Transdermal

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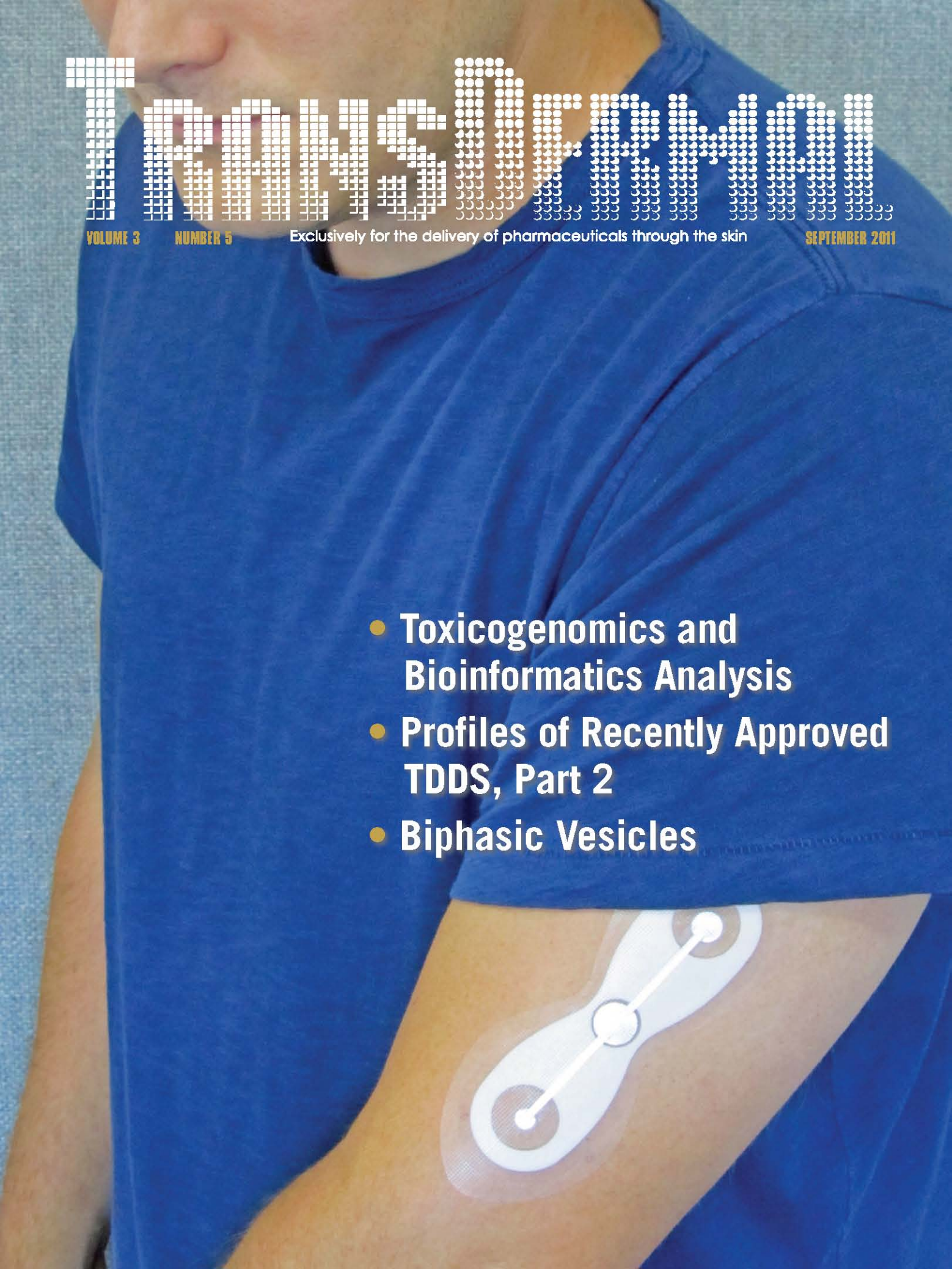

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Biphasic Vesicles: A Novel, Lipid-Based, Topical Delivery System for Large-Molecule Drugs

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Scientists recently demonstrated that biphasic vesicles—a novel, lipid-based, topical delivery system—can deliver large-molecule or macromolecule drugs into the skin. Although challenging, success with biphasic vesicles offers the potential of needle-free administration of many pharmaceuticals, including biologics [1], that medical practitioners until now could administer only by injection.

Research scientists envision biphasic vesicles as a way to deliver existing drugs in the developmental stage that previously had been shelved due to severe delivery issues. At the same time, biphasic vesicles enable the design of difficult-to-deliver molecules for a broad range of new drugs, allowing noninvasive and safe delivery through the skin.

