



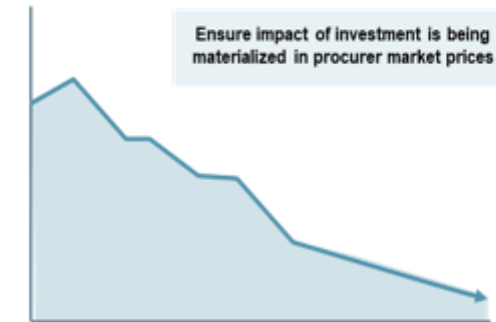
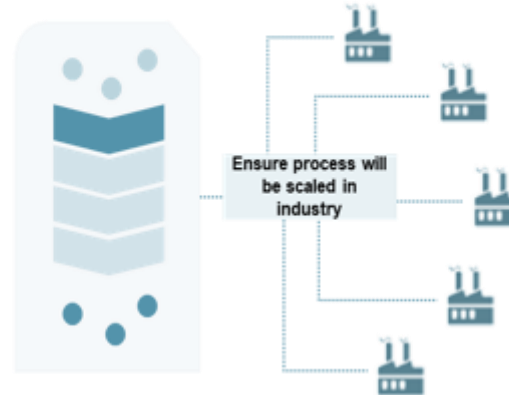
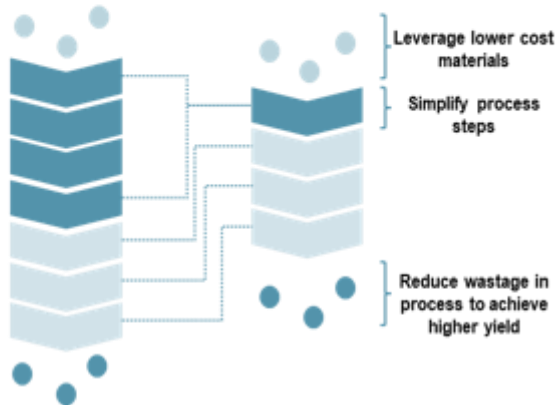
Medicines for All Institute

