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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

PSCI Webinar

Managing active pharmaceutical ingredients (API) in manufacturing effluent, Part 3

October 2016

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Our speakers

Rominder Suri, Temple University

Professor and Chair of Civil and Environmental Engineering Department at Temple University. Director of the Water and Environmental Technology (WET) Center – a National Science Foundation funded Industry/University Cooperative Research Center (IUCRC).

Ed Helmig, AECOM

Principal Engineer with AECOM with over 30 years' experience as an environmental manager and water-wastewater expert in the pharmaceutical industry. Experience includes work at Fermentation & Antibiotics, Vaccines, Formulation and Filling, Chemical Synthesis, and Biotech facilities around the world.

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Our speakers

Dan Caldwell, J&J

Toxicology Fellow in Environment, Health, Safety & Sustainability at Johnson & Johnson. His focus is science advocacy for regulatory assessment of environmental exposure to chemical ingredients. He chairs the Inter Association Initiative PiE Task Force Environmental Control Work Group.

Frank Mastrocco, Pfizer

Pfizer's Director of Environmental Toxicology for the Global Environment, Health & Safety – Product Stewardship Group. His responsibilities include environmental risk assessment support to manufacturing and product operations. He is a lead representative in the area of Pharmaceuticals in the Environment.

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Agenda

1 Introduction

3 Technology based API solutions

4 Q&A

The Roadmap commitments

IFPMA International Federation of Pharmaceutical Manufacturers & Associations

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http://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf

- Specifically, this group of diversified companies commit to:
- **Reduce the environmental impact from the production of antibiotics**, including a review of the companies' manufacturing and supply chains, and work with stakeholders to establish a common framework for assessing and managing antibiotic discharge;
- **Help ensure antibiotics are used only by patients who need them**, recognizing this requires concerted efforts from many stakeholders, through continued provider and patient education, an examination of the companies' promotional activities, sharing of surveillance data with public health bodies and healthcare professionals, and collaboration with stakeholders to reduce uncontrolled antibiotic purchase;
- **Improve access to current and future antibiotics, vaccines, and diagnostics**, including working with stakeholders to strengthen global health systems and address access bottlenecks; establishing new business models that balance access needs, appropriate antibiotic use, expanded vaccine coverage and adequate return to companies; and working to reduce the prevalence of substandard/counterfeit antibiotics in high-risk markets; and
- **Explore new opportunities for open collaborations between industry and the public sector** to address challenges in the research and development of new antibiotics, vaccines, and diagnostics, recognizing the value these bring to society.

Allergan AstraZeneca Cipla gsk Johnson & Johnson MERCK

NOVARTIS Pfizer Roche SANOFI SHIONOGI INC. SINOCHEM DSM DSM Sinochem Pharmaceuticals

WOCKHARDT

The Industry Roadmap for Progress on AMR, examples of commitments (1 of 4)

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1) We support measures to reduce environmental impact from production of antibiotics, and will:
   i. Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment
   ii. Establish a common framework for managing antibiotic discharge, building on existing work such as PSCI[4], and start to apply it across our own manufacturing and supply chain by 2018.
   iii. Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.
   iv. Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges, by 2020.

http://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf.
Published on Sept 20, 2016

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Technology Options for Removal of APIs from Pharmaceutical Process Wastewater

Rominder Suri, PhD, P.E.

Director

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– a US National Science Foundation Industry University Cooperative research Center (IUCRC)

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nsfwetcenter.org

Presentation to Pharmaceutical Supply Chain Initiative (PSCI) & Companies

October 25, 2016

WATER AND ENVIRONMENTAL TECHNOLOGY CENTER

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Background

- **Need for Pharmaceutical Effluent Treatment**
  - Water Reuse Needs
  - Detection of API in the Environment
  - Ecological Risk due to some API (feminization of fish; bacterial resistance, etc); Mixture Effects; Unlikely risk in Drinking Water
  - USGS sampling of streams near Pharma plants
  - Adverse publicity
  - Liability
  - Some regulations in certain countries
  - Some Pharma Cos. pursuing voluntary treatment of effluent
  - Precautionary Principle

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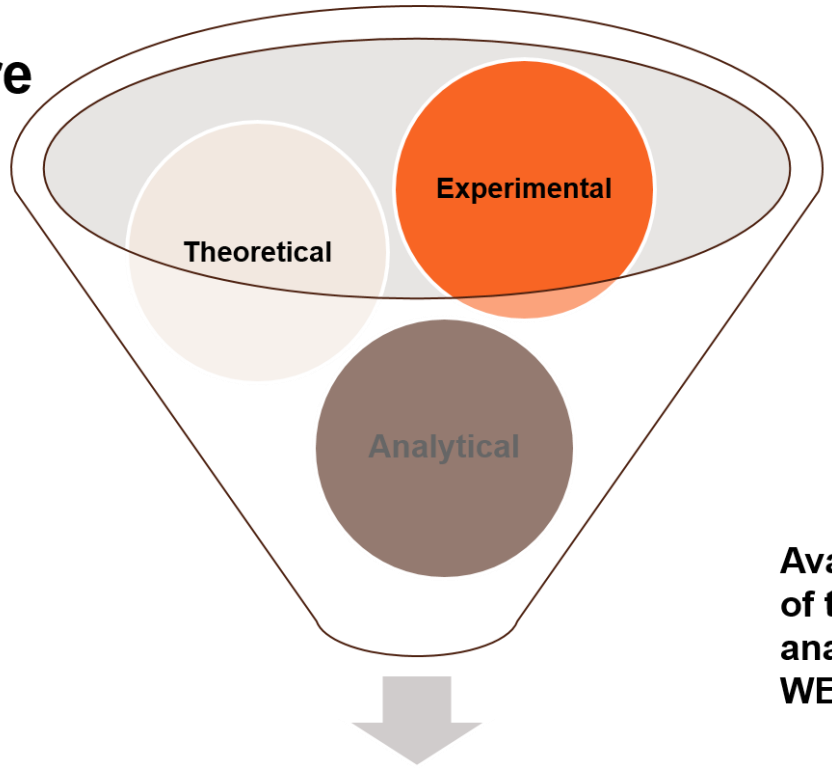
Most Pharma wastewater require



