CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220152Orig1s000

PRODUCT QUALITY REVIEW(S)

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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	220152
Applicant Name	Vanda Pharmaceuticals, Inc.
Drug Product Name	Trade Name (tradipitant) Capsules, 85 mg
Dosage Form	Capsule
Proposed Strength(s)	85 mg
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	170 mg
Rx/OTC Dispensed	Rx
Proposed Indication	The prevention of vomiting induced by motion in adults
Drug Product Description	Vanda Pharmaceuticals, Inc. has submitted this 505(b)(1) new drug application for Trade Name (tradipitant) Capsules, 85 mg for the prevention of vomiting induced by motion in adults. The drug substance, tradipitant is a selective neurokinin-1 (NK-1) receptor antagonist. It has not been previously approved or marketed in the United States. Therefore, tradipitant is classified as a New Molecular Entity (NME). Hard gelatin capsules with a white opaque body and black opaque cap. The capsules are imprinted with "VANDA 85mg" in white lettering on the cap. Each capsule contains 85 mg of tradipitant as the active ingredient and croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and (b) (4) lactose monohydrate as inactive ingredients. All inactive ingredients used in this drug product formulation are either compendial materials or materials that comply with applicable

	Code of Federal Regulations (CFR) requirements. The levels of all inactive ingredients are at or below the maximum limits specified in the Agency's Inactive Ingredient Database (IID) for oral drug products. The capsule shells are composed of gelatin, titanium dioxide, FD4C Blue, FD&C Red, FD&C Yellow, and white ink. [TRADENAME] (tradipitant) capsules are packaged as 36-count capsules in 60 cc HDPE bottle with induction sealed child-resistant caps and a 2-g silica gel desiccant. This drug product should be stored at (b) (4) 25°C (b) (4) 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Based on the stability data provided in this application an expiration dating period of 48 months is granted to this drug product.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at (b) (4) 25°C ((b) (4) 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Friedrich Burnett, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Zhengfang Ge, PhD	Hamid Shafiei, PhD/Julia Pinto, PhD
	Manufacturing	Amit Kokate, PhD	Vaikunth Prabhu, PhD
	Biopharmaceutics	Leah Falade, PhD	Tapash Ghosh, PhD
	Microbiology	N/A	N/A
	Other (specify): *Categorical Exclusion*	Zhengfang Ge, PhD	Hamid Shafiei, PhD

	RBPM	Megan Nguyen
	ATL	Hamid Shafiei, PhD
Consults	N/A	

2. Final Overall Recommendation - *Recommended for Approval*
The Chemistry, Manufacturing, and Controls (CMC) information provided in this application has been deemed adequate across all Office of Pharmaceutical Quality (OPQ) review disciplines. Several OPQ-recommended PI labeling as well as container and carton labels changes/revisions have been communicated to the applicant through the Gastroenterology Clinical Division. The Applicant has accepted the OPQ-recommended changes/revisions, and the proposed changes/revisions will be implemented in the final PI labeling as well as container and carton labels when the final labeling and labels are submitted to the application. Therefore, this application is recommended for approval, and no additional labeling addendum will be needed.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The Applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, tradipitant and the drug product, [TRADENAME] (tradipitant) Capsules, 85 mg.
- The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the overall recommendation of adequate for the facilities involved in this application.
- The OPQ-recommended labeling/labels revisions/changes have been satisfactorily addressed.
- The applicant's request for categorical exclusion from the preparation of environmental assessment has been found valid and therefore, applicant's request for the categorical exclusion is granted.