Overview of Efforts to Improve Access to Medicines
May 2021

Where We Started: Approach & Grant Deliverables



Target Selection

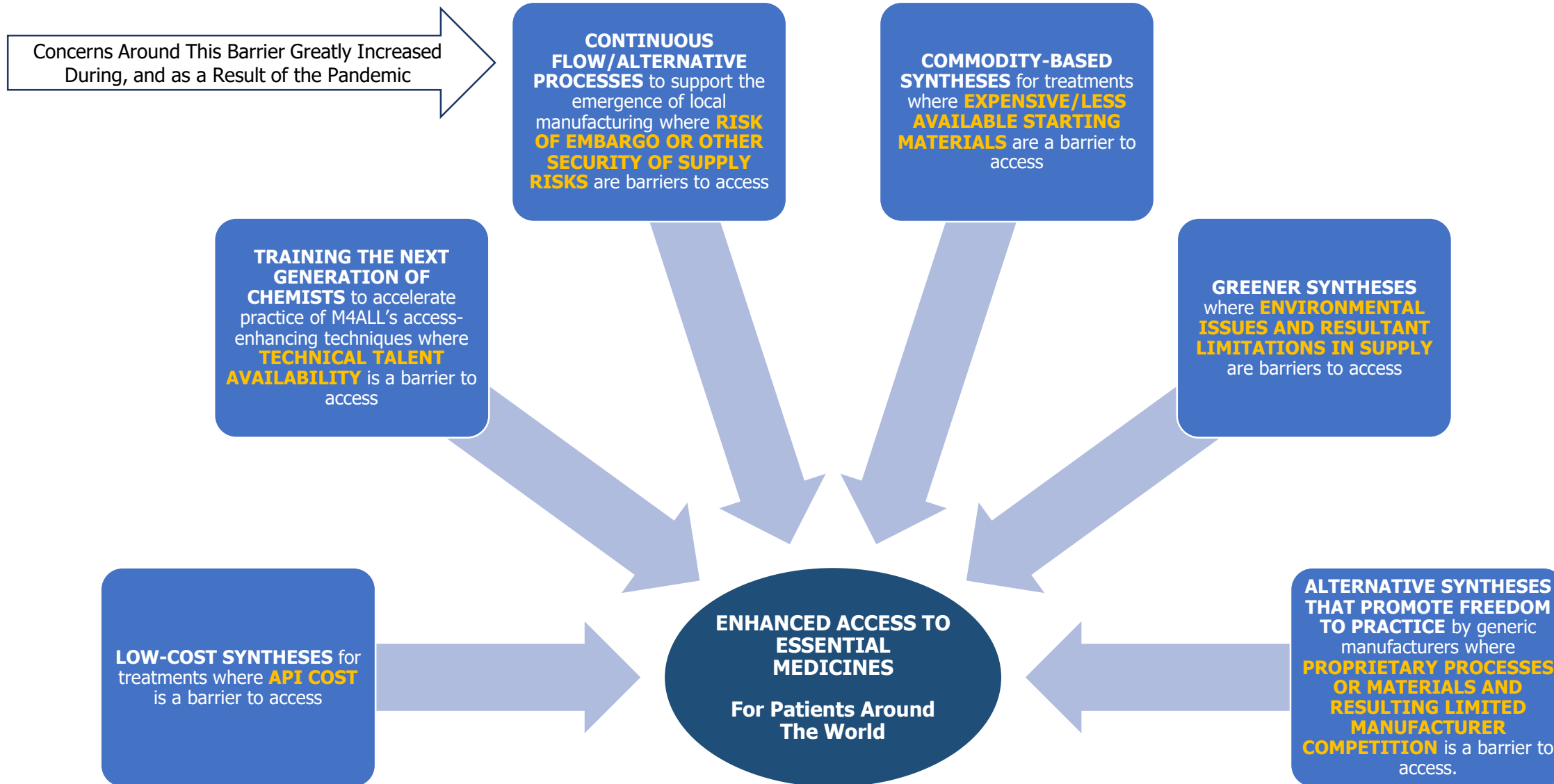


Improved Access

Key Deliverables Under 5-Year Grant (Ends 2022)

- 1) Lower the price of in-market Global Health medicines – leading to improved market access
- 2) Enable lower prices for drugs in development – leading to improved market uptake
- 3) Expand M4ALL's capacity and reduce the cost per project
- 4) Achieve sustainability beyond the 5-year grant

Where We Are Today: Mission & Core Strategies



M4ALL Key Milestones



May 2020: Award From BARDA Announced

April 2014 Nevirapine BMGF Grant

Proof-of-Concept Grant

June 2015 Tenofovir Core Grant

June 2016 Dolutegravir BMGF Grant

Planning Grant For Medicine For All Institute

July 2017 5-Year Grant: Medicines For All Institute: Scale-Up And Low-Cost Manufacturing Acceleration Plan

September 2018: Operational Effectiveness Assessment

March 2019: Governing Board Established

March 2019: Operational Effectiveness Plan Implemented

April 2019: Optimized Processes Released for FTC, DTG

Spring, 2020: M4ALL Begins Work on In-Development Treatments

Remaining In Market ARV Processes Released -- TDF, 3TC

Fall, 2020: COVID-19 Special Projects Assigned

January 2021: Remdesivir and Molnupiravir Released

Feb 2021: M4ALL subcontracted by USP for USAID PQM+

Dedicated Lab Space Created



Biotech 8 Acquired by VCU

VCU Facilities \$14.9MM

M4ALL Infrastructure Build: Research Scientists, Analytical Chemists, Market Engagement Specialists

Market Engagement & Surveillance Processes Established: Special Notice, Webinars, PDRs, and Price Tracking

Detailed Phase Gate Process Installed: Defined Phases, Decision Points, Deliverables, Governance Model