Extensive experience at WET Center on treatability of Pharmaceutical Wastewater

Availability of wide variety of technology and analytical equipment at WET Center

Customized and Cost Efficient Solution for Pharmaceutical Effluent

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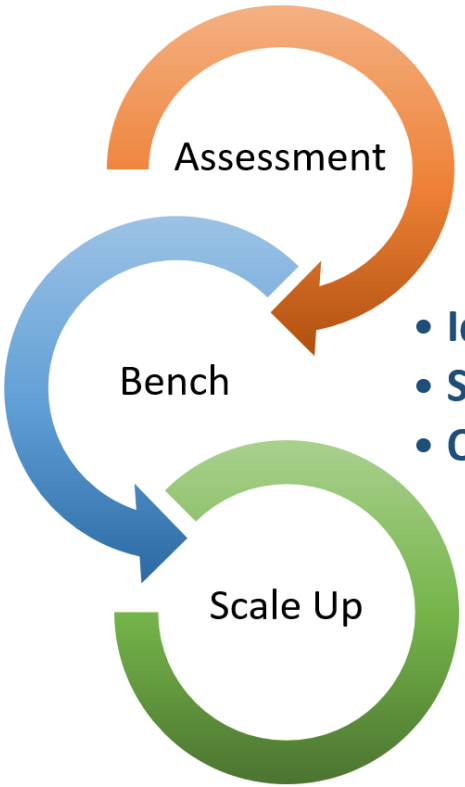
Intelligent Treatability
- rapid process prototyping



- **Identify goals**
- **Leverage existing information**
- **Establish treatment performance criteria**

- **Identify analytical requirements & methods**
- **Simulation: jar/microcosm tests**
- **Optimization**

- **Pilot Scale testing**
- **Treatment Performance: Sequence & Unit Operations**
- **Task description**

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Assessment

Identify goals and any constraints

- Define technology constraints
  - "whatever works"
  - Need it to work within existing infrastructure
- Other constraining factors (timeframe, costs, etc.)

Leverage existing information

- Establish existing information from clients, literature & database sources*
- Identify surrogate compounds if lacking data
  - Molecular similarity, etc.

Establish treatment performance criteria

- "Treat to" Level, PNECs, etc.
- Flow rates

***WET Center Database (>300 APIs) - extensive coverage of**

- **treatability**
- **ecotoxicity (PNECs)**
- **occurrence**

Using the WET Center API database: a Knowledge based approach

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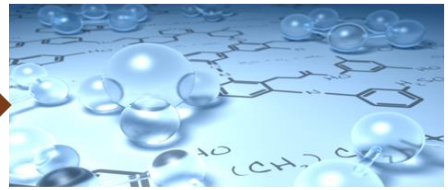
Data Sets

Example: Compound of interest - Gemfibrozil





Occurrence

In N.A:

- Max conc range: 5-790 ng/L
- Median conc range: 5-260 ng/L
- Top 100 in US prescriptions and environmental loading

Treatability

WWTP % removals

- Secondary: 40-75
- MBR: 80
- MBR/RO: 100
- RO/NF: 45-99
- O3: 98
- PAC: 50

Ecotoxicity

- PNEC = 10400 ng/L

Aquatic Risk Assessment

- MOS = 13 – 2080
- (MOS margin of safety = PNEC/ Occurrence concs)

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NSF

Bench

Approach

- Consider any required processes & configurations
- Wastewater matrix – characterize if not known
- Identify analytical requirements (detection limits) & methods of analysis*
- Conduct feasibility tests for different technologies
- ID most efficient sequence (for hybrid systems)
- Optimization studies for most promising solutions

***WET Center Analytical Capabilities Full range**
- **Multiple UPLC MS/MS & TOF systems**
- **GC/MS/MS; GC/MS/P&T**
- **Ion Chromatograph**
- **TOC; ICP/MS**

