Chapter

Copaxone® in the era of biosimilars and nanosimilars

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1.1 INTRODUCTION

1.1.1 Nanotechnology, Nanomedicine and Nanopharmaceuticals: Terminology and the Issue of Size

Rapid advances and product development in nanomedicine are in full swing as it continues to influence the pharmaceutical, device and biotechnology industries [1-3]. It is driven by collaborative research, patenting, commercialization, business development and

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technology transfer within diverse areas such as biomedical sciences, chemical engineering, biotechnology, physical sciences and information technology.

Although various “nano” terms, including “nanotechnology”, “nanopharmaceutical” and “nanomedicine,” are widely used, there continues to be confusion and ambiguity regarding their definitions. In fact, there is no precise definition of nanotechnology as applied to pharmaceuticals. This fact haunts regulators, drug companies, patent offices, policy-makers, researchers and legal professionals [4-9]. In particular, regulatory agencies and governmental entities such as Food and Drug Administration (FDA), European Medicines Agency (EMA) and US Patent and Trademark Office (PTO) continue to grapple with this critical issue.

The term nanotechnology is a bit misleading anyway given that it is not one technology but an umbrella term encompassing several technical/scientific fields and processes and properties at the nano/micro scale [7-9]. Various definitions of nanotechnology have sprung up over the years. Some label it as the manipulation, precision placement, measurement, modeling or manufacture of matter in the sub-100 nm range [10], or in the 1 to 200 nm range [11, 12]. Others point to a size ranging from 1 to 1000 nm in both nanotechnology and pharmaceutical science [13-16]. This latter definition may be the most appropriate. Even the FDA, which has not adopted any “official” regulatory definition in this regard, now uses a loose definition for products that involve or employ nanotechnology that either: (i) have at least one dimension in the 1-100nm range; or (ii) are up to 1000nm, provided the novel/unique properties or phenomenon exhibited are attributable to these dimensions outside of 100nm [8]. In other words, it appears that the FDA in recent years has correctly stretched the upper limit to 1000nm, albeit “unofficially.” This clearly highlights the importance of establishing a uniform “nano” terminology for harmonized regulatory governance.

Given this backdrop, and given the fact that there is no international scientifically accepted or uniform regulatory definition/nomenclature pertaining to “nano” [7-9], the following practical definition of nanotechnology has been previously proposed, one that is unconstrained by an arbitrary size limitation [9]:

“The design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property.”

Size limitation below 100nm is frequently touted as the basis of novel properties of nanopharmaceuticals; however, this is simply not critical to a drug company from a formulation, delivery, or efficacy perspective because the desired or novel physicochemical properties (e.g., improved bioavailability, reduced toxicities, lower dose, or enhanced solubility) may be achieved in a size outside this arbitrary range. For example, the plasmon-resonance in gold nanoshells that imparts their unique property as anticancer thermal agents is because their size is around 150 nm, not less than 100nm. Similarly, the enhanced permeability and retention (EPR) effect that makes nanoparticle anticancer drug delivery an attractive option, typically operates in a range of 100-400 nm.
Liposomes in a size range of 150-200 nm have been shown to have a greater blood residence time than those with a size below 70 nm.

This does not imply that any size will do while delivering nanopharmaceuticals. For example, submicron materials are essential for biological distribution of biopharmaceuticals for safety reasons [17]. Particles greater than 5μm can often cause pulmonary embolism following intravenous injection [18]. Therefore, submicron particle size is preferred for all parenteral formulations. In ophthalmic applications, the optimal particle size is less than 1μm because microparticles around 5μm can cause a scratchy feeling in the eyes [19].

Just like nanotechnology, there is no universally accepted definition of nanomedicine. The European Science Foundation [20] defines nanomedicine as:

“[T]he science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.”

The National Institutes of Health (NIH) Roadmap for Medical Research in Nanomedicine [21] defines nanomedicine as:

“An offshoot of nanotechnology, refers to highly specific medical interventions at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve.”

Although numerous nanodrugs have been routinely used in medicinal products for decades without any focus or even awareness of their “nano-character,” it is only within the past two decades that they have been highlighted due to their potential of revolutionizing drug delivery [22]. Obviously, the “Holy-Grail” of any drug delivery system is to deliver the correct dose of a particular active agent to a specific disease site while minimizing toxic side effects and optimizing therapeutic benefit; this is generally not achievable via traditional drugs [22-26]. However, this potential now exists through engineered nanopharmaceuticals.

Many liquid nanopharmaceuticals are colloidal drug delivery systems of 10 to 1,000nm [26]. Their nano-character – functional complexity and application potential – is related to one or more of the following properties [25-26]:

- nano-scale dimensions/small size (high surface area-to-volume ratio);
- reduced toxicity;
- controlled-release property;
- altered/modified pharmacokinetics;
- enormous compositional range and variety of therapeutics and carriers that can be formulated/package;
- superior biological distribution and targeting capabilities due to the ability to attach specific targeting moieties;
- various delivery route potential (oral, topical, intravenous, subcutaneous, etc.);
- variety of shapes/geometries (Figure 1);
- crystallinity;
aspect ratio; and surface charge.

There are numerous potential advantages of nanopharmaceuticals, and harnessing them depends on various factors such as their mode of delivery and specific class employed [25-29]. Some of these advantages include:

- increased bioavailability due to enhanced water solubility of hydrophobic drugs because of the large specific surface area;
- ability to protect biologically unstable drugs from the hostile bioenvironment of use/delivery/release (e.g., against potential enzymatic or hydrolytic degradation);
- extended drug residence time at a particular site of action or within specific targeted tissue and/or extended systemic circulation time;
- controlled drug release at a specific desired site of delivery;
- endocytosis-mediated transport of drugs through the epithelial membrane;
- bypassing or inhibition of efflux pumps such as P-glycoprotein;
- targeting of specific carriers for receptor-mediated transport of drugs;
- enhanced drug accumulation at the target site so as to reduce systemic toxicity;
- providing biocompatibility and biodegradability;
- offering a high drug-loading capacity;
- providing long-term physical and chemical stability of drugs; and
- improved patient compliance.

