Research overview and regulatory experience on mechanistic modeling for generic dermatological drug products

2021 CRCG PBPK workshop

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Day 1, Session 2: Modeling of Dermal Drug Products

Khondoker Alam, PhD

Pharmacologist

Division of Quantitative Methods and Modeling, Office of Research and Standards,
Office of Generic Drugs, CDER | U.S. FDA

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

- Scope of mechanistic physiologically-based pharmacokinetic (PBPK) modeling for alternative bioequivalence (BE) approaches for generic dermatological drug products

- Research roadmap towards developing mechanistic dermal PBPK models

- Use of dermal PBPK modeling and simulation approaches in regulatory space

General BE Study Recommendations for Topical Dermatological Drug Products

- **In Vitro characterization based BE approach**
  - Qualitative (Q1) and Quantitative (Q2) Sameness or '*No Difference*'
  - Physicochemical and Structural (Q3) Sameness/Similarity
  - IVRT (In Vitro Release Test)
  - IVPT (In Vitro Permeation Test)
- **In Vivo study to demonstrate BE**
  1. In vivo comparative clinical endpoint BE study
  2. Other in vivo studies -
     A. BE study with PK endpoints
     B. Vasoconstrictor study
     C. Adhesion study
     D. Skin irritation and sensitization study

Use of Mechanistic Modeling to Establish BE of Topical Dermatological Drug Products

Comparative clinical endpoint BE study

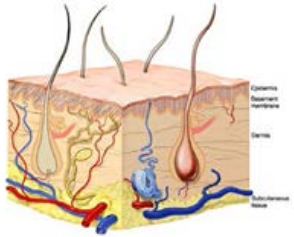
- Relatively insensitive in detecting formulation differences
- Large variability in the observed response
- Relatively costly as it requires higher subject number
- Drug development to approval time is long

Model-integrated virtual BE study

- Agency welcomes innovative approach if the proposed approach satisfies requirements of applicable statues and regulations
- Bioavailability in local tissues can be compared between test and reference drug products
- Cost effective and allows faster drug development process

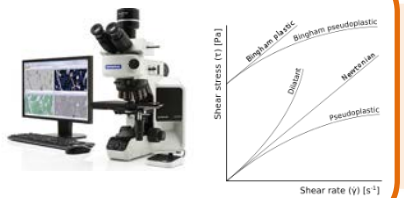
Mechanistic Dermal Physiologically-based Pharmacokinetic (PBPK) Modeling

Skin physiology



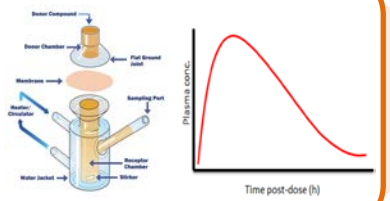
- Individual layer thickness and complexity
- Partition coefficient
- Diffusion coefficient

Formulation attributes

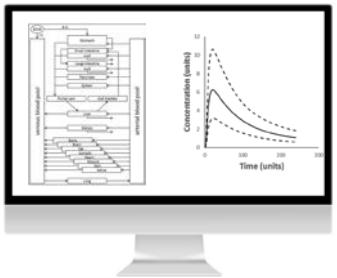


- Rheological properties
- pH, specific gravity
- Physicochemical properties
- Metamorphosis