Target Selection Process Defined: PDP Nomination, Global Health Strategy and Technical Feasibility Assessment

60-Day Plan: Sprint Process To Complete Installation of Robust Portfolio and Project Management Tools

- M4ALL Creates **Global Health, Federal and Shared Service** Divisions
- Hires Global Health COO, Federal COO, and Shared Service CFO/CAO

Throughput: 1 Project Per 18 Months

Throughput: **5 Projects Plus 10 Paper Studies** Per Year

M4ALL's Global Health Partnerships



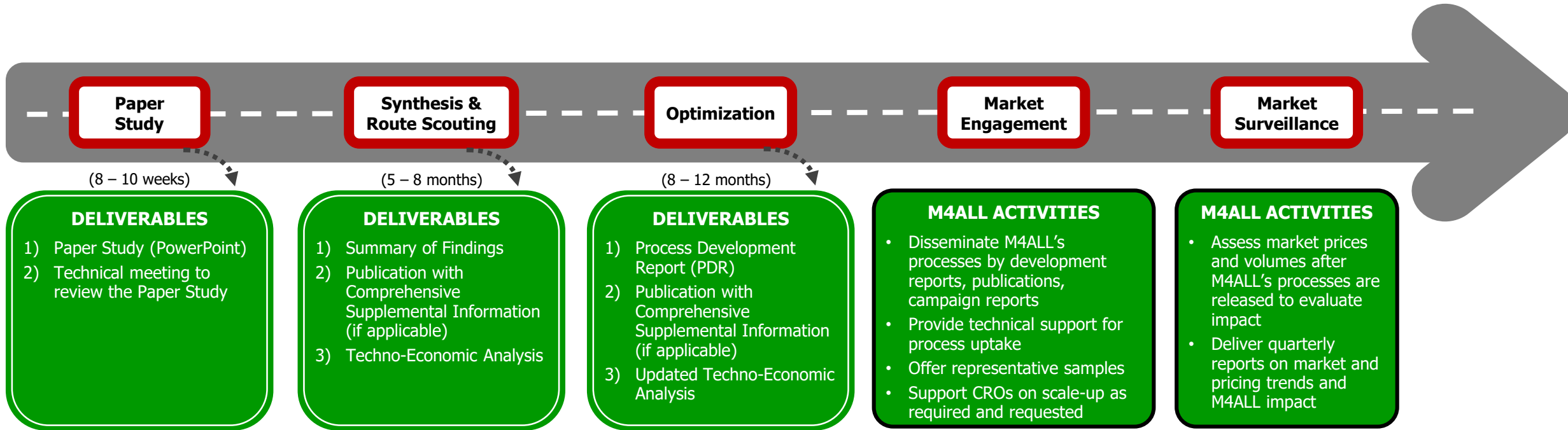
Funders



Product Development Partners



What We Do: M4ALL Service Offering



- **A proven-effective end-to-end process for in-market global health treatments (steps 1-5)**
- **ALSO, a customizable process (steps 1-3, steps 1 and 2, or just step 1) for in-development treatments**
 - **FINALLY, robust capacity for M4ALL's best practice paper studies (step 1)**

M4ALL's Impact Criteria Assessment Template

- The Impact Score is a subjective measure based on current information. They will be updated as M4ALL learns new information on the target

IMPACT CRITERIA

Raw Material Costs and Availability

- Would M4ALL's proposed work meaningfully reduce cost where raw materials cost is a barrier to access?
- Would M4ALL's proposed work address issues relating to expensive or less available raw materials as a barrier to access?

Impact Score: TBD

Expanding Manufacturing Base and Competition

- Would M4ALL's proposed work enable the entry of new manufacturers where limited manufacturing is a barrier to access?

Impact Score: TBD

Environmental & Safety Concerns

- Would M4ALL's work address environmental issues limiting manufacturer availability, which in turn creates a barrier to access?
- Would M4ALL's work address difficult or dangerous processes/materials that limit manufacturing capabilities?

