White Paper

Advanced Development of Domestic Manufacturing Capabilities for Critical mRNA Vaccine Components (NTPs)

For MCS-BAA-17-01
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1. INTRODUCTION AND BACKGROUND

1.1 TriLink Biotechnologies, LLC

TriLink Biotechnologies (a division of Maravai LifeSciences (NASDAQ: MRVI)) is located in San Diego, CA, USA. TriLink is a best-in-class contract development and manufacturing organization (CDMO) for the synthesis of nucleic acids, NTPs and mRNA capping analogs. TriLink has scale-up expertise and unique mRNA, oligonucleotide & plasmid production capabilities for companies focused on therapeutic, vaccine, diagnostic and biopharmaceutical breakthroughs.

TriLink's proprietary CleanCap® mRNA co-transcriptional capping technology simplifies mRNA manufacturing by removing additional enzymatic steps, resulting in high capping efficiency and improved yields over traditional co-transcriptional capping methods.

TriLink's CDMO services offer a range of manufacturing grade products from discovery-grade (RUO) to its customizable intermediate-grade - GMPLink™ to full GMP-grade with scale-up and technology transfer expertise. With its recent facility expansion to increase cGMP capacity, TriLink provides support from initial research phases through the production of commercial material. TriLink operates a quality system in compliance with ICH Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Section 19, APIs for Use in Clinical Trials, and ISO 9001:2015 standards.

TriLink, founded by Dr. Rick Hogrefe, Terry Beck, and Dr. Morteza Vaghefi, has been a pioneer in nucleic acid synthesis & manufacturing since its inception in 1996. With product and service offerings and expertise that have adapted to customer needs over the decades, TriLink remains committed to taking on challenges others simply will not. TriLink continues to expand its cGMP and general mRNA, oligonucleotide & plasmid manufacturing capacity at its new San Diego global headquarters to support therapeutic, vaccine and diagnostic customers.

1.2 Manufacturing Capabilities and Current Experience

Since 2019, TriLink has been manufacturing GMP mRNA and associated reagents in its 118K sq. ft. facility in San Diego.

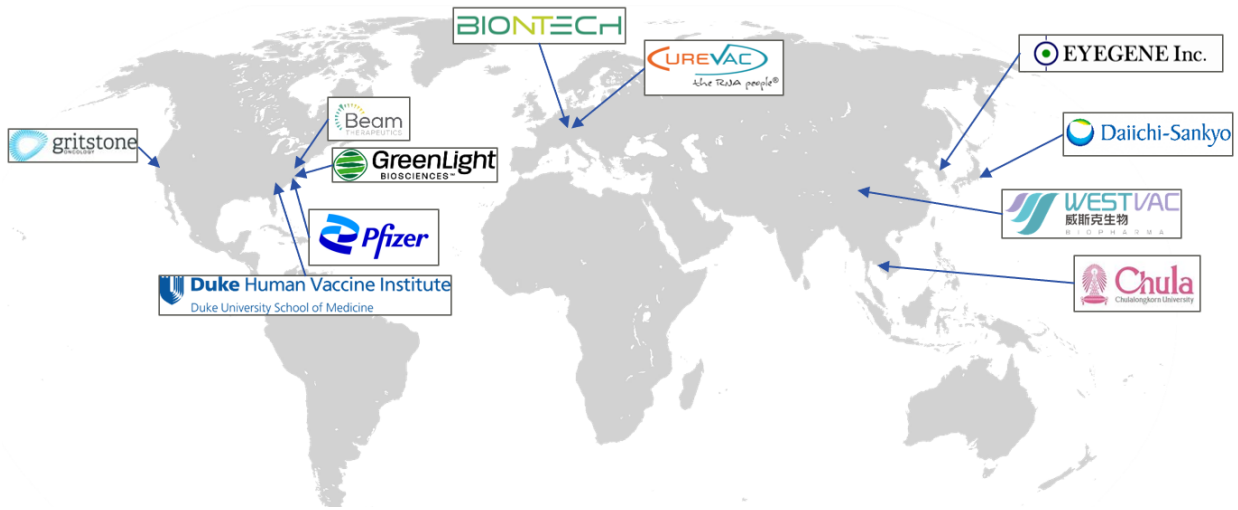
TriLink's project will significantly assist JPdL's mission of expansion of domestic capacity to 600M additional COVID vaccine doses in 6-9 months with a innovative capacity expansion plan. TriLink will serve as an effective and reliable partner to the HHS/JPdL mission of pandemic preparedness.

