

Newsletter 37

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Welcome note

Welcome to the 37th issue of our Newsletter where we present our associates in Botswana and our Key Accounts Manager.

In our Environmental Issues we have an article on floods and in the ABC of Pharmacy we continue with the term "dissolution testing".

In Corporate Social Responsibility we have the donation to the Pattihis Senior Citizens' Centre, the sponsor the first permanent prevention & test - checkpoint centre - in Cyprus etc.

In Remedica News our main focus is Remedica's attendance at the Ascendis results presentations, at the Investec Conference and at the C2C conference in South Africa, the launch of our product Imatinib in Western Europe but we also report on Remedica's party.

Finally, we take a glimpse at Cyprus' Museums. ■

Charalambos Pattihis
 Group CEO

Remedica Worldwide

Pharma Vision (Pty) Ltd, Botswana



Formerly the British protectorate of Bechuanaland, Botswana adopted its new name upon

independence in 1966. Botswana, officially the Republic of Botswana, is a non-coastal country located in Southern Africa. It is, one of Africa's most stable countries and the continent's longest continuous multi-party democracy. A mid-sized country of just over 2,2 million people, Botswana is one of the most sparsely populated nations in the world. Around 10 percent of the population lives in the capital and largest city, Gaborone. Botswana is topographically flat, with up to 70 percent of its territory being the Kalahari Desert. It is bordered by South Africa to the south and southeast, Namibia to the west and north, and Zimbabwe to the northeast.

Formerly one of the poorest countries in the world, in the late 1960s, Botswana has since transformed itself into a middle-income country and into one of the fastest-growing economies in the world. The country's diamond mining that has fuelled much of the expansion and currently accounts for one quarter of GDP. Botswana has one of the largest and most valuable diamond mines in the world. In addition, Tourism is another main industry in the country, accounting for almost 12% of GDP. One of the world's unique ecosystems, the Okavango Delta, is located in Botswana. A number of national parks and game reserves, with their abundant wildlife and wetlands, are major tourist attractions.

Remedica's local representative in the Botswana is Pharma Vision (Pty) Ltd, member of integrated healthcare group Avacare. Formed in 2001, Pharma Vision has successfully grown to become a dominant player in the Botswana pharmaceutical market. The company is primarily involved in the registration, importation and distribution of selected quality generic pharmaceuticals and more recently medical devices to both the Government and Private Sector in Botswana.

Pharma Vision has 18 staff members and a sizeable warehousing facility in Gaborone. The company strives every day to offer high quality and value added products to help people lead more enriched and healthier lives. The company remains focused on ascending the value chain in the marketing of pharmaceutical substances.

The company's aim is to be a Leading African Life Science Company that is committed to integrated



health solutions through dedicated trained personnel and to provide affordable quality products and excellent customer Service to all its clients.



Pharma Vision seeks long term, mutually beneficial relationships with its stakeholders, such as customers, business partners, suppliers and employees - always based on fair and ethical

practices. The company is committed to and will ensure at all times good corporate governance, transparency and fair dealing and will ensure that at all times it maintains high standards of systems and controls to identify and monitor material risk and safeguard its assets.



Pharma Vision's vision is: *"to continue to market and promote the sale of Generic Pharmaceuticals by dominating the domestic and regional markets. We will achieve global competitiveness while at the same time adding value to our manufacturers business. By developing our people as our most valuable asset, we move closer to develop our African footprint and strive towards leadership and dominance".* ■

Remedica News

1) Remedica attends the Ascendis results presentations and Investec Conference in South Africa.

Remedica's CEO Mr. Charalambos Pattihis and Deputy General Manager, Dr. Michalis Neoptolemos, attended the Ascendis results presentations in Cape Town and Johannesburg. The main speakers were Ascendis CEO Dr. Karsten Wellner and CFO Mr. Kieron Futter and Mr. Pattihis gave a short speech on Remedica and had a chance to chat with analysts and investors. The Remedica delegation also attended the Investec Conference in Cape Town where Mr. Pattihis gave a more extensive presentation on Remedica. All three presentations were well received by investors as evidenced by the outcome.

Whilst in Johannesburg, Mr. Pattihis and Dr. Neoptolemos visited also the C2C / Ascendis offices as well as the Ascendis manufacturing facility for pharmaceuticals where they held talks with the Pharma Division on creating synergies between the two and taking advantage of the opportunities that lie ahead.

2) Remedica at the C2C conference in South Africa.