Impact Score: TBD



Impact Composite Score: X out of 15

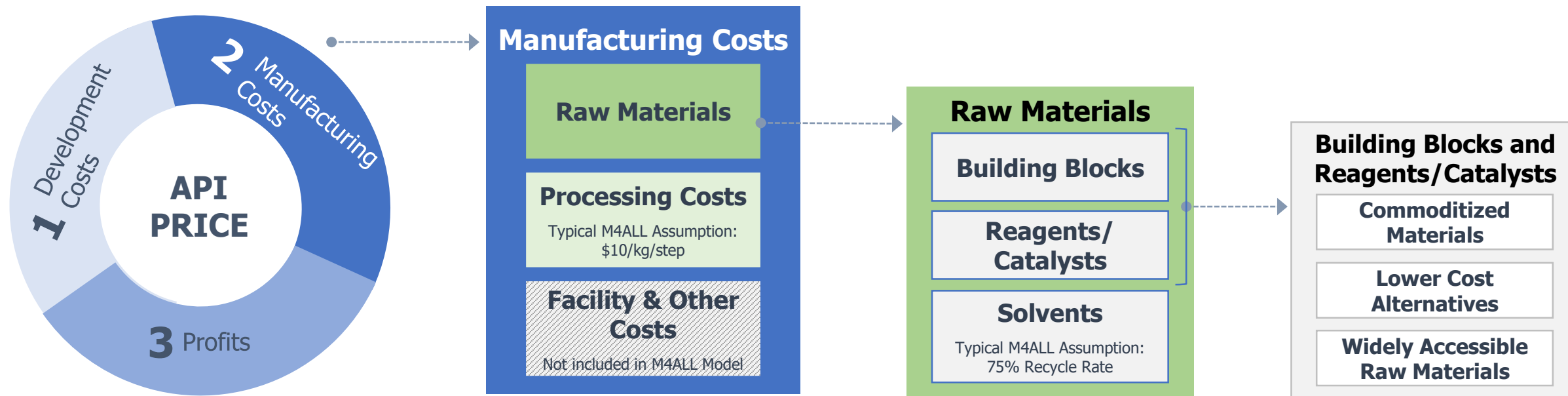
TECHNICAL PROBABILITY OF SUCCESS

Opportunity	Proposed Solution	Probability of Success

Target Priority Metric: To be established by the Gates Foundation pursuant to a separate process with PSTs and PDPs:

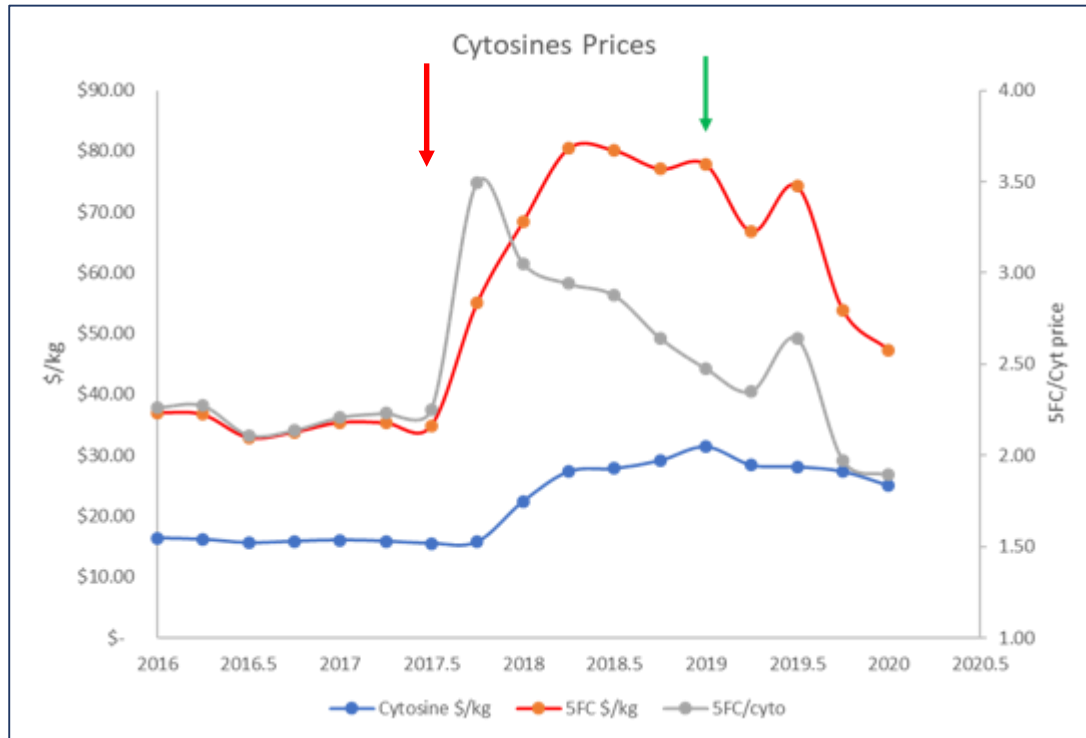
- In addition to the Impact Criteria, the drug target will be assessed based on whether it is expected to be a significant and impactful addition or enhancement to existing therapies or regimens

