

# Phynova Group Plc

June 2007

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## Key points

- A drug discovery engine
- Plant-derived medicines (Botanical Drugs) now embraced by FDA
- Efficacy and safety concerns reduced through historic use in China
- Current valuation reflects lack of understanding in new approach: shares can double as awareness grows

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**Index:** AIM

**Sector:** Healthcare

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# Phynova Group Plc



## Phynova Group Plc

PYN.L

Date:	14.6.07
Share price p	56
52 week High/Low p	95/41
Issued share cap m	20
Market cap £m	11

[www.phynova.com](http://www.phynova.com)

Company Description: Phynova Group Plc (PYN) is a UK-based, semi-virtual pharmaceutical development company focused on the discovery and development of plant-derived prescription drugs for the treatment of viral and bacterial infections, metabolic diseases and cancer.

## MEDICAL CROSS-FERTILISATION

Over many centuries the Chinese and Western medicines have influenced and enriched each other. Phynova is taking advantage of this cross-fertilisation to develop, according to Western standards, a combination of **existing** and marketed plant-derived prescription drugs and novel phytochemicals, addressing therapeutic areas where current treatment modalities are either *limited* (symptoms associated with chronic hepatitis C) or *not available* (Dengue Fever and post-operative ileus).

The novel principles introduced by the FDA's '**Botanical Drug Guidance**', specifically states that botanical and non-botanical drugs are on the **same level** in respect of clinical safety and efficacy requirements, and are in actual fact a third drug discovery paradigm running side-by-side with synthetic pharmaceuticals and biologics. Section VII of the FDA guideline specifically addresses 'marketed botanical product with no known safety issues' and allows for the development of known plant-derived drugs at a much more rapid pace.

Phynova is tapping into an under-exploited and vast 'natural reservoir of compounds' that, coupled with 'centuries' of applied knowledge, can provide tomorrow's treatment modalities at a faster pace, better risk and cost profile: thus giving considerable investment up-side.

We do not envisage Phynova to become profitable until FY2009 when we are assuming the first revenues stream will be generated from initial up-front payments for two key products and generating a positive EPS. The value of the Company lies in its long term potential development of drugs that operate in markets of vast financial size and, more importantly, that can alleviate suffering for millions of people. As discussed later in the report, the current status of the portfolio development makes an exact valuation implausible, but we see reasons for Phynova to trade at almost **double the current share price** as awareness of its potential grows. We also note the many recent examples of smaller companies developing a successful drug and seeing value accorded in a high premium take-over by 'big pharma'. Success in the future for Phynova with drugs that can combat diseases of the scale currently being targeted would lead to value being measured in the *hundreds* of millions, not the *tens* of millions.

Phynova is quoted on AIM and investors should be aware that share traded on AIM are subject to lighter due diligence than shares quoted on the main market and are therefore more likely to carry a higher degree of risk than main market companies.

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## CORPORATE OVERVIEW

Phynova Group Plc (Phynova) is a semi-virtual pharmaceutical organisation, founded in July 2002, focused on the discovery and development of plant-derived prescription drugs for the treatment of **viral** diseases (chronic hepatitis C and its symptoms and Dengue fever), **bacterial infections** (MRSA and acne), **metabolic diseases** (fatty liver) **and cancer** (breast, bowel, lung).

The Company was admitted to AIM in February 2006, raising £3.65m from mostly private investors in a round of financing that was followed, six months later, by an additional placing of 3.39m of new ordinary shares at 75p, raising about £2.5m for the establishment, among other things, of Phynova China Ltd., a wholly owned subsidiary based in Hong Kong.

In November 2006, Phynova announced the completed acquisition (approved by the Chinese Authorities) of an initial 45% stake in Botanic Century (Beijing) Co. Ltd. (Botanic Century), an early stage pharmaceutical research and development company, with an option to increase its holdings to 51%. This acquisition provides the Company with R&D facilities, access to scientists at a much lower cost than the West and three novel therapeutic compounds.

**Figure 1: Organisational structure**



*Company Data*

Phynova has a low cost structure with most of the operational aspects of the business being outsourced allowing the Company to operate optimally at a low expense rate. The Company intends to grow organically through in house drug discovery, via acquisitions and by in-licensing agreements.

The pipeline includes six drug candidates at **different stages of development** (from pre-clinical to Phase IIa) and consists of a combination of existing therapeutic compounds, derived from **botanical medicines** that have a proven track record of effectiveness and safety in clinical settings in China. As yet none of them has gone through the Western regulatory approval process. Also in the pipeline are novel phytochemical compounds. These products have been acquired or in-licensed through joint ventures or collaboration agreements with Chinese scientific organisations. Phynova intends to develop its own intellectual property at each stage of the development process and has filed multiple patent applications to protect discoveries made so far.

The combination of Chinese experience-based knowledge with Western evidence-based clinical studies should reduce the risks associated with the drug development process in terms of **failure rates, time to market and costs**. However, there are still a number of challenges related to the translation of

*Raised in total £6.2 since introduction to AIM*

*Concentrating efforts on 6 drug candidates*

*A combination of existing and novel therapeutic compounds*

clinical observations into Western research methodology given the fact that Chinese and Western medicine employ different conceptual models and empirical methods to identify, understand, and treat various groups of symptoms or disorders.

Phynova is managed by a **very experienced small entrepreneurial team** that has established long-standing relationships with scientific, policy-making and commercial Chinese institutions. These relationships have allowed them to enter into a number of collaborations with highly regarded research organisations providing access to leading intellectual and physical resources. The scientific team comprises a highly experienced Western research and development team in the **UK** based in Oxford and **researchers from China**, educated in China and in the West, with multidisciplinary and complementary scientific expertise, including in-depth understanding of pharmacognosy, medicinal chemistry, preclinical science and clinical trials and with a wealth of experience in drug development both in China and in the West.

In May 2007, the Company was nominated for the prestigious award 'UK Innovation in Drug Discovery and Development', Category 1 in 'UK Bioentrepreneur of the Year Awards 2007'. The awards are sponsored by UK Technology and Investment, a joint initiative of the UK's Department of Trade & Industry and the Foreign & Commonwealth Office. The awards ceremony will take place on July 4, 2007.

Until now, the movement toward the integration of Chinese and Western medicines has been faster in China than in the West. A crucial event in the shift toward increasing Western acceptance of Chinese medicine occurred in the US when the NIH (National Institutes of Health) published consensus guidelines on the appropriate uses of acupuncture in late 1998. More recently, in June 2004, the FDA (U.S. Food and Drug Administration) established a '**Botanical Drug Team**' and revised the regulatory framework governing the development and use of botanical drugs as outlined in the '**Guidance for Industry, Botanical Drug Products**' which finalises the draft guidance issued in August 2000.

This regulatory framework allows for the development of known plant-derived drugs at a much more rapid pace than synthetic NCEs (New Chemical Entities) or biologics. In addition several of Phynova's drug candidates have the potential to be accorded a "**fast-track**" approval process, reducing the overall time to market and development cost. Furthermore, the new framework provides for unique guarantees of market exclusivity for novel botanical medicines, as well as the acceptance of the potential synergistic combinations of bioactives. The MHRA in the UK and the EMEA Of the EU are now also considering producing similar guidelines as the FDA and both have set up committees and advisory panels.

Phynova's commercial strategy is seeking to out-license its drug candidates to pharmaceutical companies, once Phase II clinical trial has been completed or earlier should the opportunity arise, in exchange for upfront fees, milestones and royalty payments. The cash flow generated will help to fund drug development and reduce the investment risk in the Company.