There are a number of FDA-approved, commercialized nanopharmaceuticals [7, 8, 25-27, Figure 1] for the intravenous use as well as for non-intravenous delivery. However, numerous nanopharmaceuticals are still at the development or clinical trial phase. This chapter focuses on Copaxone®, a drug developed and marketed by Teva Pharmaceutical Industries Ltd. (NYSE: TEVA) and indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) [30]. In this chapter, the following equivalent terms are used interchangeably: nanodrugs, nanotherapeutics, nanomedicines and nanopharmaceuticals.
1.1.2 **Copaxone® (glatiramer acetate) and Multiple Sclerosis**

Copaxone® is a non-biologic (synthetic) complex drug ("NBCD") and first-generation nanomedicine composed of an uncharacterized mixture of immunogenic polypeptides in a colloidal suspension. The active ingredient in Copaxone® – glatiramer acetate – is a heterogeneous synthetic mixture of polypeptides comprised of four amino acids (L-glutamic acid, L-alanine, L-lysine, and L-tyrosine) in a defined molar ratio [37]. Glatiramer acetate has immunomodulatory effects on innate and acquired immunity and is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) [30]. Copaxone® is currently available as a daily 20 mg subcutaneous injection (approved in the US in 1996) and recently approved in the US in January 2014 as a 40 mg subcutaneous injection administered three times a week.

MS is a chronic degenerative autoimmune disease in which inflammatory infiltrates damage the myelin sheath and central axons, impeding neuronal conduction [60]. MS affects an estimated 2.3 million people worldwide, a majority of whom are women [61]. MS typically strikes young adults; most patients are diagnosed between ages 20-50 [61]. Symptoms of MS include visual disturbances, ataxia, weakness, fatigue, cognitive impairment, depression, sexual dysfunction, lack of bladder control and
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spasticity [60, 62]. The cause of MS is unknown; however, it is believed that a combination of several factors may be involved [63]. It is generally accepted that MS involves an immune-mediated process directed against the myelin in the central nervous system [63].

Until the development of disease-modifying therapies (DMTs) such as Copaxone®, only symptomatic therapy was available to patients. Currently there are several DMTs approved in the EU, Canada, and US for the treatment of RRMS. However, Copaxone® is unique in several ways. Copaxone® is the first drug ever to show proven therapeutic efficacy in MS and the first product to have a copolymer of amino acids as its active ingredient [64]. Copaxone® is not a single molecular entity but rather a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides of varying lengths, some containing up to 200 amino acids, with structural complexity comparable to that of proteins, if not even more complex than proteins [37]. It is presently impossible to isolate and identify pure components even using the most technologically sophisticated multidimensional separation techniques [37]. The complexity of glatiramer acetate is amplified by several aspects [37, 46, 65]: (1) the active moieties in glatiramer acetate are unknown; (2) the mechanisms of action are not completely elucidated; (3) pharmacokinetic testing is not indicative of glatiramer acetate bioavailability; (4) pharmacodynamic testing is not indicative of therapeutic activity and there are no biomarkers available as surrogate measures of efficacy; and (5) small changes in the glatiramer acetate mixture can change its immunogenicity profile. Therefore, analogous to biological products, synthetic glatiramer acetate is defined, in large part, by its well-controlled manufacturing process that has been used by Teva for more than twenty years.

1.2 NON-BIOLOGIC COMPLEX DRUGS (NBCDs) AND REGULATORY PATHWAY FOR FOLLOW-ON PRODUCTS

Medicinal products can be broadly divided into three classes: (1) small-molecule drugs, (2) biologic drugs and (3) non-biological (synthetic) complex drugs or NBCDs. NBCDs have been defined as engineered medicinal products that are not biological medicines, where the active agent or therapeutic moiety is not a homo-molecular structure but consists instead of different yet closely related and often nanoparticulate structures that cannot be isolated, fully quantitated, and/or characterized via standard analytical or physicochemical techniques [66, Figure 2]. It is also unknown which structural elements might affect their therapeutic performance [66]. As stated earlier, Copaxone® is a NBCD. In addition to Copaxone®, other NBCDs include certain liposomes and iron-carbohydrate drugs. NBCDs typically use multiple starting components and the final product(s) represents the result of complex and often proprietary manufacturing process. In this regard, if one of the starting components or the final product(s) exhibits nano-dimensions or nano-characteristics, the term nanomedicine is often employed.

Both the FDA and EMA regulate new drugs and biologics for approval and licensure. In the US, small-molecule drugs are regulated under the Food, Drug and Cosmetics Act (“FDCA”). However, biologics are currently regulated under both the Public Health Service Act (“PHSA”) and FDCA because some products also fall within the older FDCA approval route of “drugs.” Although the PHSA uses the term “biologics” when referring to biological products, there are other interchangeably equivalent terms in
this regard: “biopharmaceuticals,” “biomolecular drugs,” “biologic drugs,” and “protein product.” Branded biologics are referred to as “pioneer,” “branded” or “reference” biologics. Small molecule drugs approved by the FDA are known as New Chemical Entities (NCEs) while approved biologics are referred to as New Biological Entities (NBEs). As a result, a new drug application for an NCE is known a New Drug Application (NDA) whereas a new drug application for an NBE is called a Biologic License Application (BLA). It should be noted that because prior to the 1980s there were very few marketed biologics, the very term “pharmaceutical” or “drug” implied a small molecule drug.

The classical generic pathway for a small molecule drug relies on therapeutic equivalence to the innovator or reference listed drug (RLD). This entails being pharmaceutically equivalent (i.e., identical active substance) and being bioequivalent (i.e., comparable pharmacokinetics) established in a small volunteer study and do not require formal clinical efficacy or safety studies. The acceptance intervals must show that for bioequivalence the logarithm transformed AUC and $C_{\text{max}}$ ratios must lie within an acceptance range of 0.80 – 1.25 for the 90% confidence intervals [68]. This classical generic approval approach has been successful for many well-defined, small, low-molecular weight drugs where the analytical testing fully characterized the product.

The pathway to a biosimilar product is different. The concept of similarity was introduced in the general biosimilar guidelines published by the EMA in 2005 [69, 68]. To become authorized as a biosimilar in the EU, the applicant needs to show similarity in quality, safety and efficacy [69]. A biosimilar needs a full quality dossier comparable with that of an original biological product. The application should also contain a comparison in physicochemical and other in vitro characteristics showing no clinically relevant differences between biosimilar and innovator. Full toxicity programs do not need to be repeated and animal pharmacokinetic (PK) and pharmacodynamic (PD) studies may be used to demonstrate similarity with the original. To show clinical similarity, it is not necessary to present equivalent efficacy in all clinical endpoints for every indication for which the original product is registered. It is allowed to use a biological endpoint that is sensitive to show possible differences in clinical activity between products.

FDA published draft guidances for biosimilars in 2012 and they state that biosimilar applicants should include analytical studies that (i) demonstrate the biological product as being highly similar to the reference product notwithstanding minor differences in clinically inactive components; (ii) include animal studies including the assessment of toxicity; and (iii) provide a clinical study or studies (including the assessment of immunogenicity and include PK/PD) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for the reference product is licensed and intended to be used and for which licensure is sought for the biological product [70]. The agency also stated that they have the discretion to determine that an element described above is unnecessary [70].

