A CASE STUDY:
Regulatory Challenges and Opportunities in Developing a Novel Microarray Patch Delivery System

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PDA Parenteral Drug Association

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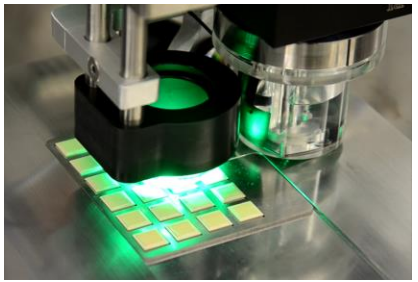
Agenda

- About Vaxxas
- Our projects and partners
- The High-Density Microarray Patch Delivery System
- Case study: US FDA pre-IND and IND application
- Regulatory challenges and opportunities

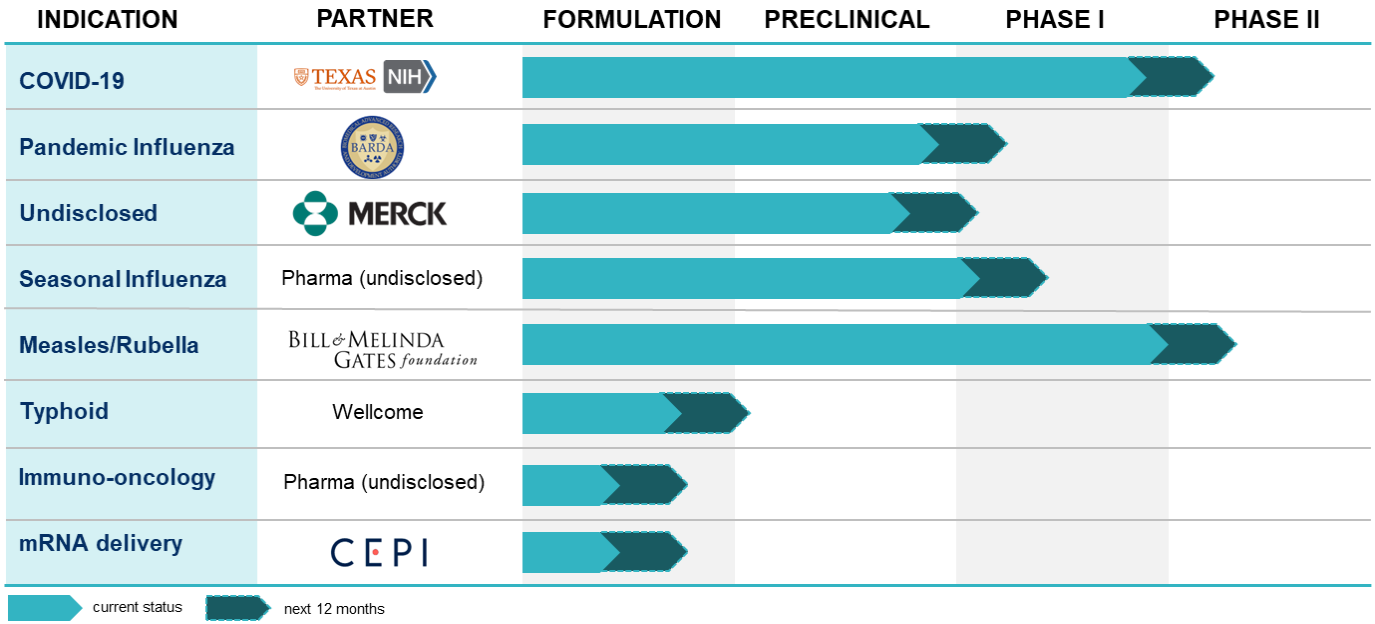
Disclaimers:
The speaker's personal opinion/interpretation may not wholly reflect the company position.
Information discussed is specific to the Vaxxas case and product.

About Vaxxas

- Australian technology based on research from the University of Queensland.
- Needle-free patch that delivers vaccine to immune-cell rich layer under the skin.
- Vaxxas Biomedical Facility opened 2023, in Brisbane, Queensland.
- R&D, pilot-scale, early commercial production.
- Rapidly growing – 140+ employees.
- Expanding vaccine pipeline and partnerships.



