

Osteoarthritis Pain Management Update

BioRestorative™ Profiling: *The New View of Hyaluronic Acid Today*

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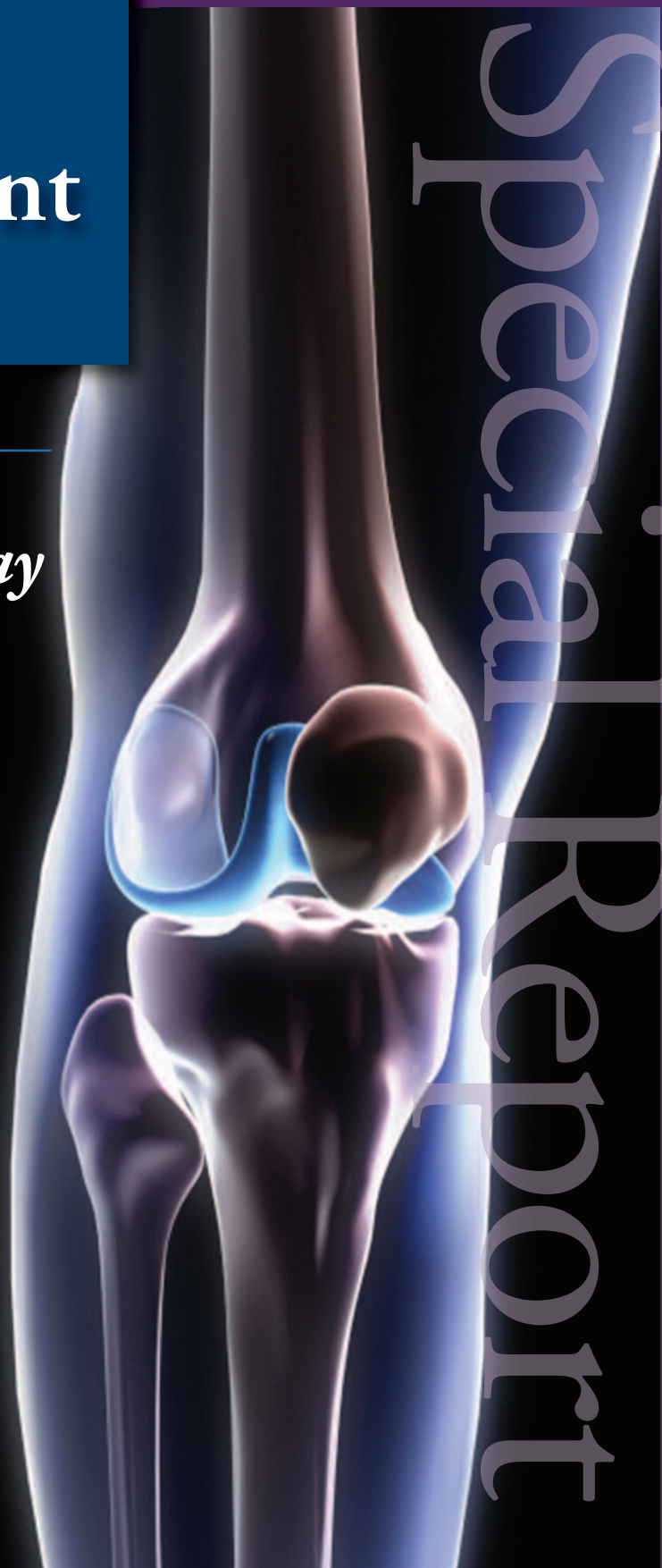
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METHODS

