Bio- Materials Analysis Technology Inc.

Abraxane® _ *Nanoparticle Albumin bounded* Paclitaxel

- *Observing the morphology and particle size distribution by electron microscopy*

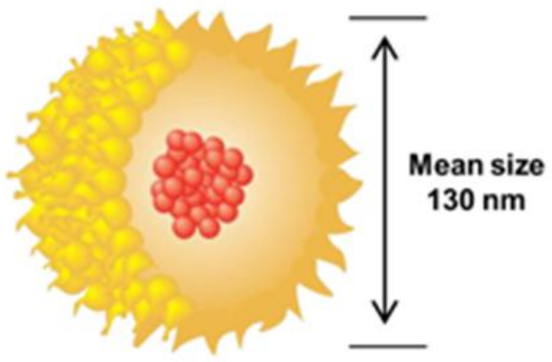
High quality electron microscopy analysis services for the regulatory requests!
Providing data support with physicochemical characterization for your products!!

Does ANDA ≈ RLD?

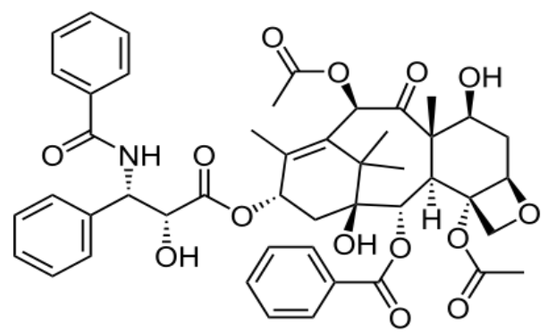
**** US FDA 2012 _ Contains Nonbinding Recommendations "Draft Guidance on Paclitaxel "***

1. In vivo Bioequivalence study with PK endpoints
2. **In vitro particle size distribution _ D_{10}, D_{50}, and D_{90}**