During their recent trip to South Africa, Mr. Pattihis and Dr. Neoptolemos also took part in the C2C conference at Arabella where Mr. Pattihis gave a presentation on his experience with the recent events concerning Remedica. They also took the opportunity to discuss matters of mutual interest that will further ensure Remedica's successful course into the future.



3) Launch of Imatinib and Abacavir & Lamivudine in W. Europe.

Remedica successfully launched Imatinib (treatment of chronic myeloid leukaemia) and Abacavir & Lamivudine (antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection) in the markets of Western Europe. Imatinib launched in Germany, France, Denmark, Sweden and Finland and Abacavir & Lamivudine in Germany and the U.K.

4) New Year's party. (photo 1-3)

Remedica recently held its annual staff party at a local restaurant. The highlight of the event was the tribute to Dr. Loukas Eleftheriou, Production Manager, who retired after 35 years of service with Remedica. He was presented with a commemorative gift and a floral bouquet. In a short speech Mr. Charalambos Pattihis, Group CEO paid tribute to "a colleague and a friend for his dedication and professionalism, hard and honest work and his tremendous contribution to the company." In addition we had two more retirements, one of Mr. George Constanti (Senior Validation Engineer) after 11 years of service and one of Mr. Stephanos Loukaides (Punches Operator) after 12.5 years of service. The event continued with the traditional cutting of the vassilopitta (the local equivalent of the Christmas cake, in which a gold coin is baked). After a rich buffet lunch, the dancing begun and, quite appropriately, this lasted for many hours.



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5) Retirement of Dr. Louka Eleftheriou, our Production Manager. (photo 4)

"After 35 years of continuous service with Remedica, words cannot express our gratitude on Dr. Louka's professional work as a colleague and a friend, who with dedication contributed greatly to the success the Remedica from the first day he was hired until the present." These were the words of Remedica's Group CEO Mr. Charalambos Pattihis during a short speech for "Loukas." After completing his studies at the Moscow Institute of Chemical Technology with a Ph.D. in Chemical Engineering, he worked for one year as assistant professor until 1982 when he joined Remedica. His name became a byword for Remedica though his position as Production Manager, where he contributed to the development and advancement of Remedica. In addition, he was an elected member of the Committee of Remedica's Provident Fund for many years. On behalf of the company's management, we would like to thank him for his loyalty and his professionalism. We wish him all the best for his retirement!

6) Remedica supported the 11th Limassol Marathon GSO held on the 18th March with a corporate entry of 68 colleagues. (photo 5-7)

In total, about 15,000 runners took part but it is pleasing to note that our team achieved the third place at the 5Km Corporate Race. ■



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Environmental Issues: Floods

Flood refers to the phenomenon where an overflow of water submerges terrain which is dry under normal conditions. According to the European Environment Agency, floods are mainly distinguished by source and mechanism of flooding. For example a flood could occur due to river or lake overflow, urban storm water combined with sewage overflow or even due to the overflow of sea water. Rivers and streams experience flooding due to heavy rain storms or even massive snowmelt that drains rapidly and accumulates into bodies of water. The mechanism of flood refers to the root cause of flooding such as natural exceedance or defence infrastructure failure.

According to the European Commission between 1998 and 2009, over 213 major damaging floods have occurred in Europe, with the most severe to be those along the Danube and Elbe rivers in summer 2002. Due to these floods, 1126 Europeans have lost their lives and about half a million people have been displaced from their homes. The economic impact of floods has been estimated to be €52 billion in terms of insured economic losses.

The European Environment Agency considers river floods as a common phenomenon and classifies it as one of the most significant natural hazards in Europe in terms of economic impact. Economic losses are induced by flooding through damage to urban infrastructure, housing and transport. In addition, floods can induce a major economic impact due to loss of agricultural production and industrial or commercial downtime. Moreover, economic losses are induced due to the huge cost of clean-up in terms of time and materials required to the removal of debris and grey water and the man hours required to execute this task.



It should be noted that river flooding is considered among others as a Climate Change indicator. As US Environmental Protection Agency suggests, Climate Change has the potential to modify the severity and frequency of river flooding. In other words floods may become more severe and more frequent in some areas where in other areas, floods may occur in limited severity and in less frequency. This occurs due to the fact that as temperatures get warmer over time, the more water is expected to evaporate from oceans and other bodies of water. This in effect alters the intensity and frequency of heavy precipitation events which affect the magnitude and frequency of river flooding.