*De-risking drug development process*

*Established relationships in China*

*Researchers with complementary scientific expertise*

*Nominated for an industry award*

*Improved regulatory environment in the US & EU*

*Seeking to out-license*

**Table 1: Summary of product development collaborations**

Date	Collaboration with	Description
Aug-03	<b>Administrators of Oxford Natural Products Ltd. - UK (ONP)</b>	4 drug candidates acquired from ONP. Royalties in a sliding scale over a period of 3 yrs (30% in yr 1, 20% in yr 2 and 10% in yr 3), on any revenues derived from these products
Feb-05	<b>Jiangxi Huiren Group Co. Ltd. (JHGC)</b> HGC produces traditional Chinese formulations and Western pharmaceutical products	Mutual R&D, regulatory and marketing support <b>IP generated through these efforts will be owned by Phynova.</b>
Dec-05	<b>Chongqing Institute of Ecological Materia Medica Co. Ltd. (CQI)</b> Private R&D organisation	Phynova acquired <b>exclusive global licence of PYN22</b> (ex option for China) to develop and commercialise any product containing CQI-01 (anti-obesity product) 33.3% royalties will be due to CQI on net revenues
Feb-07	<b>Hong Kong Jockey Club Institute of Chinese Medicine (HKJCICM)</b> HKJCICM is a publicly funded organisation and a subsidiary of the government-owned Applied Science and Technology Research Institute and the designated R&D centre on the area of Chinese Medicine by the Innovation and Technology commission, HKSAR (Hong Kong Special Administrative Region) Government	R&D collaboration to identify and develop novel anti-cancer compounds The collaboration includes The Cancer Research Institute at Birmingham University Ownership of IP and royalties retained by Phynova

Company

**Table 2: Development Status**

Project's code	Targeted therapeutic area	Development stage	Available treatments	Origin
PYN17	Symptoms associated with chronic hepatitis C	Phase IIa in US	<b>Limited</b>	ONP
PYN18	Anti-viral HCV & Dengue fever virus	Pre-clinical	<b>No specific treatment for Dengue fever</b>	In-house development
PYN22	Metabolic diseases: non-alcoholic fatty liver disease (NAFLD)/ obesity	Advanced pre-clinical	<b>No specific treatment</b>	Chongqing Institute
PYN6	Anti-bacterial(Acne & MRSA)	Pre-clinical	<b>No specific treatment for MRSA</b>	Botanic Century
PYN7	Cancer	Pre-clinical		Co-development with HKJCICM
PYN9	Post-operative ileus	Advanced pre-clinical	<b>Limited</b>	Botanic Century

Company

**Table 3: News flow since listing**

<b>DATE</b>	<b>DESCRIPTION</b>
Jul-06	Filed two patents applications covering PYN22 (obesity) and PYN18 (HCV)
Aug-06	UK Patent Office granted key patent for PYN 17 covering HCV programme
Sep-06	Raised c.£2.5m in a second round of financing
Oct-06	Established Phynova China Ltd.
Nov-06	Completed the acquisition and received the approval from the Chinese Authorities for an initial 45% stake in Botanic Century
Jan-07	FDA approved IND for PYN17 (Chronic hepatitis C) Appointment of New Chairman
Feb-07	Signed a cancer treatment collaboration with the HKJCICM
Mar-07	Appointment of Director of Business Development
May-07	Nominated for an industry award Launched Chinese website Started US Phase IIa clinical trial for PYN17

*Company Data*

To properly understand the unique environment in which Phynova is operating we now think it very useful to provide background on the science that underpins the development of **drugs derived from plants** and on the history and successes of **Chinese Herbal Medicine**:

## PLANT-DERIVED DRUGS

*Plant-based* prescription pharmaceuticals are mainly defined as single chemical entity products whereas according to the MHRA a *botanical drug* is defined as “any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations”. Plant-derived drugs contain chemicals from several groups of naturally-occurring compounds including alkaloids, terpenoids, flavonoids, lignans and phenolics.

There is a tendency to forget that quite a large number of modern medicines have their origins in botanical sources that have been used for centuries worldwide and remain relevant to current therapeutic needs. Plants continue to make important contributions in cancer, cardiovascular and infective diseases just to mention a few. In many instances there is still no viable direct commercial synthesis routes for the manufacturing of these phytopharmaceutical agents. The primary benefits of using known plant-derived medicines are their profiles being safer and more efficacious when compared to the synthetic alternatives, they offer better therapeutic advantages and risk:benefit and the potential for more affordable treatments. It is estimated that more than 25% of prescription pharmaceuticals contain plant-derived ingredients yet only a small percentage of the plants in the world have been evaluated for potential pharmaceutical use.

**The first generation** of plant-derived drugs were usually simple botanicals employed in more or less crude form. Several effective medicines used in their natural state such as *artemisia annua*, *cinchona*, *papaver sumnifum*, *belladonna* and *aloe* were selected as therapeutics agents based on empirical evidence of their clinical application by traditional societies from different parts of the world.

**A second generation** of plant-based drugs emerged after the industrial revolution, and this time their development was based on the scientific processing of the plant extracts isolating “their active constituents.” These phytopharmaceutical agents were pure molecules and some of the compounds were even more pharmacologically active than their synthetic counterparts. Notable examples were digoxin from foxgloves, quinine from *cinchona*, reserpine from *Rauwolfia*, and more recently Taxol from *taxus species*. Moreover, it is worth remembering that these compounds differed from the synthetic therapeutic agents only in their origin.

In the **third generation** a top-bottom approach was introduced, consisting of an initial clinical evaluation of the treatment modalities and therapy, as administered by doctors or as used by the community as folk medicine followed by the development of the phytopharmaceutical agent as per the standard development modality of pre-clinical and clinical studies for which in certain cases, as mentioned earlier, a shorter route to market has been introduced by regulators in the US.

It is not known exactly how many plants are used medically. It is estimated that in **Western medicine** only around 190 plant species are in use, 50 of which are considered to be in major use out of the about 250,000 plant species existing on earth and moreover only between 5 to 15% have ever been investigated pharmacologically or chemically. We think that the Chinese Herbal Medicine (CHM) uses several thousands plant extracts and the U.S. NCI (National Cancer Institute) has identified 3,000 plants that are active against cancer cells. These

*Plants constitute the origin of a large number of modern medicines*

*Three generations of plant-based drugs*

*A massive potential wealth of biological and chemical diversity remains unexplored*

figures demonstrate the **potential wealth** of biological and chemical diversity that remains **unexplored**.

**The synergistic interactions of key components found in defined botanical extracts represent a largely untapped source of new pharmaceutical products with novel and multiple mechanisms of action, highlighting Phynova's multivalent approach and potential advantage** Recent developments in plant biotechnology have created the tools to produce botanical mixtures at a level comparable to that of pure drug compounds, thus meeting the requirements of the FDA guidelines for botanical drugs.

Currently there are about 121 prescription drugs sold worldwide that contain active ingredients derived from plants including the antibiotic erythromycin, the immunosuppressive cyclosporin-A, the chemotherapy agents paclitaxel, vincristine sulphate and vinblastine sulphate, the anti-cholesterol drug lovastatin, not to mention the familiar aspirin and digoxin. **74% of these drugs were discovered through follow-up research to verify the authenticity of information concerning the medical uses of plants used by local populations.**

In mid-2006, there were 286 applications for botanical drug approvals filed with the FDA, of these 232 were INDs and 54 pre-INDs. There is a staggering increase in the application rates rising from 50 during the period 1990-1998 to 236 between 1996 and mid-2006. The largest number of submissions is represented by oncology and anti-infectives are the lowest.