The therapeutic equivalence for this third class of follow-on synthetic complex drugs or NBCDs has been a topic of conversation for the last few years. A workshop on NBCDs was held in Leiden, The Netherlands in 2009. The goal of the workshop was to work with various stakeholders, including manufacturers of original products as well as generics and biosimilars, to produce a consensus paper about the scientific issues involved in showing therapeutic equivalence of NBCDs to support the development of harmonized regulatory pathways for NBCD follow-on products [67]. Additional discussions were held on this topic at a workshop at the FIP Centennial Congress in
Amsterdam in 2012, the New York Academy of Sciences in 2012 [73], the EUFEPS Regulatory Science Network Workshop in 2012, the AAPS Meeting in 2013 and the New York Academy of Sciences in 2013 [74].

The consensus of all these meetings was essentially similar: (i) generic or follow-on biologic regulatory guidelines/pathways developed by EMA and FDA to discriminate between biologic drugs and small molecules cannot be extrapolated to NBCDs as they cannot be fully characterized; and (ii) no dedicated regulatory pathways for NBCD follow-on versions exist [68]. Due to heterogeneity and complexity, NBCDs are a diverse group of products that more closely resemble biologic drugs than small-molecule drugs. NBCDs share a number of characteristic features with biologicals including the fact that the composition is complex, the structures cannot be fully defined by physicochemical analysis, and the biological and clinical characteristics are highly dependent upon the specific manufacturing process [68, Figure 2]. Moreover, biosimilars are even better understood and the pharmaceutical ingredients in those products are better characterized than the NBCD mixtures. Therefore, the same principles that are used for biosimilars should be used for NBCDs such as the need for animal and/or clinical data and the need to show similarity in quality, safety, and efficacy. The requirements for follow-on NBCDs should be based on the biosimilar approach with specific requirements based on the science of the individual product. In summary, the new regulatory pathways developed for biologics may serve as the best example as to how to regulate follow-on NBCDs [68].

Figure 2. NBCDs therapeutic equivalence from manufacturing to safety and efficacy [from Ref. 66, reproduced with permission].
1.3 NANOMEDICINES AND REGULATORY PATHWAY FOR NANOSIMILARS

Copaxone® (glatiramer acetate), a first generation nanomedicine, is comprised of a nano-sized polypeptide mixture with molecules and molecular structures ranging from 1.5 to 550 nm in size. The data demonstrating the colloidal properties of Copaxone® and the nanomedicine attributes are discussed in detail in section 1.4.

Currently the FDA, EMA, and other regulatory agencies examine each new nanomedicine product on a product-by-product basis [71]. There is generally a lack of recognition that nanomedicine products need their own therapeutic category or regulatory pathway [71]. However, as the first generation nanomedicine products are coming off patent, the regulatory agencies will need to determine what the requirements are for a follow-on nanomedicine product or nanosimilar. As many of the NBCDs are also nanomedicines, the requirements for follow-on NBCDs and follow-on nanomedicines are facing the same lack of clarity and need for regulatory pathways.

The EMA recently published a paper on next-generation nanomedicines and nanosimilars. They note that in order to demonstrate similarity, there is a need for stepwise comparability studies to generate evidence substantiating the similar nature, in terms of quality, safety, and efficacy of the nanosimilar and the originator/innovator nanomedicine [72]. As nanomedicines differ significantly in their complexity and nature, a case-by-case or product/class specific approach for their evaluation might be necessary [72]. This article also stresses that any drug developed to be comparable to innovator’s must demonstrate equivalence in terms of quality, safety, and efficacy before a market authorization can be granted [72]. In addition, given the degree of complexity of many nanomedicine products, special scientific considerations may be required to ensure this equivalence of performance [72]. The EMA has also published reflection papers on intravenous liposomal products developed with reference to an innovator product and nanosized colloidal iron-based preparations developed with reference to an innovator product. To date, there is no reflection paper from the EMA or guidance document from the FDA for glatiramer acetate.

The FDA, on the other hand, continues to state that they will regulate nanomedicine products under their current regulatory frameworks and that their current frameworks are sufficiently robust and flexible to consider nanotechnology and nanomedicine [42], a view not shared by many experts [7, 8, 26].

1.4 COLLOIDAL AND NANOMEDICINE PROPERTIES OF COPAXONE®

Copaxone® is produced using well-established solution polymerization techniques [52]. The nanoscale size of glatiramer acetate molecules are an intrinsic process-related property associated with its chemical nature. The consistent manufacturing process employed by Teva creates a mixture of glatiramer acetate polypeptides with an average molecular weight (MW) ranging from 5000-9000 Daltons (the MW distribution of the glatiramer acetate components spans a range of 2,500 – 20,000 Daltons) [37]. The polypeptides in glatiramer acetate appear to range from approximately 20 to 200 amino acids in length, with an average polypeptide length of about 60 amino acids [53]. The theoretical length of glatiramer acetate molecules ranges from 3 to 30 nanometers (nm), with an average of about 8 nm for the peptide of 7000D MW. However,
as described further below, the molecules and molecular associations in glatiramer acetate appear to reach up to 550 nm.

The FDA has defined the term “colloid” for regulatory purposes as “a chemical system composed of a continuous medium (continuous phase) throughout which are distributed small particles, 1 to 1000 nanometers in size (disperse phase), that do not settle out under the influence of gravity; the particles may be in emulsion or in suspension.” [54]. While this definition, which appears to be derived from Dorland’s Medical Dictionary for Health Care Consumers [55], is generally considered accurate, a more precise scientific definition is as follows [56]:

*A colloid, or disperse phase, is a dispersion of small particles of one material in another. In this context, ‘small’ means something less than about 500 nm in diameter (about the wavelength of visible light). In general, colloidal particles are aggregates of numerous atoms or molecules, but are too small to be seen with an ordinary optical microscope. They pass through most filter papers, but can be detected by light scattering and sedimentation.*

Regardless of the definition applied, Copaxone® unquestionably is a colloidal suspension. Glatiramer acetate nanoparticles are within the typical colloidal size range of 1 to 1000 nanometers (1μm) (denoted as radius (r) in Stokie’s law) and are uniformly suspended in a continuous medium (mannitol solution). The mannitol solution is a “true” solution, i.e., it is a homogenous solution in which the ratio of solute to solvent remains constant and in which all of the solute particles have diameters less than 10^7 centimeters (<10 nm), and the mannitol in solution cannot be centrifuged or filtered from the solution. As such, the aqueous mannitol solution constitutes a continuous medium. The glatiramer acetate nanoparticles dispersed in the mannitol solution do not precipitate under the influence of normal gravitational forces, even when stored at 2-8°C for up to 2 years; thus, Copaxone® is stable under these conditions.