1.2.1 TriLink Manufacturing

TriLink is the supplier of "CleanCap®", an essential NTP material in mRNA vaccine manufacturing, including COVID-19 vaccines. **TriLink is the sole supplier of the CleanCap® reagent to Pfizer/BioNTech for their COVID-19 vaccine and an integral part of the supply chain**. To date, TriLink has manufactured CleanCap® for all Pfizer doses, in excess of 1B doses manufactured, demonstrating a proven integration of process/capability into an FDA regulated product.

TriLink supplies CleanCap® for COVID-19 vaccines worldwide:

Figure 1: TriLink Customers using CleanCap® in COVID-19 vaccine programs



1.2.2 CleanCap® for other MCM Needs

The CleanCap® material can be used in many applications of mRNA technology that will be utilized for medical countermeasures in the future, including: gene editing (CRISPR, Base Editor), cell therapy (e.g. CAR-T, TCR), gene replacement, vaccines, self-amplifying mRNA and antibody production.

1.2.3 mRNA Manufacturing

TriLink also manufactures the mRNA molecule directly for many vaccine programs.

1.3 Key Project Personnel

Brian Neel, Chief Operating Officer

Brian joined TriLink with over fifteen years of experience as a leader in the life sciences and diagnostics industries. He has significant experience in a wide array of manufacturing operations in life sciences and worked in chemistry and molecular biology-based operations with Life Technologies (acquired by Thermo Fisher) for over thirteen years. Brian has a passion for continuous improvement in operations management and has held key site leadership roles in organic chemistry, bioproduction, and enzyme purification technologies across organizations within 3 different states, including Synthetic Genomics and GenMark. He received a B.A. in Microbiology from the University of Missouri, Columbia.

Michael Houston, Chief Scientific Officer

Mike brings over ten years of experience as a leader in the biotech and pharmaceutical industries to TriLink. Mike worked as VP of Therapeutic Development and later as CSO at PhaseRx, where he developed mRNA-based therapeutics. Mike served as Vice President of Chemistry and Formulations for Marina Biotech, where he led a team in the development of siRNA-based therapies and LNP-based delivery systems. He has significant experience in peptide-based therapeutics, as demonstrated in his role as VP of Preclinical Chemistry and CMC at Ascent Therapeutics. Mike also served as Senior Director of Chemistry and Formulations at Nastech Pharmaceuticals . He received a Ph.D. in bio-organic chemistry and a B.Sc. with honors in chemistry from the University of Waterloo in Ontario, Canada.

Jeremy Horton, VP of Manufacturing Operations

Jeremy joined TriLink with over twenty-three years of experience in leadership roles within Manufacturing, Quality, Supply Chain, R&D, Program Management, Customer Alliance, Facilities, EHS, and Engineering across Pharmaceutical, Medical Device, Semiconductor, and Aerospace Industries. His pharmaceutical experience ranges from early phase I/II manufacturing to commercial launch and lifecycle management of commercial drug products. He is a Master Black Belt and Lean Six Sigma Expert who is a proven change agent. Jeremy received a master's degree in Chemistry and MBA from San Diego State University and has earned the following certifications: ASQ Pharmaceutical cGMP, ASQ Six-Sigma Black Belt (SSBB), APICS Certified Production & Inventory Management (CPIM), PMI Project Management Professional (PMP), ASQ Certified Quality Manager (CQM) & Certified Quality Engineer (CQE), CFA Level-1, SUN Java Programmer (SCJP).