Therefore, this applicant is recommended for approval from the OPQ perspective with expiration dating period of 48 months.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate

Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	220152
Assessment Cycle Number	1
Drug Product Name	[TRADENAME] (tradipitant) capsules

Assessment Recommendation: Adequate, pending agreement on final labeling

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	See recommendation below
Patient Information	Adequate	
Instruction for Use (IFU)	N/A	
Container Labels	Inadequate	See recommendation below
Carton Labeling	Inadequate	See recommendation below

Brief Description of Outstanding Issues:

The NDA is recommended for Approval from the labeling perspective pending the implementation of editorial recommendations listed in Section 4 at the end of this review. Dr. H. Shafiei, the SPQA, will add the final labels to the combined CMC assessment once the labels are finalized.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001	12/30/2024	Prescribe information, patient information
0026	11/7/2025	c/c labels

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name(s)[3]	Adequate	Established name: tradipitant
Route(s) of administration	Adequate	- "capsules, for oral use"
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	- capsules
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

Assessment: *Adequate*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not	Adequate	- (b) (4)

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
crush or chew extended-release tablets, instructions for mixing with food).		
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	capsules
Strength(s) in metric system	Adequate	85 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	- white opaque body capsule with "VANDA 85mg" printed on the black opaque cap.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

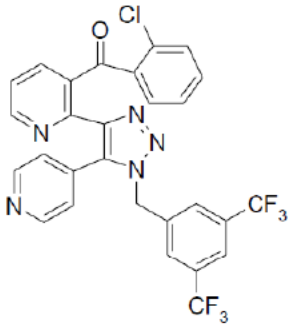
Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	- "Tradename (tradipitant)"
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	- capsules
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency	N/A	

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	- The excipients are arranged to alphabetic order. - Removed (b) (4) - The following hard gelatin capsule and the colorants are included in the inactive ingredients: The capsule contains gelatin, titanium dioxide, colorants FD&C blue No 1, FD&C red No 40, and FD&C Yellow No 6.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	- a substance P/neurokinin 1 (NK1) receptor antagonist
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	{2-[1-(3,5-Bistrifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl)-methanone with molecular formula $C_{28}H_{16}ClF_6N_5O$, and molecular weight 587.9 
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	- Tradipitant is a white to off-white crystalline powder. It is practically insoluble in water, soluble in methanol, and slightly soluble in isopropyl alcohol and simulated gastric fluid (b) (4) - [TRADENAME] is (b) (4) as white opaque capsules with black caps imprinted with "VANDA 85 mg" for oral administration, each containing 85 mg tradipitant.
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	-
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	- TRADENAME (tradipitant) capsules 85 mg

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	- 85 mg
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	- Bottle of 36
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	- white opaque body and black opaque cap, hard gelatin capsules, printed with "VANDA 85 mg" in white on the cap
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	- protect from light and moisture

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	- at controlled room temperature, 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature - added "[redacted] (b) (4)"
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	- HDPE bottle with child-resistant cap and a 2-g desiccant pouch

Assessment: *Adequate*

1.2.5 Other Sections of Labeling

None

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	- Distributed By: Vanda Pharmaceuticals Inc. Washington, D.C. 20037 USA

Assessment: *Adequate*

2.0 PATIENT LABELING

No Patient Labeling. A Patient Counseling Information is provided in section 17 of the labeling and acceptable

3.0 CONTAINER AND CARTON LABELING[24]

(b) (4)

[redacted]

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Carton and Container Labeling Resources
[25] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[26], (font size and prominence) [§ 201.10(g)(2)].	Inadequate	Yes	- "Tradename", established name should be ½ size of the trade name
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	85 mg
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Inadequate	Yes	- Add "for oral use" in the c/c labels
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	Yes	36 capsules
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	Yes	- Add Lot number and expiration date in the c/c labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	(b) (4)

[26] Established name = [Drug] [Route of Administration] [Dosage Form]

[27] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[28] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
			(b) (4)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See	Adequate	Yes	

[29] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Prescribing Information" [§ 201.5 & 201.55].			
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[30]	N/A	Yes	
And others if space is available.	N/A	Yes	

[30] USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Inadequate*

- Established name should be ½ size of the trade name.
- Add "for oral use" in the c/c labels.
- Add Lot number and expiration date in the c/c labels.

(b) (4)

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The following editorial change has been communicated to the applicant

(b) (4)

The following changes for the C/C Labels have been communicated to the applicant

- Established name should be ½ size of the trade name.
- Add "for oral use" in the c/c labels.
- Add Lot number and expiration date in the c/c labels.