Informing model parameters

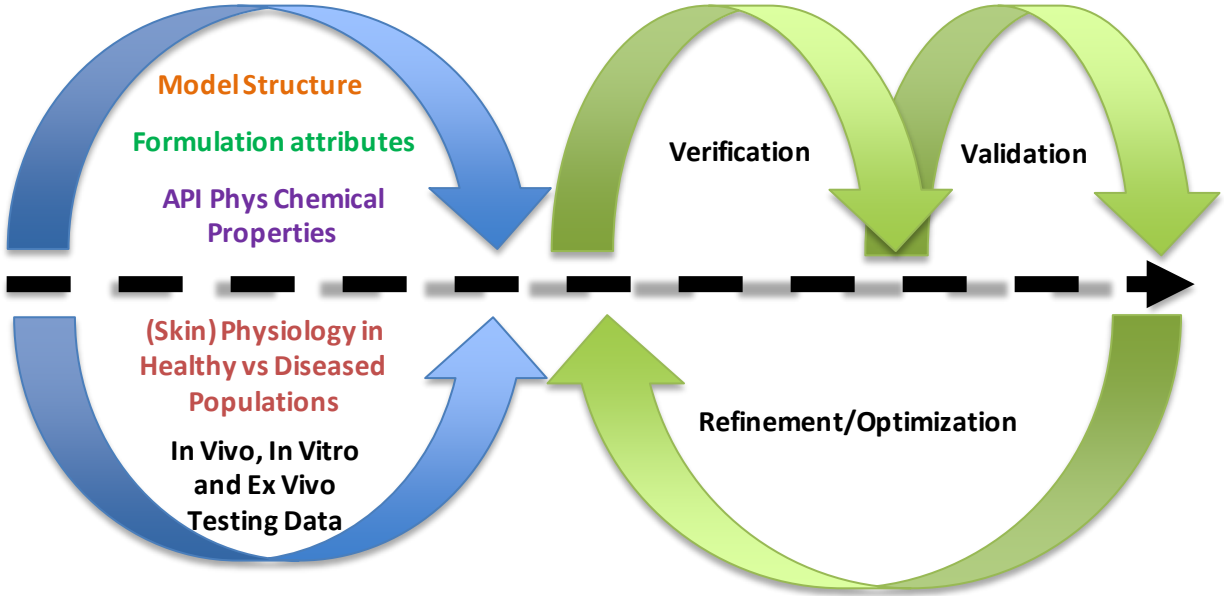


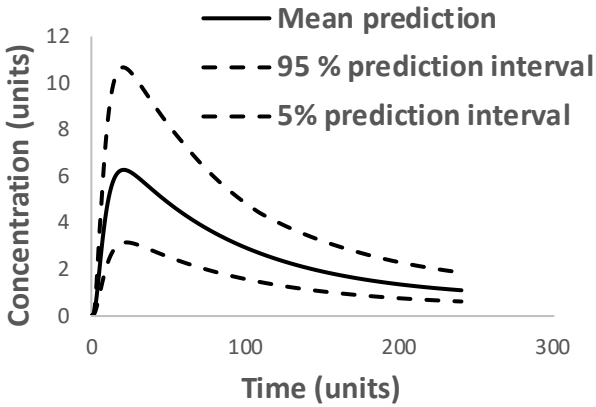
- IVPT studies
- Skin biopsy
- Microdialysis
- Systemic PK data



Mechanistic PBPK model

Dermal PBPK modeling to predict local and systemic bioavailability: Overview





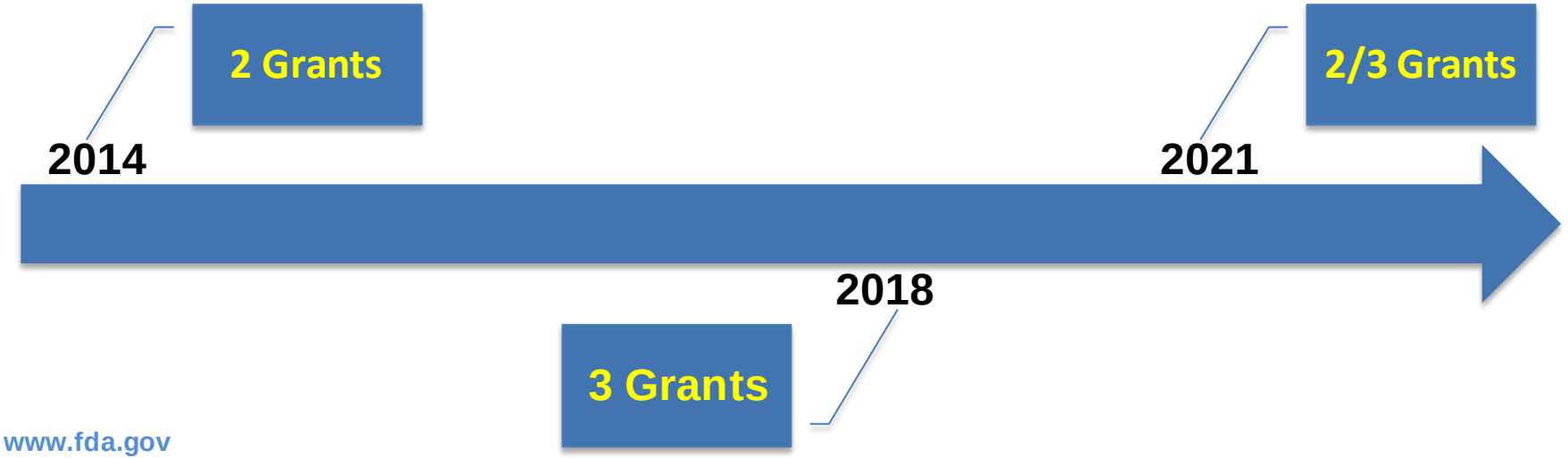
Virtual BE of topical drug products

API = Active pharmaceutical ingredient

Research Roadmap towards Developing Mechanistic Dermal PBPK Model

Major research focus:

- Realistic description of skin physiology
- Incorporating formulation attributes
- Virtual BE of topical drug products



Generic Drug User Fee Amendments (GDUFA)-Funded Research is Aimed to Close Knowledge Gaps

- Realistic description of skin physiology in in silico tools
  - Improve understanding on skin physiology in healthy and diseased populations
  - Develop and validate in silico healthy and diseased skin models
- Identify drug product-specific informative formulation attributes for semi-solid dosage forms
  - In vitro characterization of selected drug products
  - Incorporate formulation attributes in in silico tools
  - Define a safe space for drug product quality attributes
- Improve our understanding on interplay between skin physiology and drug product quality attributes
- Develop and validate in vitro, ex vivo, and in vivo methodologies that can be used to assess the in vitro and in vivo performance of drug products applied on the skin
- Develop and validate in silico tools
  - To establish in vitro-in vivo relationships (IVIVR) that can be used to predict unknown scenarios
  - To perform virtual BE assessment for topical drug products

Generic Drug User Fee Amendments (GDUFA): Regulatory Science/Research

Grant	Grant Duration	Institute	Grant No.
Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability	2014-2018	Simcyp, Ltd	1U01FD005225
Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	2014-2019	University of South Australia	1U01FD005232
Characterization of key system parameters of mechanistic dermal PBPK models in various skin diseases and performance verification of the model using observed local and systemic concentrations	2018-2020	Simcyp, Ltd	1U01FD006521
Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations	2018-2020	SimulationsPlus, Inc	1U01FD006526
Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems	2018-2020	University of Queensland	1U01FD006522
PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform	2018-2021	Children's Hospital of Los Angeles	1U01FD006549
Progressing integration of in vitro topical formulation characterisation, release and permeation data to the next level - PBPK based extrapolation to bioequivalence assessment in virtual populations	2021-2023	Certara UK,Ltd	1U01FD007323
Dermal Drug Product Quality and Bioequivalence Assessment through Advanced MAM and PBPK Simulation	2021-2023	SimulationsPlus, Inc	1U01FD007320

Research Aiming to Develop Mechanistic Dermal PBPK model

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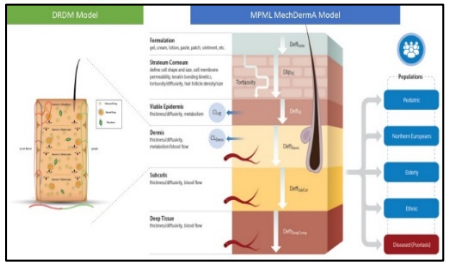


Grants:
- 1U01FD005225
- 1U01FD006521
- 1U01FD006522

In collaboration with –
- University of Queensland
- University of South Australia

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

University of South Australia

University of South Australia

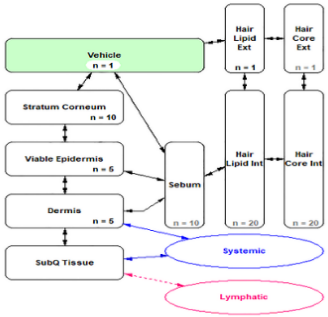
Grant: 1U01FD005232
In collaboration with
Goethe University Frankfurt

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Dermal PBPK Model

Grant:
1U01FD006526
In collaboration with industry partners

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS



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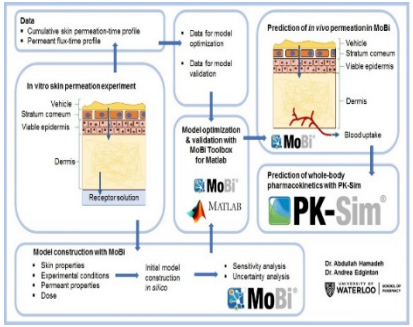
University of South Australia

Grant:
1U01FD006496
In collaboration with
University of Surrey

UNIVERSITY OF SURREY



UNIVERSITY OF WATERLOO

Grant:
1U01FD006549
In collaboration with –
- University of Waterloo
- Children's Hospital of Los Angeles

