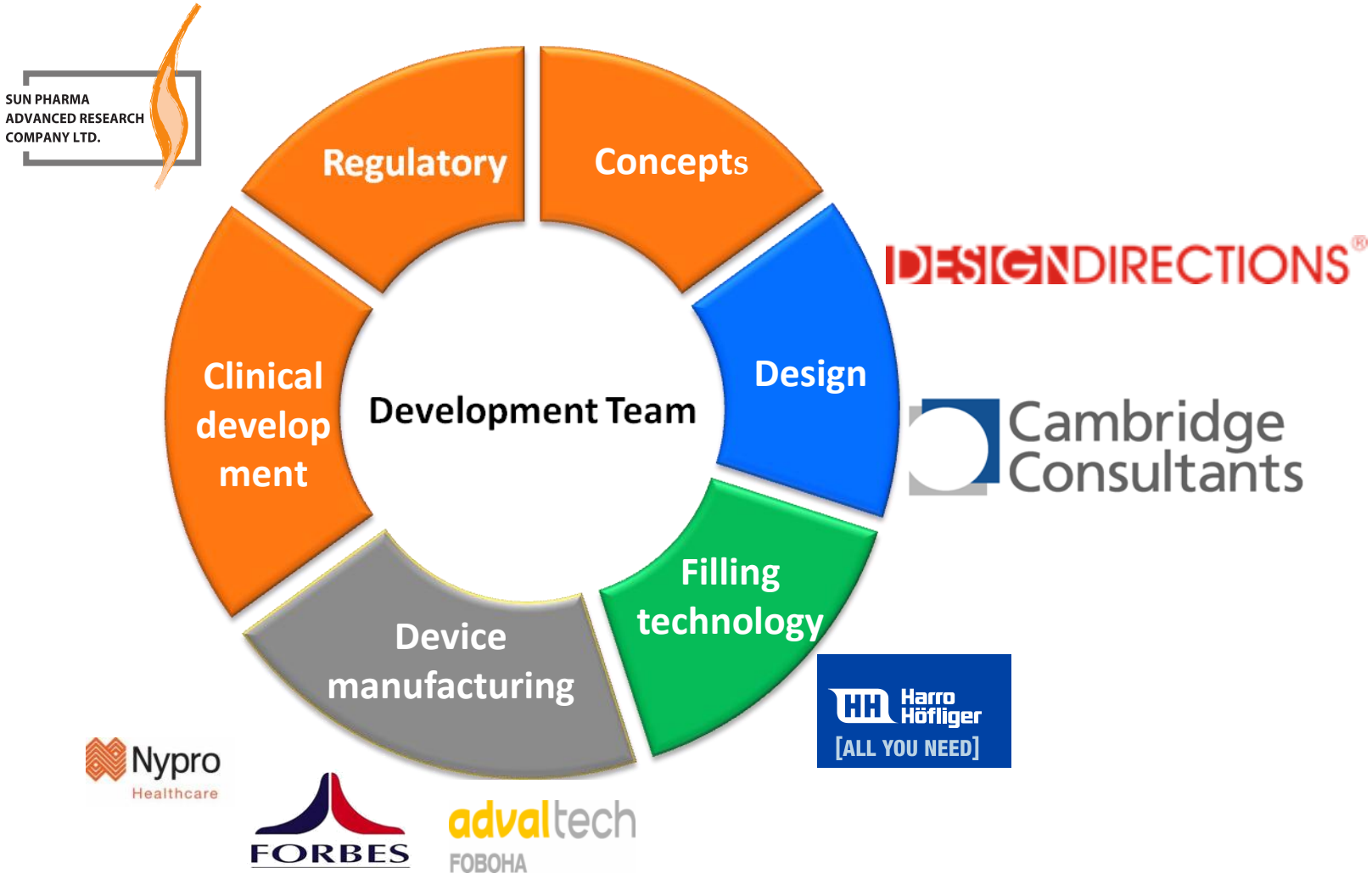
SPARC's DPI is a pre-metered, 60 dose, inhalation activated device for administration of combination of inhaled steroids and bronchodilator drugs

- Uniform dose delivery independent of inspiratory flow rate
- Consistently delivers higher amount of drug to lungs
- Eliminates double dosing and dose wastage
- Provides visual, audible and tactile feedback upon dose administration
- Glow-in-the-dark feature for easy night-time use
- Feature for assisting visually impaired, as reminder to refill device, when 8 doses remain
- Small and convenient for easy to carry.
- Compliant to the stringent USFDA and European requirements.