To quantify the market size for plant-derived drugs is a difficult task as very often the data available groups together prescription and OTC botanical, single entity, herbal medicines preparations and raw materials, however various sources have estimated that the plant-derived prescription drugs market size stands at around US\$12-15bn per annum and growing at 7-9% pa. Worldwide there is a renewed interest in botanical drugs driven by the:

- increasing number of synthetic drugs being withdrawn from the market;
- decline in the number of new leads and consequently the thinning of large pharma pipelines;
- patients' belief that natural products are superior to their synthetic counterparts;
- patients' concerns over current prescription drugs and demand for safer and more effective alternatives;
- significantly improved regulatory environment;
- national concern of increasing health care cost.

Despite all the above, large pharmaceutical companies have displayed a degree of reluctance in investing in the development of new plant-derived drugs despite the vast opportunities offered by the 'chemical factories' of the plant kingdom. The primary issues are but not limited to:

- **scientific and regulatory considerations** – It seems that many large pharmaceutical companies have overlooked the novel principles introduced by **FDA's 'Botanical Drug Guidance'** especially for those botanical drugs that have a proven track record in clinical settings. In this framework, the regulatory approval process for both botanical and non-botanical drugs have been brought to the same level in respect of clinical safety and efficacy

*Synergistic interactions and novel multiple mechanism of action*

*Possible market size of US\$12-15bn growing at 7-9%*

*Growth drivers*

*Large pharma attitude*

*New regulatory guidelines in place*

requirements. However, some degree of flexibility has been introduced in terms of timing or sequence of events to take into account i.e. the therapeutic area, history of the compound and its use (please see below 3 case scenarios as per FDA files). Other key points:

- reduced time-to-market process for those drugs that have established safety and efficacy profiles in humans and the introduction of an exclusivity period;
- there is no requirement for further purification of the extracts;
- it is not essential to identify the active constituents; and
- the regulations covering GMP (Good Manufacturing Practice) and GLP (Good Laboratory Practice) (specifically chemistry) have been extended to GAP (Good Agricultural Practice) and raw material sourcing and supply.

For **botanical INDs**, the guidance outlines 3 different scenarios that would require different levels of supporting information, depending on the available marketing data and safety concerns associated with the product:

- Initial clinical trial (Phase I and II) of a marketed botanical product with no known safety issues (Sec. VII). INDs submitted under Section VII would **require the least amount** of information to show that the product is safe for testing in humans. The IND would need to have information regarding the identity of the botanical and chemical class of the active constituent or marker compound, documentation of use (both historical and current), and limited CMC information. If the product has not been previously marketed in the United States, additional use data, including data on adverse events, CMC, and non-clinical safety information may be needed.
- Initial clinical trial (Phase I and II) of a non-marketed botanical product or a marketed botanical product with known safety issues (Sec. VIII). INDs submitted under Section VIII **require more** CMC information and documentation of use than Section VII because there is some concern with safety. If the product is the same as a traditional preparation, meets official compendia or other standards, and is used in the traditional manner, previous human experience may be sufficient to support safety. If it is not from a traditional preparation, additional non-clinical safety information may be needed.
- Expanded clinical trial (Phase III) of any botanical product (Sec. IX). Section IX INDs require more information than Section VII as well. To conduct expanded clinical studies, more detailed information on CMC and pre-clinical safety data is required. Additional toxicology studies would generally be needed to support wider use, regardless of whether the product is currently marketed in the United States or elsewhere as a dietary supplement.

**Patentability concerns** - it is generally believed that natural products cannot be patented with the same degree of assurance as synthetic compounds. Undoubtedly, it is more complicated to establish 'novelty' for those drugs that have been used over a long period of time as traditional medicine but in recent years botanical and non-botanical companies have achieved successful patent applications through the refining and defining of preparations including characterisation and modifications leading to a 'novel' compound.

**Quality Control (QC), batch-to-batch consistency** – Assuring the consistent quality of the raw material remains a concern due to existence of natural variations of endogenous phytochemicals occurring in plants. The chemical "fingerprint" of a particular species can vary widely depending on the age of the

*Section VII applicable to some of Phynova's compounds*

plant, time of harvest, soil conditions, weather conditions, and other factors. Great progress has been made in plant molecular biology, extraction and separation technologies, speed and sensitivity of molecular characterisation. In particular, the advancement of analytical methodology in recent years has provided a battery of tools to be used to characterise botanical raw materials, botanical drug substances and botanical drug products to ensure the quality and batch to batch consistency. These chemical and biological methods in frequent use include UV, IR, NMR, MS, HPLC, UPLC, HPTLC, genomics and proteomics, and most recently the introduction of metabonomics.

**Raw material supply** is perceived as an issue given that some of the plant originates in countries with limited socio-political stability even though plantation programs could be established in other more stable geographical regions.

**Table 4: Some well-known plant-based drugs**

CHEMICAL NAME	CHEMICAL TYPE	PLANT SOURCE	THERAPEUTIC USE
Camptothecin	Indole alkaloid	Camptotheca acuminata	Chemotherapeutic agent
Taxol and other natural taxoids	Diterpenes	Taxus brevifolia (and others)	Chemotherapeutic agent
Vinblastine, vincristine	Bis-indole alkaloids	Catharanthus roseus	Chemotherapeutic agent
Artemisin	Sesquiterpene lactone	Artemisia annua	Anti-malarial
Quinine	Quinoline alkaloid	Cinchona spp.	Anti-malarial
Quinidine	Quinoline alkaloid	Cinchona spp.	Anti-arrhythmic
Digoxin, digitoxin	Steroidal glycosides	Digitalis purpurea (common foxglove).	Cardiotonic
Codeine, morphine	Opiate alkaloid	Papaver somniferum	Cough relieving, analgesic
Galanthamine	Isoquinoline alkaloid	Leucojum aestivum	Cholinesterase inhibitor
Pilocarpine	Imidazole alkaloid	Pilocarpus venenosum	Cholinergic
Atropine, hyoscyamine, scopolamine	Tropane alkaloids	Solanaceous spp.	Anti-cholinergic
Diosgenin, hecogenin, stigmasterol	Steroids	Dioscorea spp.	Oral contraceptives and hormonal drugs

*Various sources*

**Table 5: SWOT Analysis of plant-derived drugs**

<b>STRENGTHS</b>	<b>WEAKNESSES</b>
Vast source of NCEs	Lack of standardised procedures
Vast therapeutic applications	Limited scientific research available for TCM as per Western standards
Large number plant-derived drugs in clinical use	Supply of raw materials
Proven effectiveness over a long period of time for existing plant-derived drugs	Quality inconsistencies in the raw material
Proven low toxicity and limited side effects for existing plant-derived drugs	Natural molecules are difficult/costly to manufacture synthetically
Shorten route-to-market for existing plant-derived drugs	Chemical and microbiological contaminations
Lower development costs and faster route to market	Stability of active ingredients
	The active components in many herbal products are not known or poorly understood
	IP ownership
<b>OPPORTUNITIES</b>	<b>THREATS</b>
Increasing issues with synthetic drugs	Lack of scientific skills in the West
New drug discovery paradigm	Lack of understanding of botanic drugs by physicians
Improved regulatory environment in the US and EU	Botanic drugs often confused with nutraceuticals
Changes in disease approach	Interaction with prescription drugs
Improved IP protection in certain major territories	Lack of understanding by the investment community
Limited scientific research available for CHM as per Western standards	

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## CHINESE HERBAL MEDICINE

Chinese Herbal Medicine (CHM), the central pillar of the Traditional Chinese Medicine (TCM), accounts for 90% of traditional medicine use, has been practiced for thousands of years and has undergone continual development over the centuries as the causes of illness affecting humans have evolved. Today it continues to play an important role in the Chinese primary care system.