The results of traditional colloidal assessments capable of distinguishing compositional features of Copaxone® at the molecular level further confirm the colloidal nature of Copaxone® [57]. These experiments, which included ultracentrifugation, DLS, AFM, cryogenic temperature transmission electron microscopy, and zeta potential testing, demonstrate the following:

- Copaxone® is composed of two, distinct populations of polypeptides, both of which are within the size range for colloids (i.e., 1 to 1000 nanometers);
- The glatiramer acetate polypeptides are stable and distributed uniformly throughout the aqueous mannitol medium;
- Copaxone® constituents can be separated into layers by ultracentrifugation and then easily reconstituted, indicating that Copaxone® is a lyophilic colloidal suspension in which the dispersed particles are well-solvated and stabilized rather than a true solution in which the dispersed particles are dissolved; and
- Copaxone® has a high zeta potential, suggesting that it is highly stable and resists flocculation and settling under normal gravitational forces.
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The results of this testing are discussed in more detail below.

Separation by Ultracentrifugation and Resuspension

Stable colloids do not “settle out under the influence of” normal gravitational forces. However, they will potentially exhibit separation of the disperse phase under increased gravitational forces, such as ultracentrifugation. The stability of colloidal suspensions is characterized by, among other things, Stoke’s law \( \frac{dx}{dt} = \frac{2r^2(d_c - d_p)g}{9h} \). By increasing gravity \( g \) through ultracentrifugation for suspensions where \( d_c - d_p \) is negative, \( dx/dt \) can be increased sufficiently to separate the suspended particles in the stable colloidal suspension.

To show that Copaxone® is not a “true” solution, a Copaxone® sample was ultracentrifuged for 24 hours at 4°C under 530,000g (“treated sample”). The sample was segregated into a concentrated layer of higher MW polypeptide moieties (a whitish, dispersed phase in the lower layer of the centrifuged sample) and a layer of lower MW polypeptide moieties (a more translucent upper layer). The upper and the lower layers of the treated sample were tested for glatiramer acetate concentrations, which were measured using size exclusion chromatography and compared with the untreated Copaxone® sample (Figure 3). The concentration of glatiramer acetate in the upper layer of the treated sample was about 1/10th of the concentration in the lower layer.

The treated sample layers were then re-mixed by vortexing, and the concentration of glatiramer acetate in the reconstituted suspension was measured again. The concentration of the reconstituted sample was equivalent to that of the original untreated sample (Figure 4).
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Figure 4. Size Exclusion Chromatography overlaid profiles of the untreated (black) and reconstituted (blue) Copaxone® samples

This testing demonstrates that Copaxone® constituents can be concentrated under strong centrifugal force, and the resulting concentrate can be easily reconstituted to its original composition. In other words, Copaxone® can be reversibly re-suspended, a property expected only for a colloidal suspension, not a true solution.

**Dynamic Light Scattering (DLS)**

DLS determines particle sizes in solution by measuring their diffusion rate (Brownian motion). Small molecules diffuse more quickly than large molecules. Molecules of different sizes scatter light at different intensities. DLS measures intensity as a function of particle sizes; however, it is important to note that DLS results are qualitative and not quantitative. The capacity of a large molecule to scatter light is significantly higher than that of a small molecule; therefore, a single large molecule can scatter light more intensely than a large population of small particles. Thus, the results of DLS should be evaluated accordingly: the area under the peak does not correlate with the number of particles (population size) represented by that peak.

Scientists at Teva developed and optimized operational DLS conditions for the glatiramoid class of compounds. Measurements were sensitive to particle sizes in the nm range (1 – 1000 nm). Robust manufacturing process was demonstrated by the reproducibility of results of multiple measurements on many different Copaxone® batches manufactured at varying time periods. DLS measurements were performed on Copaxone® diluted with a 20 mM NaCl solution and filtered through a 1.2 μm disc filter prior to analysis, and on samples obtained by ultracentrifugation at different G-forces (the upper layers and the constituents concentrated at the bottom).

DLS analysis shows that the untreated Copaxone® mixture consists of two main polypeptide populations. The first population is characterized by a distribution of particle sizes in the range of 1.5 to 15 nm, with the most abundant size of approximately 5.6 nm. The second population contains particles in the range of 20 to 550 nm, with the most abundant size of approximately 111 nm (Figure 5). The first population likely represents
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“mono-particles,” or separated molecules, which comprise the most abundant fraction; whereas the second population can be attributed to larger entities (e.g., labile intermolecular associates) that may be formed by interactions between amino acid sequences on the polypeptide chains.

Figure 5. A typical (untreated) Copaxone® DLS scan

The dispersed Copaxone® solution was exposed to ultracentrifugation at different G-forces. As mentioned above, ultracentrifugation resulted in a clear upper layer and a viscous whitish fraction. The upper layer and the material concentrated at the bottom were then tested by DLS (after reconstitution in water). At 290,000g, the upper layer still contained both “light” and “heavy” peaks (Figure 6A), whereas the lower fraction contained the “heavy” peak only (Figure 6B). Ultracentrifugation at higher G-force (650,000g) resulted in a more effective concentration of the heavy peak (Figures 6C and 6D).

Figure 6. DLS results of the Copaxone® sample after ultracentrifugation at different G-forces. The Copaxone® sample was subjected to ultracentrifugation at the conditions described in panels A-D. (A) Upper layer after 2-hour ultracentrifugation at 290,000g: two populations are observed; the relative amount of smaller particles is increased compared
with non-treated Copaxone®. (B) Bottom fraction after 2-hour ultracentrifugation at 290,000g re-suspended in water: only the larger size components are observed. (C) Upper layer after 2-hour ultracentrifugation at 650,000g: the relative amount of larger particles is even more reduced due to further separation under higher G-force. (D) Bottom fraction after 2-hour ultracentrifugation at 650,000g re-suspended in water: only the higher size constituents are observed.

Thus, after ultracentrifugation, there was a change in the profile of the suspended glatiramer acetate nanoparticles with regard to their size distribution, i.e., the larger molecularly associated nanoparticles segregated at the bottom, whereas the smaller nanoparticle associates remained in the upper layer. The extent of concentration of the larger associates at the bottom was proportional to the applied G-force value. This separation would not have been observed if Copaxone® was a true, homogenous solution.

In summary, the Copaxone® suspension was successfully separated by ultracentrifugation into several populations of constituents according to their sizes, as determined by DLS.