M4ALL Addresses Raw Material-Related Cost Drivers



- Among the three components of API price, M4ALL's approach focuses on **manufacturing costs** -- specifically, assessing the costs of raw materials (RM)
- At large production scale, raw materials are typically the primary driver of manufacturing costs, so this approach readily identifies the **major cost drivers** that could be addressed
- As part of all paper studies/projects, M4ALL evaluates the costs of raw materials **building blocks, reagents/catalysts, and solvents**
- Whenever possible, M4ALL uses **commoditized materials**, lower cost alternatives, and widely available enzymes and reagents materials. This not only reduces cost, but also improves accessibility of the processes for manufacturers
- M4ALL updates **techno-economic analyses** at various milestones during process development to provide a snapshot of cost comparisons between different synthetic routes to identify research focus areas.

Our Work on In-Market ARVs



- Chinese factory explosion affected prices (red arrow) of emtricitabine
- TLE prices increased as the supply chain for emtricitabine was impacted immediately
- Green arrow shows date of M4ALL webinar regarding synthesis of 5-fluorocytosine

M4ALL Uses a Range of Market Analytics and Market Dynamics Tools to Verify and Track Impact of Pricing

Impact on ARV In Market Drug Targets

HIV portfolio estimated to generate up to **\$65MM savings annually** if M4ALL processes are adopted

Emtricitabine (FTC)

- Developed less toxic process for key intermediate (5-FC)
- API cost impact - **16% reduction**
- Price convergence and Chinese patent filing suggests uptake of the M4ALL process
- 5-FC price decrease from \$80/kg to \$48/kg

Lamivudine (3TC)

- Developed route using commoditized raw materials to lower cost
- API cost impact - **7% reduction**
- Engagement with manufacturers for direct confirmation has been delayed due to COVID-19. However, this new process is one of the most viewed articles on OPRD

Dolutegravir (DTG)

- Developed one-step synthesis of key intermediate (amino alcohol)
- API cost impact - **53% reduction**
- Chinese suppliers have reproduced and scaled up the process and are selling to Indian generic manufacturers

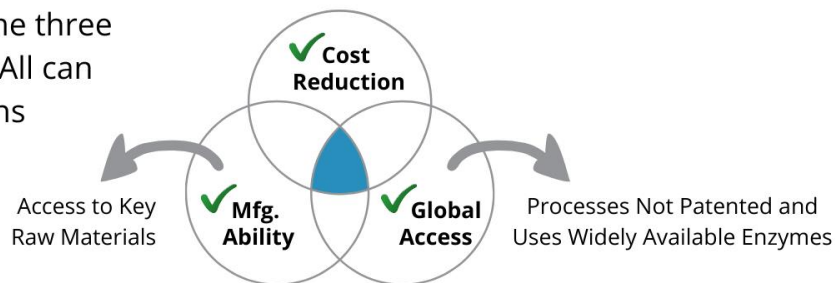
Tenofovir (TDF/TAF)