In order to tackle the impact of floods, the European Union has implemented the EU Flood Directive referring to the assessment and management of flood risks. This Directive requires Member States to assess the risks of flooding and identify the river basins and coastal areas that are more likely to experience flooding. In addition, Member States should establish plans for risk mitigation measures focused on prevention and preparedness in case where this phenomenon occurs. It should be noted that the Flood Directive requires that all prevention and preparedness plans should be publicly accessible. Moreover due to this Directive Member States are required to coordinate preventing actions between them and third countries sharing river or lake basins.

Despite the fact that floods occur as a secondary result of natural phenomena, yet the implementation of further mitigation and responsive measures has the potential to minimise their impact on individuals, society and the economy in general. ■



Corporate Social Responsibility: Remedica Cares

1) Donation to the Pattihs Senior Citizens' Centre. (photo 1)

Like other years, Remedica has sponsored the Pattihs Senior Citizens' Centre which is unique in its kind in Cyprus and for many years has made a valuable contribution to senior citizens of Limassol. Its main aim is to provide entertainment and a variety of other services to its members in order that they may be helped to become more active citizens.



2) HIV/AIDS Support Center (KYFA) - Checkpoint Centre. (photo 2)



Remedica has sponsored the first permanent prevention & test - checkpoint centre - in Cyprus under the supervision of the Ministry of Health. "Checkpoints" are prevention centres, providing services of counselling and rapid testing for HIV. A checkpoint centre is all about early testing. Early testing is essential as knowing your HIV status is key.

The sooner people are diagnosed with HIV, the sooner they can lower their viral load and even reach undetectable levels. Adequate early treatment reduces significantly the risk of transmitting the virus to other people.

A "Checkpoint" offers free, confidential and anonymous rapid HIV testing. All one needs to do is simply book an appointment by phone or by visiting the KYFA facilities in Limassol. The duration of each appointment is approximately 30 minutes and includes a rapid HIV test as well as risk assessment and reduction counselling. The HIV/AIDS Support Center (KYFA) is a non-profit organization founded in 2000 dedicated to provide support, education, information and social services to people infected with the HIV. KYFA's President Mrs. Stella Michaelidou has a vision "to build a hospice and a day center."



3) 10th Medical conference for high school students. (photo 3, 4)

Remedica sponsors the 10th Medical conference for high school students, organised by the Lanition High School, in collaboration with the Limassol Medical Association and the Cyprus Association of Children and Juvenile Gynaecology. Distinguished scientists gave their lectures and high school students from Cyprus presented their research assignments.

4) International Childhood Cancer Day.

On the occasion of the International Childhood Cancer Day, Remedica sponsored a conference organised by The Cyprus Association "One Dream One Wish" (make a wish) for cancer-afflicted children and the Cyprus Paediatric Society. The event was free of charge and open to the public.



5) International Women's Day (IWD). (photo 5)

"Every day is Women's Day!" International Women's Day (IWD) is celebrated on March 8 every year and commemorates the movement for women's rights. In 1977, the United Nations General Assembly invited member states to proclaim March 8 as the UN Day for women's rights and world peace. On the occasion of the IWD Remedica gave a bracelet of Europa Donna Cyprus to company's women, (women constitute 60% of Remedica's total employees). With this supporting efforts to raise awareness and accurate information on breast cancer. Bear in mind that breast cancer affects 1 in 9 women and 1-2% of incidents concerning men. ■



The ABC of Pharmacy:

Dissolution Testing

The disintegration test which was described in the previous edition of our Newsletter is only capable of measuring whether a dosage form such as a tablet will break up in the stomach after it is swallowed. However, it gives no indication that the active ingredient will pass into solution which is an essential requirement before it can be absorbed. This means that it will not be able to predict whether any drug will pass into the bloodstream which is an essential prerequisite to the production of a pharmacological response. This failing was brought to the notice of the pharmaceutical world in the 1970s with observations made with the natural product digoxin which had long been used as a treatment for congestive heart failure. In the UK, where both the brand leader Lanoxin and several generic versions had been available for many years, studies in human volunteers showed 7-fold differences in the blood level produced with different products. Differences were also noted between two tablets produced before and after a change in the manufacturing process by Burroughs Wellcome the manufacturer of Lanoxin. All the tablets satisfied the criteria of the disintegration test and it was eventually concluded that differences in dissolution were a better predictor of the levels of the drug passed into the blood stream. Similar observations with the drug phenytoin in the USA had led to the introduction of a dissolution test in the US Pharmacopoeia in 1970 and other pharmacopoeias began to follow suit.