Background

The administration of drugs into the human body is dependent on several factors, including the active substance in question, its pharmacokinetic profile, and the desired location of action. Because drugs administered by mouth, by inhalation, or directly to the skin (dermally) are noninvasive, scientists and medical professionals often prefer them to those requiring injection into the circulatory system. While these delivery methods may be preferable, they do have several disadvantages when compared to injections.

For example, oral administration requires efficient absorption through the gastrointestinal (GI) tract. Therefore, a drug must be resistant to the harsh physicochemical environment present in both the stomach and the intestines. The oral delivery of drugs also exposes them to first-pass metabolism within the liver that most often significantly reduces their bioavailability; that is, the rate at which the active drug enters the systemic circulation.

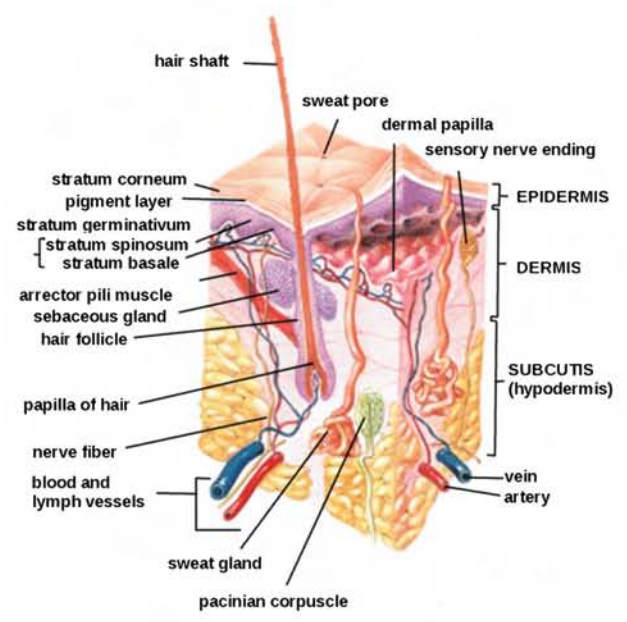
The inhalation of aerosol drugs eliminates both exposure to the GI track and first-pass metabolism. The difficulty of metering the dosage accurately coupled with the requirement for complex delivery devices, however, generally limits the use of inhaled drugs to those targeting the lungs directly.

Cutaneous delivery of drugs is complicated because the skin acts as a barrier to external contaminants, and drug delivery often requires the use of some method of physical or chemical disruption.

Structure of the Human Skin

The skin is composed of three primary layers: the epidermis, dermis, and subcutaneous tissue as depicted in Figure 1. The stratum corneum (SC) is the outermost layer of epidermis that makes the skin

Figure 1



a resilient barrier to absorption of macromolecules and even some small molecules.

The SC is composed of anywhere from 10 to 60 layers of flattened, nonliving corneocytes that are made up almost entirely of cross-linked keratin (75 to 85 percent). An intercellular matrix—composed primarily of long-chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate, and sterol or wax esters—surrounds the corneocytes.

Biphasic Vesicles: What Are They?

Biphasic vesicles are complex structures that are unique in that they are a combination of different compounds including lipids, micelles, and emulsions. The average diameter of a biphasic vesicle is one to ten micrometers (um) depending upon the specific composition of the vesicle and the encapsulated drug. Biphasic vesicles contain aqueous oil—a stabilized cationic nano-emulsion with an average droplet size of 300 nanometers (nm) [2]—and cationic surfactant micelles—average diameter of 50 nm—surrounded by concentric phospholipid bilayers, as Figure 2 illustrates.

Biphasic vesicles have an inherent ability to encapsulate a variety of therapeutic substances proportionately—most particularly pharmaceutical formulations—and can achieve a high order of subcutaneous permeability; that is, they are able to deliver drugs transdermally as previously discussed.