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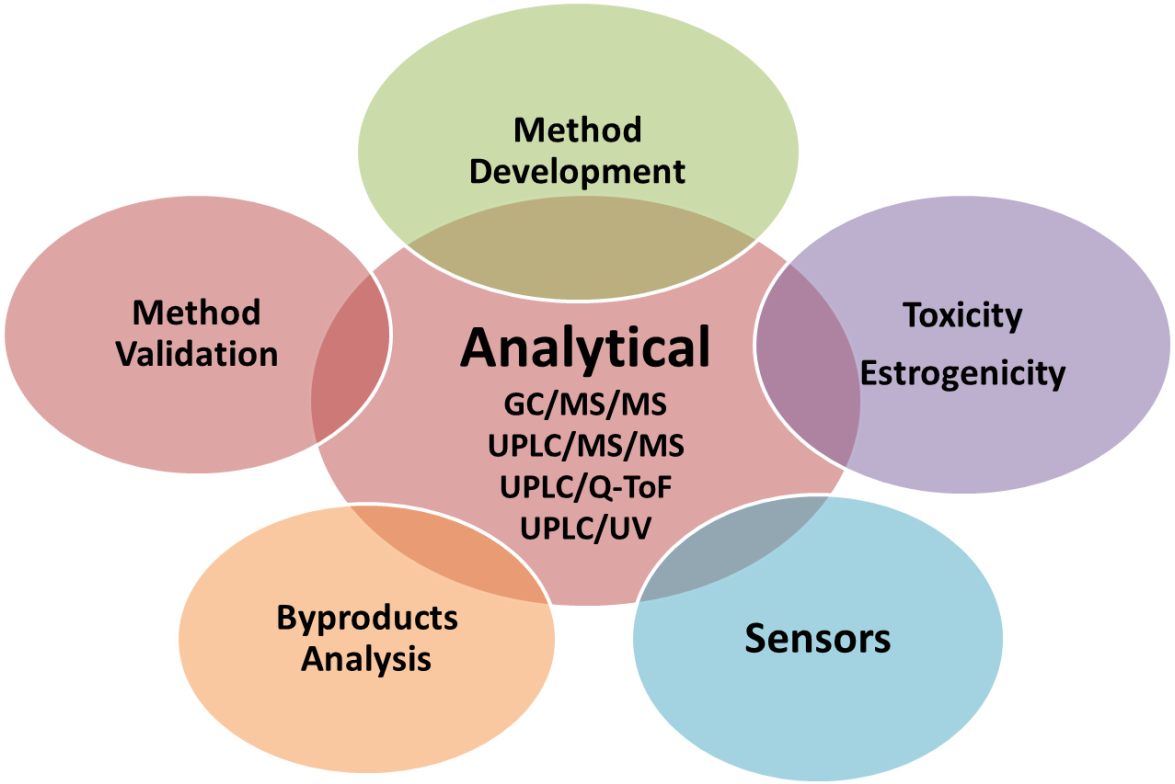
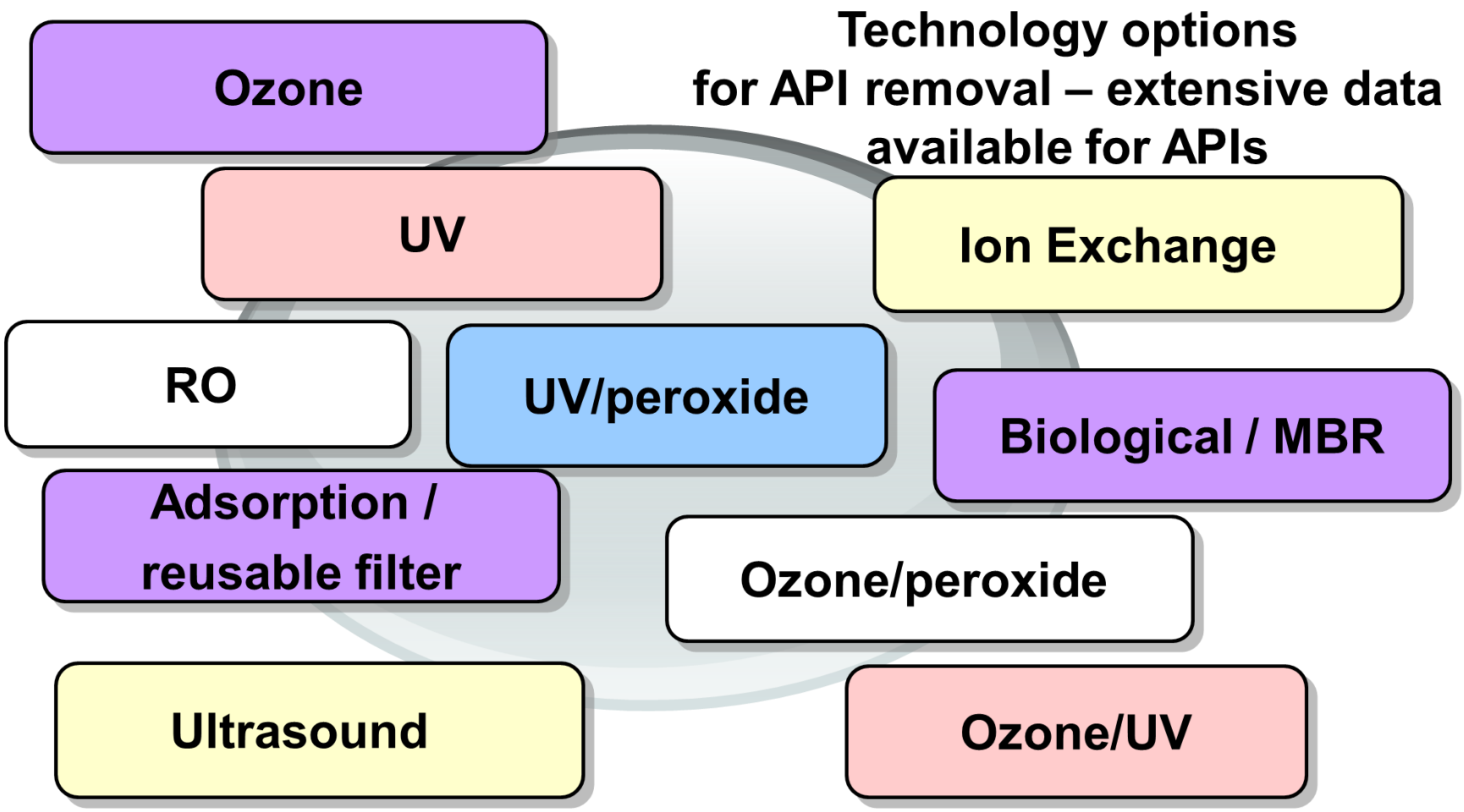
ANALYTICAL



