

Sun Pharma Advanced Research Company Ltd.
Transcript of Management Presentation
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Corporate Participants

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Sudhir Valia

Dr. T. Rajamannar

Dr. Subhas Bhowmick

Dr. Nitin Dharmadhikari

Dr CT Rao

Kirti Ganorkar



Uday Baldota: Good afternoon to all participants present in the room here, those joining us on the audio call and those on the webcast. Welcome to the Sun Pharma Advanced Research Company Limited Management Presentation and interactive session, where we are sharing updated details on the New Chemical Entity and Novel Drug Delivery System projects. This session is being recorded and a replay will be available. Just as a caution, we would be making forward-looking statements during the course of this presentation and interaction today, and this needs to be viewed in conjunction with the risk that the business faces.

During today's interactive session, we will make an effort to answer all the questions that the participants ask but if time does not permit I request all of you to please send in your questions to either me or Mira. Also we urge participants to ask questions only related to SPARC Ltd., and not ask questions related to Sun Pharmaceutical Industries Limited, for which a separate interaction is planned. I now hand over to Mr. Dilip Shanghvi Chairman and Managing Director, SPARC Ltd., who will introduce the team.

Dilip Shanghvi: Thank you Uday, and welcome to the presentation. Today on the dais with me are my colleagues, let me take a minute to introduce each of them. Immediately to my left is Dr Nitin Dharmadhikari who is based in Bombay and he looks after solid oral innovative delivery systems. Next to him is Dr. Subhas Bhowmick, who is based in Baroda. Dr. Bhowmick looks after innovative delivery system for all other dosage forms other than solid orals. Immediately left to him is Dr. Rajamannar. Dr. Rajamannar is the head of R&D, and he looks after new chemical entity development as well as drug delivery system development. Next to him is Sudhir Valia and all of you are familiar with Sudhirbhai. Next to Sudhirbhai is Kirti Ganorkar head of business development who is based in Bombay. The last person sitting on the dais is Dr. C.T. Rao, who is based in Baroda, and he looks after new chemical entity development.

This presentation is structured in such a way that Dr. Rajamannar will initially share with you the philosophy by which we are managing innovative research in SPARC Ltd. After that, Dr. Dharmadhikari and Dr. Bhowmick will introduce our innovative delivery system product list with the current status of development. After that, Dr. C. T Rao will share with you the new chemical entities and their current status of development. We are sharing with you a limited number of products for which we have a clear path available and there is some clarity of their clinical development. These are not necessarily the only projects on which we are working. We have projects across many other delivery systems and other new chemical entities that are in earlier stages, and we think that they have not reached a level at which we need to share them with you. With this, I hand over to Dr. Rajamannar.

Dr. Rajamannar: Thank you Dilipbhai, for introducing the team members including myself. As Dilipbhai mentioned I am looking after the research activities at SPARC, which includes new chemical entities as well as the novel drug delivery systems. We are going to present an update on some of the projects which we are working on, both NCE as well as NDDS. It does not mean these are the only products we are looking at. We have other products on which we are currently working, but they have to move further so that we can have clarity. I will give you some information about the kind of projects that we are working on, and what is the biological or the dosage form development for the products or projects. Some of the things may be repetitive for those who attended our last presentation. It does not mean that the contents would be the same. Especially, drug discovery can take more than a decade, so you would be talking of the same thing when you talk of Sun 1334H or Sun 597 over the next five to six years, so it will be repetitive but the additional information may be sometimes significant and for some of you it would be add on information. So how would one view that information, would depend on what is the content that you are looking at, whether you are looking at the content that you have for a product or whether you are looking at an update for all the things that we have done. So, there is



added or enhanced information available for products which we have previously shared, and there are some new products in terms of NDDS and NCE that we would be sharing.

At SPARC we have a disciplined and systematic approach to innovation. When we say disciplined that is because when we do research in pharma there are two kinds that we do. Research related to the drugs that are known, we do not need to innovate there, we need to make a quality that meets the regulatory requirement. When we say innovation, it means that we are looking at a molecule that you do not know anything about, which needs to qualify as a drug. When we are looking at a product in terms of dosage form, we know what are going to be the attributes or what are the things which may be problematic but we do not know the solution, but we need to find a solution which can change the properties of the drug. Or the NCE what you are looking at, how you can make it into a molecule, and how can it become a drug, because in normal life we see that there are several thousands of compounds which exist, but we can only take few things even for our normal survival like when we can only consume glucose. But there could be 32 different things with the same molecular formula and everything is identical but you cannot consume, they may all be toxic or they may not be digested by our systems.

So, when we talk about discipline that what we are talking about, this is our understanding, this is what we can do, and let us put our foot on strong ground and thereby we develop these activities with the team who are with us for last 15 years, who are dedicated, who are sincere and who are willing to dive into this ocean but it requires a courage, and we have a captain Dilipbhai who could, make our life easy. When we started drug discovery, we began looking for a product in steroids that will be devoid of steroidal side effects. It looks like a very simple statement, but you need to make a molecule which is a steroid, it is having steroidal property of anti inflammation but does not have steroidal property of all the other side effects, say immune deficiency, or bone disorder, or may related to diabetes, or retarded growth. There are several problems but you need to overcome these so we need to have discipline, we need to have at the same time an innovation which will offer a difference, a change of what you are looking at. And the second thing is that whatever you are doing, you should be able to see the change that is happening, you are able to see these in a predictable animal models, there is a predictable biology, which you can see, because everyone knows that steroids would have an anti-inflammatory effect. You need not have to prove that. You need to have a test steroid with specific glucocorticoid receptors binding, then that means you are bound to have anti-inflammatory action, what it is not bound to have is whether it is devoid of side effects, whether it can stay where it is required for sufficient time, and what else may be required. When you can demonstrate, that whatever is required is there, and what is not required is also not there, only then it is going to be a safer product. So, we need a confirmation that whatever are the products that we are developing, or technologies which it is solving, that we should also know side by side how it is happening, and whether we are understanding those things, and our focus is on the right indications, will it offer a sustainable market. There needs to be focus, in areas where we are sure there is going to be growth. From the beginning we are working on allergy, asthma and inflammation, over last 10 decades, there is the constant increase in the allergy, asthma, due to heavy industrialization. May be 20 years back if someone sneezes or coughs doctors will not label this as allergic cough.

Today if you go to doctor with a cough he will call it an allergic cough, so that is the change. So, you see that there is a requirement of safer drugs in these therapeutic areas. In terms of NDDS, we want to improve patient compliance, and enhance safety because there are several drugs, which are very effective in treating the condition, especially in case of cancer but not all anticancer products are safe-- they are not at all safe. If products are not safe, that means if you are able to deliver a drug where it is required at higher level and if you are able to control reaching of that drug to the healthy tissues that is going to be major advantage of your product which can enhance the efficacy at the same time they would be devoid or have minimal side effects.



For NCE, we work on validated targets where we can understand the biology and outcome of the biology, as well as understand the limitations, study how we can add with our understanding of chemistry to solve those problems, such as our approach with soft steroids. And if there is a problem of pharmacokinetics due to limitations of absorption how do we solve with the skills that we have, and those are the areas that we can contribute to, and which we can add to understanding of our knowledge and product discovery. It not only adds to knowledge but it also adds what we can take next to the higher level, what is the requirement of understanding, what is meant by new biology and new target, why we have to do, and what target we need to select, what would it offer advantages as compared to what is existing would be important for us to learn by this process. I now request Dr Dharmadhikari to discuss the technology that we have developed in last three years in terms of GRID technology and wrap matrix, what are its advantages where we are and followed by Dr. Bhowmick on nanoparticles related to some of the anticancer products, and biodegradable depot injections which talks about how one can develop product to give a long-term effect, without going everyday to the doctor and getting many injections, which one can avoid by the innovative technologies what he has worked in. And the third one is the tropical products wherein for inflammatory chronic disorders like asthma. This is a therapeutic area where steroids are used as a mainstay, but there are several disadvantages, how we are looking at a device to address this area, and now I request Dr. Dharmadhikari to initiate his presentation and finally Dr. Rao would discuss on NCE's.

Nitin Dharmadhikari Thanks a lot Dr. Rajamannar. My name is Nitin Dharmadhikari and I head the solid orals development at SPARC. I've been with Sun for more than 10 years, and after SPARC was formed, for three years I've been heading this function. I'm going to present two technologies and then the products associated with them.