Abraxane®
nab-paclitaxel



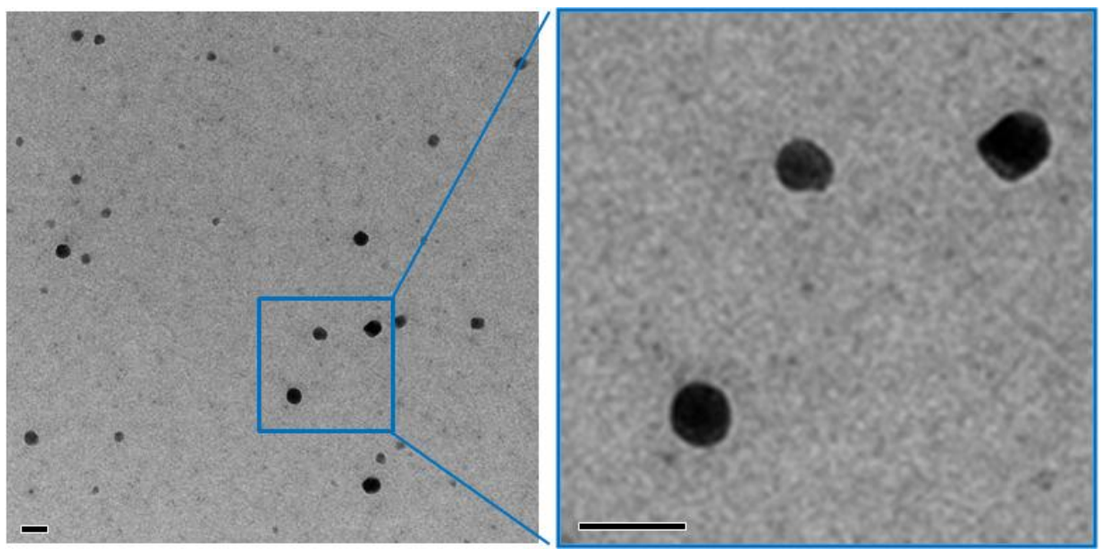
Excipient: Albumin



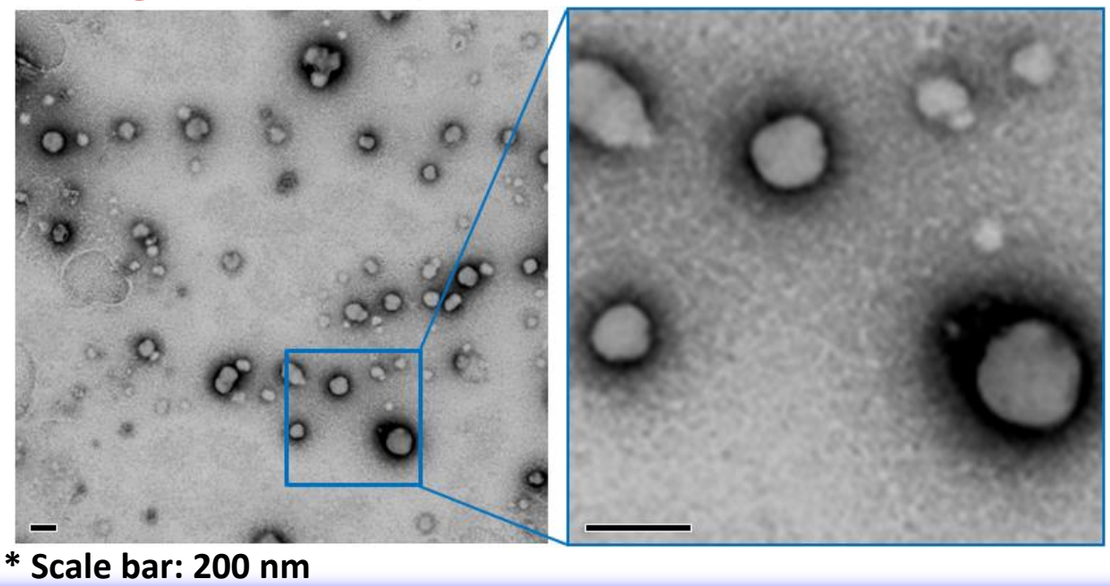
API: Paclitaxel

TEM _ *Morphology and Size distribution of ANDA vs. RLD*

➢ ***Sample in saline / Liquid TEM***



➢ ***Negative stain / TEM***



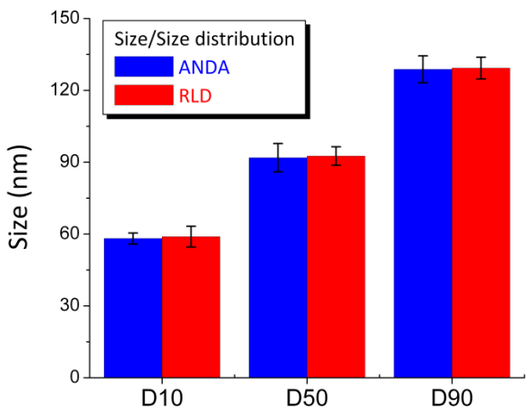
*** Scale bar: 200 nm**

Three batches of ANDA vs. RLD

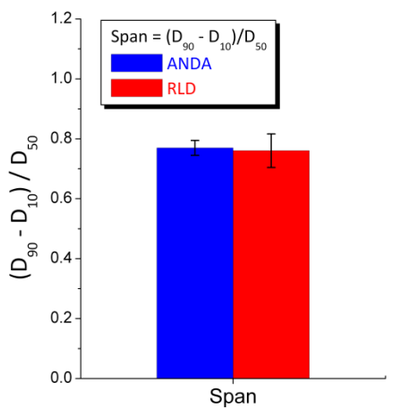
Name	D_{10} (nm)	D_{50} (nm)	D_{90} (nm)	Span	Number
A. ANDA					
Lot- #1	55.7	90.6	123.8	0.752	395
Lot- #2	60.3	98.3	134.9	0.759	378
Lot- #3	58.4	86.7	127.6	0.798	385
B. RLD					
Lot- #1	63.8	92.8	128.4	0.696	369
Lot- #2	57.3	96.3	134.2	0.799	399
Lot- #3	55.6	88.6	125.3	0.787	388

