HYBENX Technology:

An Innovative Chemical Approach to Clinical Debridement and the Eradication of Microbial Biofilm Infection and Stabilization of Necrotized Tissue.

EPIEN Medical, Inc. Saint Paul, Minnesota, USA

Abstract

Improvements in laboratory methods over the past two decades have produced a dramatic increase in the information available about the structure of dental plaque biofilm and the role of biofilm microbes in general diseases. Emerging data has now linked the inflammatory response triggered by plaque biofilm microbes with chronic destruction of oral tissues as well as with a variety of systemic disorders. Newly described features of the plaque biofilm matrix revealed that there may be a simple chemical approach to instantaneous eradication of plaque biofilm, biofilm microbes and calculus that could be formulated as a practical clinical therapeutic agent. Such an agent has subsequently been engineered as a focal liquid rinse based on a mechanism of irreversible molecular denaturation produced by a potent liquid contact desiccant. In addition to its anti-biofilm activity this rinse agent was designed to provide several other clinical benefits including localized hemostasis and debridement of inflamed and necrotized tissues. This report outlines the product design and validation processes used for the development of a family of therapeutic agents based on this novel chemical approach and named HYBENX® Technology for the purpose of commercial product applications.

Overview

Working with a team of experienced dental practitioners, EPIEN Medical has developed a new technology for improving the way that professional dental procedures are performed. The intellectual property and products that have come from this work are referred to collectively as the HYBENX® Technology. The core concept of HYBENX Technology involves the application of proprietary liquid agents to surfaces of oral and other tissues in order to alter the physical condition of those surfaces by a patented chemical cleaning process that does not involve any form of drug action. Altering the physical condition of a tissue surface in certain deliberate ways can result in therapeutic benefits for patients who are suffering from a variety of conditions. As an example, HYBENX professional dental products have been formulated to simultaneously produce a number of therapeutic benefits for dental patients on contact by instantaneously altering the physical condition of the surface of oral tissues in a highly specific manner. Upon application the HYBENX professional dental products will:

1) Reduce oral pain and discomfort
2) Remove all disease-causing microorganisms on oral tissue surfaces
3) Detach and destroy dental plaque and plaque bacteria on tooth surfaces
4) Detach and destroy infected, necrotic and dead matter from oral tissue surfaces
5) Eliminate the spread of oral bacteria into the bloodstream during dental procedures
6) Eliminate the spread of oral bacteria into the clinic environment during procedures
7) Stop inflammation and destroy inflammation promoters on oral tissues
8) Stop open bleeding and persistent oozing of blood on diseased oral tissues
9) Reduce oral tissue swelling
10) Seal and protect open ulcerations of oral soft tissue

In other words, HYBENX products can be used by dental practitioners to enhance patient comfort by instantly stopping infectious and inflammatory disease processes while sealing open wounds. They can be used to facilitate the more timely and cost effective completion of dental procedures and subsequent healing by cleansing away the accumulated tissue damage and infectious debris in a manner that

supports the natural repair process in oral tissues.

The commercial potential of HYBENX dental therapeutic agents is significant because the products are designed to be used adjunctively with existing professional procedures. The primary product design concept is that a simple brief application of a HYBENX product can be used routinely to optimize the results of any dental treatment procedure by 1) expediting completion of the procedure, 2) improving the patient experience, and 3), reducing the risk of post-treatment complications. HYBENX dental products are not designed to be a treatment for any one specific disease by themselves. They are also not designed to replace any current dental methods. They are designed to make all standard treatment techniques better. The goal of EPIEN Medical is to eventually have HYBENX products included as an adjunctive part of every dental clinical protocol.

Other significant commercial opportunities for HYBENX products in the dental marketplace are available in the enhancement of infection control measures and in the performance of preventive dental care procedures. Both of these opportunities derive from the fact that HYBENX products are based on a unique patented mechanism of action that is designed to exploit a fundamental weakness in the structure of dental plaque. HYBENX products are the only liquid agents on the market that can detach plaque from tooth surfaces within seconds and instantly kill the plaque bacteria.

As part of its business strategy, EPIEN has designed a short-term technology development plan focused on demonstrating the value of HYBENX products to the dental marketplace in various ongoing and completed clinical studies. The clinical procedures and disease topics with the highest priority for evaluation are 1) subgingival cleaning enhanced by HYBENX in chronic periodontitis, 2) disinfection of soft tissue, hard tissue and device surfaces by HYBENX in patients with infection of dental implants, 3) disinfection of chronic non-healing wounds. The protocols for these studies are either underway or currently pending funding. A study of the initial use of HYBENX in the treatment of recurrent oral ulceration has was completed and the results have been published by the Eastman Dental Institute (Porter et al.). That and numerous other publications now suggest the utility of HYBENX Products for many additional oral applications (SEE: Publications section: www.hybenx.it).

HYBENX® Products have received regulatory clearance for marketing in the European Common Market, in Canada, and in several countries of the Middle East where they have been officially designated as a low risk, Class I, Medical Devices. Another HYBENX product, HYBENX® Root Canal Cleanser, has been cleared under form 510(k) for marketing in the United States as a root canal cleanser for the removal of the smear layer. The Company plans to seek further regulatory clearances in the US after completing the initial market launch of HYBENX and completing additional clinical evaluations.

Background

It has been recognized for some time that the cause of most dental disease starts with disease-causing microbes growing on surfaces in the mouth. Bacteria, fungi, viruses and parasites are all thought to cause diseases in the mouth, but the most prevalent dental problems, cavities and gum disease, are usually linked only to bacteria.

Recent research reports show that by analyzing the genetic material from an oral sample, it is possible to definitively say that at least 1,000 distinct species of bacteria live in the mouth. Some reports suggest that there are likely to be even more species present with estimates ranging from 3,500 to 19,000. The vast majority of these bacteria have never been isolated and grown in a pure form in a laboratory. They are referred to collectively as the “uncultivatable bacteria”. Since they have not been grown in a laboratory, nothing is known about their metabolic properties, their potential role in causing disease and what drug sensitivities they may have if any. Even if the lower estimates are correct, the number of bacterial species

that could potentially be causing oral disease could be so large that it is impossible to predict when all of them will be completely recognized and understood.

Bacteria can be found on the surface of all of the hard and soft tissues of the mouth. Dental plaque on the surface of teeth is a form of bacterial colonization typically found on hard wet surfaces that is known as a microbial biofilm. The term “plaque biofilm” is now used commonly in the scientific literature when discussing dental plaque. A microbial biofilm starts to form when a microorganism attaches to a surface through a chemical interaction. The microbe then starts to replicate and at the same time recruits other microbes in the area to attach to the same surface. The microbes continue to replicate and then start to jointly secrete a polysaccharide material, referred to as the matrix. The matrix eventually turns into an amorphous layer of a mixed polysaccharide gel with unique physical properties. The matrix layer is usually populated by many different species of microbes which grow in clusters within the gel. Dental plaque biofilm is simply a thin sticky layer of a bacterial polysaccharide gel deposited on tooth surfaces that contains many different species of oral bacteria. The bacteria that live in the plaque matrix are known to adjust their metabolism so they can better function in the matrix environment. They reduce their metabolic rate and enter into a type of hibernation that has been named the “persister state”. While in this state they are resistant to the actions of many traditional antimicrobial agents because those agents depend on the metabolic pathways of the bacteria being active in order to have an effect on them.

Dental disease is believed to start when microbes in a plaque biofilm matrix for unknown reasons begin to secrete substances onto the host soft tissues that trigger the host to mount an inflammatory response. An example of this is the process by which bacteria in the plaque biofilm on a tooth surface at the gum line trigger the development of gingivitis – an inflammatory response from the host gum tissue. The inflammatory response is of course the body’s way of trying to eliminate disease-causing substances. White blood cells are recruited into the area that is under threat and they release chemicals into the area designed to destroy the invaders. However, the bacteria that are triggering the inflammation are resistant to the attack of the white blood cells. They are protected by the plaque biofilm matrix which serves as a shield. The bacteria can then continue to release inflammation-promoting signals and the host tissues continue to supply more and more white blood cells. The chemicals that the white blood cells secrete eventually build up to such a high concentration that they start to destroy the hosts own soft tissues. In other words, it is not bacterial substances that damage oral soft tissues in dental disease. It is the inflammatory white blood cells from the host that cause damage to its own tissues. The host tissue eventually is broken down and destroyed by the host inflammatory response. The dead soft tissue matter then triggers an even stronger inflammatory response from the host. This leads to a self-sustaining and repeating cycle of chronic inflammation and tissue destruction followed by more inflammation that becomes more and more difficult to control. The patient then experiences the familiar clinical symptoms – pain, swelling and bleeding – until the process is stopped through some type of professional treatment.