- Developed two-step process for the PMPA intermediate that can be converted into either TDF or TAF, eliminating reliance on adenine as with other processes
- API cost impact – **3.5% reduction**
- Mfg’s express interest due to increased supply security in the event of recurring disruptions to the adenine market

MOLNUPIRAVIR

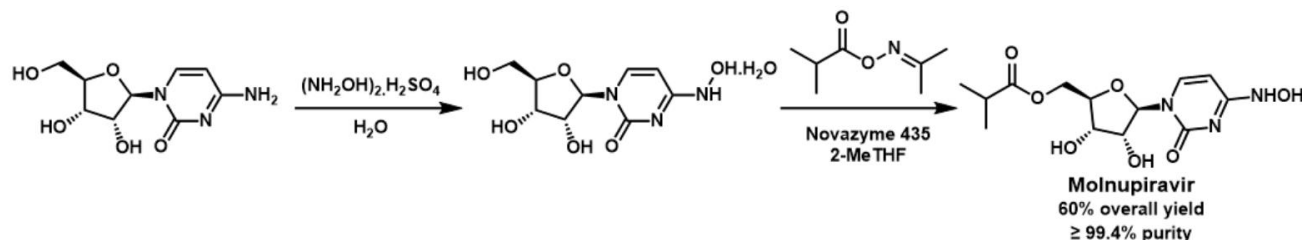
A Potential COVID-19 Treatment: Synthetic Process Research

This research illustrates the three ways that Medicines for All can impact new regimens



M4ALL Process Improvements

Key Advantages: Two-step process from commercially available starting materials and reagents
(Cytidine commercially available at >200MT/year)



Prior Art (Literature) (From Uridine)

- 5 steps
- ≤17% yield
- Key raw materials: uridine, ribose

M4ALL's Process (From Cytidine)

- 2 steps
- 60% yield
- Key raw materials: cytidine, Novozyme 435
- 7 Volumes of solvent for reaction; overall PMI of 41
- Enzyme recycle reduces effective loading to 2 wt%
- Potential savings from prior art process ~90%

Publications

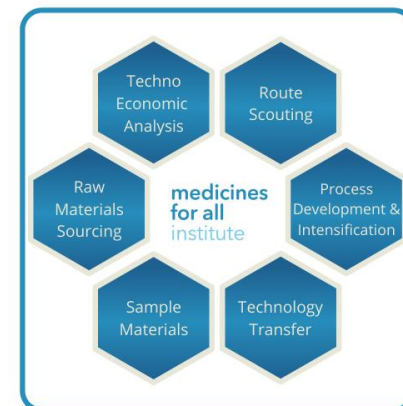
- 01 Two Enzymatic, Protecting Group-Free Routes from Cytidine (Chem. Commun.)
- 02 Chemical Route via Cytidine Acetonide (Synlett)
- 03 Chemical Route via Uridine Acetonide (European Journal of Organic Chemistry)
- 04 Follow-up to Publication 1 (ChemRxiv)

Great reception to M4ALL's work

High engagement on the follow-up publication for the enzymatic, protecting group free routes from cytidine

ChemRxiv™ >1500 views, and 250 downloads in 1 week

LinkedIn >7,500 views
21% engagement rate



Expanding The Scope of Engagement of M4ALL

Then

Global Health Treatments

Cost-Related Factors

Patients In Resource-Limited Settings

Now

All Essential Medicines

Cost AND Security Of Supply Chain Barriers to Access

Patients Everywhere In The World

World Health Organization
Model List of Essential Medicines

21st List
2019



- **developing greener syntheses** where environmental issues and resultant insecurity of, limitations in, supply are barriers to access.
- **developing alternative synthesis that promote freedom to practice** by generic manufacturers where limited manufacturer competition is a barrier to access.
- **developing continuous flow/alternative processes to enable the use of novel technologies or the emergence of local manufacturing** proprietary processes or materials and resulting limited manufacturer competition is a barrier to access.