The first technology is for controlled released products of the drugs with a narrow absorption window. So what is this absorption window? If you look at the figure on your left hand side, this is the human gastrointestinal tract. The intestine is about 4.5 meters long, and this is the place where once the drug is taken orally, it will get absorbed. For most of the drugs, out of these 4.5 meters, almost 3 meters will be available for absorption. There are different kinds of drugs, that are absorbed from only about half a meter of the intestine. There are reasons for this, there is a phenomena called transporter mediated absorption. There is a possibility that the drug does not have solubility in the intestinal fluid, or they may be getting degraded in the alkaline environment of the intestine. So what happens is that the first part of the intestine from the duodenum onwards, there is only about a half meter available for them. So, when we want to make controlled released product for such products, then there is a challenge and challenge is that the dosage form will cross this absorption window too fast and the availability of the drug will be lesser. Industry has been working on this problem for so many years and the approach taken is to retain the dosage form in the stomach, which is the most upper part of the gastrointestinal tract.

The problem with the stomach is that it wants to empty everything that it consumes so it is not able to store for a longer time, the usual transit time from the stomach is about two to three hours. So, a conventional dosage form containing the drugs with a absorption window will cross the stomach in let us say two hours, and then this half a meter of intestine by another one hour, so really you cannot make a control release dosage form for such drugs. GRID or gastro retentive innovative device is a technology which tries to answer this question. This GRID dosage form is retained in the stomach for about 8 hours. There are different mechanisms which we use to retain the dosage form in the stomach- floatation, size expansion and mucoadhesion. So, if you look at the grid technology, the key advantages with the grid technology is, it is able to retain itself in the fed stomach for about eight hours, it is flexible and soft, because something which is hard edged and retained in the stomach, you can imagine, will hurt the stomach. So, it is very essential that it does not hurt the walls of the stomach.



And then another advantage with this technology is that different types of release patterns are possible, something like immediate release and a control release combination is possible with this device. We have used our grid technology to develop Baclofen GRS Capsules. Baclofen is a muscle relaxant, it is given up to the dose of 80 mg and is given 3 to 4 times a day, it is used in the treatment of spasticity. It has a proven absorption window which has been reported in literature. So, we have developed a dosage form, capsule dosage form, which is a controlled released dosage form using grid technology, and this can be given once a day, these capsules are available in six strengths, 10, 20, 30, 40, 50 and 60 mg for individualized dosing.

We have done a large number of studies to meet the stringent USFDA requirement and then we have also done a safety study, that is a gastroscopy study to prove that dosage form does not get accumulated in the stomach. Something which is swelling, something which is floating or something which is going to get retained, there is a possibility that when the dosage form is given repeatedly, after 10 days you will have an accumulation of 10 dosage forms in the stomach of a patient. So to address that safety issue we have also done a gastroscopy study. These studies are basically to answer the possible questions from regulatory agencies like USFDA.

We have taken 505 B2 route for the US. IND has already approved by USFDA and Phase III studies with a randomized placebo control study is initiated in USA. One more long-term study is planned. In India, Baclofen GRS capsules are already registered and being marketed, 20 mg and 30 mg dosage forms are available in India. Although, Baclofen is one drug that we are sharing with you, but this technology we are using for few more drugs as well, and we will share that information once the time is right.

Now, the second technology which I am going to talk about is controlled released technology which is suitable for high solubility and high dose drugs. Controlled release, as you are aware, is a dosage form which can be given, say, once-a-day. Now, when you look at a dosage form, a dosage form like a tablet or a capsule will have a drug, and will have excipients. Usual ratio in the dosage form is something like 30%, 40% of an excipient, and the rest for the drug. Imagine a situation where drug is very highly soluble. Naturally, the drug will try to come out of a dosage form immediately, and it will be difficult to retain the drug inside the dosage form and you are looking at something like drug release over 16 to 24 hours! So, such a drug with high solubility will be difficult to formulate into a control release system. Another problem is of a high dose, let us say dose is high and the solubility of a drug is also high, then these two problems get added up, and then the difficulty in making a control release dosage form increases.

So, what are the problems? Problem will be dosage form will become very big if the solubility is high, also if the dose of the drug itself is large, then there will be an initial dose dumping because something which is water soluble will try to come out fast from the dosage form till the excipients which are suppose to control the release gets activated, until this happens, you will see the initial dose dumping. And supposing you are looking for a zero order release profile-- which is nothing but the release profile as per time. Let us say 100 mg of a drug we want to deliver in 24 hours, then 100 divided by 24 something like 4 mg per hour, that is what is desired. So if you have a high solubility, high dose drug, such zero order release will be difficult to get. Another problem will be various combinations because if you want to tailor your release profile like immediate release, immediate release plus sustained released, or something like IR plus SR plus IR, they will be difficult to make.

Wrap matrix system which is Sun Pharma's proprietary system is based on pre-defined, precise and selective surface exposure. The key advantages of this technology is it can handle high solubility, high dose drugs, in a smaller dosage form because it uses less excipients. It also has the flexibility to make



various release profiles like IR + SR +IR so it is a highly flexible technology, which can be adopted for the drugs, which are highly soluble as well as high dose.

Another point which I would like to explain to you is that the technology has an ability to create a unique kind of a pharmacokinetic profile which will be difficult to copy as a generic. So, it will become difficult for the generic copiers, because Wrap can have a differing release profile, certain release profiles in a fasted state and certain release profile in a fed state-- so it can create such a pharmacokinetic profile which will be difficult to copy by generics. These are the products which we are developing using wrap matrix technology-- there are six products which are under development across therapeutic classes: antiepileptic, antihypertensive, cardiovascular, there is a skeletal muscle relaxant. These drugs have their unique problems, something which has a higher solubility, high dose, one of the CNS drugs has a ultra high solubility, very hygroscopic and so on, so difficult to handle drugs, difficult to formulate into various dosage forms. So, there are six products under development using this technology.

With this I request Dr. Bhowmick to present the injectable and topical products.

Subhas Bhowmick: Good afternoon. Thanks Dr. Nitin for the introduction. I'm Subhas Bhowmick, working with Sun Pharma for last 19 years and then after this separation of SPARC from SPIL for last three years I am heading this NDDS platform technology based on injectables and topical dosage forms. In NDDS platform technology, the drug is known, our focus is primarily on increasing patient compliance, making the drug easy to use or administer, and enhance safety. If you can enhance safety and offer better therapeutic index, it should be accepted by regulatory agencies. So, based on this ease of use and simplicity concept, a few technologies are developed which are at an advanced stage, so I will explain the status.

One of the technologies is nanoparticle technology. Many companies are working with this nanoparticle technology and it is very difficult to stabilize a nanoparticle and specially if you are working with anticancer drugs which are very difficult to solubilize, So lot of surfactants has to be used for solubilization, but these are very toxic in nature, and also has some inherent properties like hypersensitivity reactions. Patient has to use or is treated with pre-medications like steroids and antihistamines, since anti-cancer drug itself is toxic, and with this added toxicity of the surfactants, it limits the dose of this drug to be administered. Conventional anticancer drugs are administered to the patient as a low dose, so the challenge is, can we develop a product which can be administered at a higher dose, but not causing toxicity. Another problem with anticancer drug is it kills tumor cells as well as normal cells, so can we develop a technology which minimizes the accumulation in normal cells and targets the tumor regions only. Here in our nanoparticle technology, the platform technology where we have selected the excipients which are not toxic and either it is approved by the USFDA or which is in the GRAS status (generally regarded as safe), since we are not using any surfactants, the excipients used are not toxic, so we expect that a higher dose can be administered. And there is no requirement of special infusion set, which is normally a problem with surfactants. There is no need for an inline filter either.

In Paclitaxel Injection Concentrate (PIC) we have used this nanoparticle platform technology, and in preclinical trials we observe 30% higher drug concentrations in tumors. The product as shown in picture is a clear solution and it forms nanoparticles when it is diluted, also the nurse can make an infusion solution directly, the excipients of composition is itself a self dispersing system. The drug is stabilized by forming a nanoparticle and stabilized within this infusion solution only. The infusion time is very short. Normally the conventional Taxol-like drugs have three hours infusion time but our infusion time is about



30 minutes, so that is also an advantage, the patient does not have to stay for a longer time in the nursing home or hospital.

We have done a human trial Phase I clinical study with 36 patients where we observed a DLT*** (dose limiting toxicity) of 325 and the therapeutic dose of 295, it is actually very high dose compared to the conventional drug. In this study we have seen no hypersensitivity reaction, there is no premedication requirement, and objective response rate that is efficacy is 33% compared to Abraxane, and 21% compared to Taxol. So, we see that our PICN is highly efficacious, and no disease progression was observed in any patients to date.