The ultimate answer to preventing oral disease is to prevent disease-causing microbes from triggering an inflammatory response in the first place. This is commonly done by working to eliminate as much dental plaque biofilm as possible with routine professional preventive care and home-based dental hygiene methods. These techniques are primarily based upon mechanical removal of dental plaque supplemented by application of antimicrobial chemicals in mouth rinses and toothpastes.

The best treatment method for any particular inflammatory dental disease process depends on how severe it is and how much tissue damage has already occurred. In general, however, professional treatment strategies have been based on the idea that healing of the soft tissues can start only when everything that promotes continuing inflammation is removed and all destructive inflammatory processes are resolved. That is the only way to stop the ongoing cycle of chronic inflammation and

allow natural tissue repair mechanisms to proceed effectively. This requires that the diseased tissue be cleared of all microbial pathogens and, depending on the situation, also cleansed of all dead tissues debris and inflammatory exudates. Therefore, common dental treatment procedures are designed to make the diseased tissue areas as clean as possible by using various mechanical cleaning techniques supplemented by the application of standard antimicrobial agents to suppress new bacterial growth.

The Limitations of Current Standard Dental Therapeutic Techniques

The bottom line with dental treatment procedures is that the cleaner you can make a diseased area of tissue and the longer you can maintain it that way, the more successful you will be in stopping any ongoing destruction and the more likely it will be that the tissue will heal. The currently accepted standard professional dental procedures are all somewhat mechanically limited in their ability to eradicate diseased tissue and the offending bacteria at the molecular level. These limitations are presented in separate categories immediately below.

1) The limitations of mechanical dental cleaning methods

There are a variety of well-known standard mechanical approaches to the professional removal of dental plaque including methods such as manual scaling and powered ultrasonic scalers. Dental plaque biofilm has physical properties that can make effective mechanical removal time consuming. Plaque has extreme visco-elastic characteristics such that it binds tenaciously to the surfaces of hard tissues and cannot be easily detached and washed away completely with oral rinses alone but usually requires application of mechanical shear forces. The supragingival and subgingival anatomy of the tooth adds to this problem as it often contains areas that may be covered by plaque but with limited physical access for applying a mechanical technique. As a consequence of the extreme adhesive properties of plaque and the limitations created by tooth anatomy it is often impossible to adequately remove plaque biofilm from teeth using mechanical techniques alone. Some mechanical techniques simply smear the plaque around on the tooth surface while not removing much of it.

Essentially all currently used professional methods are less than totally satisfactory for the simple reason that plaque biofilm pieces generated by mechanical shear force still contain viable microbes. While most pieces of viable plaque biofilm that are liberated are removed by rinsing, some viable attached pieces remain behind. These residual pieces readily seed the re-establishment of plaque.

2) The limitations of antiseptics and antibiotics

Antiseptic oral rinses and topical antibiotics have limited efficacy against the bacteria living within dental plaque biofilm. One of the most important features of microbial biofilms is that the microbes that live within them are known to be generally resistant to the action of typical antiseptics and antibiotics. There are many reasons offered in the scientific literature for this non-specific resistance. The critical fact is that these agents must be used at much higher concentrations and for much longer periods of time to kill microbes living in oral biofilms than to kill microbes living outside of biofilms. This has greatly limited their usefulness in the treatment of common oral diseases that originate from plaque biofilm microbes. A related concern is that an antiseptic or drug may initially be somewhat effective against biofilm microbes, but using it for an extended time at high concentrations will lead to emergence of specific drug resistance that could spread rapidly due to the proximity of the bacterial colonies that cohabitate in a plaque biofilm.

It is also critical to remember that antibiotics and antiseptics are fundamentally limited in efficacy because they only attack the microbes themselves and they do nothing to eradicate the plaque matrix. Failure to eradicate the plaque matrix increases the risk of recurrent disease through reformation of viable plaque biofilm bacterial colonies. They also do nothing to reduce the risk of ongoing inflammation through removal of tissue debris and other inflammation triggers.

3) Limitations of common dental agents

There are a variety of agents that are commonly used in dental procedures to prepare tissue surfaces for restorations, bonding or sealing procedures. Among these are solutions of phosphoric acid, EDTA, citric acid, alcohols, volatile organics, surfactants, antiseptics, antibiotics and sodium hypochlorite (bleach). It has been demonstrated that all of them have limited ability to eradicate plaque biofilm and biofilm bacteria except for the sodium hypochlorite solutions. Hypochlorite solutions have had very limited use in plaque removal procedures however due to the fact that through inadvertent contact they can rapidly damage normal healthy oral tissues.

3) The limitations of uncommon methods

There are two techniques currently being marketed for the treatment of infection and inflammation in the mouth that have yet to become widely used. One is the soft-tissue laser technique and the other is the photo-dynamic therapy technique.

The soft tissue laser uses heat generated by laser energy to destroy plaque biofilm and necrotic tissue. This technique is thought to have not gained much popularity because it requires a substantial investment in equipment, a substantial investment in training and is not without risk of harming healthy tissue. It suffers some of the same challenges as the standard mechanical techniques in that the laser may not be able to access all of the surfaces that are covered with biofilm or dead tissue.

Photo-dynamic therapy refers to a technique wherein a light activated non-specific antimicrobial agent is placed in contact with an infected surface where it is absorbed by microbes. A specific light frequency is delivered by a fiber optic device to activate the antimicrobial agent and kill the microbes. This method has the same limitations of standard antiseptic and antibiotic agents in that it does not do anything to remove biofilm matrix or inflammatory debris.

4) The limitation of methods that are currently in development

There is ongoing research to develop new antiseptic agents and antibiotics that can overcome the resistance of plaque microorganisms. As explained earlier, it is now understood that thousands of different species of bacteria colonize the oral cavity and that the vast majority of them have never been studied in a laboratory. It has not yet even been determined how to isolate and grow these bacteria in a laboratory so that their metabolism can be studied and their potential role in dental disease determined. Without this information it is difficult to say that any particular antiseptic or antibiotic will be ultimately effective in the treatment of dental disease because there may be many more untested pathogenic bacteria in the oral cavity that have simply not yet been identified as such. The work of identifying all of these agents and developing drugs to control them will likely require many years and an incalculable amount of resources. This makes the research into the development of alternative antibiotics and antiseptics impractical at this point in time.

It has been proposed that a simpler approach for developing a method to control oral bacteria is by aggressively studying the mechanisms by which plaque biofilm is formed since the majority of oral bacteria live in biofilms. This research process has suffered from the same types of problems that are found in other antiseptic and antibiotic research, namely, there are simply too many different species present and they appear to all use somewhat different mechanism to regulate their behavior in a biofilm environment. The goal of producing products which are effective at stopping biofilm formation specifically by disease-causing bacteria appears to be impractical at this point.

The HYBENX® Approach to Improving Professional Dental Therapy

In order to understand HYBENX Technology it is important to first recognize that HYBENX products act by a patented chemical mechanism that is unlike the mechanism used by any other antimicrobial agent or tissue cleansing product currently available to the dental community. As a result, HYBENX Products can

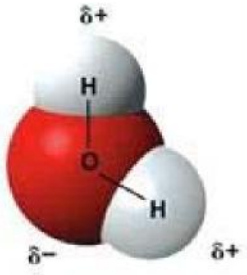
accomplish things unlike any other dental product.

For some of its actions, the HYBENX Product may best be categorized as an antimicrobial tissue cleanser or a tissue conditioning, focal rinse agent. However, typical dental cleansers are most often simple aqueous solutions of antiseptic agents that function primarily as passive mechanical rinses. They may secondarily provide an antiseptic benefit by exposing tissue to antiseptic chemicals during application, but this is a minor action compared to their mechanical rinsing action. HYBENX products work in a completely different manner. They actively detach pathological matter from surfaces during application by exerting a superficial denaturing action on contact through a proprietary chemical process. This denaturing activity assists the mechanical rinsing action of the product in removing the targeted material. HYBENX products are probably best described as “active” cleansers and conditioners that effectively pull infectious materials and biofilm off of the tissues whereas the other types of dental rinses can be considered as “passive” because they usually just carry away the debris that has already been somehow mechanically detached.