(b) (4)

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, OPQ/OPQAII/Division VII/NDPB4

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Julia Pinto, Ph. D.
Branch Chief, OPQ/OPQAII/Division VIII/NDPB3

Zhengfang Ge

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Date: 12/18/2025 04:03:09PM
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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

NDA Number	220152-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Tradipitant Capsules/85 mg
Route of Administration	Oral
Applicant Name	Vanda Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	Anti-emetics/Division of Gastroenterology (DG)
RLD/RS Number	N/A
Proposed Indication	For acute prevention of vomiting induced by motion

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant seeks approval for its Tradipitant (VLY-686) Capsules, 85 mg under the 505(b)(1) pathway. The Active Pharmaceutical Ingredient (API) is a selective inhibitor of the human neurokinin-1 (NK-1) receptor. The proposed indication is for acute prevention of vomiting induced by motion.

The Biopharmaceutics review focuses on the evaluation and acceptability of 1) the proposed dissolution method and acceptance criterion, and 2) formulation bridging, with key finding summarized below.

1) Dissolution Method and Acceptance Criterion:

(b) (4) The current Applicant provided an evaluation report justifying the selection of the dissolution medium, surfactant concentration, volume, and rotation speed. The Applicant's proposed a dissolution method using USP Apparatus II (Paddle) with sinkers at 75 rpm in 1000 mL of 0.01 N HCl with 0.2% SDS. The proposed method is discriminating to different polymorphic forms ((b) (4) and particle size distribution (PSD). Manufacturing process parameters were evaluated such as (b) (4) . However, the dissolution profiles were

found to be similar when comparing to the target batch and is therefore the method not discriminating to these changes in manufacturing process parameters.

The acceptance criterion proposed is Q (b) (4) % in 30 min. Based on the individual unit dissolution data at Stage 2 testing on the clinical and registration batches, the proposed acceptance criterion is data-driven and deemed adequate.

The Applicant's proposed dissolution method and acceptance criterion are deemed acceptable for batch release and stability testing of the proposed drug product.

2) Formulation Bridging:
During the development program, several clinical studies were performed on tablet and capsule formulations. However, the final to-be-marketed (TBM) 85 mg capsules were used in Phase 2 and Phase 3 pivotal studies. The capsules used in the pivotal studies will be manufactured at the same site as the TBM product ((b) (4) Therefore, from a Biopharmaceutics perspective additional formulation bridging is not needed.

Recommendation:
From the Biopharmaceutics perspective, NDA-220152-ORIG-1 for Tradipitant Capsules, 85 mg, is recommended for **approval**.

FDA-Approved Dissolution Method and Acceptance Criterion:

Apparatus	Speed	Medium/Temperature	Volume	Acceptance Criterion
II (Paddle) with sinkers	75 rpm	0.01 N HCl with 0.2% SDS/37±0.5°C	1000 mL	Q= (b) (4) % in 30 min

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Seq 0001	12/30/2024

Highlight Key Issues from Last Cycle and Their Resolution:
This is the first review cycle.

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Assessment:

The drug substance has low solubility and high permeability and can be classified as BCS Class II.

Solubility:

The equilibrium solubility was assessed from pH 1.0 to 7.4 at 37°C for 24 hours. The criterion to meet high solubility is 85 mg/250 mL=0.34 mg/mL. The criterion is not met in all pH media without surfactant. Therefore, the solubility is considered low.

Table 1. Equilibrium Solubility in Buffers pH 1.0 to 7.4

Medium	pH	Solubility (mg/mL)
0.1 N HCl	1.2	0.02
0.01 N HCl	2.0	0.00
0.01 N HCl containing 0.10% SLS	2.0	0.66
0.01 N HCl containing 0.20% SLS	2.0	1.06
0.01 N HCl containing 0.30% SLS	2.0	1.04
50 mM acetate buffer	4.5	0.00
0.2 M phosphate buffer	6.8	0.00
0.2 M phosphate buffer	7.4	0.00

Permeability:

The Applicant submitted Study No. 20VNDAP1GLPS607 investigating the in vitro permeability and gastrointestinal (GI) fluid stability of VLY-686 according to the BCS Guidelines. A validated Caco-2 cell monolayer model was used to determine the permeability. Due to the low solubility of the API, it was not possible to evaluate 1%, 10%, and 100% of the highest strength in 250 mL. Therefore, dosing solutions were prepared at a nominal concentration of 80 µM. The apical-to-basal (A-to-B) P_{app} was greater than that of the high permeability reference compound, minoxidil (

Table 1). The bidirectional permeability results showed that the API permeates Caco-2 cells primarily by passive diffusion (***Table 3***). Therefore, the drug substance can be classified as highly permeable. The GI stability was assessed

at 60 min in SGF and 180 min in SIF. More than 90% of the nominal concentration of API remained after the stability experiments.

Table 2. Unidirectional (A-to-B) Permeability and Recovery of VLY-686 and Reference Compounds

Parameter	Analyte		
	VLY-686 (0.130 µM)[a]	Minoxidil (10 µM)	Atenolol (100 µM)
P_{app} (10^{-6} cm/s)	18.7 ± 3.5	2.68 ± 0.67*	0.0619 ± 0.0161*
Recovery (%)	86.1 ± 13.1	102 ± 5	92.9 ± 3.0
Mass Balance (%)	144 ± 24[#]	Not determined	Not determined

The results are presented as mean ± standard deviation (SD); n=4.

[a] Mean measured concentration of the dosing solution prepared as described in Section 9.4

* The atenolol P_{app} was less than 1.00×10^{-6} cm/sec and the ratio of minoxidil P_{app} to atenolol P_{app} was greater than 3 for each replicate, confirming monolayer integrity.

[#] Mass balance was supramaximal due to the pre-incubation of the cell monolayers with the test article, followed by a post-experiment rinse with MeCN:HBSSg (1:1, v:v), which extracted the test article from all compartments, including the donor chamber.

Table 3. Bidirectional Permeability of VLY-686

Parameter	Direction	Mean Measured Dosing Concentration 0.615 µM
P_{app} (10^{-6} cm/sec)	A-to-B	32.4 ± 13.3
Recovery (%)		94.0 ± 29.9
Mass Balance (%)		121 ± 14[#]
P_{app} (10^{-6} cm/sec)	B-to-A	19.0 ± 3.4
Recovery (%)		136 ± 21[$]
Mass Balance (%)		170 ± 27[#]
Efflux Ratio*	B-to-A / A-to-B	0.586

The results are presented as mean ± SD; n=6 for P_{app} and recovery, n=3 for mass balance.

* Efflux ratio was calculated using the mean A-to-B and B-to-A P_{app} values.

[$] B-to-A recovery was supramaximal (> 100%) because the measured 45-minute donor concentration was higher than the measured initial donor concentration. There is no impact on the calculated permeability, because P_{app} is normalized to the initial donor concentration, and the mean measured initial donor concentrations in each direction were comparable (relative percent difference less than 3%).

[#] Mass balance was supramaximal due to the pre-incubation of the cell monolayers with the test article, followed by a post-experiment rinse with MeCN:HBSSg (1:1, v:v), which extracted the test article from all compartments, including the donor chamber.

Dissolution:

See section B.2.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

(b) (4) . The current Applicant (Vanda) adopted the method for their 85 mg capsule formulation. (b) (4) . The details of the method development are found in Module 3.2.P.5.6[1]. Vanda (b) (4) submitted a method evaluation report. The original dissolution method used USP Apparatus II (Paddle) with sinkers at 75 rpm in 1000 mL of 0.01 N HCl with 0.2% SDS.

In using this method, the Applicant observed stability failures for one of the clinical batches after storage at accelerated conditions. This was due to cross-linking from the capsule shell. As per USP <711>, Tier 2 testing conditions with 375,000 units/L of pepsin were added to the dissolution procedure.

Dissolution data on the to-be-marketed (TBM) product was submitted in multi-pH medium. The most favorable medium was confirmed to be 0.01 N HCl with 0.2% SLS, which is in line with the equilibrium solubility results (

Table 1).