Center Equipment

Technology options for API removal



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Factors Affecting Technology Selection

Objective – reuse or discharge; i.e. level of treatment (PNEC etc)

Type of APIs and their concentration

Site requirements / Preference

At Source or Blended ww treatment

Wastewater Characteristics

- Significant impact on technology performance
- BOD / COD ; pH ; surfactants ; alkalinity; other

This may require pre-treatment

Based upon the analysis of the site wastewater, may need to perform bench-scale tests to select/verify appropriate technology

Scale Up

WET Center Test Platform
- WERF recognition

WET Center Pilot Scale Testing

- Scale up of all treatment technologies
- Use “real” wastewaters for testing

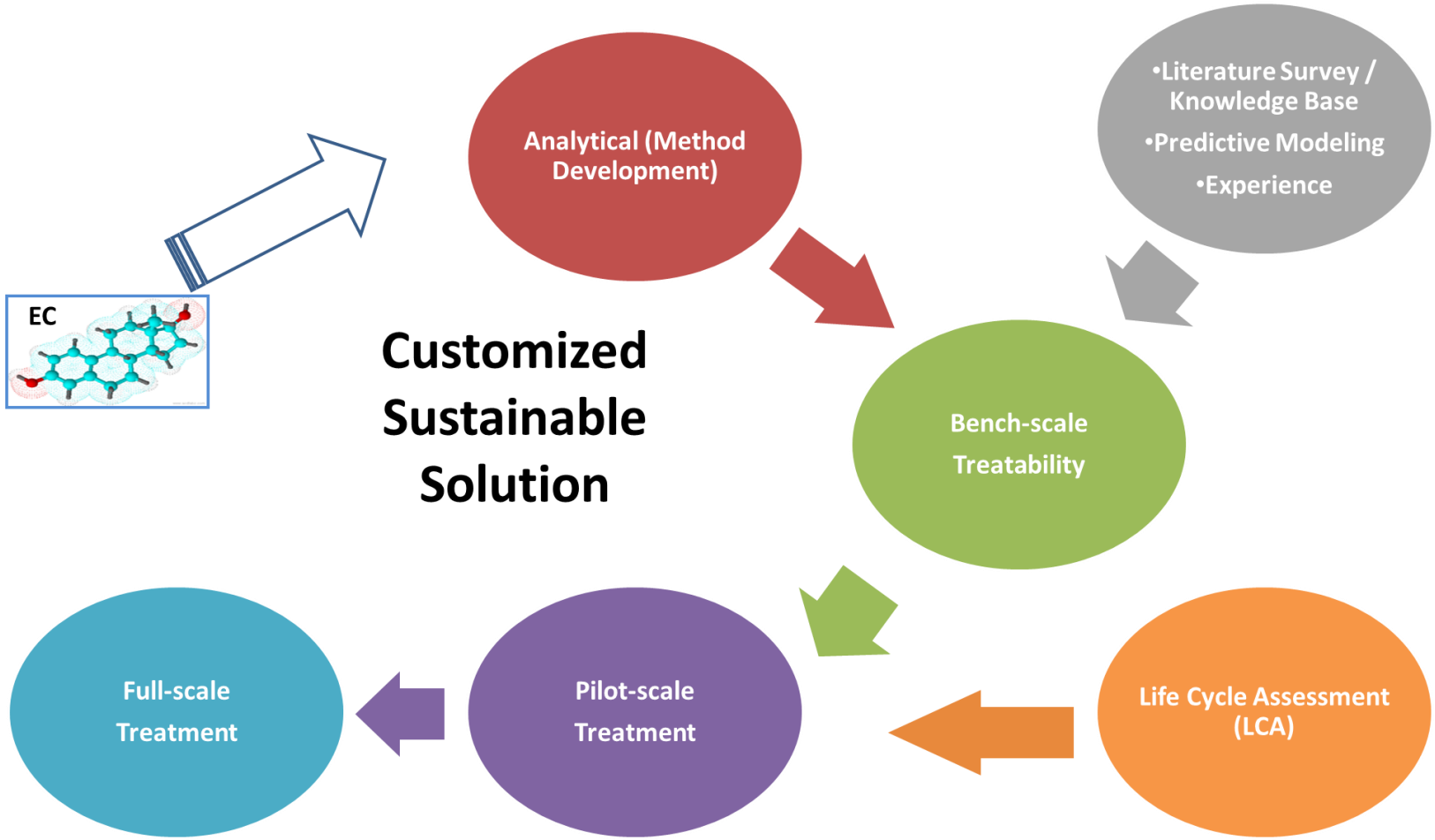
Treatment Performance: Sequence & Unit Operation

- Flexible configurations using mobile units

Variety of in-process sensors & analysis

Post treatment toxicity testing available

Summary


EC
Analytical (Method Development)
•Literature Survey / Knowledge Base
•Predictive Modeling
•Experience
Customized Sustainable Solution
Bench-scale Treatability
Full-scale Treatment
Pilot-scale Treatment
Life Cycle Assessment (LCA)