Jeff Whitmore, VP of Commercial Operations

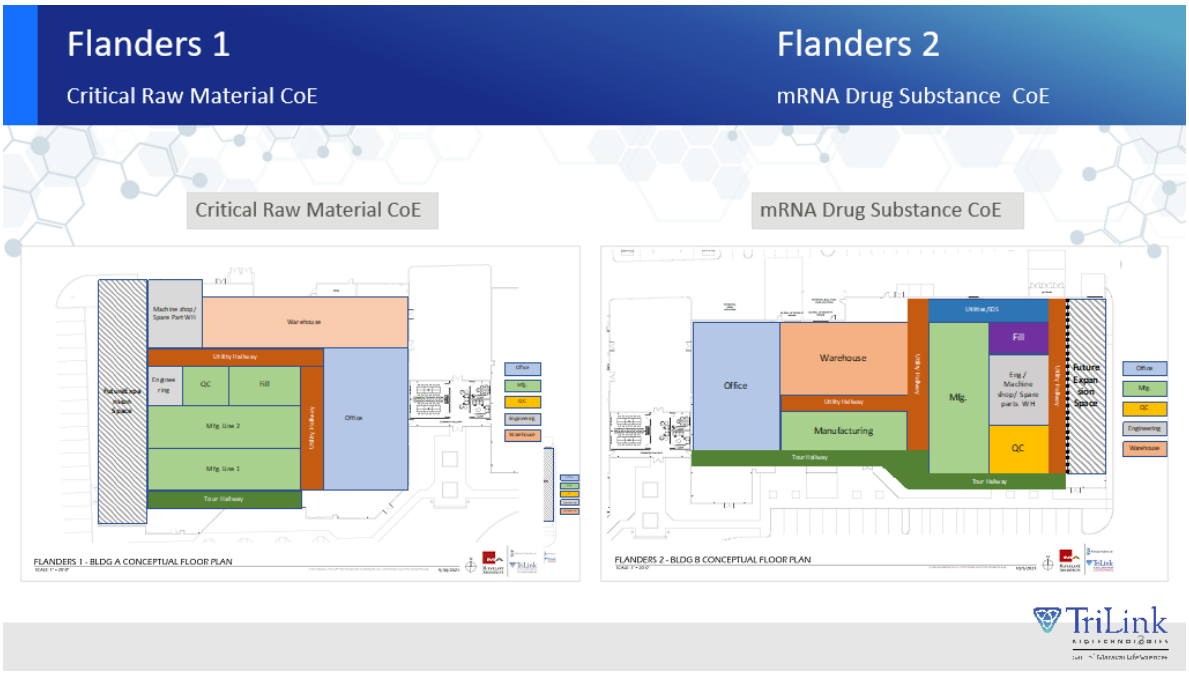
Jeff leads all commercial operations and strategy at TriLink with over twenty years of experience in life science commercial leadership and general management. Jeff served as President and Founder of United Bio Channels, an international consulting group specializing in supporting companies in growth and market expansion phases prior to joining TriLink. Earlier in his career, Jeff held a variety of commercial leadership roles in life science companies including Singulex, Protein Simple, Alpha Innotech, Molecular Devices, Bio-Rad Laboratories, and Cargill Inc. He received a B.A.Sc. in Biochemistry and Molecular Biology from the University of Wisconsin-La Crosse.

2. PROPOSED CAPABILITY SOLUTION

2.1 New Manufacturing Facility

TriLink is proposing a US (San Diego, CA) **innovative facility expansion** to manufacture materials and finished product for all aspects of the mRNA vaccine manufacturing supply chain, including small molecules, capping reagents, plasmids and mRNA.

Figure 2: Proposed New US Manufacturing Facility – Flanders Centers of Excellence



TriLink will be able to manufacture the following products to assist with JPdL's mission of expansion of domestic capacity to 600M additional COVID vaccine doses in 6-9 months. This will **advantageously facilitate the domestic response to vaccinate the US population**.

Table 1: Specific Products/Capabilities Provided

	Small Molecule (Critical Raw Materials)		Biologics (API)
	CleanCap®	**NTPs**	**mRNA**
JPdL Question			
Describe potential uses for each product	Raw materials for vaccine, cell therapy, gene therapy, sequencing, and *in-vitro* diagnostic manufacturing. Materials for academic, biopharmaceutical, and diagnostic research		Pre-Clinical through early Commercial API and future Drug Product for vaccines and gene therapy therapeutic indications
Current throughput (units/year) *Single Shift Operation*	52 kg/year	30 kg/year	400 g/year
Proposed increase (units/year) *Single Shift Operation*	52 kg/year	30 kg/year	1.2 kg/year
Final capacity (units/year)	104 kg/year	60 kg/year	1.6 kg/year
Timing when available	2022	2022	2022
Pre-Clinical - **Clinical Phase I-III** Market demand for each product (US and ROW/ 2022)	10 kg US 8 kg ROW	10 kg US 8 kg ROW	4 kg US 2 kg ROW
Commercial Market Demand US + ROW 2022	40 kg US 30 kg ROW	73 kg US 50 kg ROW	4 kg US (Non-Covid) 2 kg ROW (Non-Covid)
Pre-Clinical – Clinical Phase I-III What % of US demand will be met by this facility?	100%	60%	40%
Commercial What % of US demand will be met by this facility?	100%	40%	40% ~ 2022 and beyond non-covid demand