Today TCM is the most commonly practiced non-Western medicine and is viewed as far safer and less expensive than Western medicine, while being more effective at actually addressing the underlying causes as TCM believes "curing the root" of a disease and not merely in treating its symptoms. TCM offers a more patient-oriented approach that encourages a high degree of practitioner-patient interaction that is not excessively dependent on technology. CHM formulations are customised to address each patient's condition, and while taking into account biomedical diagnoses and laboratory, the formula prescribed by the CHM practitioner focuses on the TCM diagnosis. The movement toward the integration of Chinese and Western medicines has been faster in China than in the West, as most resident Chinese do not see TCM and Western medicine as being in conflict. In fact, **medical students in China have to take courses in both Western and traditional medicine**, and actively implement their cross-cultural knowledge in hospitals and teaching clinics.

Scepticism about TCM in the West often stems from the fact that those Westerners who advocate its use have lost faith in conventional medicine and repel any scientific explanation, and have somehow stereotyped the East as mystical and unscientific place. Although the above sounds discouraging, **CHM has been fully recognised for its medical and scientific merits in the West** and the proof of this is the considerable number of leading multinational pharmaceutical companies that have strengthened their R&D facilities and have signed extensive collaboration agreements to combine modern drug discovery approaches with those of CHM.

In November 2006, Novartis announced plans to invest about US\$100m in the construction of an integrated biomedical R&D facility in Shanghai's Zhangjiang Hi-Tech Park that will become an integral part of the Group's global R&D development network and staffed with scientists primarily recruited from Shanghai's academia, biotech and pharmaceutical research institutions. The initial area of research will be **infectious diseases that cause cancer** focusing primarily on liver cancer triggered by hepatitis viruses. Around a third of the 400m people infected with Hepatitis B in China and is estimated the about 300,000 patients will die each year in mainland China.

Prior to this investment, Novartis had already a series of important research collaborations with Chinese organisations. In 2001, it signed a six years agreement with the Shanghai Institute of Materia Medica (SIMM) to identify and test traditional medicines for pharmacological properties for the treatment of a wide range of diseases including diabetes, cancer and CNS (Central Nervous System) disorders. Other collaborations includes: WuXi PharmaTech Co. Ltd., Chinese University of Hong Kong National Institutes of Biological Sciences (NIBS) and Kunming Institute of Botany.

The German pharmaceutical company Merck KGaA and Hutchinson MediPharma Ltd, Chi-Med's wholly-owned R&D subsidiary, entered into a research agreement

*"Immortality governs change"*

*The most commonly practiced non-Western medicine*

*Western and Chinese medicine used in combination*

in November 2006 for the discovery of novel plant-derived anti-cancer therapies. Like Novartis, Merck had a presence in China prior to this agreement by entering the OTC market in 2003.

AstraZeneca was one of the first multinational companies to conduct large-scale international multi-centre trials in China and to establish a clinical research unit. Since 1996, the company has conducted 37 clinical research projects in China, with just over a third still going on. In addition, AstraZeneca has cooperated with local regulatory authorities on drug safety and clinical trials management.

### **Chinese pharmaceutical market size**

China is the 9<sup>th</sup> largest pharmaceutical market in the world and is expected to become the 5<sup>th</sup> largest by 2010. Within Asia, China is the 2<sup>nd</sup> largest after Japan (US\$55bn) and worth approximately US\$20bn, followed by India (US\$8.8bn), South Korea (US\$6.3bn) and Taiwan (US\$4.3bn). Government spend on healthcare has doubled in the period 1998-2003 to US\$8bn and despite this increase the healthcare capacity has not been able to keep up with China's overall growth.

### **Chinese pharmacopoeia**

China enjoys a large territory, various geographical features, and different types of climate. These factors have given rise to different ecological environments, which enable it to grow a great variety of herbal plants. This makes China the country with the most number of herbal medicines in the world. The current standard pharmacopoeia in China contains some 10,000 medicinal substances. Individual medicinal substances are dried and processed in numerous ways altering the original functions and chemical components of each substance according to fit the patient's needs. On average, an herbalist will regularly employ some 200-400 substances in his/her clinical practice.

## **CHINESE REGULATORY ENVIRONMENT**

Since May 2005, the Chinese Government has introduced significant regulatory changes in an effort to modernise its pharmaceutical industry and bring it in line with international standards, making it more transparent and aiming to repair a dented reputation that has been plagued in recent years with corruption, counterfeiting, poor quality control, ever-changing and inconsistent application of regulations.

The former State Drug Administration has been reorganised and is now called the State Food and Drug Administration (SFDA) and has jurisdiction over pharmaceuticals and medical devices (including food, health foods and cosmetics) at national level and generally serves the same functions as the US FDA.

The SFDA has the final say in the authorisation process to issue pharmaceutical manufacturing licenses, approve pharmaceutical advertisements and wide investigative and enforcement powers. The local FDAs are responsible for preliminary evaluation of applications including data auditing process prior to submitting to SFDA for final approval.

Recent legal and regulatory changes include modification of new drugs definitions, abolishment of administrative protection mechanisms, simplification of filing procedures, clarification through new and updated technical guidelines and standardisation of manufacturing processes.

*AstraZeneca multi-centre clinical trials*

*Globally the 5<sup>th</sup> largest market by 2010*

*SFDA = US FDA*

*Combination of national and local government regulations*

Law on the Administration of Pharmaceuticals and its Implementing Regulations are the key statutes, these are supplemented by a number of other regulations dealing with specific issues such as distribution, manufacturing licenses, GMP and good supply practice (GSP), labelling and packaging, advertising, pricing, import-export, etc. Also, local government authorities have endorsed their own policies, which in certain circumstances supplement and modify some of the national regulations often creating inconsistencies and making the understanding of the legal requirements very hard.

A substantial number of foreign pharmaceutical companies have established their presence in China through a host of options, which includes the setting up a wholly foreign-owned enterprise, forming a joint venture with a Chinese counterpart or by acquiring a local organisation. The process of establishing a new pharmaceutical enterprise with foreign investment typically involves going through several rounds of approvals which include the foreign investment authority review of the corporate documents and/or acquisition documentation, then obtain a Provisional Business License, a Pharmaceutical Manufacturing License, a full Business License, and finally a GMP Certificate. Other approvals required could include environmental and safe production.

To export pharmaceuticals to China the exporter is required to appoint a local agent to handle the application procedure with the provincial FDA and at the end of the process the SFDA issues a Pharmaceutical Import Registration Certificate that is valid for 5 years that consents the import of the product via approved ports with the assistance of a licensed importer.

Pharmaceutical distribution by foreign entities remains restricted and is subject to a strict market access evaluation. Any new application for the establishment of a wholesale or retail distribution network is required to comply with the terms set out in the Opinions on Strengthening Supervision of Pharmaceuticals and Promoting the Development of a Modern Logistics for Pharmaceuticals.