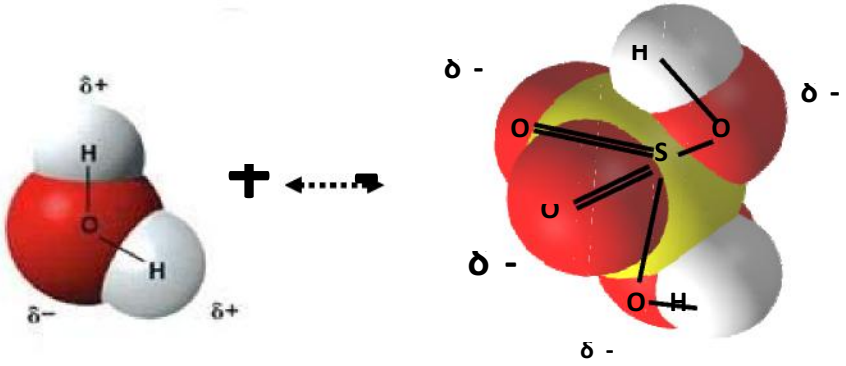
The HYBENX product attacks everything that promotes the destructive cycle of oral tissue inflammation that is the hallmark of the common dental diseases. At the same time, the product destroys and cleans away dead necrotic oral tissue debris so that tissue repair is not delayed. It assists dental practitioners in the performance of dental procedures by converting bloody, swollen and fragile ulcerated oral tissues into clean, tight and sealed blood-free sites that can be treated more easily. In a matter of seconds HYBENX products can achieve a level of disinfection and debridement of diseased oral tissue that would take much longer to achieve by any other mechanical or chemical method if it was even achievable at all by those methods.

Molecular Mechanism of Action of HYBENX Technology Dental Products

HYBENX dental products are powerful liquid contact desiccants due to the fact that they contain concentrated blends of sulfonic/sulfuric acids which have a strong affinity for water. A sulfate group has a polar internal structure with the oxygen atoms on the outer surface of the group carrying a strong negative surface charge. Water molecules also have a structure with significant polarity which gives it a negatively charged surface on one side and a positively charged surface on the other. A sulfate group in water can be thought of as resembling one large magnet pulling on many smaller magnets by matching up its large negative surface (negative magnetic pole) to many small positive surfaces of water molecules (positive magnetic poles). Water molecules become reversibly bound to a sulfate surface through an electrostatic interaction known as a hydrogen bond where the positive charge on the surface of the hydrogen atoms of the water molecule is attracted to the negative charge of on the surface of a group of oxygen atoms in the sulfate group.



Water Molecule Dipole Structure
6- = Negatively Charged Surface
6+ = Positively Charged Surface



WATER SULFATE

The strength of any hydrogen bond with water depends primarily on the strength of the polarity of the group that is pulling on the water molecule. Sulfate groups actually compete to bond available water molecules with other types of polar molecular groups in their vicinity. The group with the highest amount of "unsatisfied" polarity will have greater affinity for water and will pull it away from the other groups and hold it in a stronger hydrogen bond.

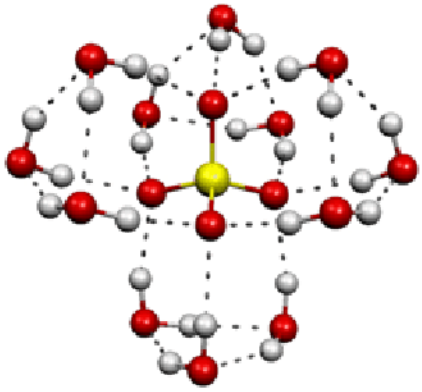
Highly concentrated sulfuric acid has a minimal amount of water bonded to it. In that condition it has a net affinity for water that is so strong that it will literally make its own new water molecules. It does this by pulling hydroxyl groups and hydrogen atoms, the components of water, from nearby molecules and then combining them on its surface through a chemical process referred to as a dehydration elimination reaction.

The strong desiccating effect that concentrated sulfate solutions can have on human tissue is actually caused by their ability to successfully compete with the components of the tissue for the water molecules that they have. Concentrated sulfate groups have a stronger polarity and a greater attraction for water than most tissue components. A pure sulfuric acid "burn", for example, is actually an area of tissue where sulfates on a surface have pulled so much water from the underlying tissue that the tissue components have become permanently desiccated, precipitated, denatured and coagulated. The technical term for this process is "Coagulative Necrosis". Highly concentrated sulfuric acid can destroy tissue components by causing dehydration elimination reactions to happen on a tissue surface. Elimination reactions literally break apart the molecules of important tissue components. The coagulative necrosis process produced by less concentrated sulfate solutions does not break apart the molecules, but rather denatures them and coagulates them so they lose their normal shape and can no longer function, but they are not broken apart.

The amount of coagulative necrosis that is produced by contact with sulfates depends in part on how resistant a particular tissue is to the passage of water through it. For example, healthy intact keratin on a skin surface resists the flow of water through it so it provides some protection to the underlying tissue from desiccation by sulfates. However, the amount of coagulative necrosis that is produced also depends on the total quantity of sulfates and how much water they have already bonded before being put on the tissue. In other words, the more concentrated a solution of sulfates is, the more likely it can compete for water molecules with any types of surface and it will coagulate almost any surface. The more you dilute sulfates with water before they contact tissue, the less severe any subsequent desiccation and coagulation of tissue will be regardless of the condition of the surface.

As water molecules become attached to the sulfate surface they form into a contiguous layer of water referred to as a "shell". If additional water molecules become available, they will form layer upon layer of additional shells around the sulfate group like layers of an onion. As each shell forms, the affinity of this

hydrated sulfate for additional water is progressively decreased because the net negative polarity is diminished by the added dilution with water. The strength of the water affinity of a solution of sulfates at any point depends on how much water has already been added to the solution. As more and more water is added, the sulfate group will at some point be covered by so many layers of water shells that the net polarity of its negatively charged surface is minimal and it can no longer compete to pull water from other hydrogen bonding groups.



Water Shell around a Sulfate Group
Hydrogen Bonds (----) Form Between
Hydrogen of Water and Oxygen of Sulfate

The desiccation intensity level of HYBENX products is set during formulation by creating the necessary number of water shells around the sulfate groups through water dilution. This reduces the net negative polarity to the desired level so that the final product does not have sufficient desiccation strength to cause either a destructive dehydration elimination reaction or coagulative necrosis on contact with healthy intact tissue, but they are still able to compete effectively with polar molecules in fragile pathological tissues for any accessible water molecules that are being held by a hydrogen bond mechanism.

The fact that HYBENX products can readily compete for the hydrogen bonded water on certain oral tissues surfaces is the most important factor in its mechanism of action. Water that is attached to organic tissue molecules, such as proteins, lipids and carbohydrates, by hydrogen bonds is essential for maintaining the structure and function of those molecule and for the integrity of the tissue that they form. When HYBENX successfully competes and absorbs water away from a molecule, the molecule's structure becomes unstable. Chemical groups on the desiccated molecule will react to the loss of water by collapsing together into a new arrangement that is stable but is also now nonfunctional because it is abnormal. The individual structures within the desiccated tissue are said to become denatured. Molecular denaturation within tissues leads to the coagulation of those tissues at a gross level. In other words, HYBENX produces molecular denaturation and tissue coagulation of the superficial layer of fragile damaged tissue surfaces on contact through a rapid irreversible desiccation mechanism.

HYBENX simply desiccates certain kinds of oral tissue surfaces to the point of denaturation and that is all they can do. They do not have sufficient desiccation intensity to cause destructive elimination reactions. And they also do not acidify tissue. In order for any acid to dissociate and acidify its environment, it has to have sufficient water available to permit dissociation and the creation of oxonium ions to transfer the acidic protons. The components of HYBENX are so concentrated and have such a high affinity for water that they do not allow sufficient proton transfer into tissue until the hydrogen bonding capacity of the sulfate is exhausted and unbounded water molecules are readily available. This does not happen until a typical sulfate solution concentration is very low at approximately 5-10% by weight but it also depends on what else is in the environment.