Children's Hospital LOS ANGELES

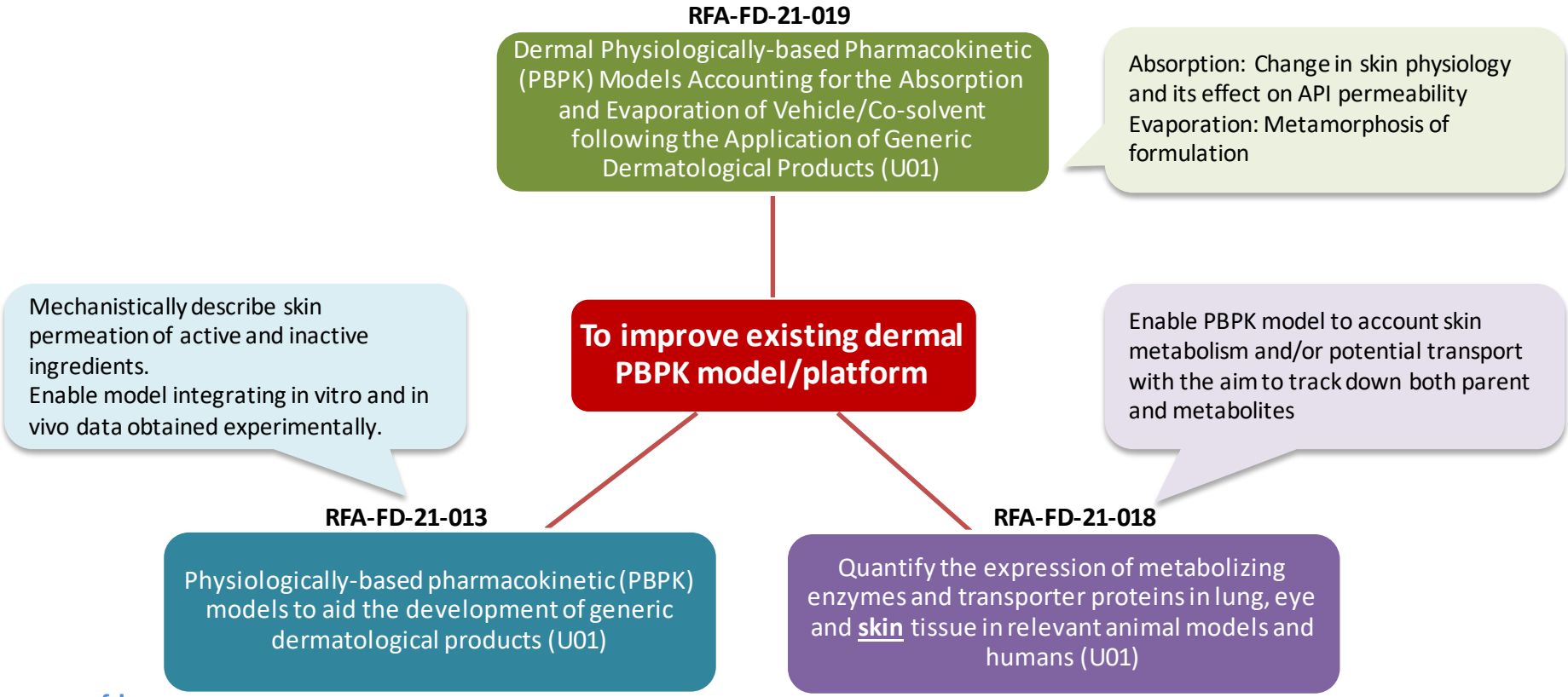
Key Outcomes From GDUFA-Funded Research

- Development of mechanistic dermal PBPK model: skin physiology and formulation attributes
- Development of skin disease model, e.g., acne/comedone, atopic dermatitis, psoriasis
- Developing IVPT module: model IVPT study results
- Developing vasodilation model: vasodilation/constriction in the dermis
- Enabling "Two Sites" for the application of drug product to resemble real life scenarios, e.g., apply topical product to face and shoulder simultaneously
- Incorporating inter- and intra-subject variabilities