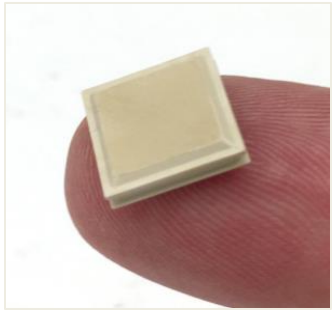
Vaccine clinical programs & partners



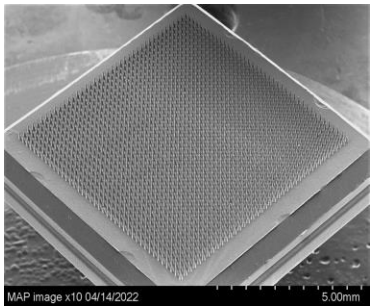
- Eight funded programs: pre-clinical and clinical studies.
- Three studies completed, > 500 participants.
  - x2 monovalent H1N1 flu (Seqirus)
  - x1 measles/rubella
- Two Phase I studies underway.
  - Covid-19
  - Seasonal influenza
- Readiness for first Phase II studies.

Publications: Forster et al, PLoS Med 17(3) e1003024, 2020; Fernando et al, Vaccine, 36, 2018.

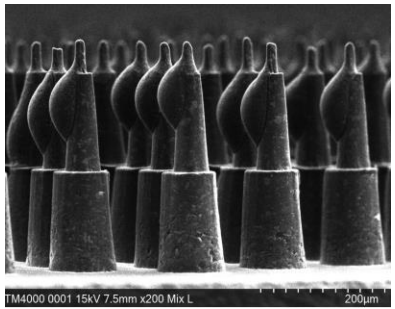
High-Density Microarray Patch (HD-MAP) Delivery System



Polymer HD-MAP

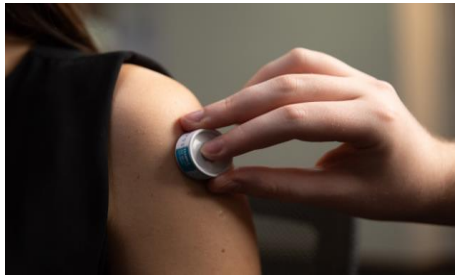


High-density array



Vaccine coated micro-projections

HD-MAP integrated in a single-use applicator



Apply & press, hold, remove

Potential benefits

- Vaccine delivery to immune-cell rich epidermis and dermis.
- Reduced antigen required.
- No needle/syringe.
- Dried formulation
  > reduce/eliminate cold-chain.
- Lower-skilled or self-administration.
- Improved global vaccine accessibility
  > hard-to-reach areas, pandemic response.

Case Study: US FDA Pre-IND and IND Application

Aim

- Phase I clinical study with a pandemic influenza vaccine, administered using the HD-MAP delivery system.
- Conduct study in Australia under TGA Clinical Trial Notification (CTN) scheme.
- Also, obtain FDA Investigational New Drug (IND) approval.

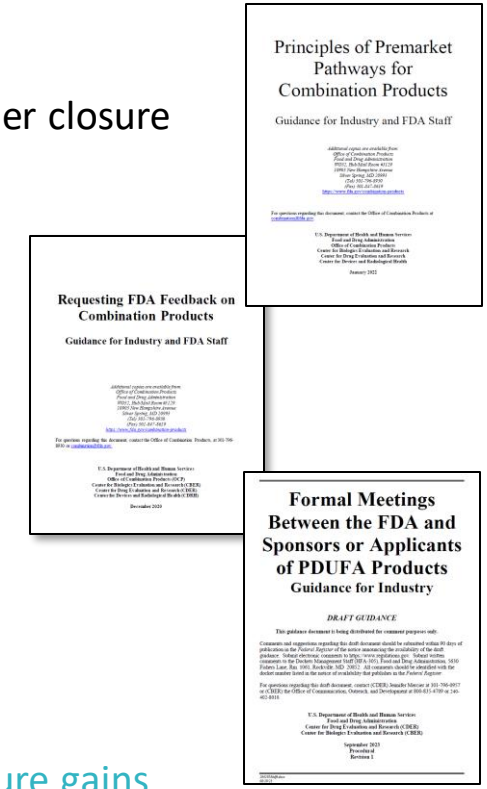
Status

- Pre-IND FDA ‘meeting’ complete.
- Addressing FDA feedback.
- IND application targeted for 2024.

Why an IND?