STARHALER™ – Designed by Best-in-Class Global Development Partners



3 simple user steps: ready when required, no preparation required

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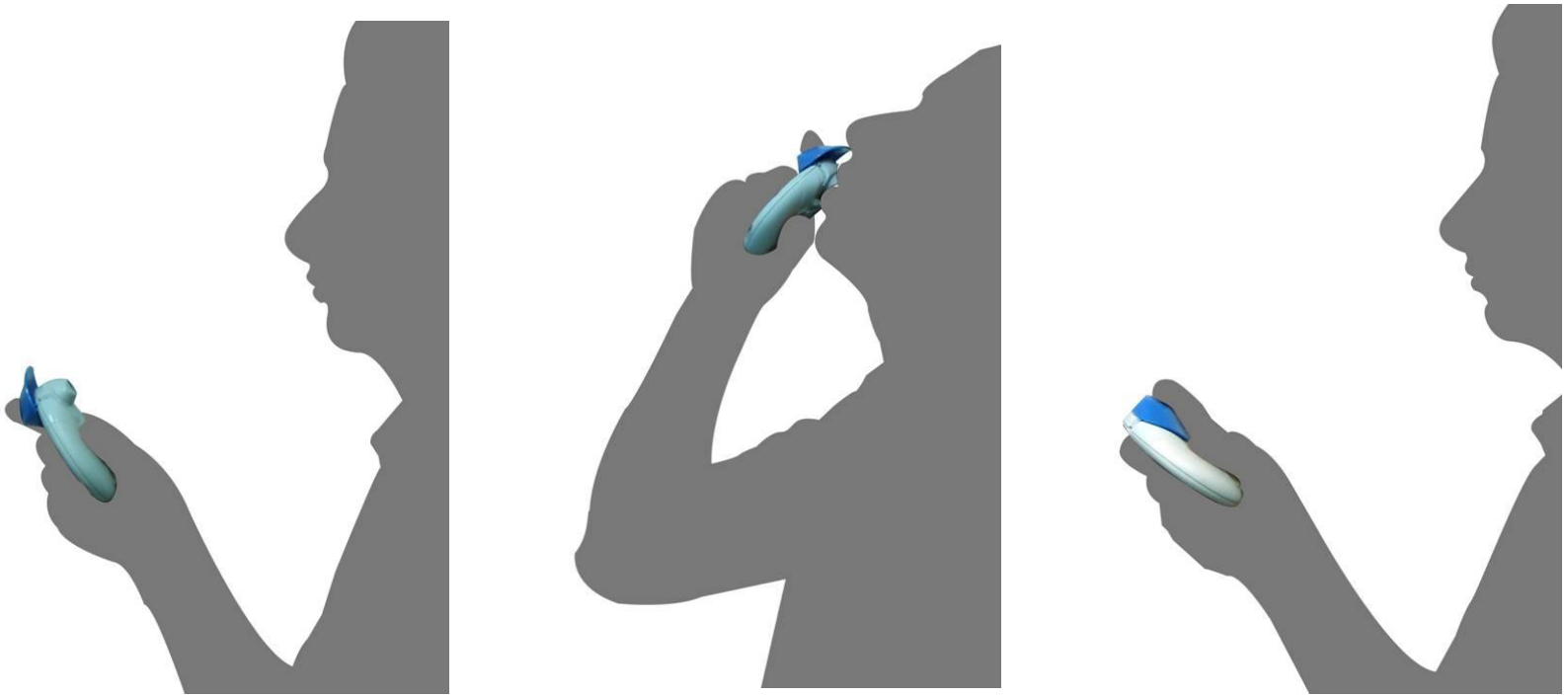
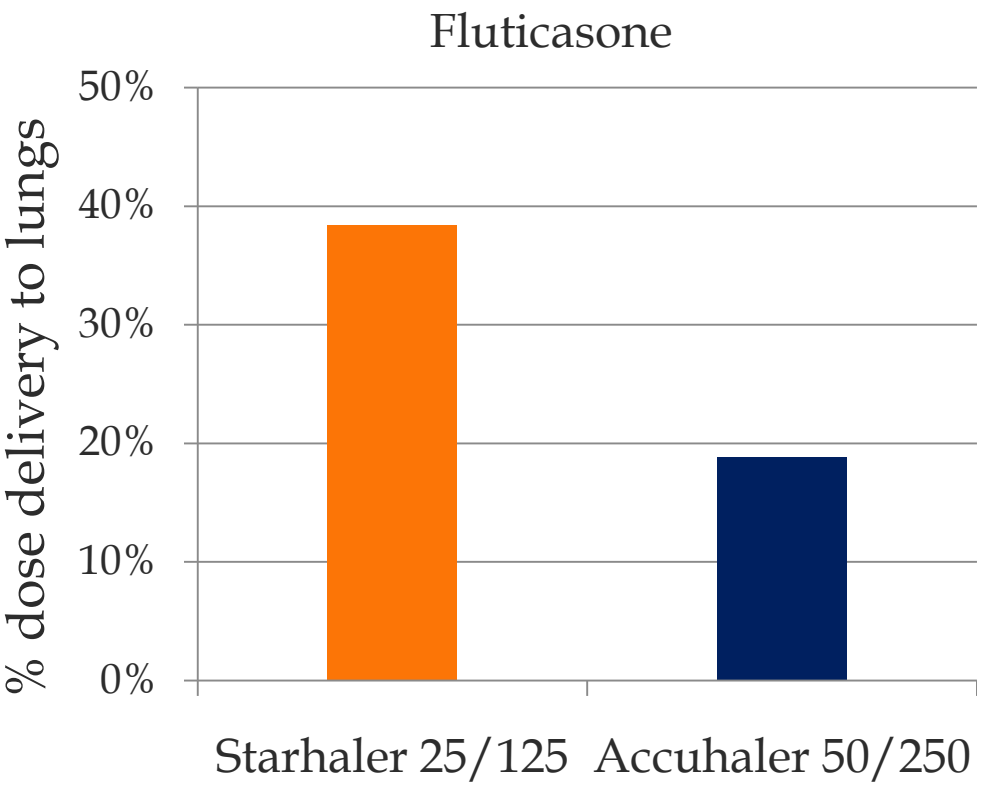
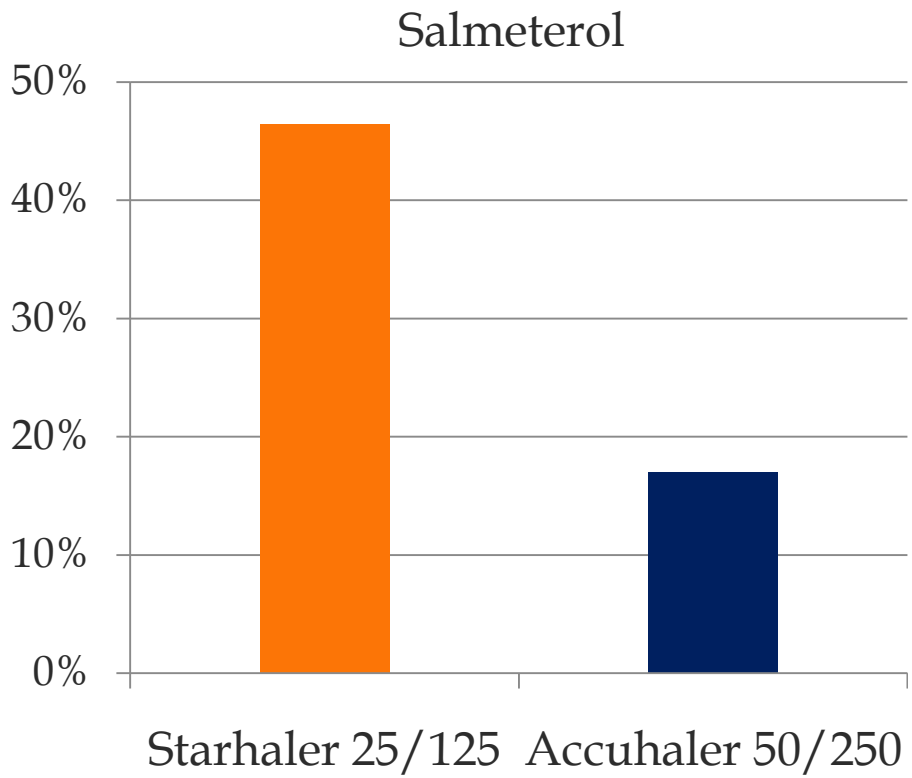