Pharmaceutical products in China have been patentable since January 1993, when the country accepted the Patent Cooperation Treaty (PCT). Before the Patent Law of the People's Republic of China was amended, pharmaceuticals were specifically excluded from the patent system. Patent protection may be granted for inventions, designs, and utility models. These applications must be filed in Chinese and are examined by the Chinese Patent Office for formalities and substance. In order to obtain a grant, an application is examined for subject matter, novelty, inventiveness, sufficiency of disclosure, and practical applicability.

Experience has shown that the courts are generally **not equipped** to expeditiously handle infringement actions brought by national and foreign entities, although this is slowly changing with the establishment of specialized IP courts in a number of provincial capitals. The Administration for Industry and Commerce is responsible for enforcement of registered trade-marks and unregistered rights pursuant to the Anti-Unfair Competition Law. The Administrative Authority for Patent Affairs is responsible for the enforcement of patents and designs. The administrative authorities' powers are broad, and include powers, which are quasi-judicial in nature.

*Several rounds of authorisation to set-up a new foreign organisation*

*Pricing policy*

## PHYNOVA R&D PIPELINE

Over many centuries the Chinese and Western medicines have influenced and enriched each other. Phynova is taking advantage of this cross-fertilisation to develop treatment approaches and compounds with, according to Western standards, an improved efficacy and safety profile and a faster route to market, that ultimately will result in the achievement of significant cost efficiencies.

Phynova is concentrating its development efforts on six drug candidates that are at differentiated development stages, as illustrated in the table below, addressing growing therapeutic areas for which limited treatment alternatives are currently available. PYN17 has recently received a UK patent and the application process in other major international territories has been almost completed.

Table 6: R&D reminder		
Phynova's Code	Targeted therapeutic area	Development stage
PYN17	Symptoms associated with chronic hepatitis C	Phase IIa in US
PYN18	Anti-viral: HCV & Dengue fever	Pre-clinical
PYN22	Metabolic diseases, fatty liver/obesity	Clinical trial expected to start in Q1 2008
PYN6	Anti-bacterial	Early pre-clinical (in-vivo)
PYN7	Cancer	Pre-clinical (in-vivo)
PYN9	Post-operative ileus	Clinical trials expected to start in Q4 2007

*Company Data*

Looking at each candidate in more detail:

### PYN17 - Symptoms associated with Chronic Hepatitis C

PYN17 is initially being developed as an oral **stand-alone** therapy for the treatment of symptoms and liver inflammation associated with chronic hepatitis C and could also be developed as a **combination therapy** to be used with peg-interferon and ribavirin, as well as a treatment to prevent the progression of liver fibrosis associated with a number of viral, metabolic and drug induced disorders.

The compound is a novel formulation consisting of **four** botanical extracts derived from **three Chinese** plant species and **one Western** plant species). Individually they have been used to treat a range of liver diseases in Asia and Europe and have a long history of safety and very little or no toxicity.

The pharmaceutical grade raw material is commercially available and supplied by two manufacturers (The Institute of Medicinal Plant Development, Beijing, China and Indena Spa, near Milan, Italy).

A four week Phase IIa clinical study started in the US in May this year. The trial is a randomised, double-blind, placebo-controlled, multi-centre (5) study in which safety and efficacy will be evaluated in 36 patients suffering from chronic hepatitis C, who have not responded to pegylated interferon and ribavirin or are not suitable for such treatment typically on account of the side effects and risks associated with these treatments. Endpoints (safety and efficacy) will be monitored through validated tests, including reporting of adverse events, health related quality of life (QoL) scores and liver function tests to assess patients'

*Dual development opportunity*

*4 botanical extracts of Chinese and Western origin*

*Phase IIa clinical trial just stated in the US*

response and alleviation of the symptoms and liver inflammation associated with the disease. Preliminary data is expected in calendar Q4 2007.

Prior to this trial Professor Graham Foster completed in May 2005 a small study at the Royal London Hospital which demonstrated that PYN17 decreased symptoms and markers of liver inflammation associated with chronic hepatitis C, in a safe and clinically meaningful way.

The Company is currently in active consultation with the FDA regarding the design the Phase IIb clinical trial involving 6 months of treatment with PYN17, which is expected to start in 1Q'2008. It will be a randomised, double-blind, placebo-controlled, multi-centre, powered study and will include over **200 chronic hepatitis C patients**.

Phynova has received a considerable number of enquiries from large pharmaceutical companies and a presentation dossier is being prepared as we go to print.

### About Chronic Hepatitis C symptoms

Chronic hepatitis C is the most common liver disease currently seen in clinical practice. The incubation period, from the time of exposure to the virus until the onset of the disease, is 1 to 6 months. Early symptoms include poor appetite, nausea, aching muscles and joints, abdominal pain and light fever. Patients going onto develop chronic disease (around 80%) experience fatigue, reduced vitality, abdominal discomfort below the right ribs and aching muscles and joints, although not all patients develop obvious symptoms. HCV can be present for as long as 20 years without presenting any further problems. In other patients, however, chronic hepatitis C can lead to long-term disability, cirrhosis of the liver, liver cancer and liver failure requiring transplantation. In many patients, symptoms increase as the disease progresses, particularly with the development of cirrhosis, liver failure and liver cancer, although in some patients symptoms develop quite late in the progression of the disease.

### Statistical data

Since its discovery and characterisation in 1989 HCV has become a global health issue. It is one of the 10 leading causes of infectious disease deaths worldwide with an estimated 250,000 reported deaths per annum. Recent data from the WHO (World Health Organisation) shows 170m individuals chronically infected with the virus and 3 to 4m are newly infected each year. There are geographical differences in the prevalence of the disease. In Europe, prevalence varies from 0.01% up to 5%. In Africa rates of up to 51% have been reported, Egypt alone has an infection rate of 22% due to the use of contaminated glass syringes in a nationwide schistosomiasis campaign. The highest prevalence is reported in Asia and Africa, whereas the prevalence of the disease is lower in industrialised countries like North America, Northern and Western Europe.

### Available treatments

Antiviral drugs such as pegylated interferon (sub-cutaneous injection), alpha taken alone or in combination with ribavirin (oral) can be used for the treatment of persons with chronic hepatitis C, but the cost of treatment is very high. Treatment with interferon alone is effective in about 10% to 20% of patients. Interferon combined with ribavirin is effective in roughly up to 50% of patients. Ribavirin does not appear to be effective when used alone. Both these drugs,

*Designing Phase IIb*

*Huge global health concern*

*170m individuals infected*

*250,000 deaths per annum*

*3 to 4m new cases each year*

*Compliance and side-effect represent considerable issues with existing treatment modalities*

No specific treatment available for Dengue fever

however, are associated with unpleasant and serious side effects. Compliance and side effects represent considerable issues for practitioners and patients alike. Global market size estimated to be around US\$10bn by 2010.

## **PYN 18 – Anti-viral for the treatment of Chronic Hepatitis C & Dengue Fever**

PYN18 is an *in-house* discovery and contains a purified active fraction derived from PYN17. It showed strong *in vitro* inhibition effect on HCV replication. If confirmed by further clinical studies, PYN18 would be the world's first drug of botanical origin, which has anti-HCV properties. Phynova filed a patent for HCV in 2006 and is currently assembling the necessary information to present the paperwork to the relevant Patent Office for Dengue Fever, a tropical, mosquito-borne disease for which there is **no specific treatment available**, only supportive therapy.