It is noteworthy that the re-suspension in water of the larger molecularly associated nanoparticles from the material obtained at the bottom of the tube resulted in the observation of only the larger particles in suspension. This indicates that the larger particles are labile intermolecular associates of several nano-sized “mono”-molecules arranged in a thermodynamically preferable disposition and thus are relatively stable. The observation of the two distinct populations of particles in the original analysis further supports this conclusion. If the suspension were merely a mix of agglomerates, one would have expected a continuum of particle size distribution over the range. The appearance of two distinct populations of particles shows that Copaxone® is a colloidal system that is more complex than a mere suspension of agglomerated particles and is actually comprised of a unique microstructure of two particulate populations. In other words, this DLS testing demonstrates that Copaxone® is comprised of thermodynamically stable, nano-sized association complexes.

**Atomic Force Microscopy (AFM)**

AFM is a type of scanning tunneling microscopy. AFM produces images of the surface ultrastructure of a substance with molecular resolution under physiological conditions. The samples are dried with nitrogen prior to scanning. The resolution of this technique varies from about 0.1 nm to the sub-micron range. In an AFM experiment, the size (length, width, and height) of individual particles can be measured and the results can be visualized in three dimensions.

A typical topographic image of a Copaxone® dried sample is shown in Figure 7. A Copaxone® aliquot from a syringe and a placebo sample from an identical syringe were dried with nitrogen on a flat support, and then scanned to produce the surface ultrastructure with molecular resolution. AFM analysis of Copaxone® samples revealed dispersed “dot-like” and “string-like” components. In the placebo syringes, no such entities were apparent, indicating that the particles observed in the Copaxone® samples did not originate from mannitol or from any part of the syringes (i.e., they are characteristic of glatiramer acetate).
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Figure 7. Typical topographic image of Copaxone® and placebo bulk solutions. AFM analysis of Copaxone® samples (left) from a bulk solution in a syringe revealed dispersed “dots” and “strings” particles. In the placebo syringes (right), no such entities were visible, indicating that the particles observed in the Copaxone® samples (left) did not originate from mannitol or from any part of the syringes (they are characteristic of glatiramer acetate).

The DLS study above indicated that the population of larger sized particles under the peak on the right (Figure 3) (about 110 nm average size distribution) can be concentrated at the bottom of a tube by ultracentrifugation. In order to characterize the strings detected by the AFM technique in the Copaxone® sample and to investigate correlations between the results of the DLS scans and the AFM images, samples described in the DLS study above (the bottom fractions) were diluted with water, dried with nitrogen and analyzed.

AFM images for those fractions from a Copaxone® batch (at a higher resolution) are shown in Figure 8. The concentrated “heavy” material appeared to contain the same string-like entities seen in the untreated Copaxone® samples (Figure 7, left), although, as expected, at a higher concentration. No round shaped particles were detected in the lower layer. By contrast, analysis of the upper layer revealed none of the string-like particles present in the lower fraction, which correlates with the data obtained by DLS testing indicating two subpopulations of particles with different average sizes, and supports the assumption that the strings are the larger sized particles in the Copaxone® sample.
Figure 8. Topographic image for “heavy” fraction from Copaxone®, separated by ultracentrifugation. Results shown in this figure complement results of the DLS study, in that AFM established that the heavier population of Copaxone® polypeptides consists of string-like entities of variable sizes.

Together, DLS and AFM confirm the colloidal characteristics of Copaxone®, which maintains a homogenous appearance throughout its 2-year shelf life (i.e., contains polypeptide particles of different sizes that do not precipitate under gravity) but can be separated into subpopulations under ultracentrifugation. Both methods also demonstrate the presence of stable polypeptide particles within the colloidal size distribution range (1 – 1000 nm).

**Cryogenic temperature transmission electron microscopy (Cryo-TEM)**

Cryo-TEM is a method of obtaining high-resolution, direct images of molecules or molecular assemblies in their native environment. Thus, it can elucidate the nature of the basic building blocks that make up a sample, covering a wide range of length scales from a few nm to several microns. Rapid freezing of the sample under study prevents alterations to the sample and eliminates potential structural changes, redistribution of elements, and/or the washing away or evaporation of substances originally present in the sample [58]. This technique was used to confirm results of DLS and AFM testing, and to eliminate the impact (if any) of sample preparation on the size, shape, and type of Copaxone® molecular assemblies.

A drop of Copaxone® was placed onto a TEM copper grid to prevent the formation of ice crystals and analyzed at -170°C. The samples were analyzed in different locations on the grid, using variable magnification, in an attempt to detect the potential existence of both larger and smaller structures in the sample. A placebo (mannitol solution) was tested as a control (Figure 9).

Copaxone® samples tested under the same conditions appear quite different (Figure 10). They largely contain three populations of particles dispersed in the continuous mannitol solution: fibers (or strings) of 60-300nm length, spherical particles of ~ 4nm, and globules of ~30nm; the latter are consistent with the globules in the placebo
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sample.

Figure 9. Typical Cryo-TEM results for a placebo (mannitol solution) sample: (A) Moderate magnification, (B) High magnification. The sample contained globule particles, with varying sizes of $30 \pm 5$ nm, as indicated by the black arrows. These globules most likely originated from the silicon oil droplets present in the syringe.

Figure 10. (A) Cryo-TEM image of typical structures present in Copaxone® samples. Images B through E are enlarged areas of image A. (B) Fibers of 60-300 nm length and width of 6 $\pm$ 1 nm; (C) Spherical particles of ~4 nm in diameter; (D) Globules of ~30 nm in diameter (also detected in placebo samples, see Figure 5, above); (E) Black frost particles (not related to the sample).
Results of Cryo-TEM analysis support results of DLS and AFM testing. Examination of native structural features of the Copaxone® sample, as in the DLS and AFM experiments, revealed two populations of glatiramer acetate nanoparticles dispersed in the aqueous mannitol phase:

- One population of Copaxone® nanoparticles were spherical with sizes of $4 \pm 2\text{nm}$ (Figure 10C), which correspond to the smaller polypeptide moieties shown on the DLS scans (Figure 5, peak on left), and with the “dot-like” structures on topographic AFM images (Figure 7, left).
- The second population of polypeptides appeared as “strings” with lengths of ~60 to 300nm (Figure 10B), which correspond with the DLS peak indicating larger moieties (Figure 5, peak on right) and the topographic images from the AFM analysis showing elongated fibers (Figures 7 [left] and 8).

The polypeptide’s particle size distribution and their dispersion in the continuous mannitol aqueous phase shown in the Cryo-TEM study provide additional evidence of the colloidal nature of Copaxone®.

**Zeta Potential**

The stability of colloidal suspensions “is determined by the balance of attractive and repulsive forces between individual particles. The repulsive force prevents two particles from approaching one another and adhering together” [57]. If the repulsive force is sufficiently high, the colloidal suspension “will resist flocculation and the colloidal system will be stable” [57].