- Agency feedback and interaction
  - Novel dosage form, route of administration, formulation, container closure
  - No equivalent products are registered
  - No specific guidelines or standards
  - R&D > commercial pathway and agency expectations unclear
- Multiple FDA Meeting Types
  - Pre-IND (Type B), Type D (issues), INTERACT (novel/development)
- Pre-IND Meeting Request
  - Questions and background package
- IND Application
  - 30-day evaluation
  - Requirement for US-based clinical studies
  - IND is 'on-going'

Increased resourcing + Extended timelines = Future gains



Pre-IND – CMC Question Focus

- Confirm Combination Product classification and Primary Mode of Action (PMOA)
  - Varies globally
  - Defines how product will be regulated
- Confirm Vaxxas manufacturing responsibility
  - Drug Substance and/or Drug Product
- Confirm Common Technical Document (CTD) requirement, structure and content
  - Location of device/vaccine/combination information
  - Data expectations for a Phase I submission
- Other regulatory requirements for a combination product

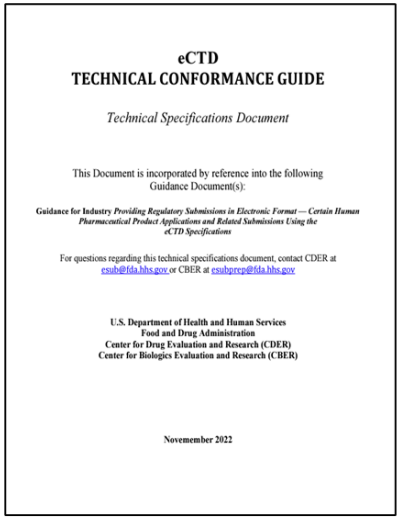
FDA Response - Product Definition and Responsibility

- Combination Product (defined under 21 CFR 3.2(e))
  - A product comprised of two or more regulated components, that are physically, chemically or otherwise combined or mixed and produced as a single entity.
    - ✓ Single-entity combination product = **Biological constituent + Device constituent**
    - ✓ Biologic constituent = vaccine formulation
    - ✓ Device constituent = HD-MAP (base and projections) + applicator assembly
  - Regulated in accordance with PMOA
- Primary Mode of Action (PMOA)
  - The single mode of action of a combination product that makes the greatest contribution to the combination products overall intended use(s)
    - ✓ Vaccine provides the PMOA
    - ✓ Center for Biologics Evaluation and Research (CBER) is lead Center for review

      ∴ Submission = IND/BLA
- Vaxxas is a Drug Product and Combination Product manufacturer

FDA Response – CTD Structure and Content

- CTD dossier structure
  - Separate Drug Substance module for device components
  - Device documentation in 32R
  - Include a Reviewers Guide in Module 1
- For a sterile product
  - Aseptic process validation: agreement on approach
  - Device component sterilization: description, validation method, impact on quality of parts
- Finish Product Specifications
  - Additional methods, set acceptance criteria
- Defined container closure system components
  - Container closure integrity testing
- Investigational product labelling – 21 CFR 312.6(a) and 21 CFR 812.5, or waiver.



eCTD
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry ***Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications***

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

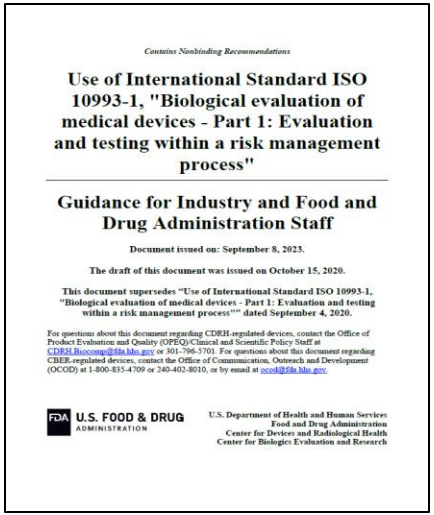
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Novemember 2022

p20 – Section 5. Combination Products

FDA Reminder – Biocompatibility Testing

- For Phase I IND, evidence of biocompatibility testing of **skin contacting parts** in accordance with ISO-10993-1.



Contains Nonbinding Recommendations

Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 8, 2023.

The draft of this document was issued on October 15, 2020.

This document supersedes "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"" dated September 4, 2020.

For questions about this document regarding CDRH-regulated devices, contact the Office of Product Evaluation and Quality (OPEQ)/Clinical and Scientific Policy Staff at CDRH.Biocomp@fda.hhs.gov or 301-796-5701. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – long term (> 30 d)													
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	X	O	X		X					
		C	X	X	X	X	O	X	X	X		X			
	Breached or compromised surface	A	X	X	X	X	X								
		B	X	X	X	X	X	X		X					
		C	X	X	X	X	X	X	X	X		X	X		

Applicator Bottom Part

HD-MAP Part

FDA cGMP Expectations

- Combination products must demonstrate compliance to the cGMP expectations for **each** of the constituent parts.