Phynova is seeking an **early development out-licensing deal** for these two medical applications and the management has confirmed that a considerable level of interest has been shown by a number of large pharmaceutical companies for the PYN18-Dengue Fever.

## **PYN22 – Non-Alcoholic Fatty Liver Disease (NAFLD)**

PYN22 has been in-licensed from the Chongqing Institute of Ecological Materia Medica Co. Ltd. This compound contains a highly purified active fraction from one plant extract and is in an advanced pre-clinical development stage, expected to be in the clinic sometime in IH'2008. A patent is being filed in the UK.

### **About NAFLD**

NAFLD is a liver disorder defined as a significant lipid deposition in patients without a history of excessive alcohol ingestion. The pathophysiological mechanism underlying NAFLD is currently unknown, although the close link with obesity, a growing problem that has reached epidemic levels in the U.S and other industrialised nations, has suggested a role for insulin resistance. In severe cases of NAFLD the disease spectrum includes nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and liver failure. Currently there is **no specific treatment** for NAFLD. Global market size estimated to be c. **US\$1bn**.

## **PYN6 – Anti-bacterial**

PYN6 is being co-developed with Botanic Century as an anti-bacterial treatment for MRSA and acne. This compound contains a purified active fraction from one plant extract and is in a pre-clinical development stage, expected to be in the clinical phase sometime in 2009. Phynova is receiving a high level of interest from large pharmaceutical companies especially for the acne compound.

### **About MRSA**

MRSA (Methicillin Resistant *Staphylococcus Aureus*) is referred to as the 'superbug'. It's estimated that one in three healthy people carry the bacteria on their skin, in their noses or in the back of their throats. Infection happens if the bacteria enter the body through a cut, a graze or any break in the skin, either accidentally or deliberately (i.e. drip or surgery). MRSA is treatable but the resistance of the MRSA bacteria to certain types of antibiotics makes treatment more difficult. Most strains of MRSA can be treated with the antibiotics vancomycin and teicoplanin given by injection or through an intravenous drip.

No specific treatment available

**Long-term, targeted treatment is not currently available.** Global market size estimated around **US\$1bn**.

### About Acne

Acne is a skin condition typically affecting the skin of the face, back, neck, chest and arms of adolescents and the severity of the condition can vary from minor inflammatory lesions to frank fibrosis. Most people affected are aged between 12 and 25. However, men and women in their 30s and 40s can also suffer with acne. There are many treatments available to help deal with the condition, but none have proved very effective. Global market size is expected to be over **US\$2bn** by 2010.

### PYN7 – Anti-cancer

PYN17 is being developed in collaboration with HKJCICM and the Institute of Cancer Studies in Birmingham. It is based on products used in China for the treatment of different cancers and contains extract from one plant. Although in early development stage, from the initial screening it appears active in a number of solid tumour assays. PYN7 could be used in combination with existing cancer treatments to treat a number of common cancers with a high prevalence and high unmet medical need. IP is being created.

### PYN9 – Post-Operative Ileus (POI)

Botanic Century is developing PYN9 for the Chinese market with Phynova retaining the exclusive global rights.

All the pre-clinical trials have been conducted in China following the Chinese regulatory procedures. An IND application as been filed with the SFDA and possible approval is expected by the end of October. Three clinical trials have been scheduled over a 2-year period with completion expected in late 2009 early 2010. Initial IP been filed with the Chinese patent office and international filing will follow through PCT (Patent Cooperation Treaty) in July 2007.

On the basis of the positive in vivo motility preclinical data carried out by Botanic Century, Phynova is planning to continue the preclinical and clinical development of PYN9, particularly as there is currently no effective treatment available and very few products in development.

### About POI

Post-Operative Ileus (POI), a transient impairment of bowel motility usually considered an inevitable response to surgery and one of the most common causes of prolonged hospital stay following abdominal surgery. It is believed that POI also occurs as a result of the use of opioids. Current treatment modalities include the avoidance of opiates and when possible the use of epidural local anaesthetics. Other potentially effective treatments include early enteral feeding and less invasive surgical procedures. **No targeted pharmacological treatment is currently available.**

### Drug in development (late development stage)

- **Entereg® (alvimopan)** is a first-in-class small molecule, peripherally-acting mu opioid receptor (PAM-OR) antagonist designed to block the adverse side effects of opioid analgesics on the GI tract without blocking their analgesic effects. The development of this product was recently stopped due to the

occurrence of serious side effects including heart attacks and cancer in Phase III trials.

**Table 7: Forward Events (calendar)**

DATE	DESCRIPTION
Q4 2007	PYN17 – Results from Phase IIa in US
Q4 2008	Start of PYN18 clinical trial
H1 2008	Start of PYN22 clinical trial
H12008	PYN17 – Phase IIb in US expected to start
2009	PYN6 – Starting clinical trials
2008/2009	Possible out-licensing agreements
Q4 2009/Q1 2010	Completion PYN9 clinical trials in China

*Company Data/ ED*

## INTELLECTUAL PROPERTY

Phynova has filed four patent applications with one granted, whereas Botanic Century has filed two patents covering the Chinese territory and one under the Patent Cooperation Treaty (PCT). The Company intends to increase patent protection as discoveries are made during the course of their activities, which include research programmes, acquisitions and future manufacturing activities. The same strategy will be applied to trademarks and design rights.

**Table 8: Patents issued and filed by Phynova Ltd.**

Title	Patent Ref. No	Status
Botanical drug or dietary supplement	GB2428974	Granted
Plant based medicament for the treatment of Hepatitis C	EP1732578	Pending
Extracts of <i>Scutellaria</i> for the treatment of SARS	EP1734976	Pending
Antiviral product	GB0612025	Pending

*Company Data and UK Patent Office*

**Table 9: Trade marks**

Description	Trade Mark Ref. No	Status	Registration date
PHYNOVA	2417807	Registered	3rd November 2006
Phynova	2417819	Registered	3rd November 2006
Device only	2433905	Registered	21st September 2006

*Company Data and UK Patent Office*

## FINANCIALS AND VALUATION

Phynova is still a scientific project with no current revenue generating activities. It has a lean cost structure which we expect to change over time as its corporate and operational needs evolve to accommodate a growing organisation. The Company has said clearly that it is within their long-term strategy to become a fully integrated pharmaceutical company.

The largest expense on the P&L is represented by R&D and is expected to increase significantly in the next couple of years, as 2 additional compounds are expected to enter the clinic in late 2007 and early 2008. Also a PYN17 (200 patients) Phase IIb clinical trial is due to commence sometime next year and the development of the remaining pipeline is constantly moving forward.

In October 2006, Phynova raised £2.5m through the placing of 3.39m ordinary shares at 75p. Part of the proceeds was used for the establishment of Phynova China Ltd and to pay £465,000 in cash toward Botanic Century's acquisition. The Company's burn rate is around £180-200k per month whilst there is now an estimated cash position of £2.5m. Therefore we expect that Phynova will probably come back to the market for additional funding, unless in the short-term an early commercially-attractive out-licensing agreement is secured, which could well be a possibility: the Company has clearly stated that it is a feasible option for them to take with regard to PYN18-Dengue Fever and PYN6-Acne.

Phynova faces the normal uncertainties associated with a development pharmaceutical company i.e. regulatory and financial. Also, they operate in the emerging 'third drug discovery paradigm', which is still not *fully* understood. Yet as we have already noted the intrinsic possibilities are vast as the 'natural reservoir of compounds' and 'centuries' of applied knowledge can provide tomorrow's treatment at a faster, better risk and cost profile.