The apparatus which was first used (therefore known as Apparatus I) consists of a cylindrical glass vessel with a hemispherical base (similar to those used as reaction vessels by organic chemists) which is capable of holding 1 L of fluid. The top of the flask should have a flanged rim on which a lid can be placed and this should bear a number of openings, one of which must be central. This circular hole must be wide enough to allow a 10 mm stainless steel shaft to pass through so that it can be connected to a variable speed motor. A cylindrical stainless steel mesh basket (approximately 22 mm in diameter and 37 mm long) is attached to the lower end of the shaft. The basket must be capable of being taken apart and this is most easily achieved by clips which are fixed to the plate which forms the top of the basket but which is an integral part of bottom of the drive shaft.

The method used to carry out the test starts with the introduction of the required amount of degassed fluid (typically water, or 0.1M HCL or buffer solution) which is allowed to attain a temperature of 37°C ($\pm 0.5^\circ\text{C}$) by immersion of the dissolution flask in a glass-sided thermostatted bath. The dosage form is



placed in the basket which is clipped together and then lowered into the dissolution medium. The motor is set to the required speed and started. Samples are withdrawn from a point half-way between the top of the basket and the surface of the medium, are filtered and then assayed. The fluid is replaced with fresh medium or its removal can be accounted for by calculation. The test is continued until all the dosage form has been dispersed or dissolved and it must be repeated with 5 further units.

There is a slight difference in the design of Apparatus II in that the basket is replaced by twin-bladed paddle, 75 mm in diameter. The method of use is essentially the same as that with Apparatus I except that the dosage form is placed at the bottom of the flask where it will assume a central position because of its shape. If, as sometimes is the case, the dosage form floats then it can be weighted down by insertion in a helix formed from wire or glass. Apparatus I & II can be used for either tablets or capsules and both are modifications designed to allow the evaluation other types of dosage forms such as transdermal patches. There are two further types of dissolution apparatus (Apparatus III & IV) included in the pharmacopoeias that are more complex and intended to be used to characterise modified release dosage forms and provide the opportunity to change the dissolution medium during the test in order to reflect the changing environment in the gastrointestinal tract.

As long as the sampling times are appropriate for the rate at which the drug dissolves the curve of amount dissolved against time can be plotted and this will allow a standard to be set for inclusion in the specific product characteristics for the dosage form. It is of course essential that this does not alter significantly throughout the shelf- life of the product. The general pharmacopoeial standard for dissolution of immediate release products is that not less than 75% of the labelled content should dissolve in 45 minutes. In some cases either a more strict or lenient standard will be directed to be used.

Manufacturers usually endeavour to exceed this official requirement and produce systems which release more of the drug in less than 45 minutes since this is quite possible using modern excipients. If these rapid dissolution rates are used in a medicines license application then the dissolution test must be demonstrated to be sufficiently discriminatory that it will be able to detect any minor formulation and manufacturing changes.

Following its success as a means of ensuring that a drug will dissolve in gastrointestinal fluid following its introduction in 1970 researchers began to realize that it might be able to use the test to predict whether a drug would be able to be absorbed and exert an effect *in vivo*. As more and more information became available on an increasing number of drugs, the regulatory authorities accepted that in cases where the drug had appropriate properties and under some conditions then an application for a generic product could allow a waiver for the need to do an *in vivo* bioavailability study in human volunteers provided that the formulation was qualitatively and quantitatively similar to the brand leader and the dissolution profiles were similar. This relaxation which essentially replaces an *in vivo* study with an *in vitro* test should reduce the cost of marketing a generic product, resulting in a lower sale price without compromising quality, safety or efficacy. ■



Remedica People

Key Accounts Manager, Mrs Stella Stylianou Charalambous



In this issue we present our Key Accounts Manager, Mrs Stella Stylianou Charalambous, born and raised in Nicosia, Cyprus. After graduating from a private English high school she was awarded her first degree by the Cyprus Institute of Marketing and then continued her studies obtaining a Master's degree from Essex University.

Prior to joining Remedica as secretary, up until 1997 she was employed in one of the largest groups in Cyprus as personal assistant to the General Manager. Due to her hard work, abilities and enthusiasm she was promoted as personal assistant (PA) to Remedica's founder, the late Mr. Chris Pattichis. Her professionalism and punctuality help her to be promoted in 2005 to the position of Key Accounts Manager, with responsibility to manage important clients such as non-profit organisations and company's representatives. Throughout the years she has participated in various seminars, workshops and training courses all of which have enriched her knowledge in her field.