Device works irrespective of orientation of device: no dose spillage

Easy to use by pediatric, adult, and geriatric patients

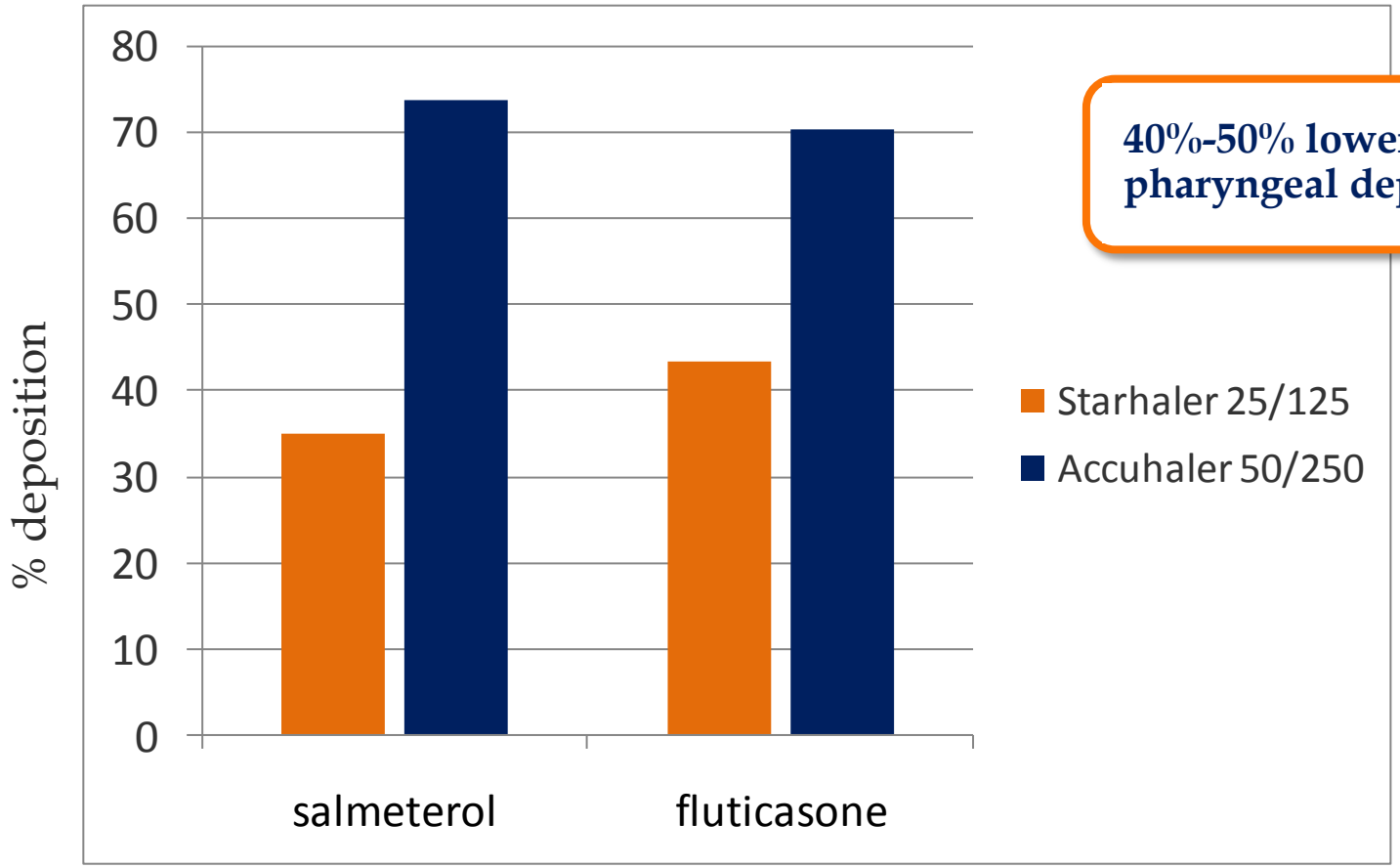
Product performance: >100% higher drug delivery to lungs*





** Based on In-Vitro Studies*

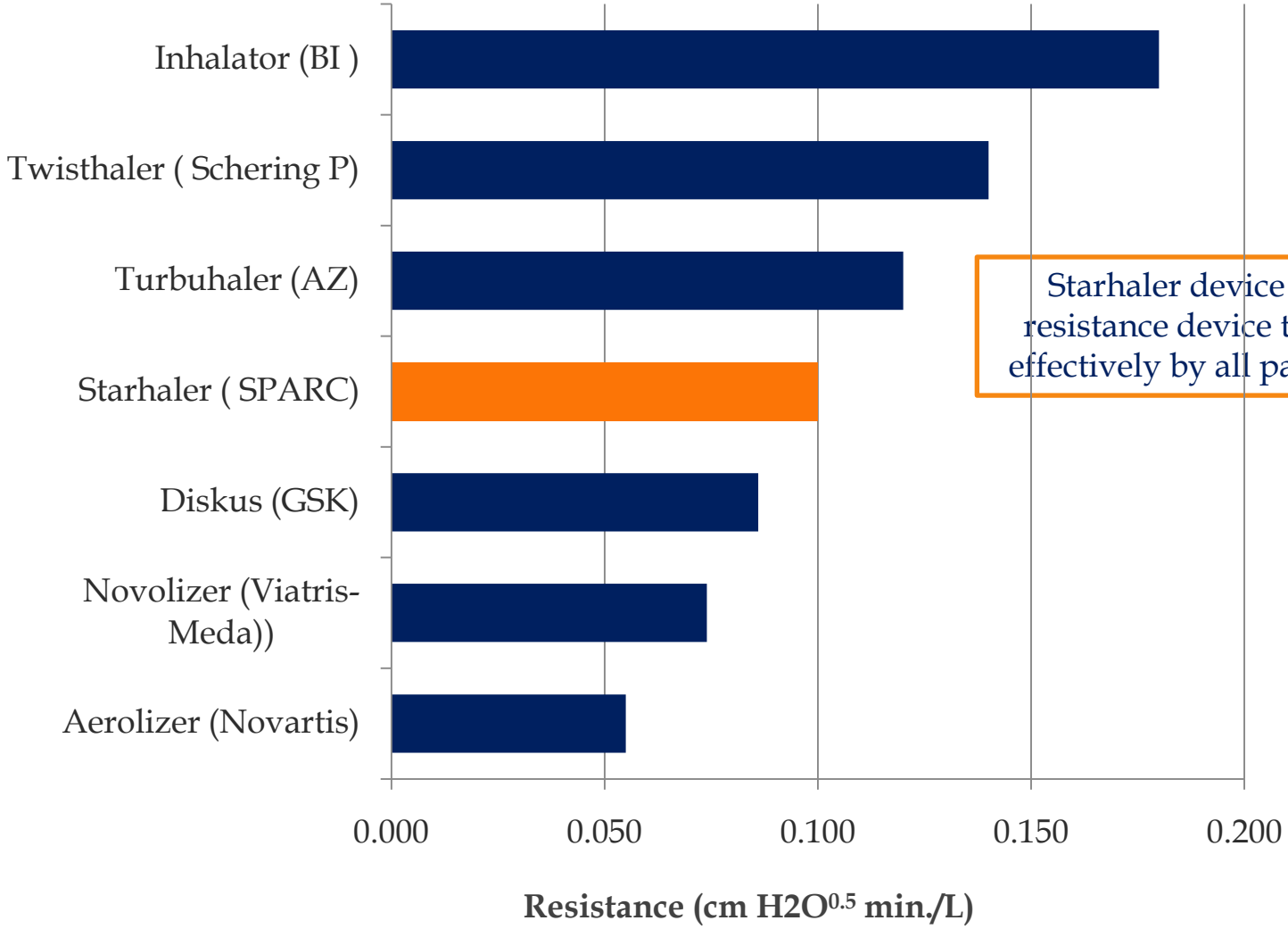
Product performance: Significantly reduced Oro-pharyngeal deposition*