Our objective is to file through section 505 B2 for the US, so we have already done a pre-IND meeting with US-FDA and got this guidance, and finalized the protocol and shortly we will initiate Phase II and Phase III study both in India and US. All Indian studies that we have done and proposed are as per GCP so which will be acceptable to any regulatory agency.

Another project I am going to talk about is docetaxel nano dispersion, also developed on the basis of nanoparticulate platform technology, where we have used excipients which are non toxic. So that higher amounts of docetaxel can be injected. Docetaxel is a highly insoluble drug, and very toxic at high concentrations. In a preclinical study, we have seen that our Docetaxel nanoparticle injection is 7.5 times safer to dose than conventional Docetaxel. The dose and toxicity with Docetaxel are predictable and linear, so whenever there is an issue with the patients getting a high dose, doctors can decide to give a low dose. So, we expect to have a pre-IND meeting this year 2010-11, and have initiated a Phase I study in India in solid tumor patients.

Biodegradable depot technology is another technology we are working on. In some chronic diseases, patients have to use injections daily, sometimes multiple times also, which is highly inconvenient. If we can develop a product which can be injected either intramuscularly or subcutaneously, where the drug is released through out the one month and three or six month period, so that will be the challenge. There are some depot products already available, but they have inherent problems. One of the products available formulated with a very high polymer to drug ratio-- that means one has to inject a very high volume of injection intramuscularly or subcutaneously, which is very inconvenient and painful. The product in the market is available as an implant where we have to use a 14 or 16-gauge thick needle, and sometimes it requires special training for the caregiver. The onset of the drug is delayed, and sometimes there may burst effect - delivering all the drug at one go, so there is a need to develop a product which can give consistent release of the drug, and uniform blood levels throughout the treatment period.

In this platform technology we have used a biodegradable polymer, and we have reduced the drug polymer ratio so that the injection volume is very low. Regarding the availability of the drug, the onset is immediate and blood levels are uniformly maintained throughout the treatment period. With this platform technology, we developed two products, one is the Goserelin the available product Zoladex is an implant which requires as I told you a 14 to 16 gauge needles and special training and sometimes you have to use anesthetic agents before you implant, which is highly inconvenient. Whereas the products we developed have a lower injection volume and the particle size is small, so it can be easily injected intramuscularly and subcutaneously.

In a similar way, we have developed Octreotide depot injections, and we compare the efficacy and bioequivalence of this product, with a series of studies. Our development plan is that the IND filing will



be made for both the products in quarter one 2011-12, and we have initiated Phase III clinical trials in India.

Our next technology is a dry powder inhaler. The DPI, dry powder inhaler delivers the drug to the lung by aerosolisation. Products are available in the market but the problem is that delivery of the drug to the lungs is very low, and in many of the products there is a possibility of double dosing. Usually, asthmatic patients have compromised lung function. That means they are not able to inhale properly, so inspiratory flow rate that we see today may be different than the next day, which means the amount of drug deposited into the lungs will vary. So if we can develop a device which is independent of inspiratory flow rate, that will be our challenge. Also, the development of this dry power inhaler requires meeting stringent regulations which is very complex. In our DPI device which is shown here, there are lots of features. One important feature is uniform dose delivery; this is a breath-operated delivery system so once you inhale only then you will get the dose. Operating this device is very simple-- open, inhale the dose, and close-- it is a simple three steps process, it is not a very complex process. When inhale only, then it will be operated --so otherwise if you do not inhale it will not get activated and the patient will not get any dose. So, the two important advantages of this are uniform dose delivery which is independent of the inspiratory flow rate, designed in such a way that it will offer a consistent dose irrespective of the inspiratory flow, there are features also that the patient will get feedback, like some visual audible tactile feedback, and glow in dark features also which make it easy for night time use, and some features that assist the visually impaired, when last eight doses remain, something will protrude from this device. So there will be an imbalance which will help this visually impaired patients. It is very small and convenient to carry.

We have done human clinical trials with half of the dose of the steroid equivalent, that is, salmeterol 25 mcg and fluticasone 250 mcg compared to the marketed salmeterol 50 mcg dose and fluticasone 500 mcg dose-- even then the efficacy we have observed is similar. There is a graph presenting the PEFR* (peak expiratory flow rate) of this clinical trial and FEV 1** (forced expiratory volume in the first second) and in both PEFR and FEV-1 there is no significant difference between the innovator product and Sun product.

The pathway for filing in US is the 505 B 2 route, and we have done Phase III study in India and we expect the launch in India very soon.

Another technology is for delivery of the ophthalmic drugs. Ophthalmic drugs like prostaglandins are insoluble and require very high concentration of surfactants like benzalkonium chloride which are very toxic so the challenge is to solubilize this drug without the use of surfactant to avoid the toxic effect on ocular tissues. Since these drugs are used for the treatment of glaucoma, in which treatment has to be life long. Safety is the prime importance for these types of dosage forms. We developed a technology called SMM technology, the swollen micelle microemulsion technology, which is a platform technology where the drug is solubilized and stabilized with the help of a polymer and it is BAK free i.e., benzalkonium chloride free product, and even then it is stable at room temperature. The product we have developed on the basis of this technology is latanoprost ophthalmic solution. It is a clear colorless BAK-free solution and is stable at room temperature whereas the product available in the market is stable at 2 to 8 degree centigrade, which is highly inconvenient to the patient. It demonstrates the improved safety profiles and comfort characteristics.

In a clinical trial done using 100 subjects, we found that the efficacy of this product, i.e., reduction of IOP which is equivalent to the innovator products, in long run the safety to be tested. Since we are not using benzalkonium chloride, it is expected that it will not be toxic to ocular tissues and will be safe to the tissue organs. Filing will be through the 505 B2 route, our IND is approved at US FDA and discussed



with US FDA and we have finalized the protocols for Phase-III study. Phase-III study will begin soon in this quarter, and in India we are expecting the launch very soon.

One more ophthalmic drug delivery technology is GFR technology. There are many drugs for the treatment of glaucoma which are to be instilled twice a day and even thrice a day. Formulation development for once a day is very critical because it is a short acting drug. We developed once a day technology for this type of product. It is a Gel-free Reservoir technology where we have used a blend of polymers in such a way that these polymers increase the viscosity without the loss of any clarity and flow property. There is no blurring or stinging on the eye. One of the products we developed using this technology is Timolol Maleate ophthalmic solution. We have done a clinical trial where we have compared our once a day product against twice a day dosing of Timolol maleate, and we found that there is no significant differences in the reduction of intraocular pressure, so it is equally efficacious as once a day as compared to twice a day dose.

Phase-III clinical study has been completed in India, and we will be launching this product in India shortly, as also in other non-regulated markets.

So, with this I will now request my colleague, Dr. C. T. Rao who will be updating on the NCE projects. Thank you.

C. T. Rao: Thank you Dr. Bhowmick and a very good afternoon to all of you. I am Dr. C. T. Rao. I am basically an organic chemist. I have been associated with Sun Pharma since 15 years and since the last 8 years I am involved in the NCE or drug discovery research program, the new drug discovery program. Today, I will be updating on some of the NCE candidates. In the last investor meeting, all these products were discussed, but we will provide you with the updates on these products. It doesn't mean that we are working only on these products, we are working on several other targets and several other products, but at appropriate time we will be coming up with details of those products.

To start with, we started our drug discovery program about 10 years back, when we were all novice to drug discovery, Drug discovery was completely new to us then. So, our approach was to start with the targets, which were well-established, therapeutic areas where the biology was well-known. With incremental understanding of the entire process of drug discovery and with better understanding of biology, we planned to gradually graduate into newer complex targets and development of more complex drugs.