Zeta potential is a measure of the electrokinetic potential in colloidal systems. The magnitude of the zeta potential gives an indication of the stability of a colloidal system. If all the particles in suspension have a large negative or positive zeta potential then they will tend to repel each other and, as noted above, there is no tendency to flocculate. However, if the particles have low zeta potential values then there is no force to prevent the particles coming together and flocculating. The dividing line between stable and unstable suspensions is generally taken at either $+30\text{mV}$ or $-30\text{mV}$. Particles with zeta potentials more positive than $+30\text{mV}$ or more negative than $-30\text{mV}$ are normally considered stable [59].

Representative zeta potential results for three Copaxone® batches are shown in Figure 11 and results are summarized in Table 1. Placebo (mannitol solution) exhibited a zeta potential that was about 5mV.
Figure 11. Zeta potential of three Batches of Copaxone®

As shown in Table 1, these zeta potentials are approximately 34-37 mV, indicating the stability of the colloidal solution through strong electrostatic repulsion of Copaxone® moieties, which prevents their flocculation. Zeta potential results confirm the physical stability of the Copaxone® suspension.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Batch</th>
<th>Zeta potential (mV)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
</tr>
<tr>
<td>Copaxone</td>
<td>1</td>
<td>36.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>37.4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>34.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>-</td>
<td>5.5</td>
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Table 1. Summary of Zeta Potential Results

**Summary of Test Results**

The results of these studies – ultracentrifugation and reconstitution, DLS, AFM, Cryo-TEM, and zeta potential – complement each other and, together, confirm that Copaxone® is a stable, lyophilic colloidal suspension. These studies show that under adequate centrifugal force, Copaxone® can be separated into layers exhibiting different concentrations that are easily re-dispersed back to the original concentration upon vortexing. They demonstrate the presence of solvated, stable, nano-sized molecules and associations dispersed homogenously within the aqueous mannitol solution. The
sufficiently high zeta potential values attest to the stability of the colloidal suspension caused by electrostatic forces in the product. The dual population of small and large nanoparticles observed in the analysis is supportive of the unique and distinct microstructure of the Copaxone® product.

1.5 IMMUNOGENICITY

There is one aspect of Copaxone® that raises special safety and effectiveness concerns that merit heightened vigilance with respect to the approval of potentially interchangeable follow-on glatiramer acetate products. In particular, glatiramer acetate is an immunomodulator. In other words, the drug is intended to achieve its therapeutic effects by interacting with and modulating a patient’s immune system over an extended period of time. For this reason, Copaxone®’s package insert warns that chronic use has the potential to alter healthy immune function as well as induce pathogenic immune mechanisms, although no such effects have been observed with Copaxone® [30].

As discussed above, due to the complexity and inexorable link between the manufacturing process and quality, the follow-on products almost certainly will differ from Copaxone®’s active ingredient in structure and composition because it will be made using a different manufacturing process from that used by Teva. Although it is not possible to fully characterize and compare the complex mixtures, these differences are revealed by using sophisticated analytical techniques. Purported generic glatiramer acetate products have been approved in India, Argentina, and Mexico. A variety of physicochemical tests have been done on these products and they have been proven to be similar to Copaxone® in some basic features, however different in the bulk composition of constituents using methods for analysis of complex closely related molecules such as biologics. A widely used analytical tool for characterization of biologics in the context of biosimilars is the ion mobility mass spectrometry (IMMS) [75]. The ion mobility method applies multidimensional separation techniques based on size, shape, charge and mass of the molecules in the mixture and this is capable of separating isomeric peptides that chromatographic techniques cannot. The analysis produces a 3-dimensional heat map to highlight intensity differences of peptides at various mass/charge and drift times. The difference between the intensities of heat maps for the generics as compared to Copaxone (result of subtraction of generic heat map from that of Copaxone) show highlighted areas indicating different polypeptide populations compared to those of Copaxone® lots tested [Figure 12].
A quantitative assessment of these differences in heat maps was used that integrates the intensity values within these highlighted areas to produce a total intensity value or TIV. If the composition of a sample was exactly the same as the reference Copaxone®, the heat map would theoretically have no highlighted areas and a TIV=0. Conversely, heat maps with more highlighted areas signify a greater difference to the reference Copaxone® and will have a higher TIV. As shown in Figure 13, the TIVs of Copaxone batches are within a narrow range of its inherent batch-to-batch variability, whereas the generics were 8-13 fold higher [Figure 13]. These results clearly indicate profound difference in size, shape and charge of the constituent polypeptides in Copaxone® compared to purported generic products.
Because Copaxone® is an immunomodulator, a follow-on product characterized by different constituent population could have significant and unpredictable differences from Copaxone® in its immunological mechanisms, raising major safety and efficacy concerns. The potential risks associated with follow-on products include increased immunogenicity, immunotoxicity, induction of additional autoimmune disorders, lack of efficacy, and exacerbation of MS disease processes. Moreover, because of the nature of both RRMS and Copaxone®, these risks may not develop for months or years and, once apparent, may be irreversible. It is thus critical to ensure that any proposed follow-on product has a long-term immunogenicity profile that is comparable to Copaxone®’s before approval. This can only be done based upon data from appropriate clinical testing.

Glatiramer acetate is a highly immunogenic antigen-based therapy, and anti-glatiramer acetate antibodies are detected in all treated patients and animals [31]. These antibodies, however, do not neutralize biological activity or clinical efficacy and are not associated with local or systemic adverse effects in RRMS patients receiving chronic treatment [32-34]. In fact, some evidence suggests that anti-glatiramer acetate antibodies may enhance the biological activity of Copaxone® [35].

The anti-glatiramer acetate antibody profile (titers and isotypes) changes with repeated glatiramer acetate administration, resulting in a unique response profile over time. In RRMS patients, anti-glatiramer acetate antibody levels peak between 3 and 6 months of treatment initiation, and then gradually decline [30]. Anti-glatiramer acetate antibodies are mainly of the IgG class. Studies conducted by different groups report that, initially, anti-glatiramer acetate IgG-2 antibodies predominate but with continued treatment, antibodies gradually shift to the IgG-1 isotype, which is consistent with the

![Figure 13. Total Intensity Values (TIV) Obtained from comparison of Heat Maps of Various Copaxone Batches and Generics](image-url)
glatiramer acetate-reactive T cell shift from a Th1 to a Th2 phenotype [31]. After months of treatment, anti-glatiramer acetate IgG-4 antibodies become evident [34].

Evidence of anti-glatiramer acetate IgE antibodies is equivocal; investigations by Teva indicated that anti-glatiramer acetate IgE antibodies were infrequent and at low levels, not dose-related, and their detection was not associated with clinical adverse events or hypersensitivity reactions [36].