40%-50% lower Oro-pharyngeal deposition

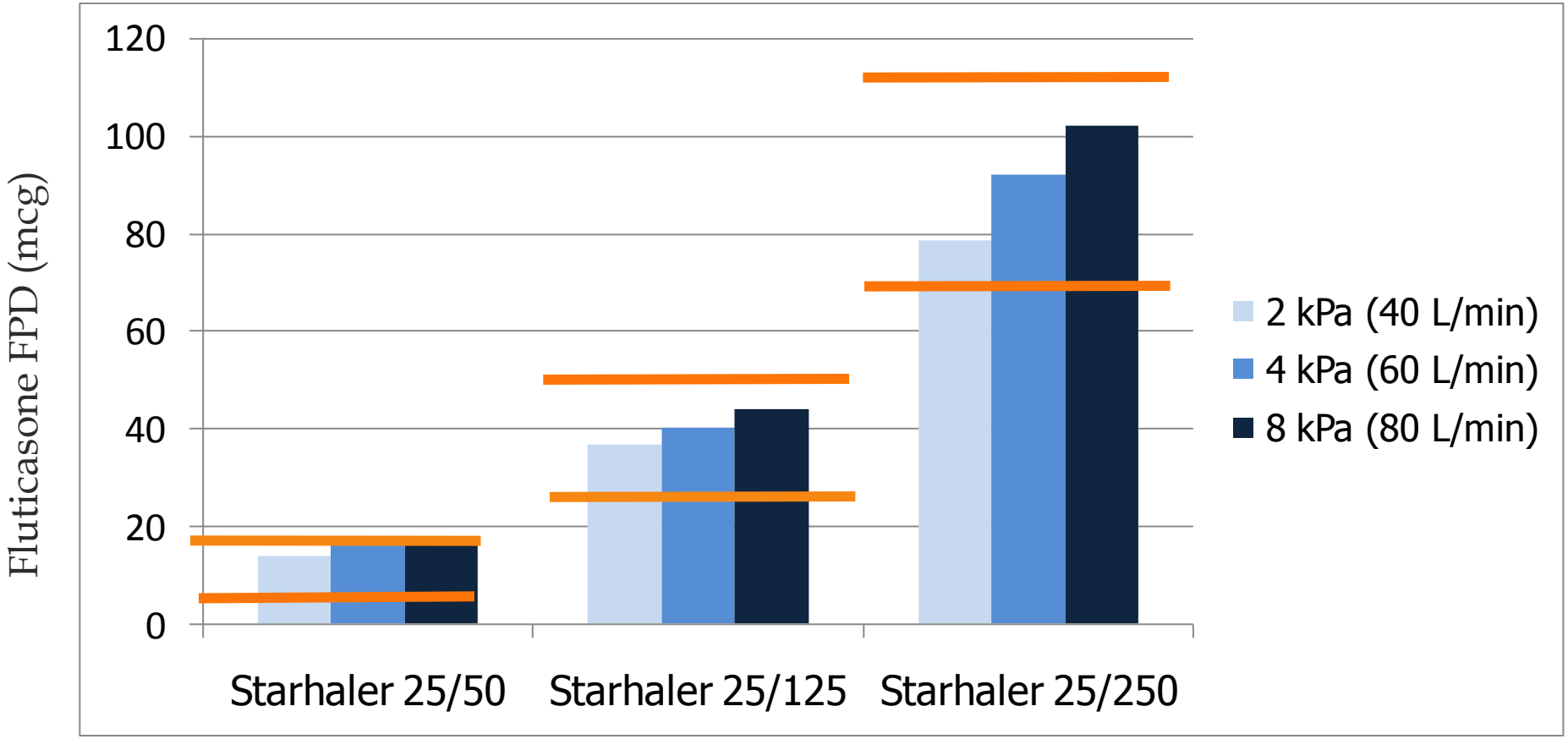
** Based on In-Vitro Studies*

Device Resistance



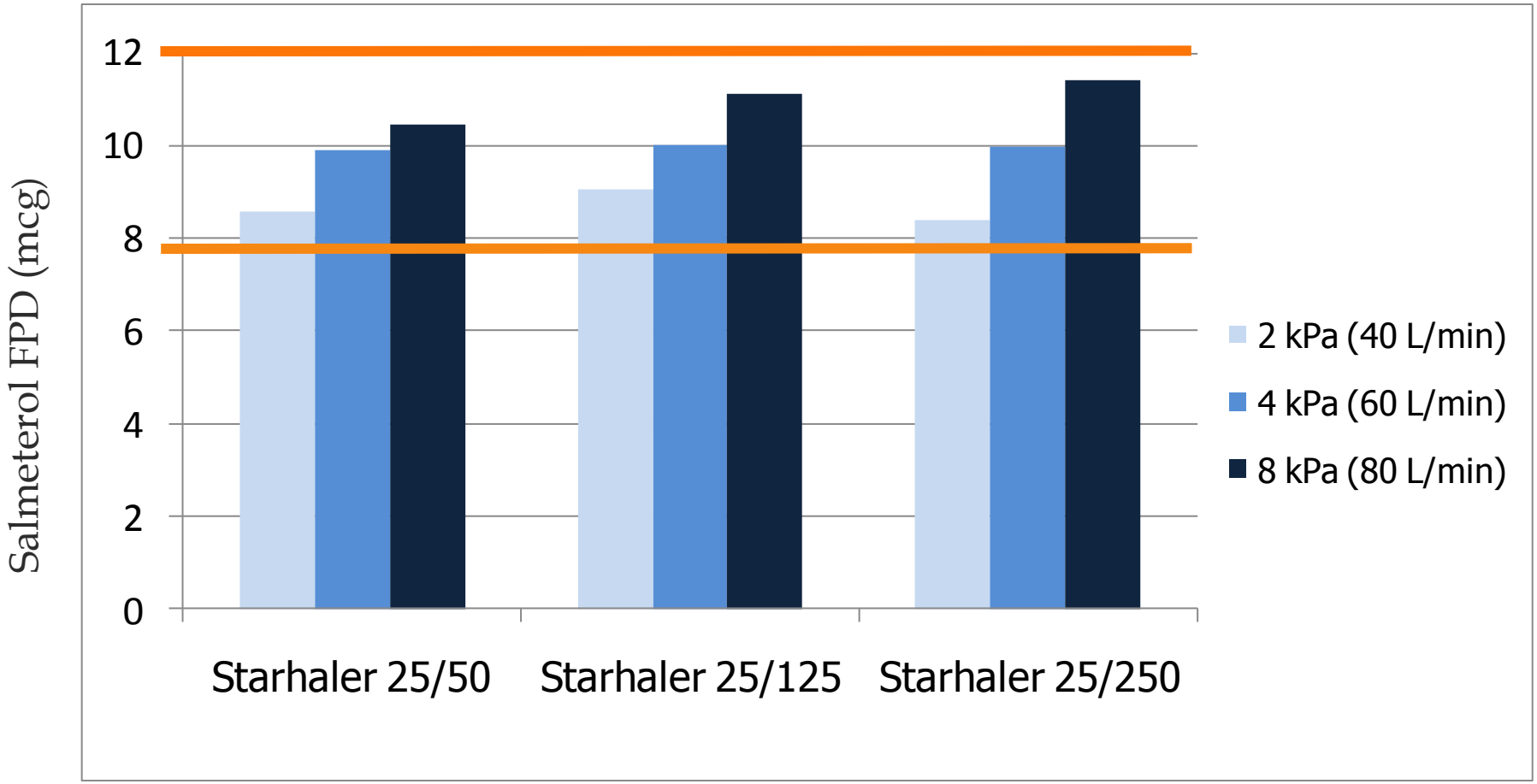
Starhaler device is a medium-resistance device that can be used effectively by all patient population