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(b) (4)

(b) (4)

Discriminating Ability

(b) (4)

The 10 mM HCl dissolution medium can discriminate (b) (4) polymorphic forms (b) (4) .

(b) (4)

[redacted]

Batches were manufactured with drug substance lots with different particle size distributions (PSD). The lot with the largest PDS had the slowest release rate and would not meet Q (b) (4) % in 30 min.

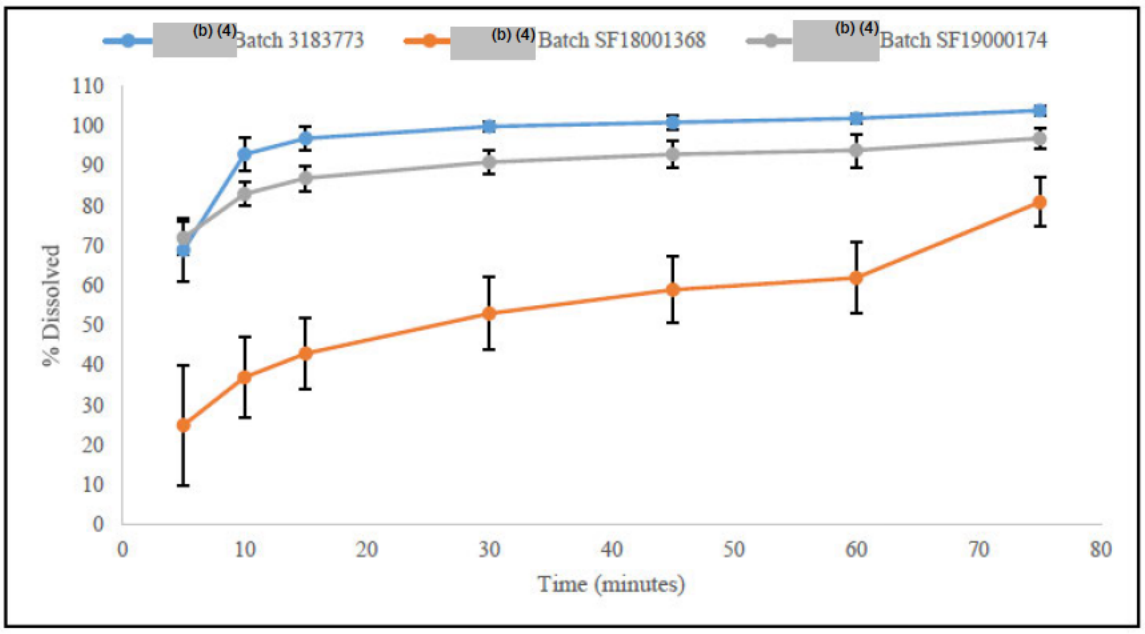

Figure 6. Dissolution Profiles for Batches with Different Drug Substance Particle Sizes, n=12

Manufacturing process parameters were evaluated (b) (4)

The dissolution profiles of the aberrant batches were similar to the target batches. This is likely because the solubility of the API is the greatest in the dissolution medium with 0.2% SDS. Therefore, the dissolution method is not discriminating to changes in the manufacturing process parameters.