For proposed follow-on glatiramer acetate products, the risk of unwanted immunogenicity is significant. Even if a follow-on glatiramer acetate product has very similar properties to Copaxone® and is produced by a method that is basically similar to the Teva process, the efficacy, safety, and the immunogenicity of the follow-on product can still differ markedly from those of Copaxone® [37]. Several product-related factors can influence the immunogenicity profile. Potential immunogenic risks associated with antibodies to a proposed follow-on glatiramer acetate product include: (1) formation of immune-complexes; (2) development of drug neutralizing antibodies; (3) hypersensitivity reactions; and (4) induction of additional autoimmune disorders.

Anti-glatiramoid antibodies with a different repertoire than that of anti-glatiramer acetate antibodies could lead to formation of immune complexes. Immune-complex deposition in the glomeruli can cause kidney damage over time, becoming clinically evident only after long-term use of the drug [38-39]. In preclinical studies of chronic glatiramer acetate administration to rats and monkeys, there were marginal and only equivocal signs of glatiramer acetate and complement localization in the glomeruli [30]. Localization of immune complexes in the kidney was not found in a longer, 2-year bioassay [36]. Immune-complex disease, presenting as glomerulonephritis, was not seen in clinical studies of glatiramer acetate and was reported only once during extensive post-marketing experience with Copaxone® [36]. In contrast, in a toxicity study of chronic administration of the higher molecular weight glatiramoid TV-5010 to rats, dose-dependent glomerulonephritis attributed to immune-complex deposition was observed at all tested TV-5010 dose levels [40]. This finding reinforces the importance of conducting chronic toxicity studies of proposed follow-on glatiramer acetate products, as longer-term adverse effects such as glomerulonephritis may not be apparent in short-term studies.

While anti-glatiramer acetate antibodies do not inhibit (but may enhance) the therapeutic activity of Copaxone® [31], slight variations in the primary, secondary, and tertiary structure of the active ingredient in a proposed follow-on product may result in the induction of anti-drug antibodies with neutralizing activity. Experience with different recombinant tumor necrosis factor alpha (TNF-α) antagonist drugs demonstrates the variety of antibody profiles possible for individual agents within the same drug class. Anti-infliximab antibody level is associated with decreased therapeutic response, whereas, anti-etanercept antibody level does not appear to influence drug effectiveness or adverse events [40]. The influence of anti-adalimumab antibodies on drug efficacy and adverse events is controversial; serum adalimumab concentrations can be dramatically lower in patients with anti-adalimumab antibodies, possibly because of increased drug clearance due to immune-complex formation [40].

Antibodies to many therapeutic peptides have been reported to induce hypersensitivity. NBI 5788, like glatiramer acetate, is an APL of MBP. NBI 5788 caused a relatively high rate (9%) of hypersensitivity reactions in MS patients in a phase II clinical trial, leading to early discontinuation of the study [41]. Hypersensitivity reactions can be immediate and are usually mediated by specific IgE antibodies, which trigger clinical signs and symptoms of variable severity, from benign urticaria to life-threatening
bronchospasm, angioedema, or anaphylactic shock. Importantly, long-term follow-up of patients who received NBI 5788 showed that even short-term therapy with an APL can induce long-term persistence of altered responses to both the APL and the native protein/peptide [45].

Pathogenic antibodies and T cells can induce autoimmune reactions. When an epitope on an exogenous peptide or protein bears similarities to amino acid sequences on an endogenous protein in body constituents (molecular mimicry), anti-exogenous-protein antibodies can neutralize the biological activity of the endogenous protein, leading to severe adverse events [43-44]. Glatiramer acetate originally was designed to mimic/resemble the encephalitogen, MBP [46] and preclinical and in vitro studies show that glatiramer acetate is cross-reactive with MBP at the cellular and humoral levels [31]. Despite this cross-reactivity, glatiramer acetate is not encephalitogenic (the encephalitogenic potential of Copaxone® batches is routinely tested by Teva). Rather than induce MBP-specific T cells, in vitro and ex vivo studies have shown the opposite: glatiramer acetate inhibits expansion and induces anergy of MBP-specific T cells [47-49]. Similarly, although monoclonal anti-glatiramer acetate antibodies can cross-react with MBP, polyclonal anti-glatiramer acetate antibodies from treated patients do not, and glatiramer acetate does not induce auto-reactive antibodies [31].

Because the active amino acid sequences in the glatiramer acetate mixture responsible for its efficacy are unknown, it is impossible to predict whether follow-on products will have the same efficacy as Copaxone®. They could have a weaker anti-inflammatory effect and/or enhance a pro-inflammatory environment, further exacerbating MS pathogenic processes. A reduced anti-inflammatory effect would provide less effective control of MS relapses, which would be difficult to detect in the post-marketing environment, since MS relapses and progression of disability are not completely abolished by any MS therapy. On the other hand, creation or amplification of a pro-inflammatory environment would likely increase relapse rate and progression of disability, or worse, e.g., have a profound encephalitogenic effect. Clinical trials of non-glatiramoid APLs of MBP in MS patients have shown that very strong responses to the APL can augment disease-related immune responses to the native antigen or produce intolerable immune-mediated secondary effects, including hypersensitivity reactions [41, 45].

Clinical experience with CGP77116, which, like Copaxone®, is an APL of MBP, exemplifies this risk. CGP77116 was associated with unexpected pro-inflammatory encephalitogenic effects, inducing brain inflammation that necessitated early termination of a study in RRMS patients [50]. In contrast to results of in vitro studies, CGP77116 in vivo caused substantial expansion of CGP77116-specific T cells that were cross-reactive with native MBP—a necessary prerequisite for “bystander suppression.” However, rather than stimulate an anti-inflammatory T-cell phenotype, the majority of activated CGP77116-specific T cells were of a pro-inflammatory (Th0/Th1) phenotype. Moreover, in some patients, worsening disease could be linked to CGP77116-induced expansion of MBP-specific T cells, which likely exacerbated pathogenic demyelination [50].

Finally, the potential for the development of cross-reactive neutralizing antibodies must be assessed before any regulatory authority approves any follow-on glatiramer acetate product intended to be used interchangeably with Copaxone®. Switching between two complex polypeptide products with subtle differences in structure and/or composition may increase the chance of cross-reactivity, a phenomenon that has
been observed with interferon beta products [51]. Upon switching from Copaxone® to a follow-on product or using them interchangeably, antibodies formed against Copaxone® may neutralize the activity of the proposed generic product and vice versa. If this were the case, patients would be left without any effective treatment. Again, there is no evidence that progression of neurologic disability associated with untreated MS can ever be reversed.