Consistent drug delivery at varying flow rates: data for fluticasone*



** Based on In-Vitro Studies*

Consistent drug delivery at varying flow rates: data for salmeterol*



** Based on In-Vitro Studies*

Equivalent clinical efficacy at "*half the dose*" of Seretide Accuhaler®

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Randomized, Comparative, Active Controlled, Multi-Center Study in Asthma Patients in India

- Comparing
  - SPARC DPI containing Salmeterol **25mcg / Fluticasone 250mcg** (TEST) &
  - Seretide Accuhaler® –(Salmeterol 50mcg / Fluticasone 500mcg) (REFERENCE)
- Treatment duration = 4 weeks, N = 113

Study Outcome

- **Equivalent efficacy** to Seretide Accuhaler® on all primary and secondary end points
- SPARC's DPI demonstrated **statistically and clinically significant improvement vs. no treatment baseline in all efficacy parameters studied**
- Efficacy of SPARC's DPI in improving lung function demonstrated by:
  - Reduction in use of rescue medication
  - Day and night time asthma symptoms
  - Global impression of change rated by subjects and investigators

Equivalent clinical efficacy at "*half the dose*" of Seretide Accuhaler®

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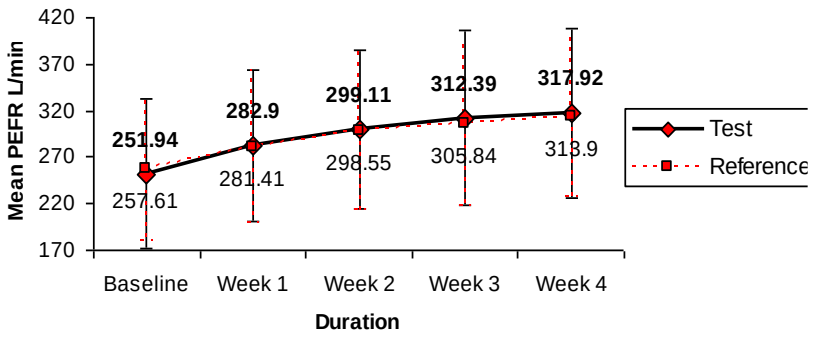
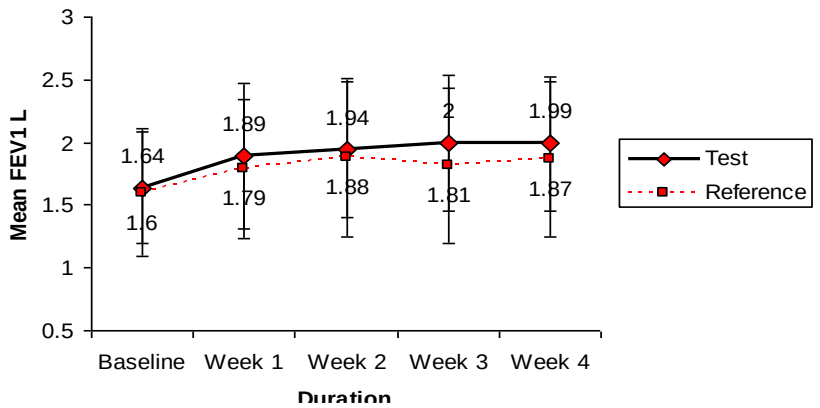
Average Morning PEFR by Treatment Group by Treatment Week (n = 107)



* p < 0.0001 for change from baseline

FEV1 from baseline to week 4 (n = 107)



* p < 0.0001 for change from baseline

- **TEST =** SPARC's DPI containing Fluticasone 250mcg/Salmeterol 25mcg
- **REF =** GSK's SERETIDE ACCUHALER® Fluticasone 500mcg/Salmeterol 50mcg

Future development plan

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US –505(b)(2) route.

- Pre IND meeting completed.
- IND filing in FY12

India

- Phase III study completed
- To be launched in Q3FY12

DPI Platform : Summary

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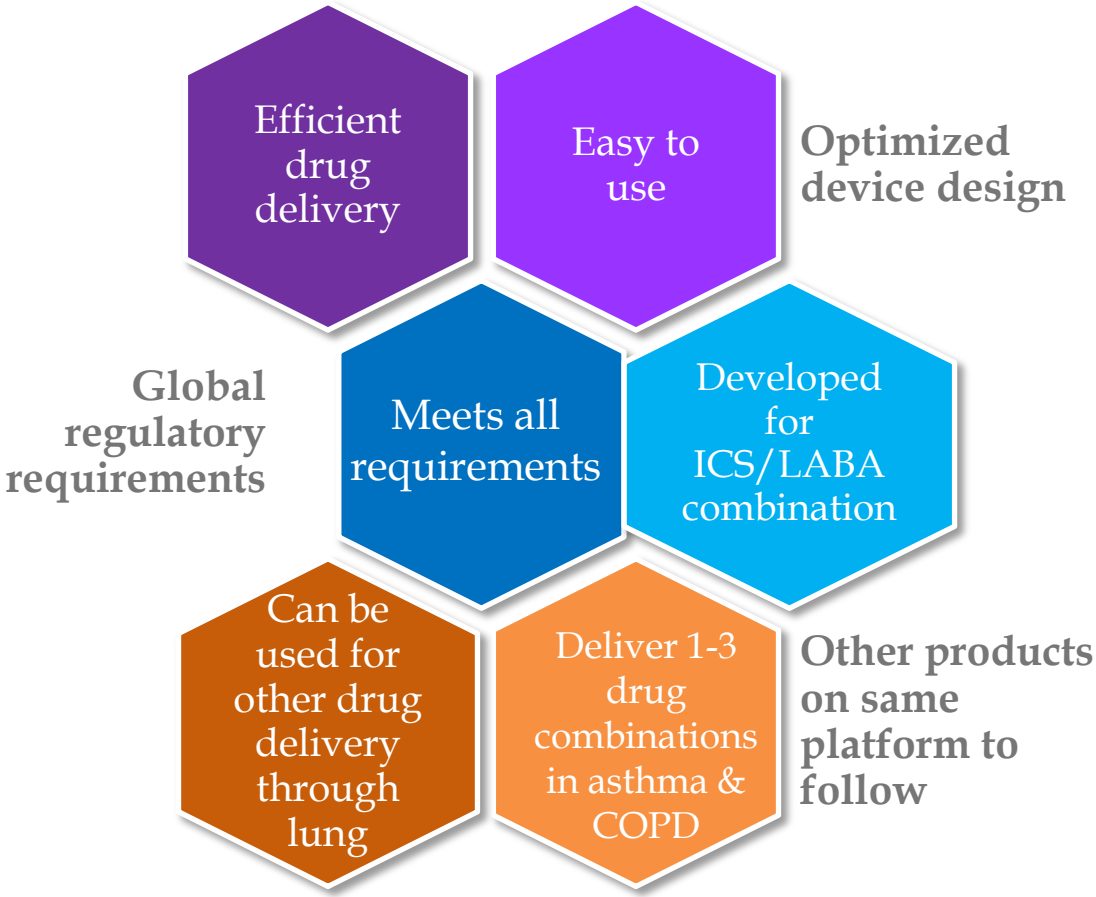