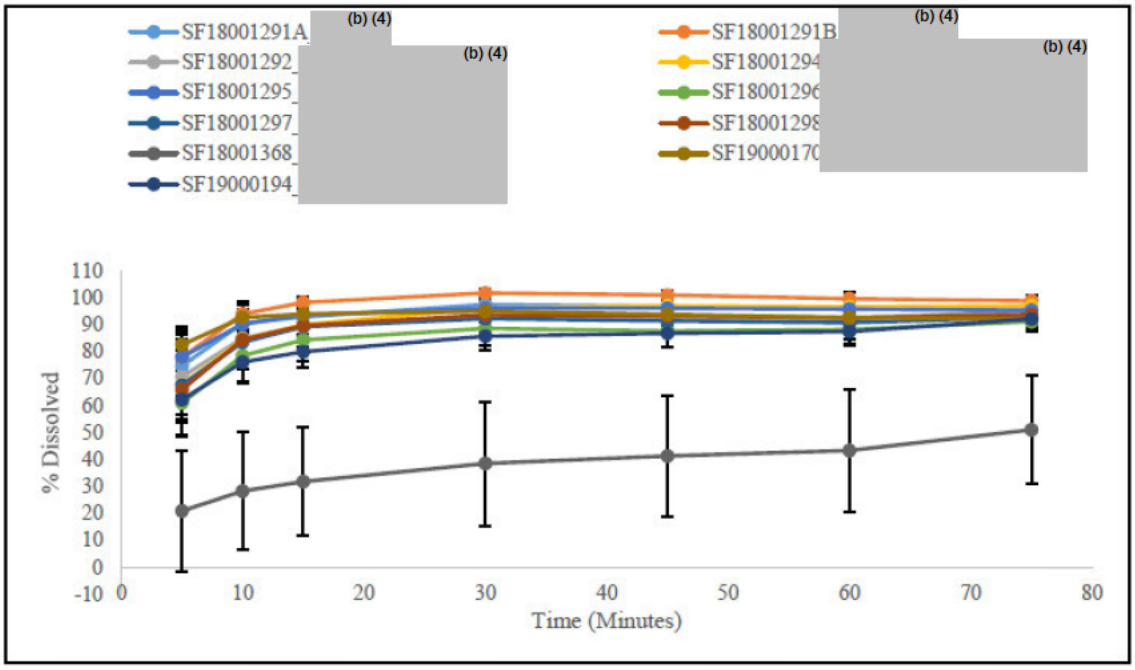

Figure 7. Dissolution Profiles for Process Parameters Variation Capsule Batches, n=12

Acceptance Criterion

Dissolution data was submitted on 7 clinical and registration batches equivalent to stage 2 testing (n=12). The Applicant proposes "Q=(b)(4)% in 30 min." This Reviewer confirmed that the data in the summary table matches the individual unit data submitted by the Applicant in Excel format[2]. Based on the individual unit data, the proposed acceptance criterion is acceptable. The acceptance criterion can reject batches that are outside of the PSD specification.

Table 4. Clinical and Registration Stability Batches

Manufacturing Batch Number	Manufacturing Date	Packaging Batch Number (Bottle ct., type)	Stability Start Date
3182857RS	September 9, 2019	3183772 (b)(4) stability) 3183775 (36 ct. clinical)	Oct 7, 2019
3182859RS	September 9, 2019	3183773 (b)(4) stability) 3183776 (36 ct. clinical)	Oct 7, 2019
3182860RS	September 9, 2019	3183774 (b)(4) stability) 3183777 (36 ct. clinical)	Oct 7, 2019
3176903R	March 14, 2019	3178053 (36 ct. clinical)	May 3, 2019
3170529R	July 19, 2018	3170596 (36 ct. clinical)	Oct 4, 2018
3168921R	May 17, 2018	3169141 (36 ct. clinical)	July 24, 2018
3167344R	April 11, 2018	3167684 (36 ct. clinical)	May 24, 2018

Table 5. Dissolution Results for All (b) (4) Clinical Batches, n=12

Batch No.	% Dissolved (n = 12)							
	Time (minutes)	5	10	15	30	45	60	75
3183775	Mean (%)	49	83	91	98	100	100	101
	Range (%)	(b) (4)						
	RSD (%)	23.4	9.9	6.0	4.1	2.9	3.1	2.9
3183776	Mean (%)	58	90	98	103	104	105	105
	Range (%)	(b) (4)						
	RSD (%)	10.9	5.7	4.7	2.9	2.2	2.2	2.0
3183777	Mean (%)	68	91	97	102	104	105	105
	Range (%)	(b) (4)						