** Span = $(D_{90} - D_{10}) / D_{50}$*

D_{10}, D_{50}, and D_{90}



Span



* ***ANDA:*** Abbreviated New Drug Application, ***RLD:*** Reference Listed Drug

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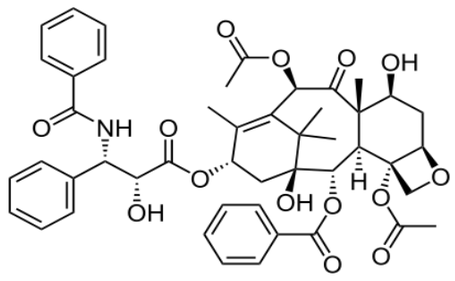
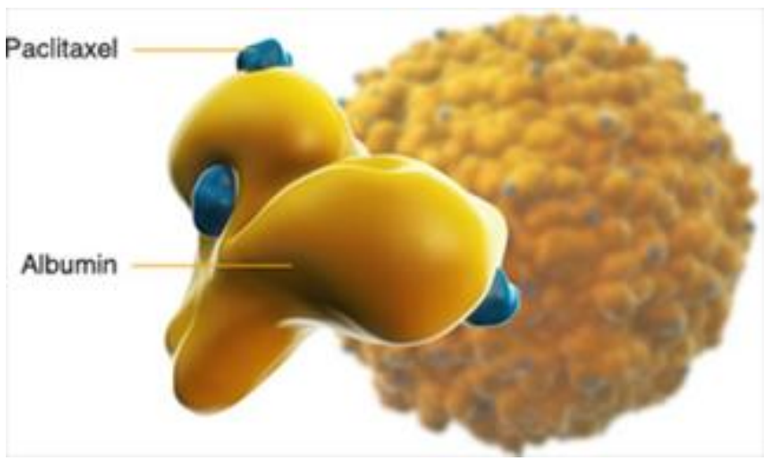
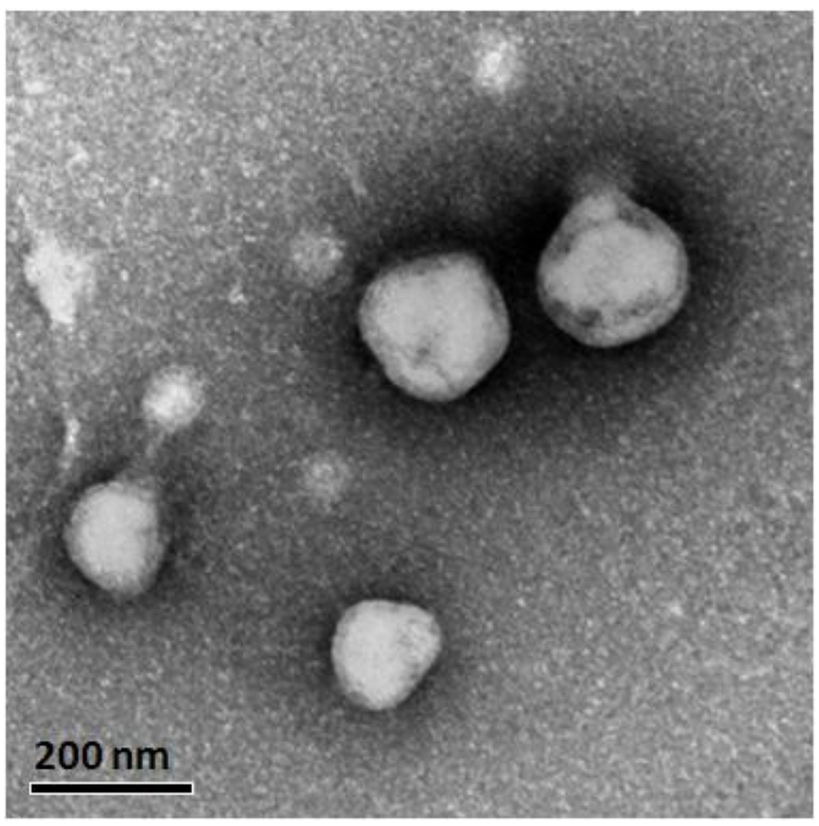
Abraxane® Analysis

_ Analyzing particle size distribution by transmission electron microscopy

Does ANDA ≈ RLD?







Contains Nonbinding Recommendations

Draft Guidance on Paclitaxel

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Paclitaxel

Form/Route: Suspension/Injectable

Recommended Studies: 2 studies

2. Type of study: In Vitro Particle Size Distribution
Design: In vitro bioequivalence study on at least three lots of both test and reference products
Strength: 100 mg/vial
Additional comments: None

Parameters to measure: $D_{10,}$ $D_{50,}$ and D_{90}

Bioequivalence based on (95% CI): Population bioequivalence based on D_{50} and span $(D_{90}-D_{10})/D_{50}$ or polydispersity index

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As per 21 CFR § 314.94(a)(9)(iii), the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the corresponding reference listed drug product. In addition, firms are recommended to obtain assurance from OGD that the test product has the same in-vitro characteristics as those of reference listed drug product prior to conducting any bioequivalence study for submission. Additional in vitro characterization are recommended to demonstrate the sameness between the test and reference products in terms of particle morphology, particle size, surface potential, paclitaxel crystallinity, fraction of free and bound paclitaxel or albumin in reconstituted suspension, nature of bond between paclitaxel and albumin, and in vitro release kinetics. In addition, albumin, the only excipient in the final product, is critical to the formulation. The characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product is also recommended. The in vitro characterization tests are recommended to be conducted on three batches of the ANDA and RLD products (at least one ANDA batch should be produced by the commercial scale process).