Construction of this facility will expand the US-based capacity for mRNA vaccine production and especially for the CleanCap® capping reagent, a critical raw material in the supply chain. **TriLink will be able to meet 100% of current US demand for capping reagents and 32% of US NTP demand for mRNA vaccines with this facility**.

3. INNOVATIVE SOLUTIONS

3.1 CleanCap® for mRNA Vaccines

mRNA capping (or 5' capping) is highly regulated in eukaryotes and play a crucial role in cellular processes, including translation initiation, splicing, intracellular transport and turnover. Manufactured mRNA does not have the same capping as mammalian cells so a modification is required in order to ensure function. Historically, this has been performed using multi-step enzymatic capping procedures.

CleanCap® technology is a proprietary, co-transcriptional 5' capping solution that generates a natural Cap 1 structure. Proper mRNA capping is critical to the production of the most biologically active and least immunogenic mRNA. TriLink scientists developed CleanCap®, the next generation of capping technology, as a solution to the low capping efficiencies (mCAP/ARCA) or high enzyme costs that are associated with traditional capping methods. CleanCap® is efficient, elicits high yields of capped mRNA, and provides the highest quality mRNA 5' cap structure available today.

Figure 2: Manufacturing Benefits of CleanCap® vs. Traditional Enzymatic Capping

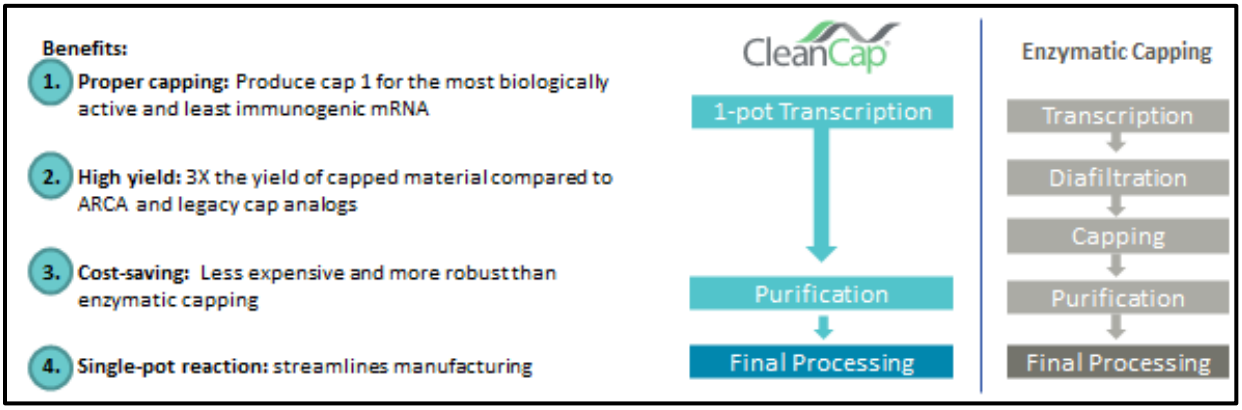


Figure 3: CleanCap® Single-Reactor Manufacturing Process vs. Traditional Enzymatic Capping