More on the Reaction of HYBENX Products with Tissue Surfaces

When HYBENX products are put in contact with a tissue surface the resulting reaction depends on the tissue structure and whether or not the surface is healthy and intact. Since the mechanism of action of the product requires the absorption of water, it will produce a significant coagulation reaction more readily on those tissues that more readily allow the passage of water to the surface.

For example, placing a HYBENX product on intact normal keratinized epithelium for several minutes has no noticeable impact on the tissue. The cellular structure of the healthy tissue is such that it acts as a protective barrier preventing passage of water through the tissue to the surface. Since no desiccation can occur, no tissue denaturation or coagulation can occur. At the other extreme placing the product on ulcerated tissue produces an immediate coagulative response. The necrotized tissue on the bed of an ulcer readily gives up its water and becomes rapidly desiccated by these products because it has no intact protective layer on its surface. Since damaged and diseased tissue surfaces are typically less resistant to the desiccating action of these products than healthy intact tissues, HYBENX products can be regarded as selective for damaged and/or diseased tissue.

As desiccation-susceptible tissues become coagulated by the action of these products, their surfaces can become covered by a dense thin membranous layer that is formed directly from tissue debris. This surface layer of coagulum then becomes thicker as contact with the product continues. Eventually it becomes more and more difficult for HYBENX products to absorb more water from the tissue surface because the coagulated layer becomes too thick and dense to allow any further passage of water. At this point these products no longer have any significant effect on the tissue. In this way, the HYBENX products can be said to be self-limiting.

Reaction of HYBENX Products with Microbial Biofilms

The interaction of HYBENX products with the surface of microbial biofilms is a special case of the utility of this product technology. Microbial biofilm is the name for the most common form of wet surface colonization used by bacteria and fungi. A microbial biofilm most often starts to form when a microorganism attaches to a hard surface in a wet environment such as a tooth or an open wound. The microbe then starts to replicate and at the same time recruits other microbes in the area to attach to the same surface. The microbes continue to replicate and then at some critical point they start to jointly secrete a polysaccharide material referred to as the extracellular matrix. The matrix develops as an irregularly shaped layer of aqueous polysaccharide gel. The matrix layer is eventually populated by many different species of microbes which grow in clusters, or colonies, within the gel.

Research conducted over the past two decades suggests that the vast majority of microbes in the world actually live within a surface microbial biofilm, including many that are located within the human body. The US Center for Disease Control has stated that up to two-thirds of hospital acquired infections may be present as microbial biofilms on such surfaces as the lining of upper and lower airways, urinary tract spaces, sinus tissues, gastro-intestinal mucosa and chronic skin wounds. Dental plaque is an example of a typical microbial biofilm on the human body.

HYBENX products have a unique ability to quickly eradicate dental plaque and plaque bacteria because of its unique ability to denature biofilm matrix through a potent desiccating action. As stated above, the matrix of microbial biofilm, including dental plaque has an aqueous polysaccharide gel structure. The matrix has significant adhesive properties that make it highly resistant to removal by mechanical shear forces alone. It is also resistant to commonly used dental cleansers and antiseptics. However, because the plaque matrix has no protective structure on its surface that prevents it from being desiccated, HYBENX products can very quickly denture them. The desiccation of plaque microbial biofilm in this manner causes the matrix and the microbes within it to become coagulated and shrunken. The biofilm material precipitates and contracts together to the point where it detaches from the tooth surface. It is

this action of the products that makes them highly effective as dental therapeutic agents for the removal of dental plaque and the eradication of plaque microbes. It compensates for the limitations of mechanical anti-plaque techniques and the limitations of antibiotics and antiseptics against biofilm microbes.

It should be emphasized at this point that the recognition and demonstration of the utility of contact desiccation as a mechanism to eradicate dental plaque and other microbial biofilms is a key element of the intellectual property of EPIEN Medical and it is described in its patents. As noted above all standard dental plaque removal techniques involve application of mechanical shear forces, either powered or manual. Plaque Biofilm is notoriously resistant to mechanical shear forces so none of the standard methods are very easy to do well. HYBENX products are the first formulations to exploit a structural weakness of the biofilm matrix to easily and quickly eradicate it together with the plaque bacteria. HYBENX products are the only products on the market that can safely and effectively do this. The development of unique, clinically useful liquid formulations with potent desiccant activity for professional dental use and the methods to safely implement them constitute additional key elements of the Company's intellectual property.

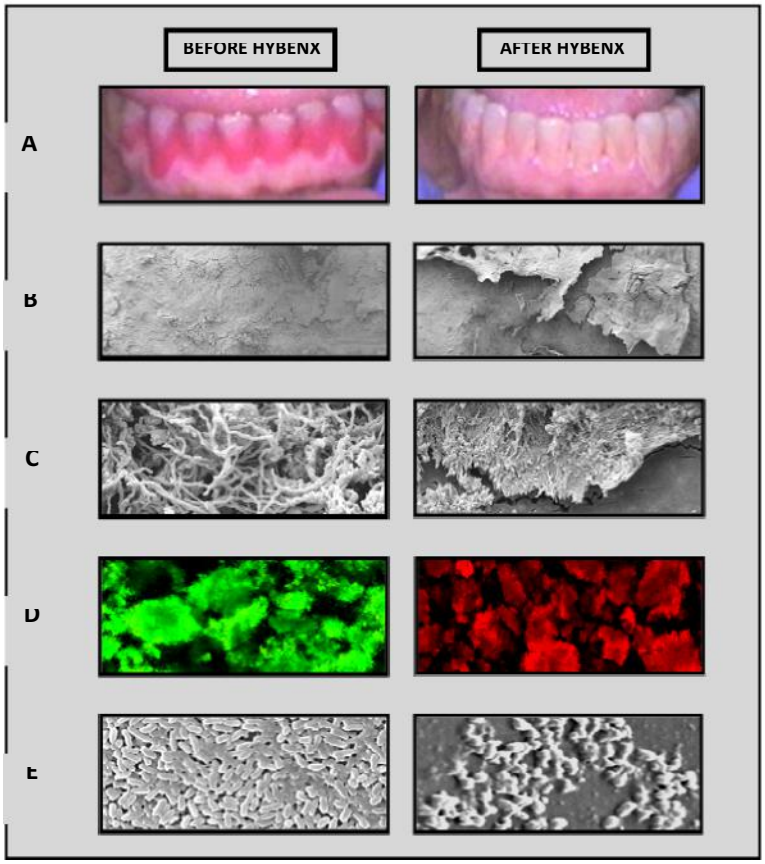
Application Techniques and Key Indications for HYBENX Products in Professional Dental Care As noted previously, HYBENX products are designed to be used in combination with standard dental treatment methods. They are typically formulated as dense, moderately viscous liquids that are readily soluble in water. They are intended to be marketed in glass vials and as pre-loaded syringes.

HYBENX dental products are usually applied focally using a small irrigation syringe with a plastic dental applicator tip, but they can be applied by other means such as with a swab, a probe or wooden applicator stick. The product is left in place for 5 – 60 seconds depending on the situation and it is then rinsed away with water and evacuation. The mechanism of action of the product and its application methods are designed so that HYBENX products can be easily incorporated into any dental procedure without any conflicts.

An application of HYBENX products is intended to be performed whenever a practitioner determines that it would be beneficial to do so. As is the case with many such technologies, the benefit of HYBENX products is most obvious when treating more severe dental conditions such as when patients present with a very heavy build-up of dental plaque and calculus. An application of HYBENX to the supragingival tooth surfaces for 30-60 seconds before starting mechanical scaling will denature, coagulate and detach most of the plaque and calculus so that they can be removed much more easily. A post scaling application of HYBENX will guarantee removal any residual plaque that the mechanical scaling process may have missed.

Another example of a difficult situation would be when patients present with severe inflammatory damage to an oral tissue with pain, swelling, bleeding and necrotic tissues involving pulp or periodontal tissues. A thorough steady rinse of the site with HYBENX will cause all of the necrotized tissue to denature and detach from the surface so the surface is cleansed of debris. Any bleeding or oozing of blood will be stopped by the coagulating action of the product. Any ulcerations of the tissue will be sealed and the edema will be reduced by the intense desiccation properties of the product. The net effect will be to convert a field of inflamed necrotized fragile tissue and blood into something that is clean, dry, solid, disinfected and ready for whatever repair or restoration procedure that is appropriate.