Figure 2

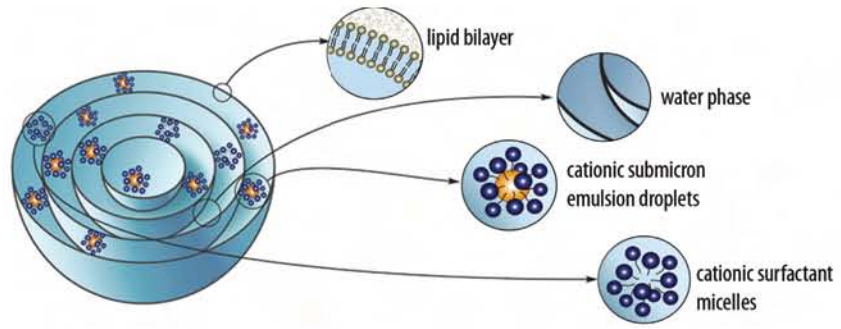
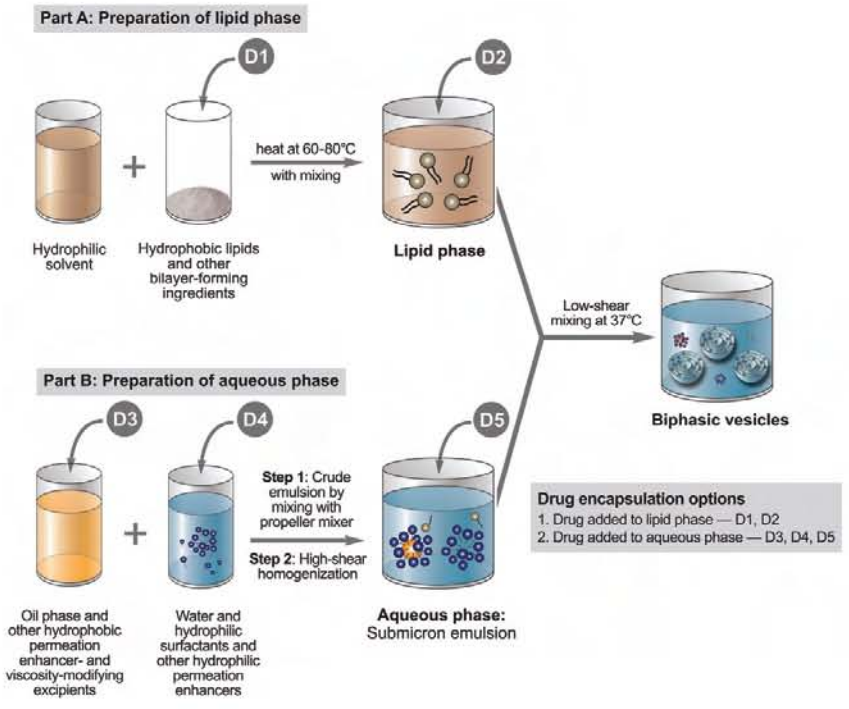


Figure 3



Preparation and Process

Biphasic vesicles are complex in form, and scientists most often produce them in a multistep process. The first steps in the process include the creation of a lipid phase and an aqueous phase (Figure 3). The lipid phase consists of hydrophilic solvent and hydrophobic lipids that are mixed together with a low-shear mixer. The aqueous phase is a two-step process that uses high-shear processing [3] to create an oil-and-water submicron (nano) emulsion. The high-shear process insures that the submicron emulsion is stable and uniform with an average droplet size that falls within a 200 to 500 nm range. This droplet size ensures the formation, stability, uniformity, and bioavailability of the biphasic vesicles, and at the same time, allows the formulation to meet the high standards of efficacy that the FDA has established.

During the development process, formulation scientists produce biphasic vesicles in small batches typical of laboratory-scale volumes. These amounts may be as small as a gram or less. Like most any drug or drug delivery system, the process requires scalability for pilot- and production-sized batches. The high-shear process enables the scalabil-

ity of biphasic vesicles while it also maintains the integrity of the laboratory formulation throughout scale-up and industrial production.

Biphasic Vesicles for Dermal and Transdermal Drug Delivery

Delivery of drugs through the skin includes two classes that are associated with distinct purposes.

Dermal Delivery involves delivery of a drug into the skin itself for dermatological treatments, vaccinations, or cosmetic applications.

Transdermal delivery also uses the skin as the application site and introduces the drug for transport into the circulatory system.

The delivery of drugs transdermally provides a convenient route of administration that bypasses the GI tract, first-pass metabolism, and many of the complications associated with injectable drugs. Because the skin is extremely effective at protecting the body from external pathogens and toxins, however, formulation scientists must design both dermal and transdermal delivery systems to circumvent its barrier properties.

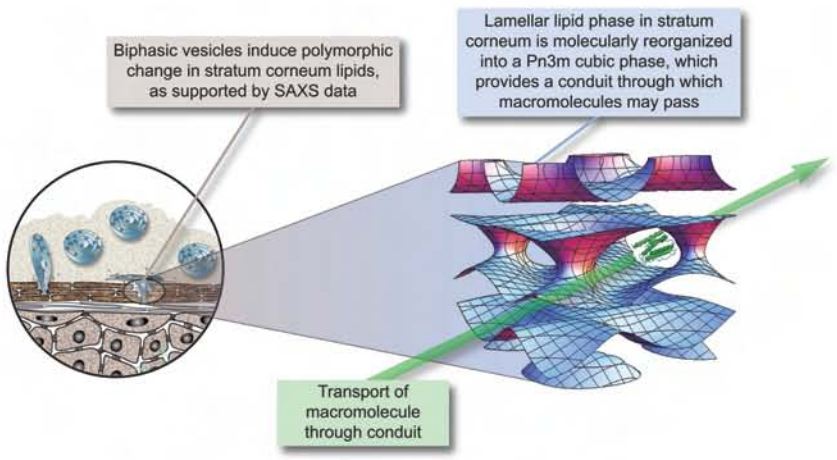
In general, scientists think that absorption into the skin occurs through: (a) an intercellular route, typical of lipophilic substances; (b) the appendages (hair follicles and sweat ducts) or (c) an intracellular route, more typical of hydrophilic substances.