So our first candidate in the NCE program is an antihistamine. The target is for allergy treatment. As it was already discussed probably earlier, that histamine is one of the primary mediators for allergic disorders such as rhinitis, urticaria, and also some of the dermal disorders. Having an antihistamine which blocks the affects of the histamine that is released by competitively binding to the H1 receptor would be a simple target with simple biology to make a new drug. Now what are the desired attributes what we are looking for in the new antihistamine? So, just as in other products, the first requirement is that the pharmacology should be very clear. It has to be very selective to the target where it has to act, and the second aspect is the pharmacokinetics. So in case of antihistamines, it is known that many of the older antihistamines cross the blood brain barrier and lead to sedation by blocking the histamine receptors in the central nervous system. So, if you have an antihistamine that doesn't cross the blood brain barrier, and also has a quick onset of action because allergic reaction is also instantaneous, it would be an advantage. Some of the drugs which were developed as antihistamines or were at an advanced stage, sometimes also after marketing, were dropped, like terfenadine and astemizole because of cardiac safety issues. So it is very important to have in the preclinical stage itself established



cardiac safety. An added advantage would be to have drugs which can be taken by the oral route as well as other routes of administration, for example, ophthalmic, if you consider allergic conjunctivitis, if you can put a drop and alleviate the symptoms of conjunctivitis that would be an added advantage. The other thing is to have anti-inflammatory potential. Because allergy is ultimately an inflammatory disorder and if you have a drug with additional anti-inflammatory effects that could also act as a prophylactic treatment. For 1334H which is our first clinical candidate, we have established the complete pharmacology. In the biological studies, we found that it is the candidate, which meets most of the attributes what we have just discussed. There are already a lot of antihistamines in the market, with a few of these attributes may be, but not all attributes, or they may have all the attributes, but not to the magnitude that is required. So, if you have an antihistamine, which is effective and with a higher magnitude of the desired attributes, that would be a good candidate. For 1334 H, we have established with data from preclinical studies. We had very high efficacy in allergy models and a high safety index. We have demonstrated that it doesn't cross the blood brain barrier through radiolabeling studies, and also has low potential for also drug-drug interaction. This is important because antihistamines are taken along with other drugs which can interact with the liver's cytochrome system and lead to drug-drug interactions. After having established all this in preclinical trials, with the safety aspects, and toxicology we had undertaken Phase-1 trials in Europe on 127 healthy volunteers. We found the drug to be safe up to 8 times the expected clinical dose. That is what we have tested, we have not gone beyond that, because we thought it is not necessary. And we have done three Phase-II studies on a total of 419 patients. One study was for SAR in US, and two studies in India, one for chronic idiopathic urticaria and one for the perennial allergic rhinitis. In these studies we have established the proof of concept of its efficacy and to a certain degree on the safety.

What we were also looking at, is whether the drug can be administered by other routes of administration, like an ophthalmic solution. As I said, in an allergic reaction such as in allergic conjunctivitis, an ophthalmic solution that would be a great advantage. So, we found that 1334H at 0.3% concentration had similar or slightly better effect than one of the currently marketed products olopatadine.

So having established oral efficacy now in Phase-II studies, we have to do certain other studies which include the renal and cardiac safety, mass balance, etc, and in preclinical the chronic toxicity which is a requirement for Phase III studies. And ophthalmic is an area we feel where one can come to the market much faster. We have completed pre-IND meeting with USFDA for the ophthalmic indication, and plan to begin Phase-I clinical studies in India in 2010, and IND filing in US we plan to do after completion of the Phase-I studies in India.

Our second NCE program was on soft steroids, some of you who would have probably seen our earlier program we had a molecule known as S461. We have done further studies in this area and today we have a new molecule which is SUN-597, which has a better or a superior profile than SUN-461. Just to brief you, as already Dr. Rajamannar was mentioning; steroids are by far the most effective drugs for treating inflammatory disorders. However, on chronic treatment steroids have serious side effects like they can hamper growth, induce diabetes mellitus, Cushing syndrome, osteoporosis, and immune suppression. So people can become susceptible to infection. To some extent, people are scared of steroids, but for inflammatory disorders, these are probably the best drugs known so far.

Now how do we make a steroid, which is very effective and at the same time, it doesn't have the damaging side effects? How do we address this issue? So one of the issue is how we design a molecule which retains the activity of the steroid, but once administered especially by the topical route (talking of steroids for topical use like asthma, dermatitis or ophthalmic use like conjunctivitis) it produces local action at the site of inflammation, but once it is absorbed into the system, it breaks down very rapidly



so that systemic side effects are avoided. And these (side effects) are all due to absorption of the drug in the system. So it is a challenge to have a drug which will act locally, produce sufficient activity for sufficient duration at the site of action, but at the same time, once absorbed doesn't have side effects.

Such a steroid is termed a soft steroid. And what are the attributes that are desired? It should have high efficacy at the target organ that is the site of inflammation, long duration of action, so it should not break down at the site itself, and it should be suitable for topical therapeutic application, and should not have good absorption. Even when you talk of topical steroids for asthma even though that are marketed are not oral, but when they are given into the lungs a substantial part goes into the GI tract, absorbed through the GI tract or may be through the lung tissue it goes into pulmonary circulation as well. Absorption can create side effects. So if you have a product with low systemic bioavailability and rapid inactivation on systemic absorption, it would be very desirable. When we talk of steroids for psoriasis where the steroids have to be applied for the long period of time, with most marketed steroids, you can have one of the side effects which is skin thinning which leads sometimes to aggravation of problems. So if you have low potential for skin thinning for dermal product, and low potential for intraocular pressure for ophthalmic product (because steroids when they are given for long time in the eye, they can increase intraocular pressure), and overall if you achieve good activity with a low side effect profile, what you are achieving is a high therapeutic index for the drug. Such a steroid would be an ideal steroid without the drawbacks of the steroids. So SUN-597 as I said, is a soft steroid with superior pharmacological profile than SUN-461 which we had earlier been looking at. SUN-597 has high binding affinity for the glucocorticoid receptor and is selective to the glucocorticoid receptor. So, it doesn't interact with other related receptors.

In the design of this, what we have done is to take an inactive metabolic of already existing potent steroid, and we have modified it in such a way that it again becomes active. So it will give local activity, but once it is absorbed into the system, it will predictably break down to the inactive metabolite. So, essentially what you are doing is you will have local activity, but the molecule will be devoid of systemic side effects. So we have seen that SUN-597 has very good *in vivo* potency, efficacy, and duration in the animal models of asthma and allergic rhinitis. Also it has very low oral bioavailability which is the desired, and a very short, plasma half-life and thus very low liability for systemic side effects. So we have essentially been able to achieve in this molecule, at least establish in preclinical, those attributes that are desired. And we have proved this in animal models. We have used the asthma model where the drug is instilled into the lung and we look at the decrease in the edema. At the same time, we use thymus involution as a marker of the systemic side effect because the absorbed portion of the drug in case it is still active in system it will cause involution or decrease in size of the thymus. So, if you see, we have compared with some of the marketed potent steroids and also the claimed safe steroid like Ciclesonide along with our product, and we find that in the lung edema our drug is almost at similar potency as fluticasone propionate, but the differentiation factor here is the side effect profile. Fluticasone propionate even at 0.36 mg/kg involutes the thymus by 50%, whereas SUN-597 even at 3 mg/kg dose the inhibition was only 30%. The second aspect of corticosteroids is metabolic side effects. So with marketed steroids you have diabetes induced by steroids due to glycogen deposition in the liver, and with SUN-597, we have treated animals at 3 mg/kg dose for 3 days by the intratracheal route. And here again we find that potent steroid like fluticasone induces lot of glycogen deposition in the liver, as also ciclesonide to some extent, but SUN-597 hardly anything, so insignificant is the glycogen deposition in the liver. So, if we look at in toto, activity of the reduction in the lung edema, as well as the side effect profile (like negligible thymus involution) what we see is that we have a good therapeutic window. Now, if you have such a steroid, it is good for chronic use and also in pediatric population where the doctors are reluctant to prescribe steroids as first line therapy. So if you look at the therapeutic index in the lung inflammation model which to some extent replicates the therapeutic efficacy in the asthma, we see that fluticasone if you say take it as 4.19, ciclesonide the safe steroid is



twice safer than fluticasone, whereas SUN-597 is safer to a degree greater than 32. The second is orally; because when we take steroids by the inhalation route, part of it enters the GI tract and that can lead to systemic side effects. So we have used again inhibition of thymus and inhibition of adrenal gland, also inhibition of the body weight gain as markers for assessing the systemic side effect. So here again if you see, fluticasone, by this route, the oral route, can inhibit thymus by 50% whereas the safer steroid Ciclesonide by 29.5%, while SUN-597 is similar to placebo, like almost 0. And also in terms of the inhibition of body weight gain, it is similar to the placebo, Ciclesonide is definitely safer than fluticasone propionate. So overall what we can see is that we have a steroid which is efficacious, which does not induce side effects even if it is absorbed systemically so we don't find this also in the toxicity studies. In 30 days intranasal toxicity, no adverse effects were noted even at 2.5 mg/kg per day and similar thing in the serum cortisol level. Because there is a suppression of cortisol by steroids and that is not affected by the intranasal route even after 30 days of treatment in dogs. For allergic rhinitis the nasal route is what we are looking at, in this also we have seen very good potency and efficacy in preclinical *in vivo* models. We have used the dye leakage model, because in allergic inflammation you have increased vascular permeability which leads to nasal discharge and that can be assessed by how much of dye which we are injecting leaks to the nasal cavity. So you are seeing that the dye which leaks through to the cavity is very less and it is more or less like, fluticasone or is somewhat better and it is quite effective. So with these data our plan is to enter into Phase-I clinical trials in 2010-11 and we are quite excited about it.