The quantification of a possible deal is not an easy task. To date the FDA has approved only one plant-derived prescription drug, Polyphenon-E Ointment (Veregen™), containing green tea extracts, for the treatment of genital warts, developed by MediGene and distributed by Bradley Pharmaceuticals in the US. The approval triggered a milestone payment of US\$14m. Comparatively, Phynova's has several products addressing growing therapeutic areas for which there are no **specific treatments and very little developmental competition**, which represent an attractive 'feature' of Phynova's pipeline represent an excellent up-side.

In our financial model we have assumed that Phynova will out-license PYN17, currently in Phase IIa in the US. On the back of the successful clinical trial a second agreement will be secured this time PYN18 by the end of FY2009. Initial up-front payments could be of the order of £6.5m and thus they would reach profitability.

Valuing Phynova at this stage of its drugs development is an inexact science. Whilst our forecasts assume licensing revenue from two products out of the portfolio will be received in the next 2 years, exact timing is impossible to predict. However investors will be heartened to know that positive cash returns are achievable in a sensible time frame and **that is the significant point**, rather than taking those forecasts and discounting back a 2009 multiple for either PER or EV/EBITDA. Equally, however, the scale of projected license receipts alone

(from a mere part of the portfolio) gives some context to Phynova's current Enterprise Value (£8.6m) and Market Capitalisation (£11m): commercial success for the company would lead to cash flows justifying a NPV that is a **multiple** of the current value ascribed by the market.

### **Do not forget trade value**

Quoted (or private) direct comparators by definition do not exist for a unique company such as Phynova. However, what is a matter of highly public record is the significant premia being paid in corporate takeovers made by 'big pharma' to restock their own drug pipelines. Note that these premia are paid relative to market cap, and are not calculable as multiples of revenues that, for development Biotech companies, often do not yet exist. To take but one example, AstraZeneca has drawn much attention recently for its **£8bn** takeover of MedImmune, but smaller deals have been done by them on a regular basis in recent months to augment existing biotech platforms and pipelines eg: KuDOS (\$210m), Arrow Therapeutics (\$150m), Cambridge Antibody Technology (£702m). In 2006 the takeover premium on larger deals for quoted stocks in this sector averaged **60%**, more than *twice* the average paid over the previous 3 year period, according to Ernst & Young.

In the absence of appropriate, quoted comparables for Phynova, it is also interesting to note that William Ransomes & Son plc, who are quoted but involved in the more predictable activity of *extracting plant material* for use in consumer industries, has been profitable in the last 2 years and has a market cap today of **£38m**. Phynova clearly has execution risk as its strategy is followed, but future cash flows from a successful development of the portfolio can easily lead one to see a similar size for Phynova when it becomes profitable. Discounting back 2 years to the present time (at a conservative 25% p.a.) gives an implied current value of **£21m** - almost double the current value of Phynova today, equating to **105p share**. This is a crude calculation, but indicative of potential value. Clearly as clinical trials progress and deals are done, the visibility of revenues will become much clearer, driving the share price to a more appropriate level.

**Table 10: Profit & Loss**

<b>Yr end September</b>	<b>2005A</b>	<b>2006A</b>	<b>2007E</b>	<b>2008E</b>	<b>2009E</b>
Revenues	0.0	0.0	0.0	0.0	6,600.0
COGS	0.0	0.0	0.0	0.0	0.0
Gross profit	0.0	0.0	0.0	0.0	6,600.0
R&D	243.3	497.8	1,500.0	3,500.0	4,500.0
SG&A	363.4	1,034.1	1,300.0	1,450.0	1,550.0
AiM Listing	0.0	131.8	0.0		
	606.7	1,663.7	2,800.0	4,950.0	6,050.0
<b>EBIT</b>	<b>-606.7</b>	<b>-1,663.7</b>	<b>-2,800.0</b>	<b>-4,950.0</b>	<b>550.0</b>
Interest receivable	0.0	24.7	23.2	33.5	24.9
Interest payable	0.0	1.4			
Net interest	0.0	23.3	23.2	33.5	24.9
<b>Net loss/income</b>	<b>-606.7</b>	<b>-1,640.4</b>	<b>-2,776.8</b>	<b>-4,916.5</b>	<b>574.9</b>
<b>EPS</b>	<b>-8.7</b>	<b>-13.6</b>	<b>-14.2</b>	<b>-20.0</b>	<b>2.3</b>
Weighted Av. no. of shares	6,953	12,028	19,536	24,536	24,536

ED estimates

**Table 11: Balance Sheet**

	<b>2005A</b>	<b>2006A</b>	<b>2007E</b>	<b>2008E</b>	<b>2009E</b>
Tangible Assets	2.2	7.6	8.0	8.0	8.0
Intangibles Assets	0.0	0.0	0.0	0.0	0.0
<b>Fixed Assets</b>	<b>2.2</b>	<b>7.6</b>	<b>8.0</b>	<b>8.0</b>	<b>8.0</b>
Stocks	0.0	0.0	0.0	0.0	0.0
Debtors	204.7	254.4	255.0	255.0	1080.0
Cash in hand or equivalent	28.8	1978.0	1339.0	1659.5	2196.4
<b>Current Assets</b>	<b>233.5</b>	<b>2232.4</b>	<b>1594.0</b>	<b>1914.5</b>	<b>3276.4</b>
Creditors falling due <1yr	217.1	206.5	456.3	956.3	1756.3
<b>Net Current Assets</b>	<b>16.4</b>	<b>2025.8</b>	<b>1137.8</b>	<b>958.3</b>	<b>1520.2</b>
<b>Total assets less current liabilities</b>	<b>18.6</b>	<b>2033.4</b>	<b>1145.8</b>	<b>966.3</b>	<b>1528.2</b>
Provision for liabilities	236.1	371.2	300.0	300.0	300.0
<b>Net Assets</b>	<b>-217.5</b>	<b>1662.2</b>	<b>845.8</b>	<b>666.3</b>	<b>1228.2</b>

ED estimates

**Table 12: Cash Flow**

	<b>2005A</b>	<b>2006A</b>	<b>2007E</b>	<b>2008E</b>	<b>2009E</b>
Cash flow from Operations	-453.6	-1,586.4	-2,625.1	-4,453.0	522.0
Cash Flow from Investing	-0.7	-7.9	-475.0	-10.0	-10.0
Net Interest	0.0	23.3	23.2	33.5	24.9
Net cash flow before financing	-454.3	-1,571.0	-3,076.9	-4,429.5	536.9
Cash Flow from Financing	429.2	3,520.2	2,437.9	4,750.0	0.0
Change in liquid funds	-25.1	1,949.2	-638.9	320.5	536.9
Cash at bank beginning of the period	53.9	28.8	1,978.0	1,339.0	1,659.5
<b>Cash at bank the end of the period</b>	<b>28.8</b>	<b>1,978.0</b>	<b>1,339.0</b>	<b>1,659.5</b>	<b>2,196.4</b>

ED estimates

## BOARD OF DIRECTORS

### **Karl Watkin MBE – Chairman**

Mr. Watkin has over 25 years' experience working with China, a market critical to Phynova's business strategy and extensive public company experience. He was the chairman and founder of D1 Oils plc, a UK-based global producer of biodiesel and received an MBE for his services to UK exports in 1993. He continues to be involved with D1 Oils plc as a non-executive director. Other current directorships include non-executive director of China Goldmines plc, a gold resource company with a direct interest in a gold mining project in the province of Hunan, China. He also brings valuable expertise gained from the healthcare sector via Dermasalve Sciences plc, a developer of retail dermatology products, which he created in 2004, floated in January 2006 and currently serves as a non-executive director.