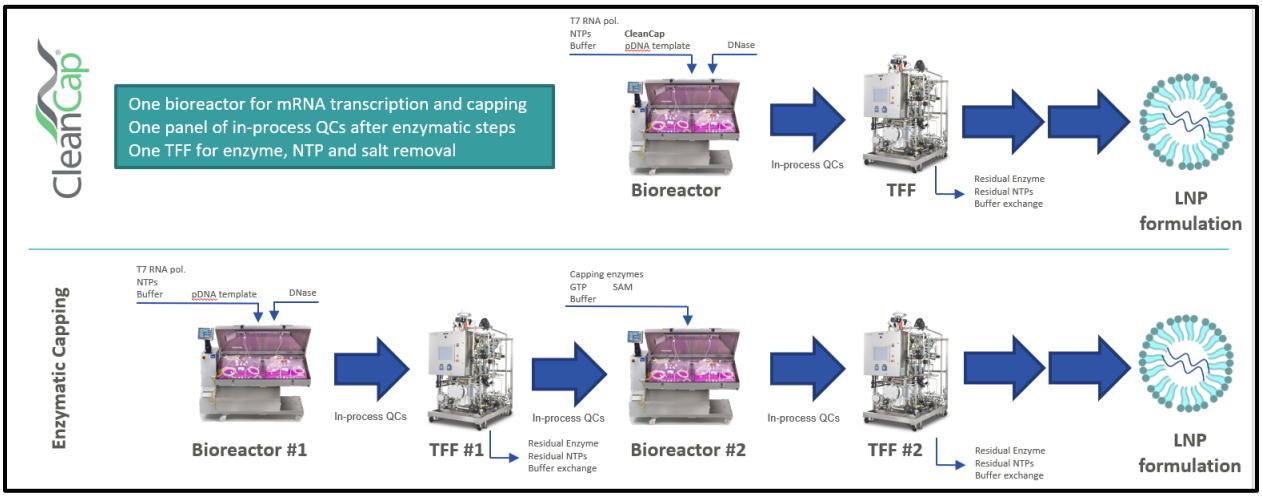
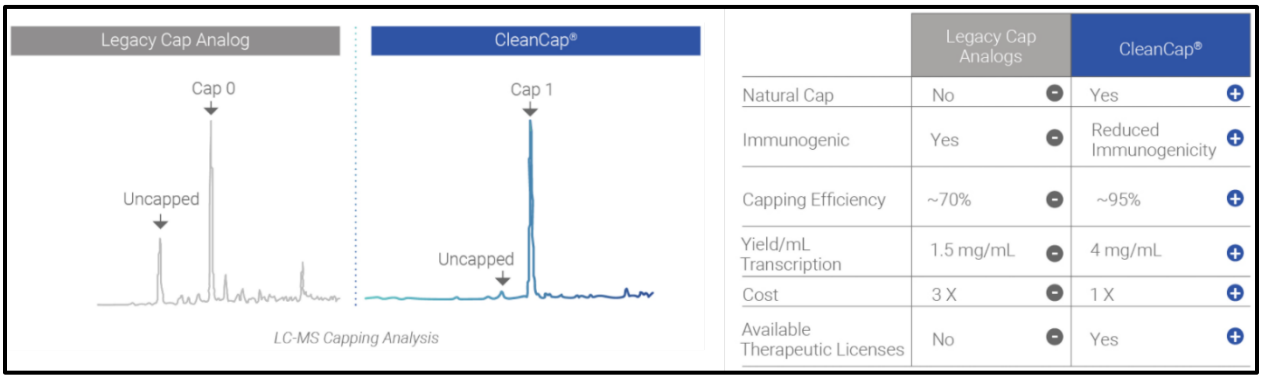


Figure 4: CleanCap® demonstrates superior performance versus legacy co-transcriptional capping methods



	Legacy Cap Analogs	CleanCap®
Natural Cap	No	Yes
Immunogenic	Yes	Reduced Immunogenicity
Capping Efficiency	~70%	~95%
Yield/mL Transcription	1.5 mg/mL	4 mg/mL
Cost	3 X	1 X
Available Therapeutic Licenses	No	Yes

3.2 Cost Benefits of CleanCap®

Even with best pricing models, alternative capping methods are > 2X more expensive than CleanCap® per mg of final mRNA product:

Figure 5: CleanCap® provides 2X cost benefit vs other methods

Method	Price (CDMO best price)	Quantity (to produce 1 mg of capped RNA)	Total Cost	Cap Structure	Reaction Vessels	Price Overrun
CleanCap	$36/µmol	1.33 µmol	$48 ✓	Cap 1 ✓	1 ✓	-
ARCA	$18/µmol	6 µmol	$108 ✗	Cap 0 ✗	1 ✓	2.25X
Enzymatic Capping	$0.04/U Vaccinia $0.01/U 2'OMT	1,000 U 5,000 U	$90 ✗	Cap 1 ✓	2 ✗	1.87X