The second thing we want to look at is the dosage form development for inhalation, because for inhaled drugs we have to look at several aspects, the particle size, the polymorphism also. So it is again a challenge to develop inhalation products for new steroids. So we plan dosage form development and sub acute toxicity studies in 2010 by the inhalation route. We are planning all these studies for both the domestic and international markets.

The second aspect, other than the NCE based on receptor target, is to look at drugs which are very efficacious-- already existing drugs-- but have poor absorption profile, or limited absorption profile. The pharmacology is very good and then the PK part, the pharmacokinetics is not very good. So how do we retain pharmacological activity in such a way that improves the pharmacokinetic aspects? One approach is through drug delivery systems which Dr. Dharmadhikari has already discussed, how through drug delivery systems we can enhance the absorption profile for such drugs-- and the second is by making prodrugs. A prodrug is a covalent derivative of the existing drug, so by making a covalent derivative, we have made a new chemical entity again, and the new chemical entity is actually not active, but it alters the entire the pharmacokinetic profile. So, by doing that in certain drugs with the narrow window of absorption, you can make them now probably absorbed throughout the entire GI tract. So what sort of attributes we look at for drugs which have narrow window of absorption or there is a transporter that is involved for transporting the drug. So there is a limitation of the transporter availability and intra-variability of the transporter expression in several individuals. So giving the drug as such could be a problem and titrating the dose could also be a problem. By pro-drug you can also facilitate absorption throughout the GI tract. What it (prodrug) should do is, once absorbed it should immediately break down to the active drug after achieving the desired transport, thereby enhancing drug bioavailability. So by this approach, since it is absorbed throughout, you have no bioavailability issues. Low toxic potential for prodrug is important because when we make a pro-drug it should not be that the extra part that we have added should create toxicity. And faster onset of action and dose dependent absorption is to be achieved which is not there in a drug with limited absorption. And it should be suitable for once-a-day administration. Where you have drug with fast elimination and also and poor absorption, it is very difficult to make a once-a-day formulation. So by pro-drug approach one could take this drug once-a-day, and also increase the scope of therapeutic application for such a drug.



Our first pro-drug already probably presented earlier is the pro-drug of baclofen, a muscle relaxant. This has been designed to transport baclofen into systemic circulation, with high bioavailability. In preclinical models, we have seen that it can convert rapidly once it has been absorbed, and in human plasma we see that within two hours it breaks down to the active drug. We have seen enhanced bioavailability in the preclinical models. We have seen higher levels of baclofen with the prodrug compared to direct baclofen. The PK parameters as well as AUC are indicators of the higher bioavailability. You can see that baclofen has AUC of 1.7, but equivalent dose with the prodrug, we have almost 8 times enhancement of the bioavailability and also if you see the T_{max}, that is the time for reaching the maximum concentration of the drug that is only 0.62. So you have brought down the T_{max}, hence the onset is also faster. Once you have the PK which is improved, it should reflect in the efficacy because you can now have a dose dependent pharmacological effect or efficacy. So by oral administration of SUN-09 we have seen that it gives dose dependant muscle relaxation with rapid onset of action and if you see the data here, we see that with baclofen there is essentially no dose dependant action. If you see 12 mg, 18 mg, or 32 mg, the efficacy has not -that is the percentage reduction in the performance of the mice is not enhanced ,but when you see the pro-drugs you can clearly see dose dependent enhancement of the efficacy. So the plan is, since in India, the IND is approved by DCGI, to commence Phase I trials in Q3 of 2010-11.

The second drug SUN-44 which already earlier has been discussed is a prodrug of gabapentin, which again has the similar problem of segmental absorption. So here again by making the pro-drug we can improve bioavailability of the drug. SUN- 44 which is a pro-drug of gabapentin is rapidly absorbed in experimental animals releasing gabapentin, and as we can see from the data, at equivalent doses you have a dose dependent incremental absorption of gabapentin, much higher than the parent drug itself from the pro-drug. Also the T_{max} is achieved in a shorter interval. So once again here also the improvement in the PK characteristic should reflect in the efficacy models. From the animal model of epilepsy, it shows much better efficacy (than gabapentin).. If you see the percentage of incidence of chronic extensor and the protection from mortality in the convulsion model, we see that it is much better in case of SUN-44 than in gabapentin, and you have dose dependency. So the current status is, preclinical safety studies have been completed and these do not indicate additional liabilities in terms of safety. As I said the prodrug itself should not be toxic, and that has been proven in the safety studies. For SUN- 44, there is a competitive product to this by XenoPort and FDA has not yet given approval to this because of some sort of toxicity which they have seen in the pancreas. We understand this is because of prodrug that they have used which has a potential for toxicity. In our case, we don't see this concern. So the developmental plan is to file IND in India and to commence and complete phase I trial in 2010-11 for this drug. Thank you very much.

Management: Thank you very much Dr. Rao. This ends the presentation and now we will begin the interactive session. We will first take questions from participants here in the room and then we will go over to participants in the audio call, and then the web cast. We can take questions now.

Participant: Good evening sir. I just want to clarify on your pro-drug of gabapentin. You just mentioned about Xenoport's product, I believe there are two developments which I would like your views on how your product compares a) is that there is a breach of patents on the composition matter on the XenoPort prodrug and b) is that FDA set back that you just mentioned. So in the light of these two, what is the prospect of your compound?

T. Rajamannar: With the XenoPort compound, in terms of toxicity they had seen in the carcinogenicity study, that is acinar cell carcinoma that means there is a problem with the pancreatic cells. The understanding of XenoPort is that it was also there in case of gabapentin and maybe it could be expected in case of XenoPort compound, but there was a dose dependent increase of incidences with



the XenoPort compound. The understanding that we have is that the structure contains about more than 10% of reactive acetaldehyde moiety. When you say any substance or any entity which has to become a drug then it should not generate various reactive moiety, it should be excreted without much of a problem without inducing or inhibiting enzyme and in this case the reactive moiety it produces can form adducts with various enzymes, various proteins and it can cause lot of damage to the liver, various organs. We are not sure that is one of the reasons that exaggerates this toxicity but we presume our product doesn't contain such kind of moiety and the fragment which gets removed would have very high water solubility, and highly hydrophilic which would excrete out without much of a problem.

Dilip Shanghvi: We applied for the patent, we yet still don't have a granted patent, since our compound is significantly different from XenoPort compound and we don't expect some of the limitations of XenoPort product in our product. We hope to be able to obtain the composition of matter patent for the product.

Participant: Can you give us some insights on your oncology products on paclitaxel and docetaxel what is the sample size, patient sample size required to get the product in the US market and is there a possibility of getting fast track approvals on this and you have compared it only to Abraxane and any comparisons required compare it to Doxil.

Management: PICN we have completed phase one study in India that is Paclitaxel nanodispersion and the Phase I study is designed in such a way that we have a combined Phase I with Phase II kind of study. So we are seeing both safety and efficacy. And as you know Abraxane is approved for breast cancer and we have two paths to go forward. We can go with breast cancer as an indication to get approved in that case to compare our product with Abraxane. And there is a possibility which is what now we are working on is to develop this product for other cancer indication, and in that case we do not have to compare ourselves with Abraxane. And the question which you asked is whether fast track is possible. There is a possibility that we may get a fast track approval because the kind of data what we have seen in Phase-I, Phase-II type of study is usually not seen in other type of products even with Abraxane. There are two things which I would like to highlight here is most of the anti cancer drugs have neurotoxicities means neuropathy and neutropenia. In 28 patients which were dosed with PICN we have not seen neuropathy in any of the patients. So this is something unheard of and this is something surprising as a result. Second is neutropenia-- we have seen almost in 40% of the cases. In Abraxane it is reported in 80% so we what we are seeing is a better safety, efficacy and kind of a profile where efficacy is almost in 33% of the patients compared to Abraxane which is in the range of 20 % ,and safety profile which is much better. So on this ground there is a possibility we may get a fast-track approval.

Management: Sample size of patients.

Management: The sample size of patients will depend on two things, one is if we are comparing it in breast cancer indication then it could range between about 600 to 700 patients, and for other indication when it is non-comparative then the sample size would be between 300 to 400 patients.