Batch No.	% Dissolved (n = 12)							
	Time (minutes)	5	10	15	30	45	60	75
	RSD (%)	10.1	8.9	5.2	2.4	2.4	1.8	1.7
3178053	Mean (%)	65	91	95	97	99	98	100
	Range (%)	(b) (4)						
	RSD (%)	11.0	5.9	5.1	4.3	4.7	4.3	1.9
3170596	Mean (%)	51	85	92	98	99	99	100
	Range (%)	(b) (4)						
	RSD (%)	14.1	9.5	7.7	4.8	4.0	3.9	3.8
3169141	Mean (%)	75	91	94	97	97	97	98
	Range (%)	(b) (4)						
	RSD (%)	9.8	5.1	3.3	2.5	2.3	2.1	1.9
3167684	Mean (%)	71	92	95	99	100	100	101
	Range (%)	(b) (4)						
	RSD (%)	12.4	7.8	6.1	3.6	3.6	3.3	3.2

(b) (4)

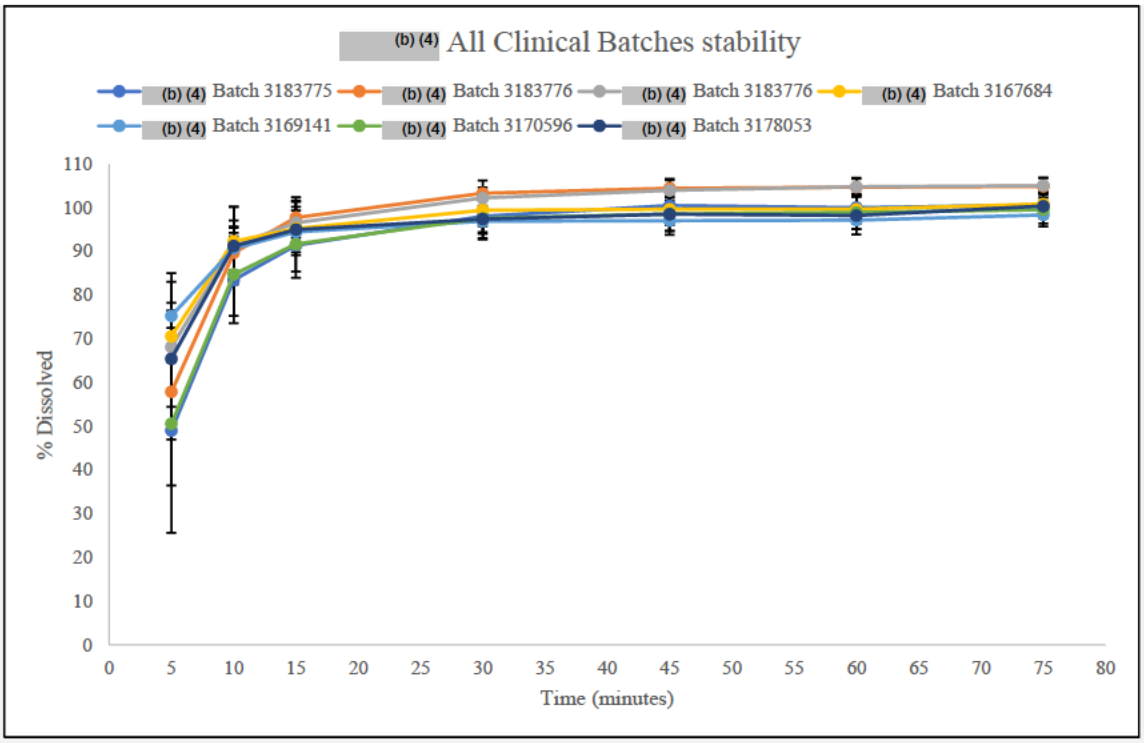

Figure 8. Dissolution Profiles for All (b) (4) Clinical Batches, n=12

B.3 BRIDGING OF FORMULATIONS

Assessment: Adequate

(b) (4)

(b) (4)

The development work was transferred to (b) (4). The (b) (4) site will manufacture to to-be-marketed (TBM) capsules.

The Phase 2 and Phase 3 clinical studies used the TBM 85 mg capsules. Therefore, from a Biopharmaceutics perspective additional formulation bridging is not needed.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name: Leah W. Falade, Ph.D.

Secondary Assessor Name: Tapash Ghosh, Ph.D.

Leah Falade

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Tapash Ghosh

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