### **Robert Miller – Chief Executive Officer**

Mr. Miller has over 20 years' experience in the natural product industry in both the United State and Europe. He is one of the main individuals responsible for the establishment of Chinese herbal medicine in the UK. He has had broad experience in the areas of product development, manufacturing, quality control and regulatory affairs relating to natural products. In 1997 he founded East West Biotech Limited, a company using proteomic technology for the development and quality control of botanical drugs whose assets were acquired by Oxford Natural products Limited ("ONP") in 1999. Following the acquisition he was responsible for business development at ONP until October 2000.

### **Edward Blair PhD - Chief Science Officer**

Mr. Blair is a molecular biologist/biochemist with 15 years experience in the pharmaceutical industry, recently as Director of Applied Diagnostics and Surrogates at GlaxoSmithKline (GSK), and is also a visiting scholar at the University of Cambridge. He has been involved in all aspects of early phase drug development from target identification and routine compound screening through pre-clinical development & Phase II clinical trials. He has developed programmes that support the strategic integration of surrogate biomarkers into the drug development pipeline from candidate selection to approval & launch. His broad therapeutic area experience includes viral, respiratory, liver and neurodegenerative disease, and also cancer gene therapy, with research aspects conducted in collaboration with esteemed UK, European and US academic groups. He is an expert in the field of virology having edited two books on the subject and has published more than 30 primary papers.

### **Stephen Marshall – Chief Operating Officer**

Mr. Marshall has a degree in Engineering Geology and Geotechnics and is a Chartered member of the Institution of Civil Engineers and the Institute of Materials, Mining and Metallurgy. He joined City Analytical Services Limited (an environmental chemical testing company) in 1994 and became managing director in 1996. He was instrumental in restructuring the business and raising development finance. The business was sold to a major UK plc in 2001.

### **Alan Brown – Finance Director**

Mr. Brown has over 20 years' experience in finance and specialises in providing financial management and financial controls for medical research companies

including Avidex, Ribostern and Prosurgrics. He has a degree in accountancy and computer science, qualified as an accountant with Dunn & Bradstreet and is a fellow of the Institute of Certified Chartered Accountants.

### **William Doyle – Non-executive Director**

Mr. Doyle is Phynova's founder and has spent the past 10 years focusing on the healthcare market. His efforts led to the US\$100m financing of enzymatic Therapy Inc., where he served as a vice-chairman, the creation of Integrative Therapeutics, Inc., a consolidation of professional distribution companies and the execution of Phynova's agreement with Hepusen in Beijing.

### **Michael Martin – Non-executive Director**

Mr. Martin has been a partner at Anvil Partners LLP since 1995 where he specialises in raising finance for management buy-outs and development capital. He previously spent 18 years in investment banking in London, New York, Paris and Dublin with Kleinwort Benson and Allied Irish Investment Bank and qualified as an accountant with Price Waterhouse.

### **John Pool – Non-executive Director**

Mr. Pool has an extensive experience in establishing public companies in the medical sector. In 1981, he instigated and was programme manager for the floatation of the first private hospital in the UK, The west Yorkshire Clinic, now a part of Community Hospitals Group plc. In 1987, he founded a private company exploiting computer-aided molecular design in drug discovery which became a subsidiary of Proteus International plc in 1990. Having led the successful floatation of Proteus International plc on the Unlisted Securities Market of the London Stock Exchange, he served as its managing director and subsequently as deputy chairman, retiring in 1995. He is a director of Medical House plc, Eirx Therapeutics plc (chairman), IDMOS plc (chairman) and Physiomics plc (chairman).

### **Dr. Ren Dequan – Co-Chairman Phynova China Ltd\***

Dr. Ren Dequan was appointed as co-chairman since September 2006, former vice director of China's State food and Drug Administration of Traditional Chinese Medicine, was president of China National Pharmaceutical Corporation. He worked closely with Wu Yi and represented China's pharmaceutical interests in the World Trade Organisation negotiations and has been a frequent speaker at the Davos World Economic Forum on improving global healthcare.

\*Dr Ren is Co-Chairman of Phynova's Hong Kong subsidiary company. He is not a main board member.

## **Senior Managers**

### **John Efthimiou MD FRCP - Chief Medical Officer**

Dr. Efthimiou practiced as a physician and clinical academic in London and Oxford University teaching hospitals, specialising in both general and respiratory medicine. His pharmaceutical clinical development experience extends over 15 years and over 120 clinical trials in a diverse range of therapeutic areas (eg respiratory, rheumatology, hepatology, oncology, neurology, dermatology, infectious diseases). He has managed a broad range of drug development programmes and clinical development teams at GSK, Novartis, Genzyme and

Almirall in senior global development roles. He is an expert in the field of respiratory disease and has published over 50 primary papers and book chapters.

### **Tony Mills PhD - Director of Business Development**

Dr. Mills is a virologist by training and has spent over 15 years in biopharmaceutical business development. He helped develop several novel viral vaccines for the animal health industry, with Glaxo and then switched to Intellectual Property (IP) brokering at BTG International. At BTG Tony was a key individual in the team that created Acambis and he also licensed IP world wide to the pharmaceutical industry. Before joining Phynova Tony directed business development at BioVex, a privately owned clinical stage biotech company in the cancer space.

### **Wendy Richings Barrow - Director of Regulatory Affairs**

Ms. Riching Barrow has worked in the healthcare industry since 1981, with SmithKline & French, Glaxo Animal Health and Cyanamid of Great Britain. At Cyanamid she was Regulatory Affairs Manager for its subsidiaries and Business Development Manager for Lederle Laboratories (a subsidiary of Cyanamid). Her responsibilities included in-licensing and out-licensing, identifying potential new business areas, and monitoring and advising on strategic developments in areas which included anti-infectives and Oncology. During this period Cyanamid registered a number of new chemical entities, and novel delivery systems for established pharmaceuticals and innovative devices. In 1995 she established Subiaco Associates, which provides consultancy services to the healthcare industry.

### **Shouming Zhong PhD - Research Director**

Dr. Zhong graduated from China Pharmaceutical University, Nanjing and received his PhD in Phytochemistry from Strathclyde University, Glasgow. He is currently a Visiting Professor of Guiyang Medical College. Shouming was previously employed at ONP as the Director of New Product Development, mainly responsible for the research and development of products containing Chinese medicinal plant materials. Previously, he was the Director of Research & Development at East West Biotech Limited, overseeing and executing the development of a number of natural products.

### **Hongwen Yu - Executive Vice President**

Miss Yu was a lecturer in the Department of Pharmacy, Shanghai University. She has worked for several companies which were developing medicines from plants. She is experienced in the development of plant-based medicines from "field to final dosage form". She has prepared the initial Chemistry, Manufacturing and Control (CMC) documents for submission to ethics committees and regulatory bodies for clinical trial approval and has successfully managed several development programmes from concept to products in clinical phase. As a Pharmacognosist, she is experienced in the authentication and quality assessment of natural products. Miss Yu also plays a key role in Phynova's business development activities in China.

## Scientific adviser

### **Brian Whittle PhD - Scientific Director, GW Pharmaceuticals plc**

Dr. Whittle has over 40 years' experience in the pharmaceutical industry and was co-founder of Phytopharm and GW Pharmaceuticals plc.

I certify that this report represents my own opinions  
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