Participant Specifically on the DPI side similar question in terms of the sample size for getting a product launched in US, and EU markets and the roll out plan, if you could give some more highlights for India and emerging markets.

Dilip Shanghvi: I think for DPI we would be significantly away from US, and specifically US approval. If you see Skye Pharma for Flutiform has been working since last almost six- seven years for getting



approval and they still have not received approval. Our product from our point of view, is significantly superior because it achieves steroid sparing affect at half the dose of steroid. Secondly which you may be aware with that all long-acting beta agonists like salmeterol-formeterol have a black box warning about potential side effects, and our product also reduces the dose of salmeterol administered to the patient. Studies that we have done is not powered to highlight the benefit that is feasible because of our dosage form to the patient. In addition to the therapeutic benefit that product has, the convenience to patient and large number of other patient friendly features that it has. We have done focus group of patient and caregiver acceptance in US as well as in Europe and our device has been found to be consistently superior compared to all other devices in market. So we have a three-stage product development strategy for this. The first phase we will focus on emerging markets because there is a significant market in these markets, and the next stage we will try and get approval in Europe as well in other regulated markets. And the final market would be the US. If you see all product development other than DPI, our approach is that how we have short term, medium term, and long term projects and long term success so there is a success of earlier products we will fund the development of subsequent products.

Participant: You had around 113 patients so far **(Inaudible)**

Dilip Shanghvi : I think it will be in thousands. If we want to do a superiority study it will be bigger, if you want to be non-superiority study you still have to be in thousands, longer duration, larger number of patients.

Participant: First is on the number of scientists it was about 150 when the companies demerged what is the number now and how could we break up in terms of NCE, NDDS?.

Dilip Shanghvi: I think number of scientist would be around 175 at this time. We don't have a break up NCE, NDDS and pharmacology area right now but that we could share.

Participant: Do you intend to go for in terms of licensing deals or PE deals or something like that?

Dilip Shanghvi: Yes we could look at licensing some of these products in markets like Japan also hopefully once we get some of the generics using the solid oral technology that we have filed in the US once they approved they will also generate royalty for SPARC so that should also take care of some operating cost.

Participant: Sir do you think the pipeline movement both NCE and NDDS is slower than your expectation or overall economic slow down has some role to play per se, whole chemistry based industry is moving slow?

Dilip Shanghvi: Let me be transparent. I think we are learning while we are doing many things for the first time. Some of the things if we had to re-do, we would do them differently. If the question is whether this is the best which was possible in the last three years in all of this, the answer is no. We could have done better and faster but as we learned I think we will use that learning to improve our speed. At the same point of time part of it is also lack of familiarity because when you are working on product development with relatively short development times, if you let us say you go to FDA and FDA is asking you for a three months tox study that means your project is automatically delayed by six months. So some of the things take time and there is no other alternative to it and FDA has a dynamic and evolving standard. FDA also keeps on changing as it learns more. So even with the best companies they need to do these studies if they really want. (inaudible)



Participant: Final question. Do you think you would be getting into biologicals some time soon or we do not see Sun talking about biologicals especially since we have seen most of the other industry players either go into biogeneric or biologicals.

Dilip Shanghvi: I am making investments(Inaudible) there is currently no such plan

Participant: Presentation spoke about launches of a few products in India in your NDDS pipeline what is the kind of market size you are looking at in India, and you also spoke about launching in to the semi-regulated markets?

Dilip Shanghvi: I think in India for most of the products we will launch you should be able to get meaningful market share because these are clearly products with benefit and we have in each of these therapy areas good relationship with customers. So we should be able to highlight the benefit and get a meaningful market share for each of the product that we will launch.

Participant: This market is similar like what have been for your other products or is there a difference?

Dilip Shanghvi: The market is just like other products, only thing is effort involved highlighting benefits promotion also resources put for ensuring publication of whatever is done clinically, that you will see is in addition to what we do for our routine products.

Participant: I am asking for a little more details on Sun 1334H. For each study we have done, quite a large studies in US and India, have you published any of your result in peer reviewed journals, or are there any more details available and what is the immediate plan about the Phase III ?

Management: The Phase II studies are conducted to check the safety as well as proof of concept but we found that based on the study that product have shown efficacy more than one dose. So our understanding is that we if we want to do Phase III clinical trial which we need to do certain studies before we can venture into Phase III actually on large size population which is required for antihistamines. One is the cardiac safety which FDA would insist that it should be safe in cardiac respect if we want to continue and there are also parallel studies which we have initiated long time ago for carcinogenicity studies which we have long ago initiated. Our current understanding is that to take the product ahead much faster than the oral route, would be the ophthalmic route, and which is also have significant advantage in respective of product. And not all the antihistamines could qualify for that. We see that efficacy that comparable to the data of the standard products that are available; it has significant advantages for that particular product in terms of aspects. So we are initiating with the Phase I clinical trial to start this for safety and then we would continue with that to take the product much faster which in that case the drug absorption should be minimum where the FDA should not have a concern in terms of other safety aspects..

Participant: Would you be publishing in peer reviewed journals for Phase II studies?

Management: We have already published some of the preclinical information. It would be coming up at an appropriate time once we have more information.

Participant: Sir can you let me know of soft steroid which I understand is probably the most dream project out here, could you just guide us a little bit more on the Phase II studies planned ahead, and what kind of timelines we are looking at before getting at clear proof of concept out there?



Management: We have completed preclinical studies and applied for IND which we got permission from DCGI. We would be initiating Phase I clinical trial.

Participant: What are the plans in the US? Have you planned any timelines out there?

Management: Yes we will be doing the discussions with the FDA to file INDs and which would be starting very soon.

I think the idea is to develop an understanding of whether in humans the soft steroid is actually soft or no, because whatever data and understanding we have if we validate that in the human study then this is a great product, so as soon as we finish the Phase I human study in nasal aero-inhalation product we will then determine the speed with which we need to do international development of this product.

Participant: One final question on the cash burn and what cash did you start with and in three years how much have you burnt and what is the outlook going forward?

Dilip Shanghvi: We will have as I see money available to operate for this year. If we are successful in getting licensing revenue and royalty from Sun Pharma for any launched product, then we may be able to introduce some product into market and may not need to raise money. If that gets delayed, then may be end of this financial year we may have to raise money.

Participant: Sir just for my understanding that this new drug delivery system in asthma that you are going to launch. If and when that is launched how much revenue would go to Sun Pharma Advanced Research? Is it on the top line is it a milestone payment?

Management: No, I still did not understand the question.

Participant: Like you spoke about new asthma product that you are coming out with at the end like a new delivery system. Now once this product is launched in the market who will be distributing it and what sort of the revenue sharing will you have for that product, you know top line payment?

Dilip Shanghvi: There is a licensing fee and then there is royalty on sales. The product is currently licensed to Sun Pharma for India alone. As clinical development continues and Sun Pharma pays for the part of the clinical development, Sun Pharma has an option to license for other markets but all of these are semi regulated markets. For regulated markets Sun Pharma does not have a right for first refusal for any SPARC technology.

Participant: On Baclofen GRS how has been the India experience in switching the prescription from Baclofen to Baclofen GRS. I am assuming that is the only once a day product in the market.

Dilip Shanghvi: We have I think around 25% market share but what it has done, is that it has also helped our immediate release Baclofen in market so let's see when we launched the product then we and Novartis had more or less 50-50% market share. With introduction of long acting Baclofen we now have almost like 75 to 80% market share. What we also see is that growth of our long acting Baclofen GRS is significantly higher than that of IR product.

Participant: Just persisting on this point. If the switch is only 25% I mean how long has the product been in the market and it is to say that the doctors are not interested with this product and so 75% of market is still jittery they don't see the clinical benefit for the patient.



Dilip Shanghvi: No the GRS product has significant premium to the immediate released product and pricing in India is always an important consideration. So that is inhibiting the rapid uptake but our marketing people are confident that it may be end of 2 or 3 years in this market it will end up being more or less 40% of the market.

Participant: And just one question on the DPI, the innovative product is still patented and more important to it are you looking at any partnerships with the innovator especially for the DPI or prodrug where innovator may still have a lot of interest in the market.

Dilip Shanghvi: We could look at partnerships once we have clarity--once we launch that product in India.

Participant: And this one is final question is on NCE. Like for NDDS, India launch would happen before launch in regulated markets. Its not very obvious if your NCE pipeline too would go the same way, if India launch would happen a lot sooner and regulated markets a lot later? Is there something stopping us from doing that? It almost looks like that we are going to do Phase I, Phase II, Phase III in US Europe simultaneously.

