LATERAL FLOW ASSAYS FOR COVID-19: GLOBAL NITROCELLULOSE LANDSCAPING

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AGENDA

- Introductions
- Project Overview
- Nitrocellulose Background
- Key Informant Takeaways
- Supply and Demand Projections
- Conclusions





PROJECT TEAM



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START OVERVIEW



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Provides high-quality research and analytic support to the Bill & Melinda Gates Foundation and global and public health decision-makers



Provides structured mentorship and training to University of Washington graduate research assistants



PROJECT OVERVIEW

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Project Rationale

- Massive COVID-19 rapid diagnostic testing demand
- Lateral flow assays for COVID-19 require nitrocellulose
- Hypothesis that nitrocellulose will become a bottleneck in scale-up efforts

Project Objectives

- Identification of manufacturing bottlenecks
- Landscaping of current nitrocellulose market
- Feasibility of alternative membrane materials



PROJECT WORKFLOW





NITROCELLULOSE BACKGROUND

LFA COMPONENTS



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LFA ANALYTICAL MEMBRANE

Function

- Control flow of sample over the test & control lines
- Bind and stabilize capture antibodies

Primary Material

• Nitrocellulose (NC)

Alternative Materials

- Polyvinylidene difluoride (PVDF)
- Nylon
- Polyethersulfone (PES)
- Cellulose



Image from Sartorius



NC MEMBRANE FEATURES

- High signal-to-noise
 - Sharp, distinct test lines
- Good antibody binding properties
 - Membrane blocking prevents nonspecific protein binding
- Flow rates specialized for different applications
- Over 30 years of continued use in commercial LFA manufacturing
- Backed with polyester film for mechanical strength



NC MEMBRANE DISADVANTAGES

- Inter- and intra-lot inconsistencies are common
 - Capillary flow time variability (5-10%)
- Flammable and < 2-year shelf life
- Requires shipping by plane and specialized storage facilities
- Low-yield manufacturing process (~50%)

From Cytiva: lot-to-lot NC inconsistency





DIFFERENT FLOW TIME OPTIONS

- Capillary flow time = # of seconds for water to wick 4 cm
- Flow rates offer performance trade-off
 - Fast flow = poor sensitivity, quick results
 - Slow flow = high sensitivity, slow results
- Companies offer range of flow time options
 - Current Mologic COVID LFA uses 200s MDI NC membrane



CN 95



CN 110

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CN 140



CN 150



Images from Sartorius

CN 180



| 13

MANUFACTURING PROCESS OVERVIEW

- 1. **Prepare Lacquer** raw NC and additives in solvent
- 2. Membrane Casting lacquer is spread into film and solvent carefully evaporated off
- 3. QC and Membrane Collection





PREPARE LACQUER

- Raw NC widely available
 - Acquired from outside vendors (e.g. DuPont)
 - NC used in many applications: paints, coatings, explosives, cosmetics
 - Characterized by viscosity rather than molecular weight
- Additives included to improve membrane features
 - Proprietary surfactants to make hydrophilic
 - Possibly other polymers (e.g., cellulose acetate)
- Lacquer composed with specific raw NC, additive, and solvent concentrations

MEMBRANE CASTING

 Polymeric membranes are typically produced via phase inversion – controlled precipitation of a polymer solution



MEMBRANE CASTING

- NC membrane pore structure critical to performance
- Polymer precipitation process determines pore structure
- Improper solvent evaporation creates vastly different pore structures



Polymer Phase Diagram – Schulze et al. 2018

QC AND MEMBRANE COLLECTION

- Quality control systems ensure membrane consistency
 - Thickness (± 20 µm)
 - Flow time (± 60 s)
 - Surface defects
- Web handling systems collect membranes into master rolls (100m x 30cm typical)



Sartorius QC System



COMPANIES PRODUCING NC LFA MEMBRANES



Leading NC Producers

- Sartorius
- Cytiva
- Merck Millipore
- mdi Membrane Technologies
- Pall Corporation

Other NC Producers

- Nupore (India)
- Shantou Ealon Membrane Co. (China)
- TEST (China)
- Ballya (China)



NC PRODUCTION KEY POINTS

- Casting lines incredibly specialized with precise environmental conditions and tolerances
- New NC production facilities take 1-3 years to bring on-line
- Process described as "more of an art than a science"



Sartorius air casting equipment



ALTERNATIVE MEMBRANES

- Most test developers agree that NC is the best available membrane and are resistant to alternatives
- Leading alternatives are synthetic polymer membranes: PVDF, nylon, PES
- Require similar air or wet casting lines to NC → same production scaleup issues
- Exception: cellulose-based LFA (3M/MIT venture)



KEY INFORMANT TAKEAWAYS (Takeaways removed from public version)

INTERVIEWS CONDUCTED



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SUPPLY AND DEMAND PROJECTIONS

(Confidential figures removed from public version)

NC MEMBRANE MARKET - 2020





PROJECTION ASSUMPTIONS

NC membranes pre-COVID demand = supply

Only NC membranes used in COVID LFAs

Global NC market size is 6B units for 6B LFAs

2B NC units allocated to COVID LFAs

NC units will not be reallocated from non-COVID to COVID LFAs



SUPPLY AND DEMAND PROJECTIONS





ESTIMATED NC MEMBRANE SHORTAGE



CONCLUSIONS (Several confidential findings removed)

GLOBAL NITROCELLULOSE LANDSCAPE

- Global increase of NC membrane capacity is limited, with substantial increase possible in 2022.
- Most optimistic scenarios still present supply shortfall against projected demand.
- Some producers may still possess some additional production capacity in the near term.
- Willingness to increase supply contingent upon promise of sustained demand post-COVID.



THANK YOU



| 31