She is a Certified First Aid person and member of many charitable foundations. Stella's enthusiasm and professionalism have helped her to develop reciprocal cooperation within Remedica, between her colleagues, her supervisors and Remedica's associates. She is married and blessed with two children, her daughter Andrea and her son Ioannis. ■

A glimpse of Cyprus: Cyprus' Museums

Cyprus is a small country that has a population of less than a million inhabitants and has a relatively impressive big number of museums. The Cypriot museums vary and can be either state foundations with big collections that employ many employees as the Cypriot Museum in Nicosia, or small private museums which operate under the surveillance of only one person and are preserved thanks to the persistence and loyalty of their owners, as the Ethnographical Museum of Pafos.

Some of the museums are accommodated in very impressive buildings as for example the Leventis Gallery in Nicosia and they have fix working hours. However, some other museums are hosted in small houses mainly in villages and in order for someone to visit these can do that following a telephone call or by requesting the key from the responsible person for the operation of the museum. All these museums consist of a rich variety of different types of museums, archeological, byzantine, historical, ethnographical museums / galleries, art centers and others.

One of the most important museums of our island is of course the Archeological - Cypriot Museum. It is situated in Nicosia and it is the main Archeological Museum of Cyprus and highlights the long history of the civilization of Cyprus from the Prehistoric years to the early Christian Period. The collections of the museum were significantly enriched by the extended excavations around the island and brings to the fore the Cypriot Archeology of the international archeological research. At this specific museum, the cultural heritage of Cyprus is exposed and of course protected contains ceramics, jewellery, sculptures and currency from the Neolithic period to the Copper Age, the days of the iron and the Greek-roman period, in order for us to be able to enjoy freely this one of a kind heritage. Some of the glorious and impressive exhibits of the museum are the statue of Aphrodite of Solon, a collection of gold jewelry and ruins of the royal tombs of Salamina. The museum consists of a stop of the cultural course of Aphrodite.

Another very important museum of Cyprus is the Leventis Municipal Museum of Nicosia. This Museum is housed in a complex of three traditional buildings within the old, walled city and is situated close to Square of Liberty. This is a historical museum of Nicosia since through this the history of the city is presented from the prehistoric age up until today. It was founded in 1984 by the Municipality of Nicosia and the Anastasios G. Leventis Foundation at the initiative of the then Mayor Lellos Demetriades. The museum opened its doors for the first time for the audience on 1989 and on 1991 got awarded with the prize "European Museum of the Year". In 2010 it was totally innovated and its space got bigger and at that time the wing "Constantinos Leventis" was added. Through the objects presented to its permanent exhibit halls the visitor travels through the history of Nicosia, starting from the formation of the region from its emergence from the foam of the sea approximately 1,800,000 years ago, the creation of the first agglomerations at about 3900 B.C. to end up to the recent years, to the last divided capital city of Europe. It is very important to underline that this museum organizes educational programs, visits and other events.

It is worth mentioning another important archaeological museum the one that is situated in the region of Limassol. It was founded on 1948 and was situated in the medieval castle of the city. After the turbulence that took place on 1964 when the castle was given to the National Guard then the Museum remained closed for a long period. On 1972 the creation of the new building which was going to host the Museum began along with the nearby District Court of Limassol. Finally, the exposition operated on March 1975 in the new building where it is still situated up until currently. Recently there have been some changes on the building in order to create a bigger exhibit space. At the Museum, there are findings that cover all the antiquity from the 10th millennium B.C. up until the end of the roman

period which come from the city and region of Limassol. These objects have been found during both systematic and saving excavations that take place in the region from the Department of Antiquities and from several foreign missions.

Of course, besides the main and big museums of islands, there are some more equally important concerning the presentation and explosion of the cultural heritage of Cyprus. Some of them are the Cyprus Folk Art Museum, the Byzantine Museum, the National Struggle Museum, the Ethnological Museum (The House of Hadjigeorgakis Kornosios), the Local Archeological Museum of Curium, the Local Archeological Museum of Palaipaphos and many more. There are also museums in villages that have a huge history behind them such as the Local Agricultural Museum of Fikardos, the Linos Museum in Kakopetria, the Commandaria Museum in Zoopigi village.

It is very important as thoughtful citizens of this island not to neglect our cultural heritage and history of our country, to enrich our knowledge on these, to support the institutions that aim to protect and preserve this rich heritage. The least we must do is to visit these museums, to learn through our visits there and to strongly recommend these to our familiar persons and not, the visit to these places. ■

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