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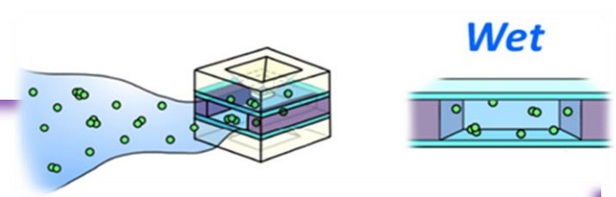
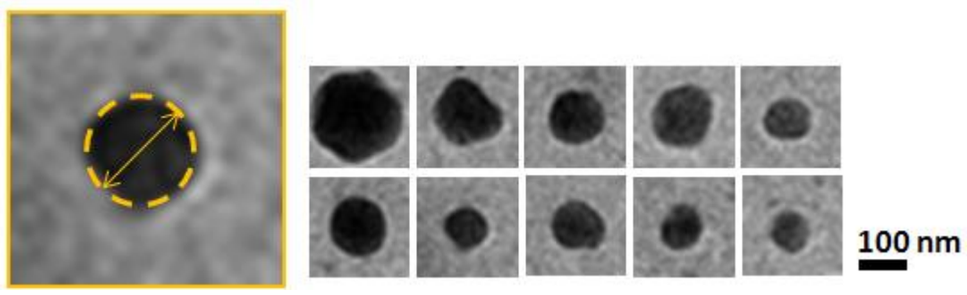
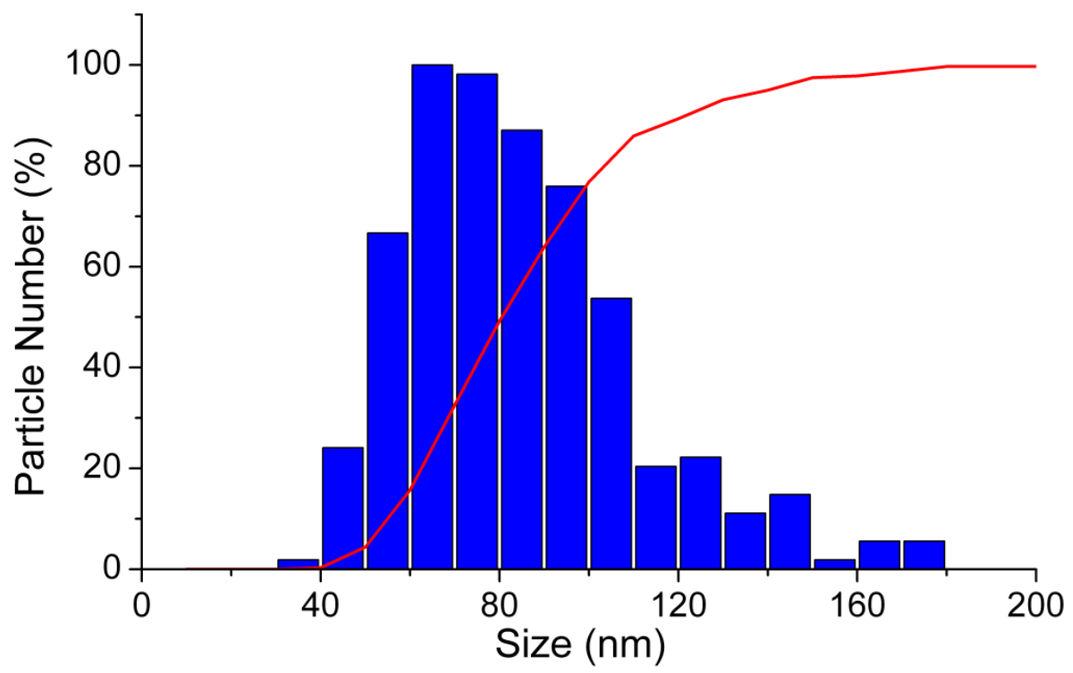
Liquid TEM _ In Saline _ Size/size distribution (D_{10}, D_{50}, D_{90})





Parameter	Size (nm)
D 10	55.6
D 50	80.1
D 90	122.2
Span: $(D_{90} - D_{10}) / D_{50}$	0.831

☐ ***Constituted particle:*** Original individual particle with defined physical boundaries.
☐ Total calculated particle n = 319



**** D50***, the median diameter, where half of the population lie below this value. ***D10***, the diameter of 10% population lies below this value. ***D90***, the diameter of 90% population lies below this value.

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