A Model For Engagement: BARDA Grant



M4ALL supplies continuous flow API processes and processing technology



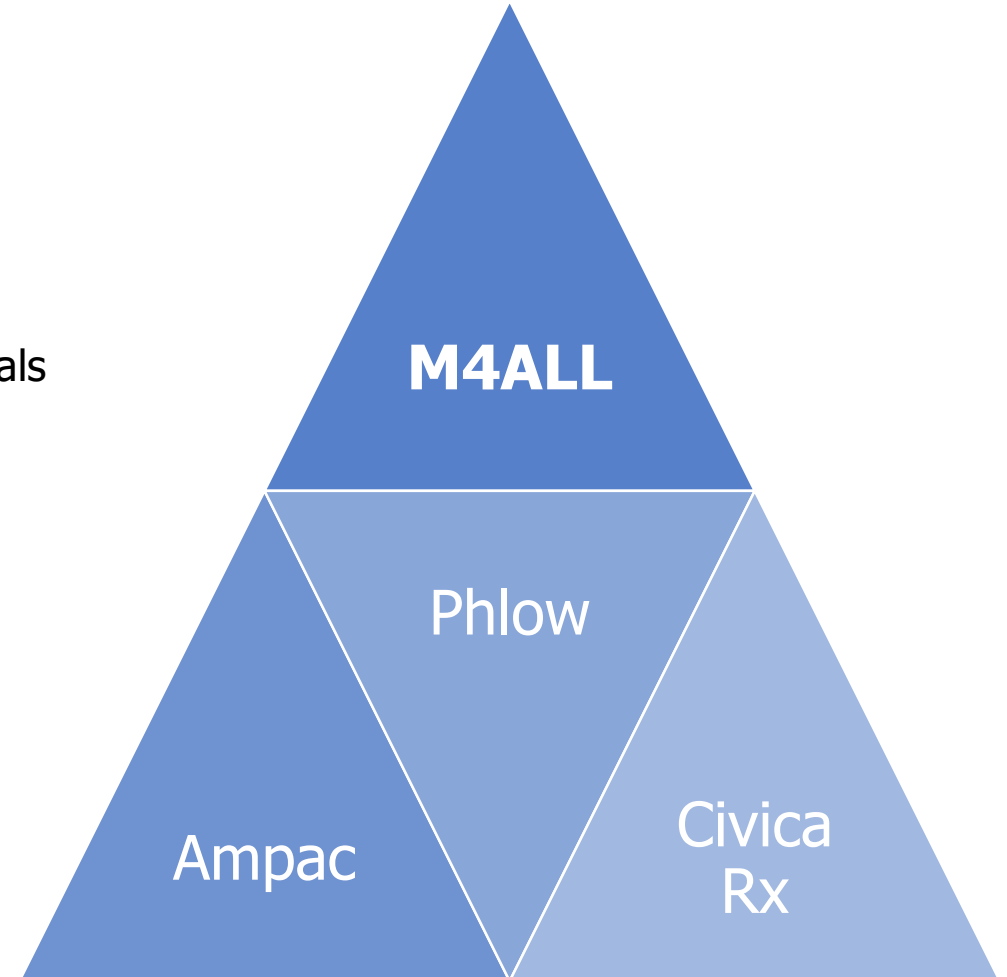
AMPAC supplies infrastructure, intermediates and starting materials



Phlow supplies cost effective API's to Civica manufacturers/strategic reserve



Direct supply of finished dosage to over 1,500 hospitals and USG



M4ALL: In Conclusion

