Non-Biological Complex Drugs

Defining and characterizing non-biological complex drugs (NBCDs) – Is size enough? The case for liposomal doxorubicin generics ('liposomal nanosimilars') for injection

Professor S Moein Moghimi, PhD; Z Shadi Farhangrazi, PhD

'Non-binding recommendations' from regulatory bodies are in place for evaluation and production of generic liposomal doxorubicin injection. However, how these nano-sized generics ('nanosimilars') should be characterized and evaluated, and particularly when the 'reference listed product' is no longer in production are among the major issues. We discuss these issues with respect to complexity of liposomal structure and vesicular population heterogeneity, and the challenges facing 'nanosimilars'.

Keywords: Adverse reactions, complement system, immunogenicity, liposome, nanoparticle size, vesicle morphology

Doxil (owned by Johnson & Johnson through its subsidiary Janssen) is the trade name of doxorubicin HCl liposome injection. Doxil is indicated for HIV-related Kaposi's sarcoma in patients with low CD4 count and extensive mucocutaneous or visceral disease as well as for the treatment of patients with advanced ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy [1]. The original patent for Doxil expired in 2009 [1]. However, there is an exclusivity extension for Doxil (an orphan designation until 17 May 2014) in combination with bortezomib (Velcade) for use in patients with multiple myeloma.

Doxil is a sophisticated multi-component nano-sized formulation and its biological performance is controlled by a complex array of interrelated physicochemical properties including liposome composition, vesicular size (curvature), morphology and surface characteristics, the internal environment, e.g. volume, pH, sulfate and ammonium ion concentration [1, 2]. The sheer complexity and the know-how of Doxil design, development and production, should indeed, offer market exclusivity and reduce the threat of generics competition even after patent expiration [3].

Since mid-2011, Doxil is in short supply, arising from voluntary shutdown of a third-party manufacturer (Ben Venue Laboratories, Bedford, Ohio, USA). Despite continued efforts to return the Ohio facility to working order, decision was made to permanently cease production by the end of 2013 [4]. Johnson & Johnson is now looking for an alternative site for producing Doxil [4]. However, in February 2013, the US Food and Drug Administration (FDA) approved a 'nanosimilar' version of Doxil (Lipodox) made by Sun Pharma Global FZE, a subsidiary of India's Sun Pharmaceutical Industries Ltd [5]. Lipodox is not approved to treat patients with multiple myeloma, as this exclusivity agreement is still intact [4].

Are Doxil and Lipodox similar? Recently, FDA generated a draft document containing 'non-binding recommendations' for evaluation of generic injectable poly(ethylene glycol)-grafted (PEGylated) liposomal doxorubicin formulations [6]. It is well known that the biophysical characteristics of liposomes can modulate their biological performance, which include vesicular stability and circulation times, enhanced permeability and retention at solid tumours, drug-release rates (at the target site) and toxicity [1]. Although, these attributes have been addressed in the regulatory draft recommendations, precision biophysical characterization of drug-loaded vesicles is a daunting task [7]. A generic liposomal formulation may show similar morphological structures (lamellarity), mean average hydrodynamic vesicular size and electrophoretic mobility profiles to that of the reference listed drug (RLD). However, the vesicular suspension (whether RLD or generic drug) may be heterogeneous with respect to many physicochemical properties. Some vesicular populations may differ from others in terms of lipid bilayer stress and defects, aspect ratios (since on doxorubicin loading and precipitation the vesicular shape usually changes from spherical to an oblate spheroidal shape) and vesicular scattering intensity (even among vesicles of the same size/aspect ratio), and surface hydrophobicity/hydrophilicity. These issues are often

Author for correspondence: Professor S Moein Moghimi, PhD, Centre for Pharmaceutical Nanotechnology and Nanotoxicology, Department of Pharmacy, University of Copenhagen, 2 Universitetsparken, DK-2100 Copenhagen Ø, Denmark

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not addressed in liposome production, but could play serious roles in liposomal 'nanosimilar' manufacturing and biological performance. Furthermore, a liposomal 'nanosimilar' may differ from the RLD in terms of the number of suspended vesicles in the vial, although the mean vesicular size (spherical equivalent) and encapsulated drug content (and drug-to-lipid ratio) may be the same between the two formulations. Here, dosing of the generic drug formulation, in terms of equivalent doxorubicin or doxorubicin/g lipid, may be the same as the RLD product, but not necessarily in terms of the number of administered vesicles. Accordingly, a generic doxorubicin HCl liposome injection may not be qualitatively the same as the RLD, i.e. Doxil. The above-mentioned changes, however, may not have a dramatic impact on vesicular circulation times (at least on the first injection), but may control the kinetic of drug release at tumour sites as well as affecting immune responses on infusion [7]. These biological differences, presumably, can only be observed in large and carefully planned studies. Indeed, small changes in liposome number will affect the total available surface area exposed to the blood, and subtle changes in liposomal surface properties can translate to large changes in the overall surface considering the large number of vesicles that are introduced into the systemic circulation. These changes, for instance, may affect the frequency of infusion-related reactions, where inadvertent complement activation is a causal factor [8]. Complement system is the first line of defense against intruders, recognizing danger primarily through pattern recognition [9]. Minor differences in liposome surface curvature, defects and characteristics can incite complement differently and through the binding of antibodies as well as different complement-sensing molecules to include C1q, mannose binding lectin, ficolins and properdin [9, 10]. Further complexity may emerge from the presence of complement activating aggregated contaminants in clinical formulations as well as vesicular structural transformation (resulting from vesicular heterogeneity) in contact with the blood that could elicit immunological reactions [9]. Indeed, morphological evidence for the presence of low-curvature oval, elongated or irregular liposomes and aggregate already exist for Doxil, which are believed to affect complement activation and consequential responses [11]. Other complications could still arise from potential differences in immunogenicity, which can only be observed in large population studies.

There are ongoing debates as how to evaluate generic or 'nanosimilar' liposomes for injection [12-14], but unavailability of the RLD product (Doxil in this case) is of concern for comparative purposes. After all, this is not about conventional bioequivalence approaches applied to a generic low molecular weight drug, which is sufficient to demonstrate comparable content, purity and clinical pharmacokinetics. With liposomes, the vesicular properties control the pharmacokinetics of the encapsulated drug as well as the toxicity profile [15]. Accordingly, various techniques must be adopted to examine key physicochemical parameters between generics and RLD products and identify vesicular population differences and systems' heterogeneity. What are needed are advanced and sophisticated characterization tools that can provide better definition of vesicular (or nanoparticle) morphology heterogeneity, size and surface heterogeneity within a typical suspension as well as technologies that can yield more homogenous drug-loaded vesicular populations [7]. In the absence of such evaluations an independently developed liposomal formulation may not have identical pharmaceutical quality attributes as the RLD product and therefore cannot be considered interchangeable in the absence of designated clinical studies. A responsive regulatory framework is therefore needed and may be applicable to broader regulation of future products of nanotechnology [16].

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Co-author

Z Shadi Farhangrazi, PhD, Biotrends International, Denver Technological Center, Greenwood Village, Colorado, USA

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