As noted above, HYBENX products are intended to be used in combination with virtually all standard dental therapeutic products and professional mechanical techniques. Depending on the specific clinical situation the unique mechanism of action of HYBENX products provides at least an additive level of combined benefits and at times a level of combined benefits that may be considered synergistic.



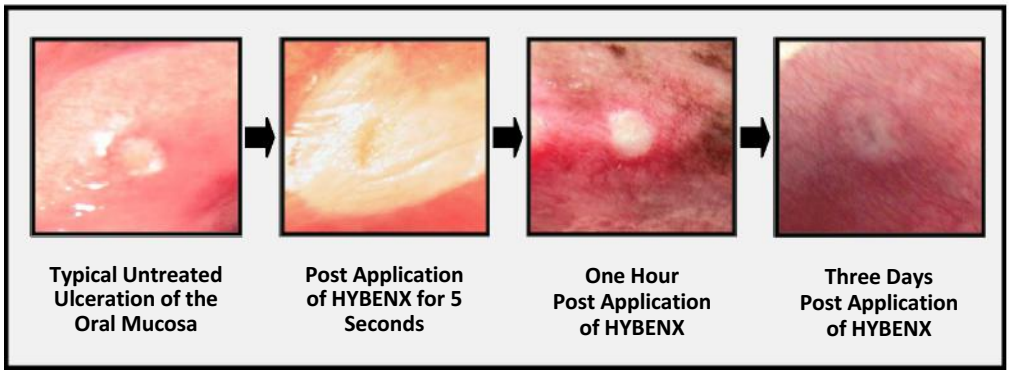
The chart above demonstrates the effects of a brief HYBENX rinse on the surface of dental plaque as seen from several perspectives. In rows A through E the image on the left shows dental plaque before an application of HYBENX and the image on the right shows how the plaque is changed by the product. The HYBENX was applied onto the surface for 60 seconds or less and rinsed with water. This was done for demonstration purposes only. HYBENX is intended for use in combination with mechanical plaque removal methods in clinical practice.

Row A – The left picture shows heavy plaque on lower incisors stained red by Disclosing Solution. HYBENX was applied for I minute and rinsed. The Disclosing Solution was then reapplied to the same teeth post rinse. The picture on the right shows that there is minimal staining by Disclosing Solution after the HYBENX treatment indicating that the plaque had been detached by the product application alone without mechanical intervention.

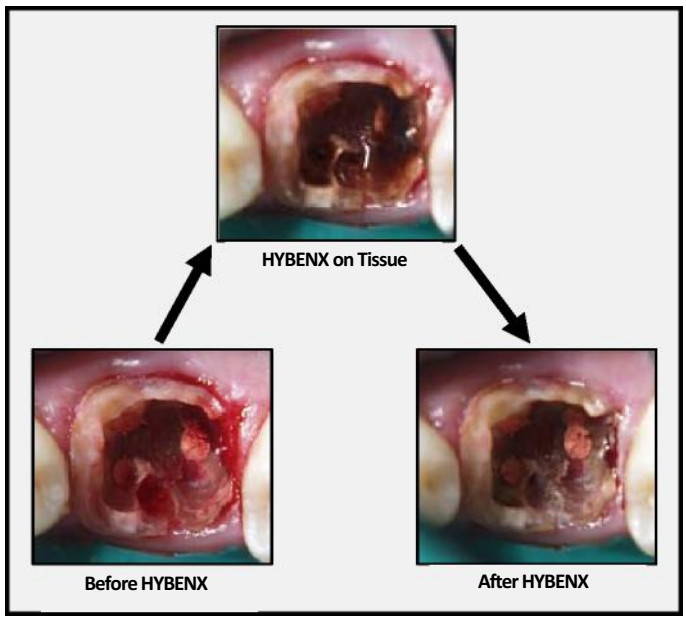
Row B (Low SEM) and Row C (Medium SEM) – Scanning Electron Microscopy (SEM) at different levels of magnification was used to examine the effects of applying HYBENX to the root surface of an extracted tooth from a periodontitis case. The left side images show intact plaque biofilm at low (B) and medium (C) SEM magnification levels and the right hand pictures shown what happens after HYBENX application. The untreated specimens show an intact layer of plaque with bacterial clusters obvious at higher magnification. SEM preparation of biofilm converts the matrix gel to a tangle of string-like structures. The post-HYBENX images show that HYBENX disrupts plaque by desiccation and coagulation so it detaches and reveals the cementum layer underneath.

Row D – Flourescent staining techniques that distinguishes live bacteria (green) from dead bacteria (red) by color was used to examine the effects of HYBENX on a human mixed species oral microbial biofilm. The images show that HYBENX effectively killed all of the bacteria in the biofilm after a simple brief application and rinse.

Row E - HYBENX was applied to a biofilm formed in vitro from a pure strain of common disease-causing oral bacteria (P. aeruginosa). The left image shows an SEM picture at high magnification of an intact layer of microbial biofilm which shows the bacteria intact and stacked up on top of each other. The right image shows that the same biofilm after a 15-second long application of HYBENX. The bacteria are desiccated and coagulated. Many have been detached from the surface. The remaining organisms have the type of degenerated appearance associated with dead microbes.



The illustration above demonstrates the use of HYBENX to treat an ulceration of the mucosal lining of the oral cavity. The far-left panel is a picture of a typical aphthous ulcer with a round elevated rim and a layer of inflammatory exudates on the surface of the ulcer bed. The second picture shows the same ulcer immediately after HYBENX was applied for 5 – 10 seconds with a cotton swab then rinsed. Note the swab-shaped white-colored area. The white color is produced by desiccation of the organic material on the surface by HYBENX. At this point the ulcer is pain-free. The ulceration is still visible as a circular depression in the middle of the treated area. The third picture shows the same site one hour after HYBENX treatment. The healthy mucosal tissue surrounding the ulcer has become rehydrated and is no longer white because healthy intact mucosa is not irreversibly coagulated by the action of HYBENX. The ulcer bed is still white because the fragile tissue on the bed of the ulcer is permanently denatured and coagulated by the product so it does not rehydrate but gets sloughed within a few days. The last picture shows the same ulcer at three-days post HYBENX treatment. The ulcer is almost completely filled in with new repair tissue and the white color is fading.



The illustration above demonstrates the use of HYBENX to quickly cleanse and prepare the surface of a caries lesion that became very large and deep due to neglect by the patient. The picture at the lower-left shows an untreated caries surface that is characterized by necrotic inflammatory debris and oozing blood. This patient also had significant pain and discomfort from this tooth. The surface of lesions such as this must be clean, dry, disinfected and free of blood and debris before any kind of definitive repair procedure can be attempted. Caries repair procedures usually require the use of adhesives and they will not bond well to wet contaminated fragile tooth surfaces. The top-center picture shows the same cavity with a HYBENX dental product delivered over the entire surface of the tooth including the bed of the cavity and the remainder of the enamel, especially along the gum line. The picture at the lower right shows what the same tooth looks like after the HYBENX has been in contact for roughly 60 seconds and then rinsed with water and air-dried. Note that the bleeding has been stopped and the base of the lesion is now cleansed, dry and ready for repair. At this point the lesion also became pain-free.

Exceptional Opportunities to Change Dentistry with HYBENX

The properties of HYBENX products and the benefits that they provide in the treatment of dental disorders are unique. There are some clinical situations where application of a HYBENX product has the potential to fundamentally change the way that a professional dental treatment method is performed. Several examples are provided here.

1) Oral Ulceration and Mucositis

Ulceration and inflammation of the oral mucosa is usually treated with a variety of topical agents that are designed to provide temporary relief of pain and discomfort while the lesions heal. These products typically must be applied repeatedly throughout each day for 7-10 days.

HYBENX products can be used to instantly relieve the pain and discomfort of mucosal inflammation and ulceration in a single application. The products are applied with a swab to the damaged area for only 5 – 10 seconds and then the lesion is rinsed with water. When HYBENX contacts damaged and infected tissue on a mucosal surface it instantly desiccates it to the point where it denatures and coagulates the debris and fragile tissue structures. This coagulation process in effect instantly converts the damaged tissue debris into a membranous layer of dense denatured disinfected tissue. This layer then acts as a protective barrier that prevents microbes from re-infecting the area of the lesion and prevents environment irritants from causing more pain. Occasionally a dental patient may defer completion of a routine dental procedure due to the pain of a mucosal lesion. A practitioner can now provide relief from that pain within seconds by using HYBENX Technology.