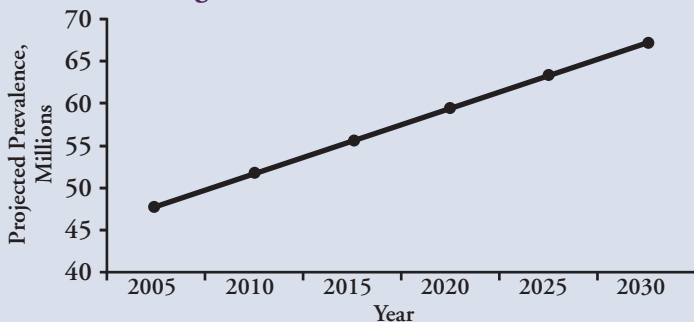
Through the sponsorship of Ferring Pharmaceuticals, an expert panel of interdisciplinary clinicians was assembled to review the beneficial properties of endogenous hyaluronic acid (HA), evaluate the available exogenous HA products to determine how they compare in their resemblance to endogenous HA, and agree on an umbrella term that would best encompass the features of the ideal HA product for both clinicians and patients. Dardine & Associates, LLC was selected to facilitate the open forum discussion, develop the draft of this special report based upon the meeting proceedings, and obtain consensus agreement from the panel of experts.

BioRestorative™ Profiling: The New View of Hyaluronic Acid Today

BACKGROUND

Osteoarthritis (OA) is estimated to affect almost 27 million Americans. Second only to heart disease as a cause of work disability, OA affects people of all ages, although the majority of those experiencing OA are adults. The prevalence of OA has increased and is likely to continue increasing as the “baby boom” generation ages, as shown in Figure 1.¹⁻³

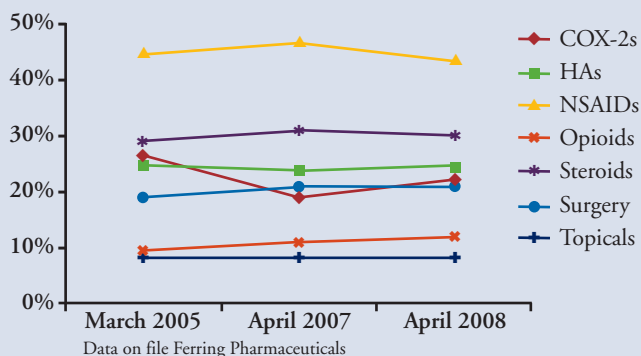
Figure 1. Projected Prevalence of Diagnosed Arthritis Among US Adults.³



The current market for OA treatments, aside from a slight decline in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and a slight but surprising upswing in the use of cyclooxygenase-2 (COX-2) inhibitors, has remained relatively stable over the past few years, as illustrated by the graph in Figure 2. In the past year, use of intra-articular steroids has dropped slightly, while the use of hyaluronic acid (HA) products has remained the same. With a goal of symptom relief and improvement in function, many clinicians believe that the HA product likely to yield the best results may be one that most closely resembles endogenous human HA.

With this hypothesis in mind, a group of clinicians in the fields of orthopaedics, rheumatology, and physical medicine/rehabilitation met in New York City in November 2008. Their purpose was to review the beneficial properties of endogenous HA, evaluate the available exogenous HA products to determine how they compare in their resemblance to endogenous HA, and agree on an umbrella term that would best encompass the features of the ideal HA product for both clinicians and patients.

Figure 2. HA Market, 2006-2008



The panel comprised the following clinicians*:

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Chairman, Department of Orthopaedics and
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New York Hospital Queens
Flushing, New York

Specialty: Orthopaedic Surgery/Sports Medicine

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**The panelists serve as consultants for Ferring Pharmaceuticals Inc.*

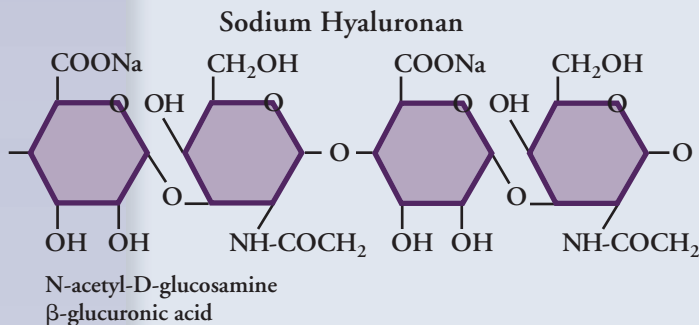
ENDOGENOUS HA

Endogenous HA is found in high concentrations in connective tissue, including skin and cartilage. HA is a key player in joint biology, supporting the viscoelastic and lubricating properties of synovial fluid.⁴