Salmeterol and Fluticasone DPI is registered in India and will l be launched by Sun Pharma in Q3 FY12.

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NDDS – Nano-particulate Injection Platform

Taxane– Market Opportunity

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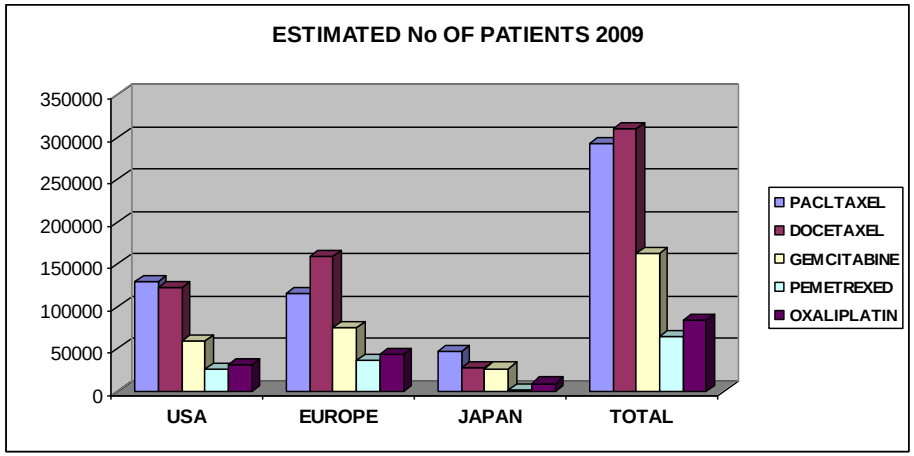
- Taxanes - Most successful drug class for solid tumors.
- Established standard of care for advanced cancers of breast, lung, ovary, prostate, cervix, esophagus and stomach, urinary tract & bladder and head & neck region.
- Both paclitaxel and docetaxel became "blockbuster" anticancer drugs because of their significantly higher response rates and survival advantages in wide range of solid tumors.
- Limitations of Paclitaxel
  - Very high incidence and severity of toxicities especially hypersensitivity reactions, neutropenia and peripheral neuropathies.
  - High incidence of hypersensitivity reactions due to use of Cremophor®.



In USA, an estimated 115,000 patients are treated with paclitaxel per year.

Taxane – Market Opportunity

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- ABRAXANE®, is the first marketed "Cremophor® free" formulation of Paclitaxel, now approved in 39 countries.
- ABRAXANE offers the advantages of no requirement of premedication, shorter 30 minutes infusion time, reduced toxicities and ability to give higher paclitaxel dose compared to conventional formulation
- ABRAXANE® commands significantly higher price compared to generic Paclitaxel. (Approx 35 times of the current generic paclitaxel price in USA and at about 2 times the price of TAXOL® in year 2000 before generics entry)
- ABRAXANE® achieved a sales of $318 million (MAT Sep'09) at an estimated 15% patient share (~ 16000 patients) from generic paclitaxel (~115,000 patients)

Paclitaxel Injection Concentrate for Nanodispersion (PICN) with its demonstrated advantages against ABRXANE, has the potential to command 15 to 20% of the patient share of Paclitaxel

ABRAXANE ® is developed by Abraxis bioscience inc, USA

Nano particulate Formulations

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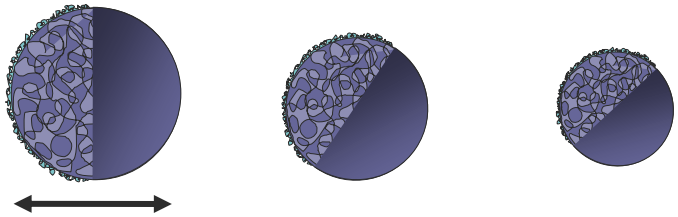
The Technology

- Novel self-dispersing nano-particle technology platform for "difficult to formulate", insoluble" anticancer drugs

Composite Nanoparticles
Anticancer Drug + Polymer + Lipid



Nanometer sized particles
i.e. 1/1000th of a human hair thickness

Key Advantages

- Uses very safe excipient with no added toxicities
- Drug molecule remains the same; not covalently bound or altered.
- Low excipient to drug ratio.
- Delivers higher dose without increased adverse event profile.
- Eliminates the need of pre-medication, special infusion bags/bottles, and in-line filters

Paclitaxel Injection Concentrate for Nanodispersion (PICN)

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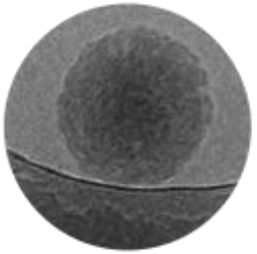
Novel formulation of Paclitaxel using SPARC's proprietary nano particle platform technology

- Achieves 30% higher drug concentration in tumor tissues compared to conventional paclitaxel
- Unlike ABRAXANE ®, quick and easy "one step" dilution and infusion preparation
- Shorter infusion time (30 min)
- Superior safety profile compared to ABRAXANE®, observed in Phase I clinical study in INDIA.

PICN as How Supplied

PICN after Reconstitution



Electron microscope image of nano particle

Safety established at high doses in Phase I clinical trial

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Study enrolled 36 patients with metastatic breast cancer and who have progressed to at least one combination chemotherapy.

Key Findings

Safety Data Analysis

- 28 patients exposed to PICN.
- Dose limiting toxicity was observed at 325mg/m^2
- NO pre-medication with high dose corticosteroids, antihistamines or anti-emetics.
- NO hypersensitivity reactions in in ANY patients
- Less neuropathy

*Toxicity comparable to ABRAXANE®**

	PICN 260mg/m^2 n= 9 , (%)	ABRAXANE®† 260mg/m^2 n=229, (%)	TAXOL®† 175mg/m^2 n=225 , (%)
Neutropenia <2.0 x 10^9/L	7 (77.78)	183 (80)	185 (82)
Neuropathy			
Any Symptoms	1 (11.11)	163 (71)	124 (56)
Severe Symptoms	0	23 (10)	7 (2)

*This comparison with large historical data of Abraxane and Taxol is for the purpose of interpreting PICN data. PICN safety remains to be established in large, randomized clinical trial

† ABRAXANE PI

Encouraging trend of efficacy in Phase I clinical study

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Key Findings from Efficacy Data Analysis

- Overall response at all dose levels 45% (10 out of 22 patients).
- Efficacy of PICN is evaluated at MTD dose level 295mg/m^2 in 7 patients
  - 6 patients achieved partial response, and 1 had disease progression in the 295mg/m^2 group with ORR of ~86%.