2) Endodontics

HYBENX can be used to completely remove the smear layer (biofilm) in the root canal during preparation for capping. In addition, HYBENX reduces bleeding and weeping which interfere with proper sealing of the canal.

3) Subgingival Cleaning in Minimally Invasive Periodontal Therapy

Subgingival cleaning is the primary technique used in the treatment of periodontitis and in the maintenance of periodontitis patients. Periodontitis is a disease where the tissue that connects the root of teeth to the jaw bone is destroyed by an inflammatory reaction to bacteria in the area. The destruction of the tissue creates a space between the tooth and gum tissue referred to as the periodontal pocket. In periodontitis this space becomes filled with necrotic tissue debris, blood and infectious microbes. The methods for treating this disease requires that the pocket by cleansed of the dead tissue and microbes so that it can heal. This is usually done by a mechanical procedure that is referred to as scaling and root planning (SRP). Antiseptic and antibiotic solutions are sometimes also applied to the pocket to suppress growth of bacteria. SRP is usually effective in milder cases of periodontitis where destruction of the tissue in the pocket has not extended very far. SRP is much less effective in cases of more severe tissue destruction where the pockets are deeper because the mechanical techniques become more difficult to perform and require more time to do well. Application of HYBENX products could potentially change the way that periodontitis treatment is performed by chemically doing much of the cleansing that is now done mechanically. When a periodontal product is irrigated to overflowing with a HYBENX product many beneficial things happen in the pocket. Everything that triggers or promotes inflammation will be desiccated, denatured and detached from the pocket surfaces so that it can be easily rinsed away. This includes microbes, blood, necrotic tissue, white blood cells and any other inflammatory mediators. Open tissues are coagulated over and sealed. Edema is reduced and as a result the gum tissue is tightened around the tooth root. Pre-SRP HYBENX irrigation together with post-SRP HYBENX irrigation minimizes the amount of mechanical scaling and mechanical trauma that has to be delivered to the periodontal pocket in order to achieve a therapeutic result. Treatment procedures are completed more quickly and patients have less discomfort when the anesthetic wears off.

Another fact to consider is that effective performance of SRP requires significant training and clinical experience. This is especially true in the case of severe periodontitis where the pockets are deeper. Subgingival cleaning that is supplemented by adjunctive applications of HYBENX does not require as much training, as much experience or as much effort to be just as effective, even in the case of deep pockets, because most of the cleansing work is done by the HYBENX product and does not depend on the manual scaling technique and experience of the practitioner.

Finally, in cases of peri-implantitis, HYBENX is particularly effective in debriding plaque from the irregular complex metal surfaces of both sub- and supra-gingival restorative structures.

4) Using HYBENX to Improve Infection Control Procedures

Infection control policies involve the implementation of procedures specifically designed to reduce the risk of spreading infectious diseases between patients and staff. Typically, many infection control methods are utilized in every dental practice including such things as mandatory use of gloves, wearing surgical masks and frequent cleaning of all clinic surfaces. These various methods are considered to work in concert with each other. Each one is viewed as an additional "layer" of protection. The decision as to whether or not any specific additional layer of infection control should be added to a clinical practice depends on the cost/benefit analysis for that layer. HYBENX products are inexpensive and easy to apply. They require no additional equipment or specialized training. They can be used to completely and instantly eradicate all microbial pathogens from any surface in the oral cavity where a dental procedure is to be performed thereby eliminating any risk of spreading pathogens during the procedure. An application of HYBENX to the same area after a procedure is completed eliminates the risk that pathogens were spread into that site by the practitioner.

5) Using HYBENX in Prophylactic Supragingival Cleaning and Preventive Care

Routine supragingival cleaning and polishing of teeth are a critical part of preventive dental care. However, reimbursement for these procedures is usually limited and fixed which means that it is important to do this work in the most cost-effective manner possible. HYBENX is most useful when doing preventive care procedures on individuals with significant plaque and calculus on their teeth. A simple brief focal application of HYBENX to the surface of dental plaque will cause it to quickly detach from the tooth surface making it easier to remove. The structure and attachment of calculus deposits are also disrupted by HYBENX so that they are much easier to remove after treatment. In other words, the more significant the plaque and calculus deposits are, the more useful HYBENX is as an adjunctive agent.

6) *Using HYBENX in Cavity Disinfection in Minimally Invasive Caries Restoration*

Cavities are caused by bacteria living in plaque on the surface of teeth when they metabolize certain carbohydrates and secrete organic acid waste products onto the tooth surface. The acid erodes the enamel mineral from the surface to the point where the dentin inside the tooth is exposed. This in turn allows the biofilm to expand into the interior of the tooth where the acid starts to erode the mineral of the dentin and softens it.

The repair of a tooth cavity requires that the infectious biofilm material that is causing the disease to be destroyed and mechanically removed from the interior dentin. In addition, the damaged dentin is supposed to be mechanically removed so that whatever material is used to fill the cavity can bond to solid healthy undamaged dentin and not to soft necrotic tissue. A major concern when performing the mechanical removal of diseased dentin has to do with how much material must be removed to have a successful outcome. Removing too little creates a risk that the restoration will fail due to persistent infection or re-infection. Removing too much creates a risk of iatrogenic exposure of the tooth pulp and subsequent pulpitis as well as a risk of simply damaging the structural integrity of the tooth to the point where the tooth is easily cracked by mechanical stress. These concerns have caused some to advocate for the development of so-called minimally invasive caries restoration techniques. The idea is that these techniques would utilize a minimum amount of mechanical dentin removal to lower the risks of pulp exposure and structural damage and would use some other means to eradicate the biofilm infection in the dentin and firm up the dentin tissue for bonding.

HYBENX products meet the requirements for developing the technology for minimally invasive cavity restorations. For example, after removing a minimum amount of damaged dentin, the cavity would be irrigated with a HYBENX agent for 60 seconds. In that time period the desiccating action of HYBENX would coagulate and kill and microbes within the dentin. The process would also denature and detach only damaged dentin tissues leaving a solid base of material for bonding the restoration material.

7) Using HYBENX to Limit the Risk of Spreading Bacteria and Other Pathogens
Whenever a mechanical dental procedure is performed there is a risk of mechanically spreading a variety of disease-causing microbes into the blood stream of the patient, and/or, into the air of the dental clinic.

It is a well-accepted fact that many mechanical processes in the oral cavity, including brushing your teeth when gingivitis is present, can lead to the spread of bacteria from the surface of oral tissues into the bloodstream which creates a condition known as bacteremia. For most patients with a healthy immune system this type of episodic bacteremia is not a significant health issue. For some dental patients, however, this level of exposure to blood borne bacteria is considered to be a serious risk to their health and they are usually provided with antibiotics when they have any type of dental procedure to limit that risk.

Many mechanical professional dental procedures, especially supragingival scaling, carry the risk of creating a splatter of particulates into the environment which consist of plaque biofilm, calculus and other oral debris. These particulates are initially airborne and while airborne they can in some cases spread and land on numerous surfaces throughout the clinic including staff and patients. When these particulates become airborne they carry with them all of the various microbes that are found in the oral cavity including disease-causing bacteria, fungus, virus and parasites.

The risk of this type of mechanical iatrogenic spread of disease-causing microbes can be reduced and perhaps even eliminated all together by using HYBENX products. If all oral tissue surfaces that are to receive any form of mechanical contact during a dental procedure are first treated with an application of HYBENX before any mechanical force is applied, then any microbes that may spread from that area will be dead and therefore no longer a hazard.

8) Using HYBENX in Difficult Clinical Situations with Limited Resources and/or Time
It is not uncommon in a typical clinical dental practice to have a patient present unexpectedly with a severe dental problem that needs immediate attention. These cases are often very challenging because they can require so much time to provide the appropriate care that they disrupt the entire clinic schedule. Sometimes this situation forces a decision as to whether or not a referral is necessary even when it is not the preferred course of action. At other times the choice of which treatment to provide may be dictated by the fact that time and resources are limited and not by consideration of the best possible clinical outcome for the patient.

Application of professional HYBENX products to the diseased tissues in the oral cavity can provide additional options for treating many of the patients who come to clinic in these types of situations. Application can be done easily and quickly by without any complicated equipment or specialty training. The application itself may stabilize the situation by immediately relieving pain and discomfort, stopping any bleeding and clearing away and infectious matter. Temporary therapeutic measures may then be taken that will allow for more time to plan and execute the appropriate definitive therapy without any undue stress. The clinic schedule can remain undisturbed and patient care is optimized.