Description

HA is a polysaccharide chain composed of repeating disaccharide units (Figure 3).⁵ HA, a fairly large molecule, turns over in about 12 hours, which is much slower than that of small solutes and proteins.^{6,7} HA is produced within the joint by synoviocytes, fibroblasts, and chondrocytes. The long molecules interact, increasing the viscosity that led to the use of HA as replacement therapy for its viscoelastic properties. HA is present throughout the body, including in skin, vitreous humor, cartilage, and the umbilical cord; its highest concentration, however, is in joint synovial fluid.^{8,9}

Figure 3. Structure of Hyaluronan⁵



HA in Healthy Joints

Within the healthy adult knee there is approximately 2 mL of synovial fluid, with an HA concentration of 2.5 to 4.0 mg/mL. HA is present in healthy joints at an average molecular weight of about 5 million daltons.⁵ HA supports joint function by providing viscoelasticity and lubrication, enhancing the shock-absorbing action of synovial fluid. HA acts as a lubricant during low-impact joint movement and as a shock absorber during high-impact movement.⁹

The mechanism of action of HA is not clear. A number of possibilities have been postulated based on current understanding of the properties and activity of endogenous HA, some of which are discussed below, but there is no direct clinical evidence to support any theory of HA's mechanism of action.

HA binds to several receptors, including CD44 receptors and receptors for hyaluronate-mediated

motility (RHAMM), on cells that are involved in OA pathology.⁸ The binding of HA to CD44 is an example of its role in maintaining communication between cells and extracellular matrix and, thus, fostering cartilage homeostasis.¹⁰ Low-molecular-weight HA has been observed to promote cytokine expression and is, therefore, proinflammatory, whereas higher-molecular-weight HA downregulates cytokine expression. When tissue becomes inflamed, polymorphonuclear leukocytes mediate enzymatic and oxidative free radical reactions that cause tissue damage. HA has been observed to scavenge the free radicals, to a molecular weight-dependent degree, protecting joints from oxidative damage. It also physically prevents the entry of polymorphonuclear cells into synovial joints. It has been suggested that when HA binds to receptors on cells, they form a mesh around the cells that inhibits interaction with the radical-generating species.⁸

HA has several “chondroprotective” qualities. In addition to helping maintain homeostasis in the cartilage matrix and counteracting oxidative injuries in chondrocytes, as mentioned above, it protects chondrocytes from apoptosis and inhibits interleukin 1-stimulated production of matrix metalloproteinases. In addition, HA plays a role in chondrogenesis.⁴

HA in Arthritic Joints

In OA, the balance between matrix synthesis and degradation is upset, and degradation begins to exceed synthesis. In arthritic joints, the rate of collagen turnover and the water content increase. Thus, HA is present at a lower concentration, typically reduced by one-half to two-thirds of the healthy concentration. Its molecular weight is also decreased substantially. The reduced concentration and molecular weight of HA lead to diminished interaction between molecules and, thus, decreased synovial fluid functionality, exacerbation of cartilage damage, and increased synovial trauma. There also is a decline in the viscoelastic properties of the HA in the joint. This alteration in HA structure and concentration during the degenerative process decreases the material's ability to effectively lubricate the joint surface and distribute the stresses associated with weight bearing.^{5,8,11}

Synovial fluid from patients with OA has been found to contain high levels of inflammatory cytokines, which are thought to induce cartilage degradation. Additionally, nociceptors of articular nerves become hyperalgesic and allodynic in OA.^{8,11} The use of intra-articular injections of exogenous HA grew out of the premise that replacing endogenous HA could restore the viscoelasticity, lubrication, analgesic, and anti-inflammatory effects lost in OA.^{5,9}