- Phase II study is ongoing with 260 mg/m^2 and 295 mg/m^2 dose comparing with 260mg/m^2 Abraxane® in metastatic breast cancer

Trend of superior efficacy in Phase II clinical study continues…

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Interim Efficacy Data Analysis of 65 patients

	PICN 295mg/m² n= 22 , (%)	PICN 260mg/m² n=20, (%)	ABRAXANE® 260mg/m² n=23 , (%)
Objective response rate (ORR)	59.1%	50.0%	34.8%

Added above are early efficacy data for ongoing PICN phase 2/3 study.

We will look at early efficacy data with following understanding:

1. Data includes CT scan reports as available in Jan 2011 for Cycle 2 , Cycle 4 or Cycle 6.
2. The study is ongoing

Key Findings from Interim Efficacy Data Analysis

Efficacy and safety of PICN in subjects with metastatic breast cancer:

- 154 out of 180 Enrolled, 86% enrollment complete
- Superior efficacy continues
- No pre-medication
- No hypersensitivity reactions
- Trend of less neuropathy continues

Trend of superior efficacy in Phase II clinical study continues…

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Percentage Reduction in Tumor Size	PICN 295mg/m² n= 12	PICN 260mg/m² N=10	ABRAXANE® 260mg/m² N=7
Percentage Reduction from baseline (Mean SD)	54.8 26.0	46.3 22.4	47.4 24.4
(Median)	51.5	33.5	39.0
Number of Patients with Complete Response	2	1	1

These are early efficacy data for ongoing PICN phase 2/3 study. We look at early efficacy data with following understanding:

1. Data includes interim analysis of data from CT scan reports as available in April 2011 for Cycle 2, Cycle 4 or Cycle 6.
2. The study is ongoing

Future development plan

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US –505(b)(2) route

- IND filing with USFDA completed and ethics committee approval obtained.
- To initiate Phase I study of a combination chemotherapy of PICN with Carboplatin Q3 FY12.

India

- A phase II/III study in metastatic breast cancer is initiated in FY11. The study has completed 86% enrollment.

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NDDS ORAL Products –Wrap Matrix Platform

Challenges in CR products with high solubility, high dose drugs

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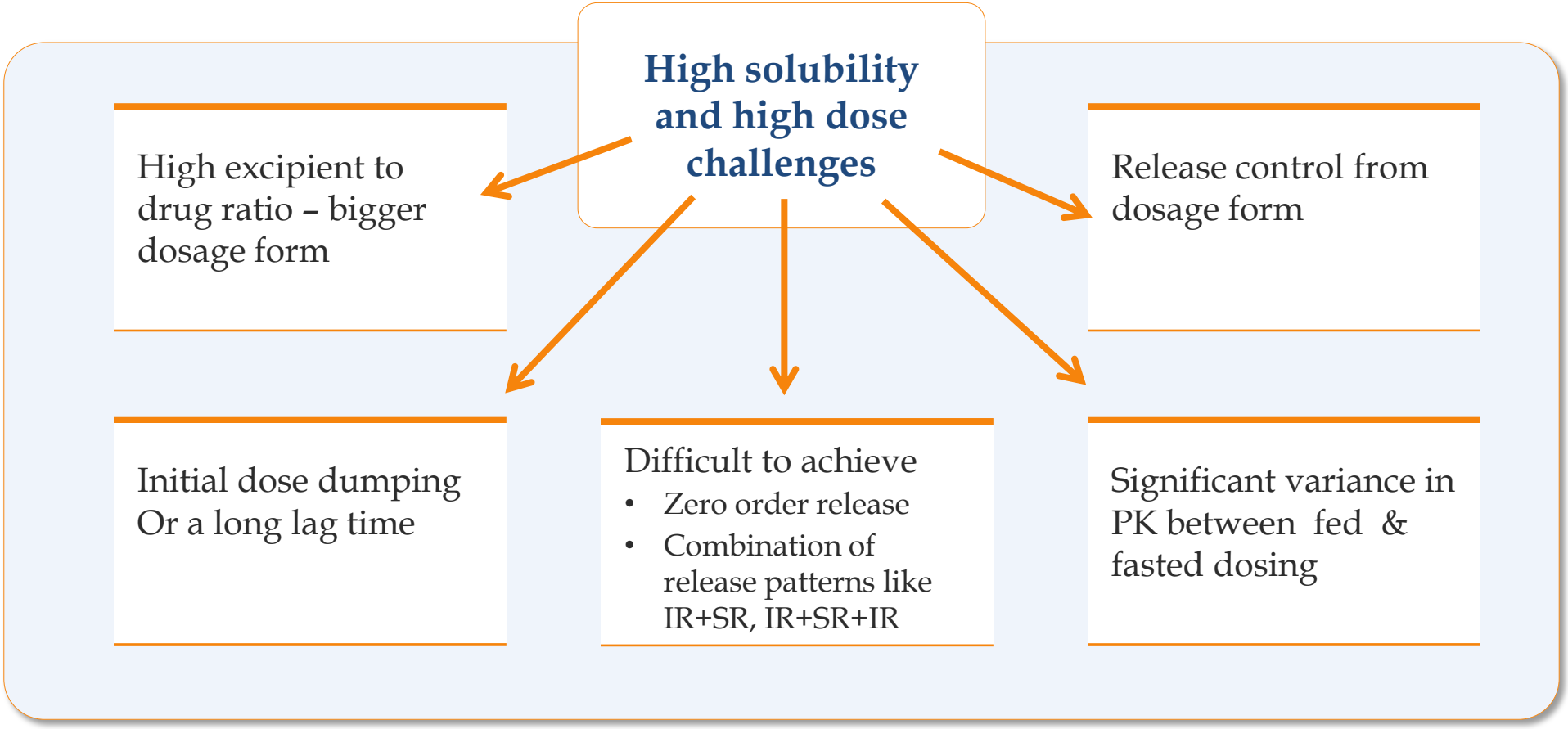

Wrap Matrix System

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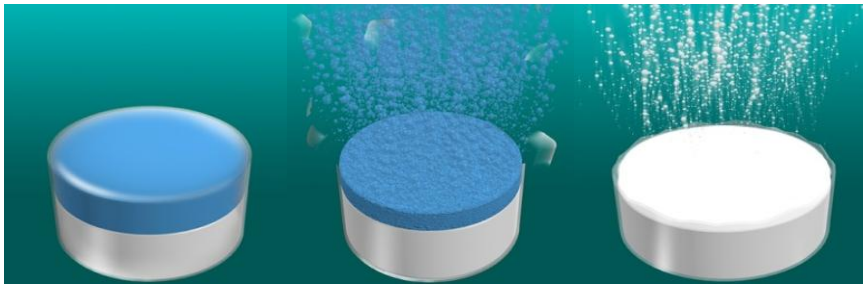
The Technology