Dilip Shanghvi: I think the idea is to develop NCE, at least in one of the regulated market along with semi-regulated market. We do not want to simply launch a product based on studies done in the semi-regulated market because clearly there would be large number of things that we need to find out about the drug which is not in the market. For NDDS which are products already in market for a long time, the potential risk of any kind of side effect which is not seen in smaller trial becoming a major issue is very limited. Thank you.

Participant: How much roughly time you would take for 1334 H to complete cardiac and renal safety studies as well as the long term tox on that compound?

Management: There are two things. One is cardiac safety study. So currently we are doing a pilot study that is ongoing. This pilot will help us in designing a pivotal study somewhere another year or so. By the time we have pivotal studies in place. Renal studies also take some time. So both studies put together anywhere between 12 to 18 months is what we are targeting.

Participant: Long term tox?

Management: Long term tox is going on parallel means already the studies are initiated and I would say they are somewhere in the middle of the studies.

Participant: By 12 to 18 months when you finish the renal and cardiac test, should that also get over or...

Management: Almost, at the same time, the chronic tox also get over by that time.

Participant: That should set the stage for Phase III , I guess once if everything goes well.

Management: That is right.

Participant: And in terms of ...



Management: And this is what I told you about is oral product on 1334H, but there is another product that is ophthalmic that is eye-drop product, and what we believe the ophthalmic track would be quite fast for us to come to the market, and all the preclinical work is almost completed means we will have carcinogenicity studies in place when we file ANDA for ophthalmic products, and there are various ways to do it faster means now there is a way without going into really patient studies we can do ophthalmic programs in next two-three years. It is complete from phase one to phase three.

Participant: That is interesting. So potentially you are saying that it could reach market faster than the oral 1334H.

Management: That is correct because we do not need to do QT prolongation or cardiac safety type of studies in ophthalmic.

Participant: And have- we I do not know whether you can share- have we looked at licensing 1334H oral by now and considering the need for funds at the end of this year as you just explained a little while ago, are we sort of looking at a greater need to monetize any of the assets now?

Dilip Shanghvi: No, I think the basic approach that is better to license products closer to market is a approach that remains constant. Even the cardiac safety study is with a view to establish that the product has lower risk of failure in Phase III study so the ability to license the product at a higher revenue is much better if we take out uncertainty of potential registrability. Rather than licensing early then there are uncertainties and then settle for a much smaller value, it is better to license when the uncertainties are removed.

Participant: That brings me to the risk part of it and I think the first slide captured it -- the measured risk-- so in the generic your company obviously has pretty solid track record in terms of sizing the risk. In this part of the business which is at the highest end of the risk how do you like and one compound where you have swapped the compound into soft steroid space. Obviously there is a decision that has gone on chucking the one versus the other, so if you can throw some light as to how you look at the risk in this riskiest business.

Dilip Shanghvi: I am still not clear as to what you are asking.

Participant: Yes, in terms of how do you manage overall risk of SPARC across various programs that you are running, each individual program will have a different risk profile. At aggregation level there is a risk of aggregation of a different size and scale. So how do you manage the risk and when do you decide to pull the trigger and kill a compound and move to the next one. Obviously we do not know many of them which are not there on the list.

Management: I think we look at risk in two broad parameters. One is the level of risk and the second is the duration of cash flow. Because one is you can have a low risk, high risk, and medium risk project with potential for failures or yes or no go. The second is risk related to when it can come to market. So when you have a potential cash flow. So the approach is that we have to have low risk, short term cash flow project as much as possible so that we are able to use that cash flow for funding medium and long term, and medium and high risk projects going forward without or with least amount of dilution. So if you broadly look at all the technologies that we are working on, the proof of concept that whether it is working or not working and whether we are achieving the objective with which we setup to start the project is feasible for us to detect at a relatively early development stage. If you see the ophthalmic product, or if you see the anti-cancer product and nanoparticle systems, conceptual proof of concept,



like whether you have higher concentration of drug in the tumor or not, whether you have higher toxicity compared to standard product or not, are very easy to find earlier. You do not have to wait for years. If there is any clinical development time which is a function both of our own experience and also availability of patients, so like these 36 patient study which is both a toxicity study or maximum tolerated growth study, also an efficacy study. So because we merged both the studies together it took us almost 1 and ½ years to get 36 patients. If we are only focused on toxicity may be we could have done in 6 months because there we can dose to all the cancer patients. So I think as we keep on learning we will keep on using our deal experience to improve the speed by which we can develop the product.

Participant: Last thing on when we demerged the company we talked about \$50 to \$60 million of R&D expenditure over the roughly three years. We have finished that and I think we have spent roughly half, about 140-150 odd crores in terms of operating expenditure if you total up. Did we over budget or have we spent less? How would you sort of reflect on that?

Dilip Shanghvi: I think our original planning included the Phase III study for 1334 H, we decided to do that after we complete the cardiac toxicity study, so that has saved some money, so as we finish this then money will get spent.

Participant: Any color or next two-three years, how should we look at in terms of spending three years or two years?

Dilip Shanghvi: No, I think we should be able to start getting the cash flow from products much faster because regulatory timeline for registering some of the delivery system product in semi-regulated market is much shorter. If we look at Abraxane in India, then Abraxane in India is expected to be a 100-crore product by next year. And if we are able to get the kind of significant benefit that we have over Abraxane in larger clinical trial, then the potential for PICN in semi-regulated market itself is very large, even before we can get approval in US or in Europe.

Participant: Thanks.

Participant: Yes, can you talk a little bit about your Baclofen ER and plans for monetizing this product because this product is in Phase III so when do you expect the Phase III to be over and **what is the time to market?**

Management: The Phase III in USA we have just initiated. It will get over in next 18 months that is the current plan, and along with the Phase III we also need to do a safety study so both put together it is somewhere between 18 to 24 months by the time we file the NDA in the US.

Participant: Okay likewise on latanoprost this is another product which is in Phase III or which is (inaudible)

Management: That is a latanoprost eye drop ophthalmic without BAK that is Benzalkonium Chloride so that study, Phase III study has also begun in US, and it is a short duration study. So it should get over from start to finish in the next one year, followed by that again we need to do a safety study in 100 patients that will take another 6 months so it is total 18 months from today.

Participant: So is there any possibility of **(Inaudible)** that you have?



Dilip Shanghvi: Well we have specifically discussed we see a lot of interest in our differentiated product but we have not carried any specific discussion for licensing. Also I think since neurology as an area is not a very large specialty it is also possible that we may decide to market the product through Sun in the US if may be we can acquire the business or we can set up our own field force because this to me is a very interesting and potentially very large product.

Participant: And can you also talk about the pricing of product in India you said significant premium can you indicate in terms of how do you decide the pricing?

Dilip Shanghvi: I do not remember exactly the pricing but I think it is around 50% premium to equivalent oral product.

Participant: And lastly on the R&D expenditure front clearly the company is now at a position where it has a lots of products in Phase III, which is a significant expenditure, the other is what the revenue we talked about. In fact you know if you look at the model why do you think it is not possible for the company to out licence the some of the other products which we have in Phase I, to enable it to do more aggressive kind of development of later stage products? So how do you decide the R&D expenditure and ability to ramp up the R&D expenditure (inaudible)

Dilip Shanghvi: What I sense in your question is that you are thinking that whether we are not spending money because we do not have money and if we have money then we can do product development faster. That is what I sense in the question. But that is not the reality. Whatever is required to develop the product is not delayed because we will not have the money or we cannot arrange for money. So licensing it for generating cash is not a decision that we help the drug get developed

Management: Dilipbhai said philosophically we would like to license the compounds at the late stage of development so that has been the basic philosophy behind licensing.

Participant: This is regarding IP situation on this products. Have you had any difficulty getting back in the India the law given that there are certain issues with CD, etc. Has your product run up against any sort of issue of issues under the new amendments to the 2005 patent law.(inaudible)

Dilip Shanghvi: Honestly I do not know so I will possibly find out and tell you but my understanding is that the products and technology are differentiated and innovative enough in terms of benefits that they provide that even under treaty they will get patent protection.

Participant: You mean certain patents have already been awarded.?

Dilip Shanghvi: I am not aware of it, so we not seeing any difficulty in getting patents.

Participant: And specifically through with baclofen again you talked about 25% share for NDDS, what is the overall market right now and do you have plans to take this product to other emerging markets, could you name some of them within the next 18 months or so if you are having any?