It is possible that specialty dental products derived from HYBENX Technology could be developed for nations and regions of the world that currently have limited resources for providing the clinic space and staffing for traditional types of dental care. As noted previously the utilization of HYBENX for the treatment of most common dental diseases does not require expensive equipment or extensive training. HYBENX can be applied very quickly and easily with minimum risk to almost any dental patient. And while an application of HYBENX by itself may not be optimal and definitive therapy, in many cases in would be a highly cost effective and ethical alternative to doing nothing or doing the wrong thing.

HYBENX Professional Dental Product Development and Regulatory History

After the initial development work on the HYBENX Technology concept was completed, work began on transforming the basic HYBENX formulations into finished professional dental products complete with regulatory clearances for marketing.

A formulation was first created that eventually became our core HYBENX professional dental product which was named HYBENX Plaque Biofilm Remover (HPBR). The HPBR formulation was then modified to create a product intended specifically for the treatment of oral ulcers, named HYBENX OralMedic (HOM). HOM is essentially just a less viscous and less concentrated variant with the exact same constituents as HPBR. Preclinical safety and efficacy testing was performed primarily with the HPBR product since the HOM product was simply a less concentrated version of the same formula.

The most critical evaluations that were performed are outlined in the table below. This testing was sufficient to meet the requirements for marketing clearance in Europe, Canada and a number of countries in the Middle East. HYBENX Products have now been used safely in over seven million oral procedures.

STUDY	BASIC STUDY DESIGN	RESULTS
Biocompatibility Test Panel per ISO 10993-1	As specified in the applicable ISO standards for this product type	HPBR/HMO passed the Biocompatibility Test Requirements
Pharmacokinetics and Metabolism in a Canine Model System	The ADME of Radio-labeled HYBENX on an oral mucosal surface and injected i.v. was studied in beagle dogs by scintillation counting and HPLC chromatography.	HYBENX was not metabolized by oral mucosal tissue. It was rapidly cleared by the kidneys and not stored when injected intravenously.
Treatment of Acute Pulp Exposure in a Canine Model System	Acute pulp exposures were created in multiple teeth in each of three dogs. Standard therapy with calcium hydroxide was compared to therapy with HYBENX at three time points using histological examination of the teeth after extraction.	Over the course of the study 25% of the pulps treated with the calcium hydroxide died and none of the teeth treated with HYBENX dies. New dentin formed faster
Treatment of Chronic Periodontitis in a Canine Model System	Beagle dogs with moderate to severe periodontitis were treated with either Scaling alone, HYBENX alone or both. Teeth were extracted at time points up to 4 weeks and examined by histological techniques.	HYBENX treatment enhanced the level of cleaning and did not cause any damage to soft or hard tissues.
Eradication of Biofilm in the MBEC Model System	HYBENX was studied in a specialized *in vitro* model system for activity against bacterial and fungal microbes living in a microbial biofilm as seen by SEM and standard microbial culture techniques	After 10-15 seconds of exposure HYBENX killed all of the microbes and denatured/coagulated the biofilm matrix

STUDY	BASIC STUDY DESIGN	RESULTS
Eradication of Biofilm in a Porcine Acute Wound Model System	Small shallow wounds were made in the back of 3 pigs. The wounds of each were infected with one of three separate bacteria – MRSA, Pseudomonas or Acinetobacter. The bacteria were allowed to grow into biofilms. The biofilms were treated with HYBENX for 1 minute then harvested for examination by standard culture techniques and by histological techniques.	HYBENX treatment for 1 minute killed all of the bacteria in all of the wounds by desiccation, denaturation and coagulation.
Eradication of *ex vivo* Human Plaque Biofilm	HYBENX was applied for 1-2 minutes on specimens on mixed species human dental plaque biofilm, both on extracted teeth and on bench specimens. Specimens were examined by SEM and confocal fluorescent spectroscopy.	1-2 minute application of HYBENX killed all of the microbes in mixed species human plaque biofilm and caused the matrix to denature, coagulate and detach from the tooth surface
Enamel Erosion in a Bovine Model System	The erosive action of HYBENX on bovine incisors was compared to the erosive action of other dental products and some acids commonly found in foods and beverages. The results were determined by SEM, hardness testing and Calcium ion release by HPLC.	HYBENX was found to be less erosive than common food and beverage acids. It was much less erosive than other professional dental products such as Phosphoric Acid, Citric Acid and EDTA solutions

Regulatory History of HYBENX Technology Products

A formal Technical Memorandum was prepared for the HYBENX Plaque Biofilm Remover product and the OralMedic product. They were sent for review and classification to the appropriate regulatory agencies in Canada and the UK. In all cases the products were classified as low risk Class I Medical Devices for purposes of regulatory control and reporting. Manufacturers of Class I products are required to perform self-regulation of their operations and certify to the authorities that they are following all necessary regulations. Class 1 products do not require additional formal review, inspections or clinical trials prior to marketing their products. Clearance by the UK provides automatic clearance to market the products throughout all of the countries of the European Union.

HYBENX products have also been cleared in several countries of the Middle East that routinely accept products that are cleared by regulators in the EU. Initial steps have been taken to obtain regulatory approval in certain Asian countries.

The US FDA has cleared HYBENX in the form of HYBENX® Root Canal Cleanser under the 510(k) protocol for the debridement of the smear layer of the root canal during endodontic procedures. Although used as a topical agent that is applied only briefly and infrequently, not absorbed, leaving no residue, and viewed as a low risk product, future embodiments of HYBENX Products may still require a formal new drug approval process. The Company has decided to postpone future costly regulatory applications in the US until the launch of the current product, and those outside the US, have been completed.

The Regulatory Process Expected for New HYBENX Dental Products and Expanded Indications

The Company intends to perform additional studies and clinical trials related to expansion of the clinical indications for HYBENX outside of the US for the near term. The regulatory classification of the product in the Canadian and European systems allows for more flexibility in performing additional development work. This should result in substantial savings of time and funding for product development before submitting any new marketing applications to the US FDA.

The Significance of HYBENX Technology for Dental Practitioners

In order for the HYBENX professional dental products to become commercially successful they must provide significant clinical advantages for dental practitioners. More specifically, practitioners will only become steady customers when they recognize that that there is a favorable Cost/Benefit ratio associated with implementation of HYBENX dental products into their daily routine.

Application of HYBENX products does not require any expensive or specialized equipment. The techniques used for applying the product require no specialized training or extensive experience. The price of the HYBENX products is set to be affordable and is in a range that is typical for other liquid agents used to prepare oral tissues for dental procedures. Therefore, the cost of bringing HYBENX dental products into a clinical practice should be viewed as reasonable and acceptable for the vast majority of dental offices.

The main benefits for practitioners to start using HYBENX dental products on a routine basis can be divided into three main categories. First, HYBENX products can improve the cost efficiency of their practice by making the performance of many procedures easier and better. Second, the availability of HYBENX products can provide additional options for many dentists to expand the types of patient care that they can provide without additional resources. Third, HYBENX products provide an answer for practitioners to the problems presented by the link being established between inflammation in the mouth and systemic disease.

HYBENX Products Improve the Cost Efficiency of Dental Procedures

HYBENX products can improve the cost efficiency of a dental practice because the they can accomplish cleansing and disinfection work using a single quick chemical process that would otherwise have to be done by more time-consuming mechanical methods and with multiple dental products. In effect, HYBENX can do much of the cleaning and tissue preparation work for the practitioner in one easy step. As noted previously, the amount of time and effort that an application of HYBENX can save depends totally on the nature of the case.

HYBENX provides its greatest benefit in cases where the disease and tissue damage are the greatest. Consider the challenge of doing subgingival cleaning of a deep periodontal pocket in a case of severe periodontitis. Mechanical cleaning of deep pockets is very difficult to do and requires extensive training and experience. However, irrigating the pocket with HYBENX is not any more difficult in the deeper pockets as in shallower ones. It requires no specialized training or expertise. In this situation HYBENX saves money by saving time. In addition, recently published reports indicate the reduced need for routine antibiotic administration in certain treatment protocols.