In recent studies at the University of Waterloo (Waterloo, Ontario, Canada), Marianna Foldvari, PhD, and her team investigated the delivery mechanism of biphasic vesicles by using *interferon alpha (IFN α)*([4], a protein used for the topical treatment of human papillomavirus infections. They employed *IFN α* as a model protein to improve their understanding of both the interaction of biphasic vesicles with human skin and the transport of macromolecules through the stratum corneum [5], as illustrated in Figure 4.

Foldvari's work revealed that biphasic vesicles delivered *IFN α* intercellularly to a depth of 70 micrometers (μm), which is well below the stratum corneum and into the viable epidermis. Data suggest that the interaction of biphasic vesicles with the SC lipids resulted in the formation of a three-dimensional, cubic *Pn3m* polymorphic phase [6] by the molecular rearrangement of intercellular lipids. The researchers believe that the formation of this cubic phase is unique to biphasic vesicles and could be an intercellular-permeation nanopathway that may explain the increased delivery of *IFN α* by biphasic vesicles.

Liposomes and submicron emulsions, the individual building blocks of biphasic vesicles, do not induce a cubic phase, and they deliver low amounts of IFN α below the stratum corneum. The researchers hypothesize that induction of a *Pn3m* cubic phase in stratum-corneum lipids could also make dermal and transdermal delivery of other macromolecules possible.

Figure 4



Looking Forward

Researchers continue to search for a more effective design for dermal and transdermal delivery systems. Despite the rapid growth of new delivery technologies, the FDA has approved only 20 transdermal drug formulations as of 2008, which demonstrates the complications associated with noninvasive introduction of drugs into the body.

For dermal and transdermal delivery to become available for use with a wider range of next-generation therapeutic agents, scientists' and process

engineers' ongoing work must establish a clear understanding of the mechanisms of barrier properties associated with new-generation drugs.

"In our recent study of the mechanism of delivery of biphasic vesicles, we observed that the structure of the vesicles is important, since its constituent ingredients, being liposomes and submicron emulsions, do not promote drug delivery," said Marianna Foldvari [7]. "Biphasic vesicles are a structurally and chemically synergistic mixture of skin permeation enhancers. It is hoped that further understanding of structural changes in the stratum corneum and skin will allow for the design of improved carriers for more efficient passage of macromolecules through the skin."

Today, more than ever, the pharmaceutical industry continues to venture into the biotechnology arena with the hope that novel therapeutic biologics (macromolecular drugs) will fundamentally reshape the pharmaceutical landscape [8]. This change will increase the desire to replace injections with a safer, noninvasive delivery method such as that offered by biphasic-vesicle dermal delivery.

A growing optimism exists within the industry that therapeutic biologics will comprise a majority of commercial portfolios within the decade.

References and Notes

1. Therapeutic biologics essentially are derived from proteins, whereas small molecular entities are derived from chemical synthesis.
2. One nanometer (nm) is equal to one thousandth of a micrometer (um).
3. For high-shear processing, see Microfluidics at www.microfluidicscorp.com.
4. Foldvari M, Badea I, Kumar P, Wettig S, Batta R, King MJ, He Z, Yeboah E, Gaspar K, Hull P, Shear NH. Biphasic vesicles for topical delivery of interferon alpha in human volunteers and treatment of patients with human papillomavirus infections. Curr. Drug Deliv. 2011, 8:307-319.
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6. Shah JC et al. Cubic phase gels as drug delivery systems. Department of Pharmaceutical Sciences, Medical University of South Carolina.
7. Marianna Foldvari, D. Pharm. Sci. and PhD, is Canada Research Chair in Bionanotechnology and Nanomedicine at the School of Pharmacy, University of Waterloo, Ontario, Canada
8. Biologics in the pipeline: Large molecules with high hopes or bigger risks? In: Biologics from Pharmacokinetics, Modeling, & Simulation. Clinical Pharmacology & Experimental Medicine. Zhou H, PhD, FCP, Section Editor. Centocor Research & Development, Malvern, Pennsylvania.

Bob Bruno, founder and principal of R. P. Bruno and Associates, possesses over four decades of experience in corporate management, marketing, sales, and engineering. Until his retirement in 2008, he was president and COO of Microfluidics International Corporation in Newton, Massachusetts, USA. He holds BSME and MS degrees in mechanical engineering from Northeastern University, Boston, Massachusetts. For more information about high-shear processing, visit www.microfluicscorp.com or contact 1-800-370-5452.

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