Device
21 CFR 820

Drug
21 CFR 210, 211

Biologic
21 CFR 600-680

- Streamlined approach (21 CFR 4.4) > distinctly interpreted 'called-out provisions'

Drug cGMP +

Devices QSR subset
820.20 Management controls
820.30 Design controls
820.50 Purchasing controls
820.100 CAPA
820.170 Installation
820.200 Servicing

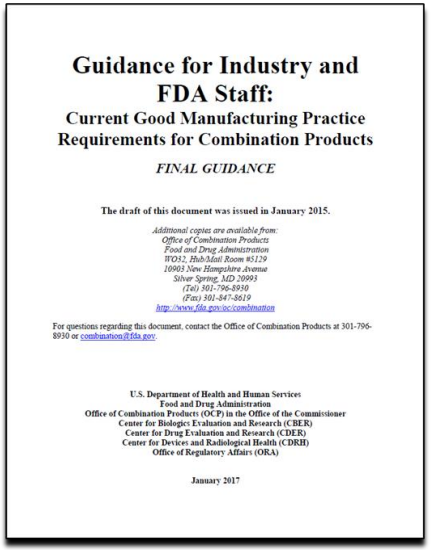
OR

Device Quality System Regulations (QSR) +

Drugs cGMP subset
211.84 Testing/approval/rejection
211.103 Calculation of yield
211.132 Tamper-evident packaging
211.137 Expiration dating
211.165-167 Testing and release for distribution, stability, special testing
211.170 Reserve samples

AND

Biologic
600-680



Guidance for Industry and FDA Staff:
Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

The draft of this document was issued in January 2015.

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Atsl Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
http://www.fda.gov/oc/combination

For questions regarding this document, contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in the Office of the Commissioner
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Office of Regulatory Affairs (ORA)

January 2017

Investigational combination products that include **device** constituent parts **are subject to design controls** under 21 CFR 820.30

FDA Expectation – Device Design Control for Phase I IND

- Design control:
  - Mandatory methodology to control the design process, include quality, and relevant expertise throughout development.
  - Includes product design and manufacturing process.
  - Meet user needs, intended uses, specified requirements.
- Demonstrate design control in IND application for **Phase I prototype**
  - At minimum, a **risk analysis with supporting verification data/information.**
  - Safety risks have been identified and adequately mitigated.
  - Product functions as intended.

➢ Introduce device design control **early** in the development process.

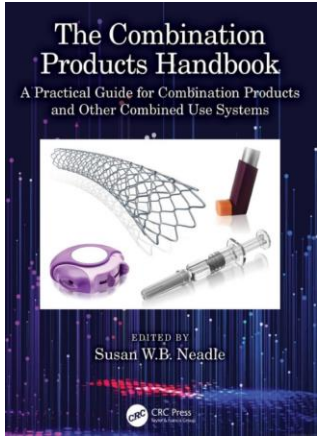
Other Areas for Understanding

- Information requirements for Phase II and Phase III stage IND
- Defining Critical Quality Attributes (CQAs)
- Managing prototype changes > Bridging
- Including Human Factors engineering/usability
- Identify global differences in regulatory requirements for licensure
- Registration submission pathways
  - FDA considers it a **new** product, even if the vaccine is approved
    - Different dose form, route of administration, formulation, material interactions, users/use environment.
  - Single and/or multiple submissions
    - Single BLA in CTD format
    - Or Master File for the 'platform'
    - Defining the submission Sponsor > vaccine or device manufacturer

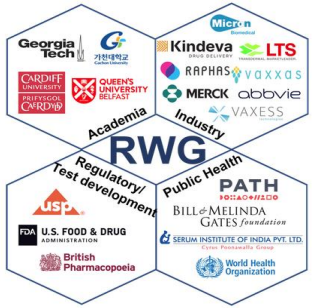
Regulatory Opportunities

Network/research/participate

- Interactions with regulatory authorities and recognized experts
- ISPE Combination Products CoP
- Combinate Podcast
- MAP Regulatory Working Group (RWG):
  - PATH MAP Center of Excellence + Cardiff University partnership
  - Inform, guide and define regulatory science of the dose form
  - Expedite clinical translation of safe and effective products
  - CMC regulatory topics e.g.,
    - Define MAP dose form
    - Identify and understand MAP CQAs
    - Develop standardized validated test methods
    - Inform microbiological requirements/specifications
  - Adopt, adapt, or develop new, standards/methods



MAP RWG



www.microneedleregulatory.org

Thank you

Session II: Global Regulatory Approach to Combination Products

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CBE Pure Solutions
Moderator

Daniel Flewellen
SeerPharma

Peter Qiu
Roche Genentech

Kerrie Way
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