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Some Recent API R&D Work Results

- Ozonation treatment for Pharma Co. in EU
- Carbon adsorption treatment system in India
- Ultrasound treatment for Pharma wastewater
- MBR/Ozonation treatment system
- Analytical Methods for Pharma Co. in Ireland
- Novel, Reusable Adsorbent Filter – Contaminants destroyed in the filter; no replacement of filter needed
- Numerous API treatability studies
- Fate of APIs at Municipal WWTPs
- Fate of APIs in Biosolids, Animal Manure and Mushroom Compost Waste
- Presence of APIs in watershed and risk

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Technology Based API Solutions

Defining the risk, evaluating options, and delivering the solution for your company

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Principal Engineer- Industrial Water and Wastewater
Process and Technology
AECOM

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Agenda

1. Business Justification and Alternatives Analysis
2. Project Development
3. Project Delivery
4. Schedule and Cost Issues
5. Path to technical solutions and four project examples

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Business Justification

What are key business drivers?

Profit

Compliance

Risk

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Examples of Justification Arguments

Driver	Justification Examples
Profit	**Cost Savings:** less expensive than sending first and second rinses off-site for incineration. **Paradigm Shift:** this is not something separate but rather it is a key *part of our production process*. We can't grow the business and/or site without this component. **Magic Kingdom approach:** build this and consider it as a ***strategic asset***. Once built customers will come to us.
Compliance	It is required or implied under the applicable laws and regulations and/or can be prosecuted under the law (see "Risk").
Risk	If we don't build this we are operating at serious risk and this risk will inevitably impact our profits and our reputation. Spend $5-25M now and proactively address problem or put $250M+ in the company environmental reserve and pay for the problem later. And remember the law is weighted on the side of ***should have known*** not ***we didn't know***!

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How do I know if I have a justifiable project?

- The PEC/PNEC is in the 100-10,000 range and even after improving process yields and house-keeping practices it is still very high.
- It is a potent, high volume, high value product and no one else can make it.
- There are sensitive downstream receptors like the intake to brewery or infant formula manufacturing facility.

Project Justification

The product/waste stream already created an incident. Some real-world examples:

- You land apply your sludge and have a permit to do so. However one day neighborhood kangaroos jump the fence, eat the sludge and die. Your companies APIs are in the sludge. Your PNEC/*aquatic guidelines* may have been too high and did not account for these species.
- Your branded API was detected in river and drinking water samples and made newspaper and internet headlines. Your API was being made upstream by contract manufacturer with “loose” API management practices and they did not realize the compound was “poorly biodegradable. *The contract manufacturer now wants the fate and effects data as well as the treatment technology that they say you should have provided as part of the deal!*
- Your “stuff” became airborne and infected livestock shutting down the local beef and dairy industry. The prime minister of your country was notified and product was temporarily banned from export.
- The fish near the plant outfall were found to be *hermaphrodite.* You make oral contraceptives at that plant site.

Business Justification

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- Step1: Recognize that you will need to create a capital project
- Step 2: Understand your companies key business drivers
- Step 3: Identify the key stakeholders and get their support
- Step 4: Show a Return on Investment (ROI)

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2. **Project Development**
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Project Development

- Starts with stakeholder engagement
- Follows your companies project development process (PDP)
- Typically involves 4 or more phases and numerous gates or hurdles including:
  - Business Justification and Alternatives Analysis
  - Preliminary Engineering and Basis for Design
  - Detailed Design
  - Equipment Procurement and Construction
  - Commissioning, start-up and operator training
  - Performance Verification and Project close-out