EXOGENOUS HA

The use of intra-articular HA injections for treating OA pain of the knee was approved by the US Food and Drug Administration (FDA) in 1997.¹² Injection of HA into an osteoarthritic joint has been shown to provide long-term improvement of the quantitative and qualitative properties of endogenous HA, increasing joint lubrication and reducing pain.¹³

The concept of viscosupplementation—removal of abnormal synovial fluid and replacement with purified HA to restore viscoelasticity—does not completely explain the analgesic effects of HA in OA pain, as the benefits derived from this procedure have been observed to outlast the residence time of HA in the joint by weeks or even months.⁸ There may be other, as yet undiscovered, explanations of HA's effect as well. For example, the fact that pain relief from intra-articular HA treatment typically outlasts HA's half-life in the joint suggests that intra-articular HA has disease-modifying properties.⁴

Despite the fact that the FDA has classified exogenous HA as a device rather than as a medicine, there is substantial evidence that intra-articular injections of HA have a pharmacologic effect.⁸ This evidence includes the traits discussed above and summarized in Table 1.

Available Products

There are several HA products on the market. The products differ in a number of ways, including source, protein content, viscosity, and molecular weight. Table 2 lists the HAs currently approved by the FDA for treating pain associated with knee OA. Most are avian in origin, and two are bioengineered via fermentation of bacteria.¹² There are also between-product differences in crosslinking and intracapsular longevity. Most of the products have short half-lives ranging between 1 day and 2 weeks. Hence, as mentioned above, sustained relief of pain for up to 1 year following injection is not a result of viscosupplementation alone but of some other mechanism or mechanisms.^{4,7} No studies of intra-articular HA are truly placebo controlled, because as soon as a needle is inserted into a joint, either to remove excess synovial fluid or to inject saline solution or active treatment, the patient experiences some relief – a placebo effect.¹⁴ This has confounded efforts to prove the effectiveness of HA.

Table 1. Potential Disease-Modifying Activities of HA⁴

Prevention of destruction

- Inhibition of expression and activity of chondrodegenerative enzymes such as metalloproteinase
- Inhibition of destructive inflammatory processes

Promotion of repair

- Stimulation of chondrocyte growth and metabolism
- Decrease of chondrocyte apoptosis
- Stimulation of synthesis of cartilage matrix components, including endogenous HA