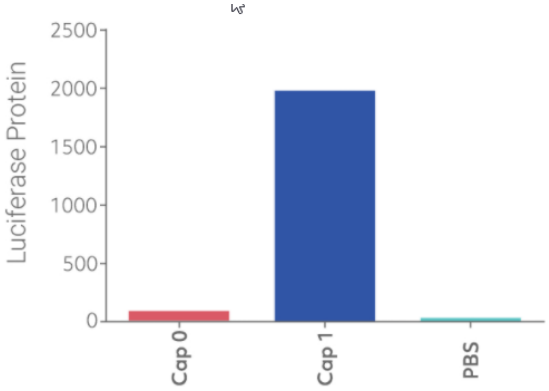
3.3 Summary of CleanCap® Innovation Benefits

CleanCap® provides:

- High capping efficiencies (95%+) resulting in more active mRNA
- Yields a natural Cap 1 Product
- Cap 1 reduces activation of Pattern Recognition Receptors
- Dramatically increased activity in vivo in liver relative to Cap 0
- "One pot" co-transcriptional reaction to produce a Cap 1 structure vs multiple purifications steps required for enzymatic Cap 1
- A significant cost benefit over other methods of manufacturing
- Accelerated advancement on CleanCap analog innovation to promote greater protein expression
- Greater than 99% purity GMP grade modified NTPs

CleanCap® results in a natural Cap 1 structure that reduces stimulation of the innate immune system of the host, resulting in unparalleled efficiency in vivo. Legacy co-transcriptional capping methods yield a Cap 0, an immunogenic cap structure that is poorly expressed in vivo:

Figure 6: CleanCap® effectiveness in vivo



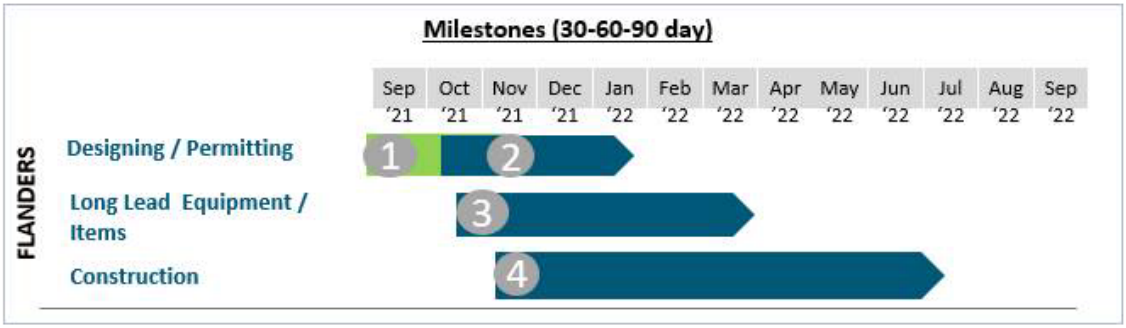
Luciferase mRNA was formulated with Lunar Lipids and injected by tail vein into mice. At 6 hours, luciferase was measured by western blot in mouse liver. Data courtesy of Arcturus Therapeutics.

4. SCHEDULE

4.1 Current Status

This facility is currently completing the design process (McFarlane Architects, San Diego CA) and a construction company has been selected (Level 10 Construction, San Diego CA). The facility is scheduled to start construction (November 1, 2021) and with anticipated completion in July 2022.

Figure 7: US Facility Expansion Construction Schedule



4.2 USG Priority Placement

TriLink would give USG orders for products made in these facilities priority over non-USG orders for 10 years after award.

4.3 USG Preferred Pricing

TriLink would give USG orders for products made in these facilities preferred pricing, not to exceed pricing TriLink offers to third parties purchasing the same products (with the same intended use) at the same or lesser volumes as those ordered by USG for 10 years after award.

5. COST ESTIMATE

The facility expansion is estimated to cost $106M, of which TriLink proposes a cost share of $54M, with $52M from JPdL.

Table 2: Cost Estimate

Area	Estimated Cost
Flanders 1 (Critical Materials) – Equipment/Utilities	$10M
Flanders 2 (mRNA manufacturing) – Equipment/Utilities	$20M
Flanders 1 and 2 Construction	$53M
Process Development / Validation (All facilities)	$23M
Total	$106M
Cost Share	TriLink: $54M USG (JPdL): $52M