- Novel oral controlled drug delivery system based on pre-defined, precise and selective surface exposure



Key Advantages

- Once-a-day dosing
- Ability to handle products with larger daily dose
- Suitable for drugs with very high solubility
- No residual drug in dosage form on evacuation
- Minimal food effect
- Difficult to reproduce bioequivalence using any other formulation technology
  - Low risk of generics

Levetiracetam ER 1000mg, 1500mg; Market Opportunity

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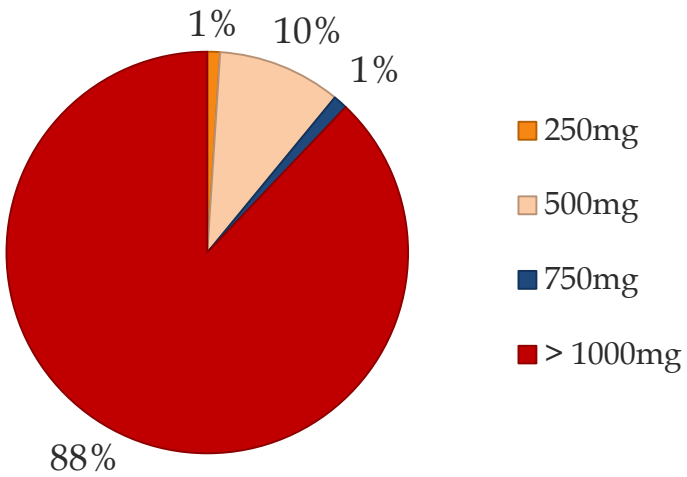
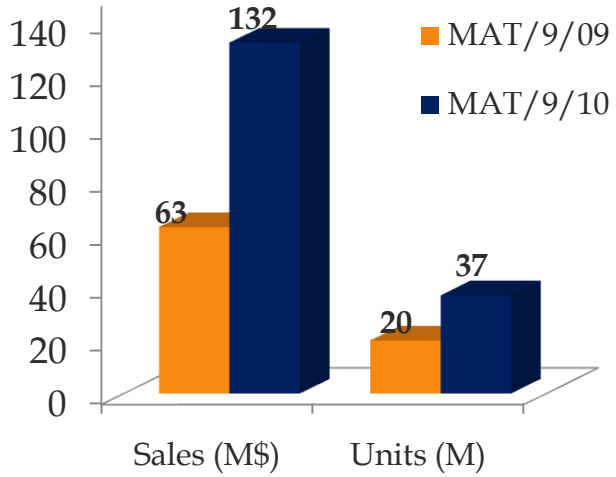
- Levetiracetam is one of the most successful anti-epileptic agent worldwide.
- Peak sales of Levetiracetam in the developed markets before the patent expiry reached ~ US$ 2 B in 2008
- 88% of Rx are for daily doses above >1000 mg requiring multiple tablets dosing per day.
- Kepra XR 500mg, 750mg rapidly growing in US inspite of generics launch suggests the need of long acting products.

Levetiracetam US Prescription data (2007)*



Keppra XR Sales Trend in USA*



Levetiracetam ER 1000mg, 1500mg

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Levetiracetam - An Antiepileptic with high water solubility and vey large dose

- Levetiracetam requires very high daily dose upto 3500mg , making it necessary for patient to take multiple tablets 2 to 3 times a day
- Levetiracetam ER tablets (Keppra XR) were launched but they provide only 500mg and 750mg per tablet hence patient still requires to take multiple tablets.
- New Levetiracetam ER Tablets are being developed using Wrap Matrix system with higher strengths of 1000mg/1500mg using SPARC's proprietary Wrap Matrix system.
- High Drug/Excipients ratio makes it possible to formulate a smaller tablet.

Current Status

- Development of 1500 mg and 1000 mg once a day product completed.
- Bioequivalent product to Keppra XR 2 X 750 mg
- Completed Pivotal Pharmacokinetic studies
- Plan to file in US as 505(b)(2) in Q3 FY12

Other Products with Wrap Matrix Technology

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A Cardiovascular agent - high dose and high solubility

A skeletal muscle relaxant with ultra short half-life

An Anticancer Agent combination with beneficial agent

CNS Agent with very high solubility

ANDAs

- ANDA product - Venlafaxine ER tablets approved in US & Europe
- Additional products based on Wrap matrix technology filed as ANDA (by Sun Pharma)

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Other NDDS Platforms

Other NDDS Platforms

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Biodegradable Depot Injections & Implants (INJECTABLE)

A technology platform of biocompatible and biodegradable *micron-sized* polymer particles that contains drug molecule in its matrix for long-term systemic delivery of drugs

- **Octreotide Depot Inj 1 Month is developed and marketed in India.**

Swollen Micelle Microemulsion (SMM) Technology (OPHTHALMIC)

"swollen micelles, micro emulsion" is a platform for solubilizing ophthalmic drugs with limited water solubility or completely insoluble ophthalmic drugs.

- **Latanoprost "BAK Free" Ophthalmic Solution is marketed in India and undergoing phase III clinical study in USA.**

Gel Free Reservoir (GFR) Technology (OPHTHALMIC)

Gel Free Reservoir technology platform consist of a unique polymer ratio that show synergistic increase in viscosity without the loss of clarity and flow property.

- **Timolol OD Ophthalmic solution is marketed in India**

Gastro Retentive Innovative Device (ORAL)

Designed for drugs with narrow absorption window; drug is retained in the stomach for longer time (~about 8 hours), thereby providing once a day dosing advantage.

- **Baclofen GRS capsules are marketed in India; ongoing SPA with USFDA for Phase III study in US**

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NCE Programs

NCE Programs

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SUN 1334H Anti Allergic

Selective H1 Receptor Antagonist

Oral Tablets and Ophthalmic Solution

Completed Phase II for Oral Tablets; Ongoing Phase II for Ophthalmic solution in

SUN597 – Soft Steroid

Topically Active Glucocorticoid Receptor Agonist

Inhalational (Asthma) , Nasal (Allergy) , Ophthalmic(Anti-inflammatory) and Skin (Dermatitis, Psoriasis) Applications

Nasal formulation in Phase I ; Other formulations are at Preclinical stage

SUN 09 – Prodrug of a marketed muscle relaxant

Developed for spasticity with once a day dosing and improved safety profile

Ongoing Phase I clinical studies in India

SUN44 -Prodrug of Gabapentin

Developed for Epilepsy/Peripheral Neuropathies

Completed Preclinical studies; Phase I to start in FY12 in India

SUN K706 – Bcr-Abl Tyrosine Kinase Inhibitor

Developed for TKI resistant Chronic Myeloid Leukemia; Active in T315I mutation

Ongoing formulation optimization and preclinical studies

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