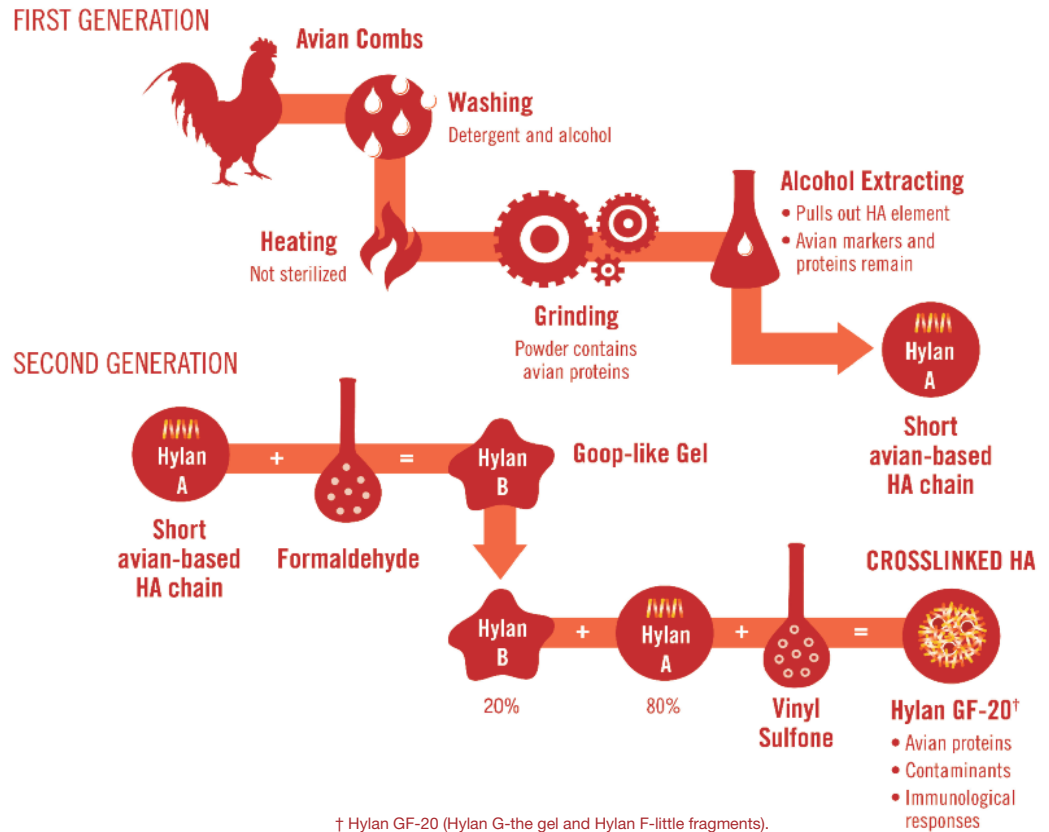
Adapted from Goldberg VM, Buckwalter JA. *Osteoarthritis Cartilage*. 2005;13:216-224.

There is substantial evidence that intra-articular injections of HA have a pharmacologic effect.⁸

Table 2. HA Products Available in the United States for Treating OA¹²

Trade Name	Molecular Weight (daltons)	Source
Euflexxa®	2.4-3.6 million	Bioengineered bacteria
Hyalgan®	0.5-0.73 million	Rooster combs
Orthovisc®	1.0-2.9 million	Bioengineered bacteria
Supartz®	0.62-1.17 million	Rooster combs
Synvisc®	6.0 million	Rooster combs

Figure 4.
Manufacturing
Differences
Between HAs*



Euflexxa

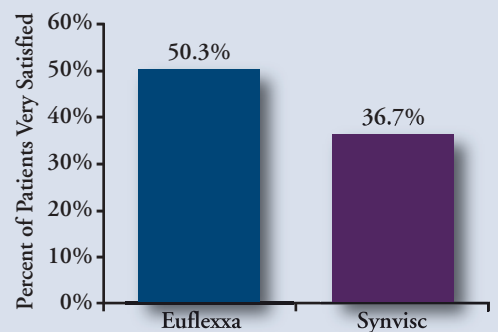
The newest HA product on the US market is Euflexxa. This HA, which was the first non-avian-derived product available in the United States, has the second-highest molecular weight of all available products. Despite the fact that the avian-derived HAs are subjected to a purification process (Figure 4), non-avian-derived HA generally contains fewer impurities and is likely to cause fewer inflammatory reactions.¹⁵

A recent double-blind, randomized study (N=321) compared Euflexxa with Synvisc, an HA whose high molecular weight is achieved via chemical cross-linking avian proteins with vinyl sulfone and formaldehyde. Overall, both products provided significant relief ($P < .0001$), although more patients taking Euflexxa (63%) than taking Synvisc (52%) were symptom free in post hoc analysis ($P = .038$). Additionally, significantly more patients in the Euflexxa group expressed satisfaction with their treatment ($P = .03$; Figure 5). Fifteen local effusions were reported with Synvisc versus only one with Euflexxa ($P = .0015$).¹⁵ It is not clear to what degree any of these advantages are attributable to the non-avian origins of Euflexxa.