Dilip Shanghvi: The size of baclofen I think in India is around 30 or 35 crores annually or may be slightly higher and I think it is must be higher because we will do around 2 crores. So may be around 44 and this is also an interesting opportunity that we are currently working on, is that baclofen is used empirically for treating alcohol addiction. So doctors are finding that once a day baclofen is very



successful in reducing alcohol consumption in patients and that is also something that we wish to along of it the baclofen for spasticity, also do that in the US is to see baclofen for alcoholism.

Participant: Is it being used already in India?

Dilip Shanghvi: It is empirically used already yes.

Participant: So it is like on basis.

Dilip Shanghvi: I think Dr. Dharmadhikari met some of the doctors so may be he can tell you.

Nitin Dharmadhikari: I think they are finding it as an interesting product of treating of alcoholism and particularly where the alcoholism is higher, so it is being used may be as an off label today. They find being once a day product it is more appealing to them giving 3 tablets or 4 tablets to an alcoholic you can imagine the difference. The difficulty is giving 3 or 4 tablets per day so having an OD product itself is an advantage in that case.

Participant: On the GRID and Wrap Matrix side, how many ANDAs have you filed using both the technology if you can just give some insight and whether any of these have been approved or on verge of approval and secondly on gabapentin essentially what is related from XenoPort side, because they have slashed team size by 50% and things like that so what is your clinical development plan post this.?

Dilip Shanghvi: I think Dr. Nitin you can say about ANDA products.

Nitin Dharmadhikari: We have filed a few ANDAs with Wrap Matrix and they are under review so it depends on FDA that carries the next stage of the review. A tablet product and innovator is a capsule and then we have tablet, and of course the generics gets an approval earlier then the generics which are expected almost one year later on the capsules so we may get some advantage because there is already an Osmotica product which is there and which is also a tablet (inaudible) are good opportunities, and then the advantage we got for Wrap Matrix is that we were not sued by Wyeth because we what they believed is that this is not infringing any of their patent and most of the other generic companies they have sued, including Osmotica, so basically the value which Wrap Matrix added to Venlafaxine was avoiding the patent litigation because there was no litigation on this product.

Participant: Actually just wanted to get an insight as to are there other products which are in similar opportunity in terms of market value size?

Nitin Dharmadhikari: I am not clear about your question.

Participant: What is the value of other products? Like Venlafaxine, are there other products which are similar in market opportunity from Sun's perspective?

Nitin Dharmadhikari: We see some but of course difficult to tell specifically about them because the ability of Wrap Matrix to meet the different kind of release profiles in vitro and in vivo in making a product although we believe that Wrap Matrix is very good for the ANDAs basically, but when it has its own flexibility which can meet the pharmacokinetic profile of the existing product. So it is a flexibility which is working well and then mimicking the product is easier for us and we have a system which has a lot of flexibility. So the different products when you look at, and then different requirements when you look at like pharmacokinetic requirements when we look at, it is useful to make different kind of products.



Participant: Thank you. Could you give an insight on gabapentin product?

Management: As mentioned already from all the preclinical data what we have, and in terms of biology what we have seen under modules are superior compared to our country which we do not make (inaudible) as a protocol we believe in whatever **(inaudible)** should not have any unwarranted toxic side effects. Into the safe manner study the product and **(Inaudible)** we need to do a lot of preclinical studies before we can start making.

Management: We can then take questions from people who are connected on the audio call.

Moderator: Sure. Ladies and gentlemen, we will now begin the question and answer session for participants connected with the audio conference call. To ask a question, please enter * followed by 1 on your touchtone telephone. Participants connected to the audio conference call may please enter * followed by 1 at this time. There are no questions from participants from the audio bridge.

Uday Baldota: Okay, we will take there are some from the web cast so I will just read out the questions and then you can take through. First question is which of the products do you anticipate to launch in the regulated markets in the next year or FY12?

Management: Nothing in regulated markets. There will be no product which we will launch next year in regulated market.

Uday Baldota: For FY12?

Management: The earliest I can think is FY 2013.

Uday Baldota: Where do you see SPARC 3 years from now in terms of top-line, which geography is SPARC concentrating in terms of revenue?

Dilip Shanghvi: No, I think once we get approval on important products in U.S., then clearly U.S. will be the largest market for SPARC.

Uday Baldota: I think this might have been answered partly, but I still read out. For how many of the NCE we already have patent and status on others if it is underway?

Dilip Shanghvi: I think we will need to give a detail response for which we are currently not ready so may be we can send it later.

Uday Baldota: Sure. What is the worldwide market for baclofen currently? What is the current sale from Baclofen GRS in India?

Dilip Shanghvi: I think we had some information about the number of patient dosed per year.

Kirti Ganorkar: We have some information. Right now, I do not remember, but baclofen being the generic product. In terms of all products which are used for spasticity, baclofen is a number one product except in Japan including U.S., Europe, and emerging market. So this is the product which is used in almost more than 50% of spasticity patients, but the exact numbers I do not know at the moment.

Uday Baldota: What is the current sale from Baclofen GRS in India?



Dilip Shanghvi: I think we do around Rs. 70 lakhs per month.

Uday Baldota: Okay. How does the bioavailability of pro-drug of gabapentin compared to that of Lyrica?

Dilip Shanghvi: You don't do comparison with Lyrica- Dr Rajmanner can answer.

Dr. Rajmanner: Lyrica and gabapentin are two different drugs and we did not compare gabapentin with respect to Lyrica.

Uday Baldota: Okay I think that has also been answered, I will still read out. What is the strategy on partnering for the U.S., any of the products being developed for the U.S. or for any of the products being developed, the strategy I think we have discussed licensing.

What is the side effect profile sedation of 1334H oral compared with that of levocetirizine?

Kirti Ganorkar: So far, we have not done a comparative study, but some studies we did in phase I comparing the sedation profile in a pharmacodynamic model where we are not seen a sedation with 1334H compared to not levocetirizine, but compared to other molecules like desloratadine, fexofenadine, and cetirizine.

Uday Baldota: Which are the other competing products in the ophthalmic segment? this is the continuation of the 1334H.

Kirti Ganorkar: 1334H, the biggest product is olopatadine. I am talking of US markets specifically is Patanol and Pataday is the number one product for allergic conjunctivitis and then there are number of other products like epinastine, then ketorolac, but the major competition is from olopatadine.

Uday Baldota: Could you highlight reasons why Sun 09 and Sun 44 have not been able to progress to Phase I in last 3 years, are you still optimistic on these products?

Dr Rajmanner: We are extremely sad for implication of Sun 09 we are expecting that some of the studies what we are conducting in various safety as well preclinical talks we will be able to translate and then file for IND. We could do reasonably fast because for any product which we want to do Phase-1 clinical trials we also need to produce a product under GMP condition and we need to formulate the product and do the stability so that when we have a stable formulated product it can be dosage using the trial. So we did anticipate some of the things which took sometime but making of the product under GMP conditions as well as the formulation and regulatory approach took more time than we expected, which we got currently approval to do, for the Phase-1 clinical trial.

Uday Baldota: Sun 44?

Management: Sun 44 is under trial and probably in the next year we will be getting.

Uday Baldota: So we are still optimistic on these products, that is the response.

Management: Yes

Uday Baldota: How do you see Depomed's Gabapentin ER impacting your gabapentin pro-drug program?



Dilip Shanghvi: I would expect Gabapentin to be a big challenge to formulate as a GRS system in terms of larger dose. My sense is that a well designed gabapentin prodrug will be a much better much more consistent bioavailability for patients.

Dr Rajamannar: I am not familiar with Depomed's formulation technology. When I see gabapentin profile in terms of level of absorption and (inaudible) formulation one can have orally but in terms of achieving higher level, I am not sure it would have a success to have such a formulation to the higher dose of gabapentin. We have pro-drug kind of molecule which can avoid the use of a specific transporter can have bioavailability a level of (inaudible) gabapentin....

Uday Baldota: Thank you and last question, details on plans to raise money by end of the year?

Dilip Shanghvi: Hopefully we will not have to raise money. Even if we will raise the money, money will be raised through a rights issue.

Uday Baldota: Thank you very much for joining us today in the presentation cum interactive session. If you any further queries, please do send it to us. I now invite all of you to join for the high tea. Thank you very much.

*PEFR: The peak expiratory flow rate measures how fast a person can breathe out (exhale) air. It is one of many tests that measures how well the lungs are working.

**FEV1: The volume of air that can be forced out taking a deep breath, an important measure of pulmonary function. The forced expiratory volume in the first second is the FEV1

***DLT: The dose of a drug that produces side effects severe enough to prevent larger doses being given