Although Copaxone® is not currently regulated as a “biological product” in the US or Europe, it nevertheless shares many of the same characteristics as biological products, including a large and complex molecular structure and concomitantly complex interactions with the immune system. Consequently, the same scientific justifications for requiring data on the risks of switching “interchangeable” biological products apply equally to proposed generic glatiramer acetate products that are intended to be used interchangeably with Copaxone®. Indeed, because Copaxone® is intended to be used chronically, and because its effects on the immune system appear to evolve over time, there is no way to predict the effect of a “switch” or for that matter, multiple switches, on safety or effectiveness without conducting adequate and well-controlled clinical trials.

1.6 CONCLUSIONS AND FUTURE PROSPECTS

The complexity of Copaxone® raises safety and effectiveness concerns that merit heightened vigilance with respect to the approval of potentially interchangeable follow-on glatiramer acetate versions. Currently there is no defined mechanism for follow-on versions of NBCDs such as certain liposomal drugs, glatiramoids like Copaxone® and iron-sugar complexes. As discussed earlier, this is because the classical paradigm for abbreviated authorizations of conventional small molecules is not appropriate or valid because NBCDs lack a homo-molecular structure that cannot be fully quantitated or characterized via conventional physicochemical analytical tools and their composition and quality generally depends upon the manufacturing process and controls. As a result, originator NBCDs are not fully characterizable, some are not amenable to therapeutic bioequivalence testing, and comprehensive regulatory evaluation and guidelines for follow-on versions of NBCDs or nanosimilars are currently not developed. Consequently, they present a challenge to regulatory bodies like the FDA and EMA, manufacturers, physicians and pharmacists.

1.7 DISCLOSURES AND CONFLICT OF INTEREST

The authors declare that no writing assistance was utilized in the production of this manuscript and the authors have received no payment for preparation of this chapter. The findings and conclusions here reflect the current views of the authors. They should not be attributed, in whole or in part, to the organizations with which they are affiliated, nor should they be considered as expressing an opinion with regard to the merits of any particular company or product discussed herein. Nothing contained herein is to be considered as the rendering of legal advice. Currently, Dr. Bawa is a Scientific Advisor to Teva Pharmaceuticals, Ltd. (Israel).
1.8 BIOGRAPHIES

Dr. Jill Conner joined Teva Pharmaceuticals in 2006 in the Medical Affairs department, where she was Director of Medical Operations, before she took her current position as Director of Specialty Life Cycle Initiatives. She currently is responsible for the life cycle management for innovative products. Prior to working at Teva, she spent several years as a medical technologist before she focused her work in drug approval research with management positions in CRL-Medinet followed by director positions in Clinical Operations/Project Management at United BioSource Corporation. Over the years, Dr. Conner has been involved with all aspects of clinical research including design and conduct of Phase I-IV clinical trials, retrospective database analyses, chart reviews, and investigator initiated trials. Dr. Jill Conner received her Ph.D. in International Health from TUI University, an M.S. in Management from Baker University, and a B.S. in Medical Technology from the University of Missouri-Kansas City.

Dr. Raj Bawa is president of Bawa Biotech LLC, an Ashburn, VA based biotech/pharma consultancy and patent law firm he founded in 2002. He is an inventor, entrepreneur, professor and a registered patent agent licensed to practice before the U.S. Patent & Trademark Office. Trained as a biochemist and microbiologist, he has been an active researcher for the past two decades. He has extensive expertise in pharmaceutical sciences, biotechnology, nanomedicine, drug delivery and biodefense-related scientific, FDA regulatory and patent law issues. Since 1999, he has held various adjunct faculty positions at Rensselaer Polytechnic Institute in Troy, NY where he is currently an adjunct professor of biological sciences and where he received his Ph.D. degree (Biophysics/Biochemistry; 1987-1990). Since 2004, he has been an adjunct associate professor of natural and applied sciences at the Extended Learning Institute of NVCC in Annandale, VA. Since 2012, he has been a scientific advisor to Teva Pharmaceutical Industries, Ltd., Israel. He previously served as patent legal advisor at Sequoia Pharmaceuticals, Gaithersburg, MD and as senior scientist at SynerGene Therapeutics, Inc., Potomac, MD. He recently served as principal investigator of two National Cancer Institute/SBIR contracts titled “Targeted nanocomplexed iron oxide for early detection with concurrent hyperthermia treatment of cancer” and “A targeted nanocomplex for early detection of lung cancer.” In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office, including primary examiner (6 years) and instructor at the US Patent Academy. He is a life member of Sigma Xi, founding director of the American Society for Nanomedicine, and co-chair of the Nanotech Committee of the American Bar Association. He has authored over 100 publications, co-edited two texts, presented or chaired at over 200 conferences worldwide and serves on the editorial boards of 16 peer-reviewed journals.

Dr. J. Michael Nicholas, received his PhD in pharmacology from the University of Tennessee Center for Health Sciences. After postdoctoral work at the University of Mississippi in Jackson he joined Mylan Pharmaceuticals in Morgantown, WV as Director of Scientific Affairs. While at Mylan he later served as Director of Scientific and Regulatory Affairs and was involved with the development and approval of both generic and branded products. Following Mylan, he accepted a position with Marion Laboratories in Kansas City in the Regulatory Affairs department. Over the years, Dr.
Nicholas has been involved with all aspects of regulatory matters including product development and approval. While at Marion Laboratories, Marion Merrell Dow and Hoechst Marion Roussel, Dr. Nicholas served as the Director of Product Approval within the Regulatory Affairs Department and directed the submission of INDs, NDAs, and their subsequent approval. Prior to his current position, he was Vice President, US Regulatory Affairs and Compliance, Marketed Products for Aventis Pharmaceuticals and was responsible for regulatory matters for approved products. Currently, Dr. Nicholas is Vice-President of Specialty Life Cycle Initiatives for Teva Brand Pharmaceuticals and is responsible for product life cycle planning.

Dr. Vera Weinstein, received her PhD in Synthetic Organic Chemistry from the Hebrew University of Jerusalem, Israel (HUJI). After several years at the HUJI as a senior lecturer, she joined Portman Pharmaceutical Industries as Chief research chemist, and was involved with the development of branded products. In 1996, Dr. Weinstein accepted a position with Teva as an Analytical Team Leader, and later as CMC Program Leader in Innovative R&D. At her present position, Dr. Weinstein is Director of Scientific Affairs, Discovery and Product Development, Global R&D, Teva Pharmaceuticals.

1.9 REFERENCES


30 | Copaxone® in the era of biosimilars and nanosimilars

Metabolism and Toxicology 6:643-660.


March 15, 2014]