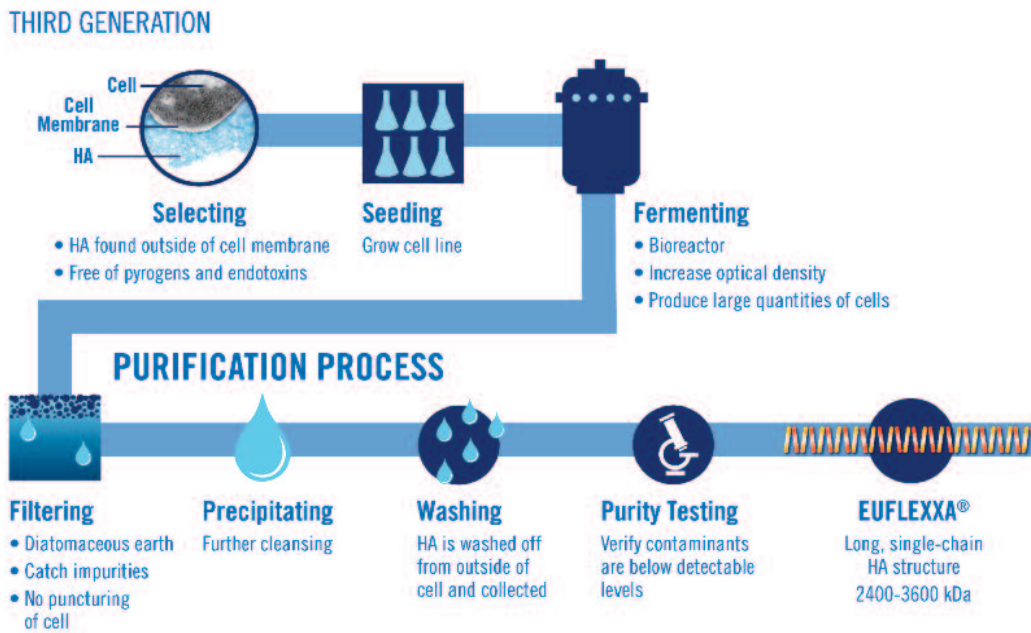
AN IDEAL HA PRODUCT

In part because intra-articular injection of HA is relatively new (less than 10 years old) in the United States, and in part because of differences in reports generated by manufacturers, physicians have varying impressions of the mechanism of action of the available products and differing opinions regarding the clinical relevance of the inter-product differences in features. In an effort to clarify these issues, the panel focused their discussions on a list of features that an ideal HA product would have and a list of possible umbrella terms to best capture those features.

Figure 5. Patient HA Preferences¹⁵



It was the opinion of the panel that an exogenous HA product that closely resembles healthy endogenous human HA in all ways, including size, structure, and molecular weight, is desirable.



*Courtesy of Ferring Pharmaceuticals Inc.

Desirable Features

An ideal HA would have high viscosity and high molecular weight; once injected, it would supplement the viscoelastic gel inside the knee, thickening synovial fluid and lubricating and protecting the joint.

- The product would be as pure as possible, containing no contaminants or animal proteins; a low protein concentration lowers the risk of inflammatory reactions and pseudosepsis. Figure 6 shows an approximate comparison of the protein concentrations of the available HA products.¹⁶
- It was the opinion of the panel that an exogenous HA product that closely resembles healthy endogenous human HA in all ways, including size, structure, and molecular weight, is desirable. A comparison of the structures of the available exogenous HAs with that of healthy human HA is shown in Figure 7.