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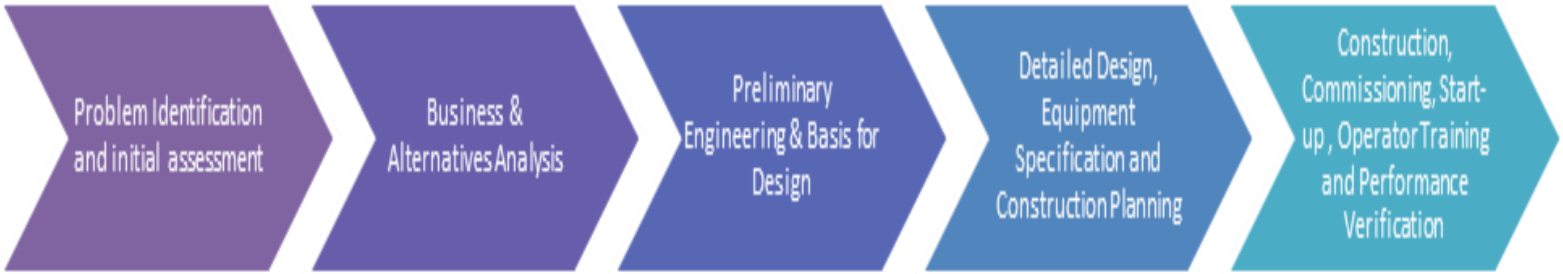
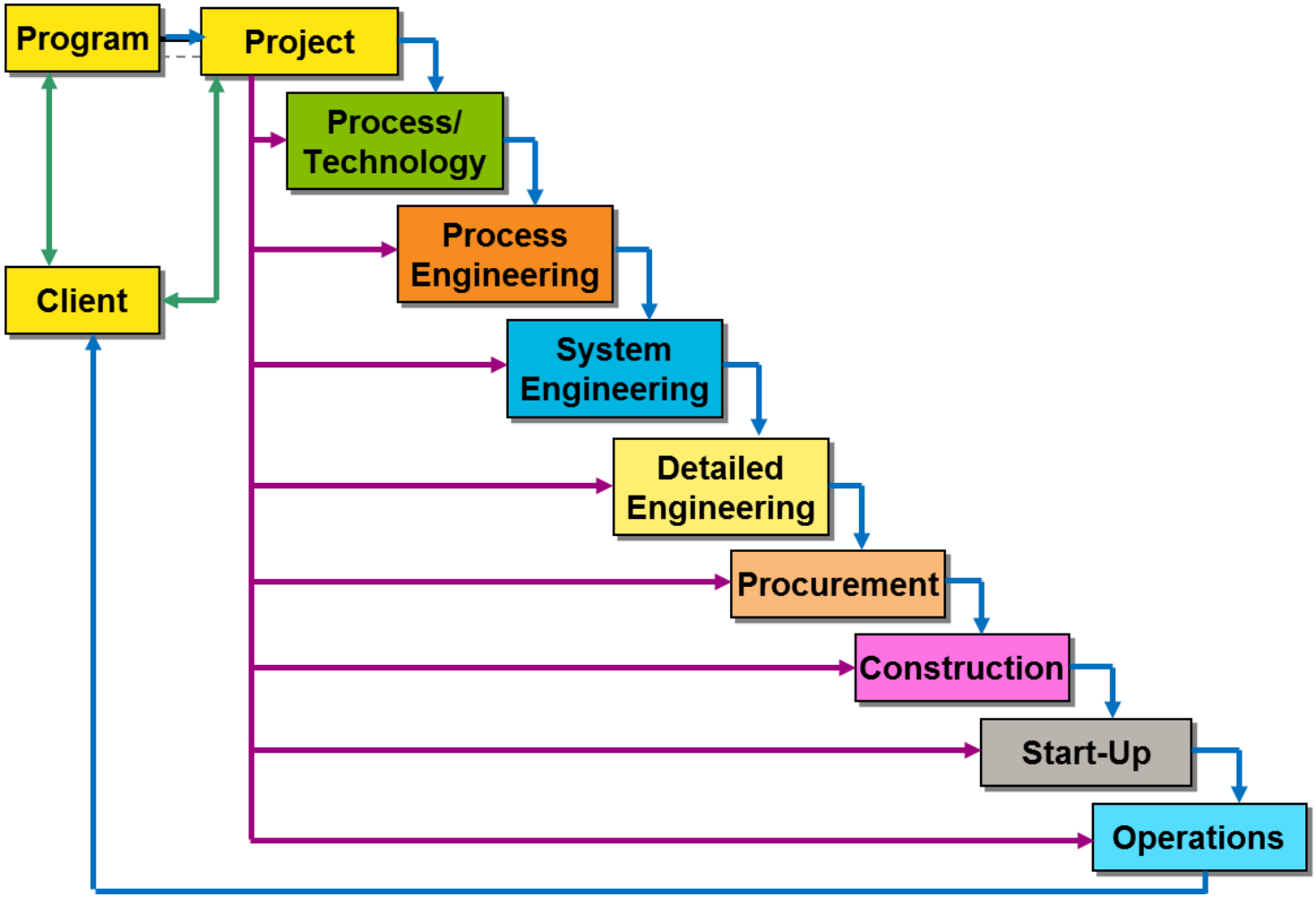
Typical Project Roadmap



Project Delivery Model



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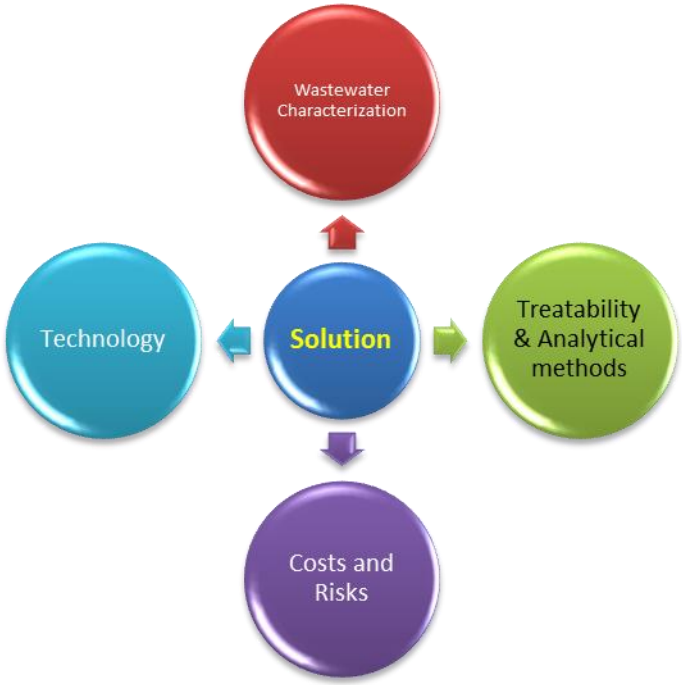
Four Key Elements of a Solution