Another example of improving efficiency is found in patient pain management. HYBENX products provide relief of pain and discomfort be stopping the inflammatory process, by reducing edema and by sealing open wounds so they are protected from environmental irritants. HYBENX reduces the need to provide medications for pain relief after a procedure minimizes the time needed to respond to patients with pain management problems.

HYBENX Products Provide New Options for Expanding Patient Care Services

Dentists in a general practice are frequently confronted with difficult cases that create problems with patient care and management of the clinic schedule. It is not uncommon for a dentist to refer such patients to dental specialists for care rather than take the time to do a procedure themselves.
For example, consider again the patient with deep periodontal pockets. It would be a common practice for some generalists to refer such patients directly to a periodontist for treatment because of the known

difficulty in cleansing and disinfecting deep pockets. A general dentist may determine that he does not have the time or expertise to handle such cases. This obviously is both a loss of near term patient revenue and a lost opportunity for future revenue if the patient never returns to the generalist for care. HYBENX is so simple and easy to use, and, is so effective in cases where the key challenge is tissue cleansing and disinfection that it can enable generalists to successfully treat many of these cases. This provides the generalist with an opportunity to retain patients and generate additional revenue. HYBENX becomes an equalizer that raises the bar on the requirements for patient referral in certain common clinical situations.

HYBENX Products Provide an Answer to a Potential Healthy Mouth-Healthy Body Mandate
There is growing evidence that chronic infection and chronic inflammation in the soft tissues of the oral cavity lead to an increased risk of developing systemic health problems, especially problems with the cardiovascular system. These findings are consistent with other data that suggests that chronic inflammation anywhere in the body is a significant risk factor for a number of serious disorders including stroke, diabetes and cancer.

As the linkage between oral health and systemic health becomes more firmly established, dental practitioners soon will be expected to do everything possible to stop oral inflammation and infection as quickly as possible. Only now they will be doing it to not just preserve dentition but to actually lower the risk of catastrophic illness. Among dental practitioners there will be concern and open questions. What will be the standard of care for patients with different levels of oral inflammation when its significance is fully recognized? How will the responsibilities and potential liabilities change? Are patients with certain pre-existing conditions to be treated differently? How will this change the cost of doing business? Will this effect reimbursement rates in any way?

An application of HYBENX is unique in its ability to address the concerns about inflammation and infection control in a cost effective manner. HYBENX professional dental products eradicate plaque, microbes, tissue debris and anything else that can trigger inflammatory infiltration into oral soft tissues. With minimal expense and effort practitioners can significantly improve their approach to the management of all types of inflammatory processes in the mouth.

Potential for Development of Additional Markets for HYBENX Technology Products
There are substantial opportunities for the development of additional markets for HYBENX Technology. The same general forms of infection and inflammatory diseases that are found in the mouth are also present on skin. For example, it is now known that chronic non-healing skin wounds, such as bed sores and diabetic foot ulcers, are difficult to heal because they become covered with a relatively thick layer of microbial biofilm that is resistant to traditional antimicrobials – a characteristic also found with dental plaque. Recently published clinical papers indicate that HYBENX Products may be a useful adjunctive debridement agent for advancing the healing process in these wounds.

Also, the topical approach to developing therapeutic agents for lesions of the skin is even more common than it is in the mouth so the treatment methods of HYBENX Technology are applicable. Cosmetic dermatology in particular is a rapidly growing area of professional medical practice that offers some exciting opportunities for using the HYBENX approach to tissue surface cleansing and conditioning in combination with popular current products.

The Company also plans to investigate parallel opportunities for HYBENX products in professional veterinary health care. Although the market for professional veterinary products is a fraction of the size of the human medical and dental markets, it would be a natural place for expansion since companion animals often develop diseases of the mouth and skin that are direct counterparts to human disorders.

Examples of Potential HYBENX Products for Therapeutic Dermatology Applications
HYBENX products should be highly effective in the treatment of minor infections and inflammatory lesions of the skin. One of the most common conditions on the skin is dermatitis, otherwise referred to

simply as a rash. A rash can develop for many reasons, only some of which involve infectious microbes. All forms of dermatitis, however, by definition include a process of surface inflammation of the skin. In more serious cases there may be edema and focal breakdown of the skin leading to small ulcerations. Mechanical trauma through scratching leads to additional surface damage, bleeding and even further inflammation. An application of HYBENX will dry out the skin surface, debride away any necrotic tissue and denature any allergens or other inflammatory mediators on the skin. HYBENX in this case could be used in combination with traditional dermatitis medications. An application of HYBENX would be used to clean, disinfect and prepare the skin surface for application of an antibiotic or an anti-inflammatory steroid which would perform more effectively because of the HYBENX preparation step.

Athletes Foot is a actually just a familiar type of infectious dermatitis that is caused by a fungus that thrives in damp warm tissue such as the skin between the toes. The fungus, known more specifically as a dermatophyte, burrows into the top layers of the skin and forms a biofilm. The biofilm layer and the covering of skin cells make the dermatophytes somewhat resistant to the anti-fungal medications that are commonly used to treat this condition. When you apply a HYBENX formulation to the skin between the toes when dermatophytes are present it aggressively desiccates the infected tissues. This dries and denatures the skin cells so that they are shed from between the toes with the fungus trapped within the layer of coagulated dead skin and debris. The HYBENX application technique uses desiccation to instantly cleanse the dead tissue away and immediately kill any dermatophytes that are present on contact. HYBENX can also be used in a combination mode with traditional Athletes Foot medications as a product for preparing the tissue by cleansing and disinfecting it before the anti-fungal is applied. This will of course make the anti-fungal more effective since the protective barrier of dead tissue and debris is removed by the HYBENX.

The therapeutic approach described in the examples above could be extended to the treatment of many more additional types of skin lesions. Virtually any type of topical disorder that involves the presence of inflammation, infection and tissue debris can potentially be treated more efficiently when the lesions are first debrided, exfoliated, cleansed and disinfected with HYBENX. This includes common problems such as acne, calluses and keratoses, but also some less common conditions such as psoriatic plaques.

Examples of Potential HYBENX Products for Cosmetic Dermatology Applications

The desiccating and denaturing action of HYBENX products can be used on facial skin that has typical sun damage, but is otherwise healthy, to improve its appearance. This occurs because the desiccating action of the product causes damaged skin epithelial cells to lose attachment to the underlying skin surface and exfoliate more rapidly than normal. When used in this manner the HYBENX formulation can be considered to be cosmetic facial exfoliants not unlike the popular cosmetic exfoliants that are based on alpha and beta hydroxyl acid technology. The exfoliating action of HYBENX Technology may in fact prove to be synergistic with the exfoliating action of the alpha/beta hydroxyl acids since they use very different chemical mechanisms of action. This would present the Company with some very exciting opportunities for the development of combination exfoliant treatments with unique efficacy due to the complementary actions of the two different technologies.

Examples of Potential HYBENX Products for Veterinary Applications

HYBENX product can be used to treat dental and dermatologic problems in companion animals in the same way that they are used in humans. For example, dogs are known to frequently develop significant gum disease and periodontitis. Canine plaque and calculus can be very difficult to remove because it gets very thick before many pet owners decide to seek treatment. Dogs are commonly treated for dental problems while under anesthesia. Using HYBENX to soften the plaque and calculus to expedite removal will shorten the amount of time that an animal must remain under anesthesia. Ear infection in dogs is also a common problem. In less than a minute an application of HYBENX to the infected outer ear tissue will kill the mites, cleanse the damaged tissue and seal any open wounds so that the dogs are more comfortable.

Traditional ear medications can then be used for home care to extend the disease free period until the lesions are completely healed.

Potential for the Development of Additional Platform Formulations and New Technologies

The focus of the research and development program at EPIEN has been the HYBENX Technology. The HYBENX Technology, however, may in fact be regarded as just one example from a potentially large class of related techniques for the treatment of diseased tissue surfaces. This class of technologies is defined by the use of non-drug chemical processes to change the physical condition of the surface of tissues in a manner that provides a therapeutic or cosmetic benefit.

In general, an R&D program in this area would focus on evaluating the potential of a variety of other desiccants, denaturants, chaotropic agents, surfactants and miscellaneous derivitizing chemicals to safely and effectively change the physical condition of a tissue surface by temporarily changing the physical microenvironment. In other words, this program would use the techniques of physical chemistry to develop therapies for diseases that have been treated with therapies derived from pharmaceutical chemistry.

Suggested Reading:

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