Figure 6. Protein Concentrations¹⁶

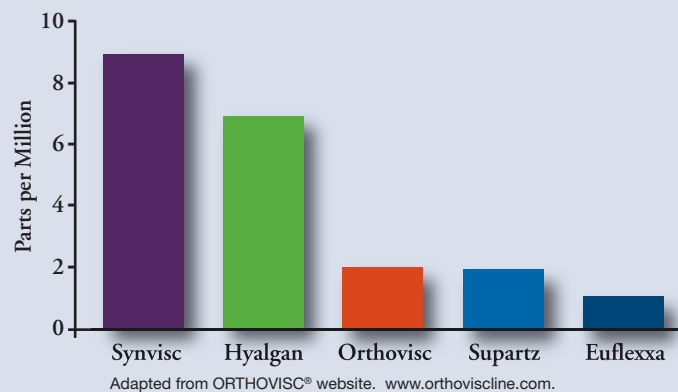


Figure 7. Comparison of the Structures of the Available Exogenous HA With Healthy Endogenous Human HA



*Artist interpretation of HA chain structure. Courtesy of Ferring Pharmaceuticals Inc.

Possible Terms

The panel then focused on deriving an umbrella term that would encompass the multiple features of the ideal HA product for both clinicians and patients, the purpose of which is to reduce confusion about the importance of individual features, as it is the opinion of the panel that the effectiveness of HA is related to its multiple features. Several umbrella terms were suggested. Following are the 3 general terms that were given the most consideration by the panel, as well as a summary of the panel members' opinions of each term.

Protective (Joint Protective, Chondroprotective, Knee Protective)

Pros: Terms incorporating “protective” describe potential protection of the joint from degradation, imply shock absorption, and suggest the possibility of protection from pain via coating of nociceptors to decrease nociceptive pain stimuli; also, these terms are considered familiar and comforting (as with cardioprotective).

Cons: Ironically, the same factor that makes these terms seem comforting (cardioprotective) also gives the impression that they are already overused and unoriginal; also, they are too limiting and do not describe the full range of potential benefits of HA treatment.

Preservative (Preserve Function, Preserve Joint)

Pros: Preserving implies prevention of loss, slowing of the degenerative process; it suggests not allowing the condition to worsen or progress, as well as extension of the life of the joint.

Cons: “Preservative” conjures up an image of a jar containing formaldehyde to preserve something stagnant; it does not suggest improvement but rather just prevention of further degradation.

Restorative (Joint Restorative, ChondroRestorative, BioRestorative)

Pros: The idea of restoration encompasses replacement of something that was there and is supposed to be there but is in lower supply and lower quality in the osteoarthritic joint; it also suggests restoration of normal, natural viscoelastic fluid as would be seen in a healthy, younger joint; additionally, it implies improved function within the joint.

CONSENSUS

The panel agreed that “BioRestorative” was the most accurate and comprehensive term to represent the collection of traits that describe an optimal exogenous HA product. BioRestorative also was considered an upbeat, proactive-sounding word, evocative of a regaining of youth. In light of the fact that the purpose of treatment for OA really is improvement in quality of life and satisfaction for patients and helping them regain a happy and active lifestyle, this term seemed most appropriate.

It was felt generally that BioRestorative suggests that an ideal HA has a restorative effect on naturally occurring synovial fluid within the joint, while it also enhances the viscosity, elasticity, and cushioning action of healthy human HA. When the term “BioRestorative” was presented to nonmedical people following the consensus meeting, they responded that it evoked a natural or holistic impression that was positive.

Finally, in their comparison of the available HA products, the panel concluded that although each of the products has some features that resemble those of endogenous HA, only Euflexxa, as shown in Table 3, has enough of those features to allow it to be discussed as best matching the BioRestorative profile.

BioRestorative suggests that an ideal HA has a restorative effect on naturally occurring synovial fluid within the joint.

Table 3. Matching Exogenous HA to the BioRestorative Profile

Features of Endogenous HA	Euflexxa (non-avian)	Hyalgan	Orthovisc (non-avian)	Supartz	Synvisc
Molecular Weight	XXX	X	X	X	XXXX
Structure	XXXX	XXXX	XXXX	XXXX	
Purity	XXXX		XX		
Minimal Protein Content	XXXX	X	XXX	XXX	X
Viscosity	XXXX	XX	XX	XX	XXXX

More Xs = closer to endogenous HA

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