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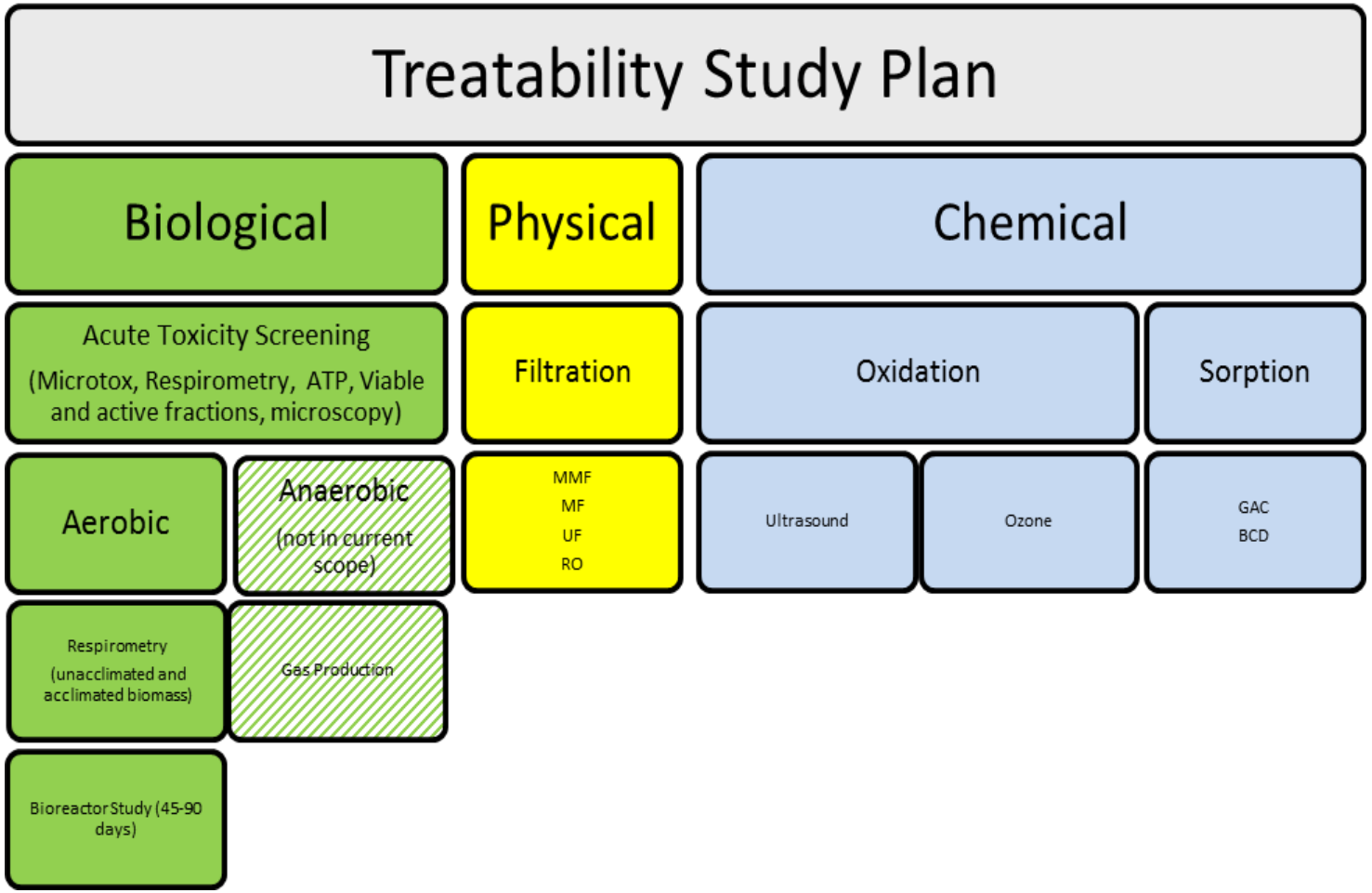
Example Technology Matrix



Understand the technology and its limitations. Know the equipment and not only the design but also the operating requirements

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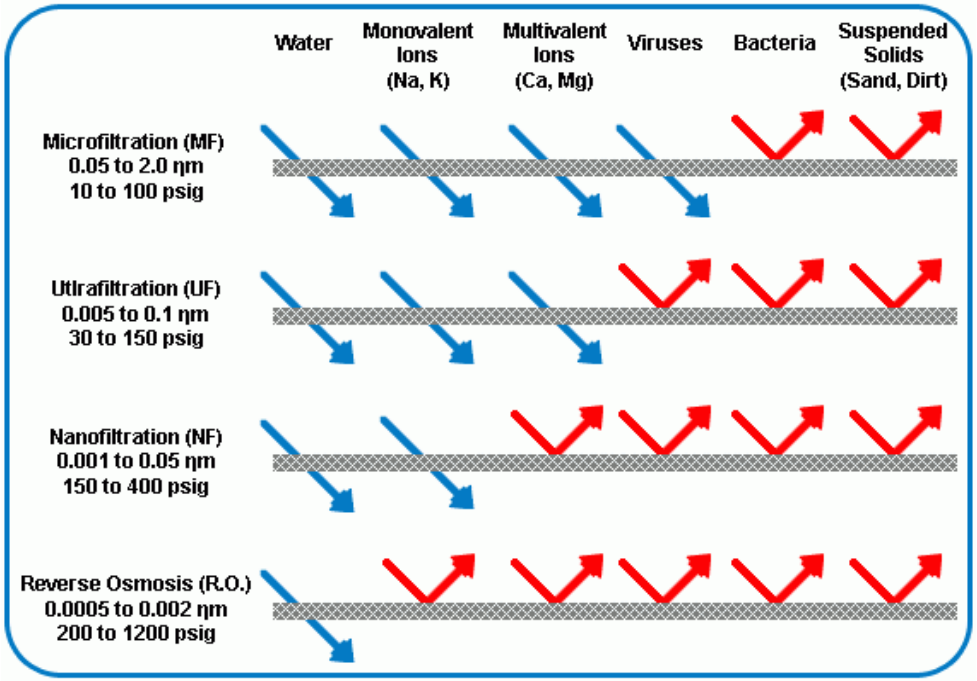
Understanding Filtration Technology