To improve the predictive power of dermal PBPK model

To increase confidence on the model to perform virtual BE assessments

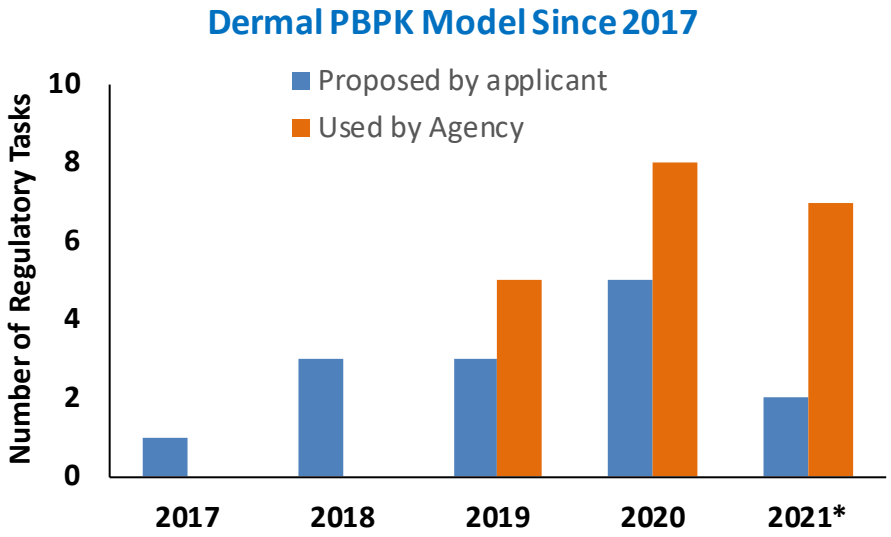
Dermal PBPK Modeling: Research Focus in FY21



*RFA = Request for Applications

Use of Dermal PBPK Model in Regulatory Space

- Model-integrated evidence for generic drug development and approval
  - Support alternative bioequivalence (BE) approaches, e.g., virtual BE studies
  - Define a safe space for critical attributes
  - Extrapolate bioavailability predictions and BE assessments from healthy to diseased populations
- Making informed regulatory decision in the review of ANDA, preANDA, controlled correspondence, citizen petition etc.
- Product-specific guidance (PSG) development and other regulatory research



* still ongoing

Science and Research Report: Locally-acting PBPK modeling

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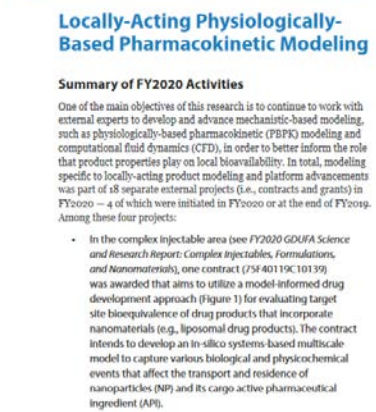

Locally-Acting Physiologically-Based Pharmacokinetic Modeling

Summary of FY2020 Activities

One of the main objectives of this research is to continue to work with external experts to develop and advance mechanistic-based modeling, such as physiologically-based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD), in order to better inform the role that product properties play on local bioavailability. In total, modeling specific to locally-acting product modeling and platform advancements was part of 18 separate external projects (i.e., contracts and grants) in FY2020 – 4 of which were initiated in FY2020 or at the end of FY2019. Among these four projects:

- In the complex injectable area (see *FY2020 GDUFA Science and Research Report: Complex Injectables, Formulations, and Nanomaterials*), one contract (75F40119C10139) was awarded that aims to utilize a model-informed drug development approach (Figure 1) for evaluating target site bioequivalence of drug products that incorporate nanomaterials (e.g., liposomal drug products). The contract intends to develop an in-silico systems-based multiscale model to capture various biological and physicochemical events that affect the transport and residence of nanoparticles (NP) and its cargo active pharmaceutical ingredient (API).

https://www.fda.gov/media/146749/download#page=60

- Summary of research activities
- Research projects and collaborations
  - New, continuing and completed grants/contracts
  - Active FDA research
- Articles, posters, presentations

Take home messages

- PBPK model-based virtual BE is an innovative alternative approach for the approval of dermal drug products
- GDUFA-funded research is set for continuous improvement of dermal PBPK model or modeling platform –
  - To improve the predictive power of dermal PBPK model
  - To increase confidence on the model to perform virtual BE assessments
- Mechanistic dermal PBPK modeling is used -
  - by the applicants to support their drug development and approval process
  - by the Agency to make informed regulatory decisions
- Academia/industry/software developing companies are encouraged to follow 'Notice of funding opportunity' to work with the Agency to achieve critical mission of GDUFA

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Questions?

Khondoker Alam, PhD
Khondoker.Alam@fda.hhs.gov

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