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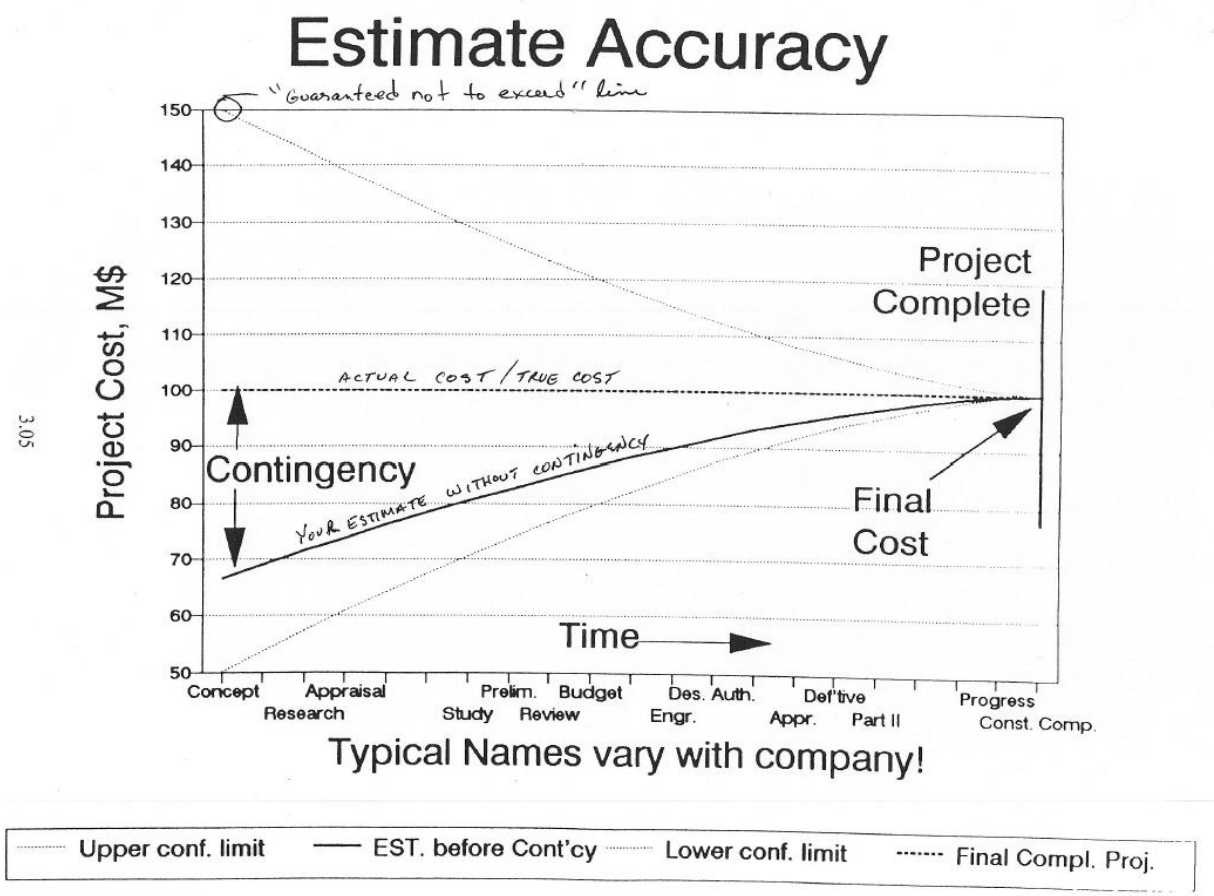
Cost and Schedule Issues

Murphy's Law: *all work expands to fill the maximum time allotted!*

….and…to spot the expert remember that he/she is the one who always seems to suggest that the project will take longer and cost more than what the other so called "experts" in the room are saying.

You will not know the precise cost until the project is completed and fully operational…..really!



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Source: Graphic: AIChE course on cost estimating.
Comments: "*school of hard-knocks*"

Time and Money

"Typical" Cost and Schedule Figures

Activity	Cost	Schedule
Bench studies	$25-$150K	4-6 months
Pilot Study	>$50K	4-10 months
Concept/Alternatives & Business Justification	>$50K	3-6 months
Design/Build	$5-$25M	18-24 months

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Example 1- Granular Activated Carbon (GAC) in India

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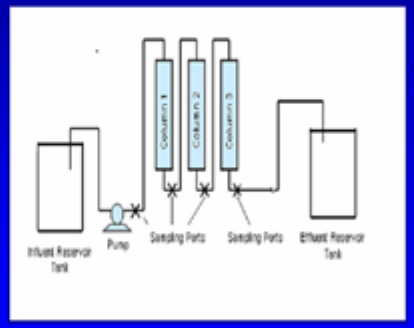
Carbon for Removal of APIs from Pharmaceutical Plant WW

Compounds Evaluated and C_o (ng/l).

1. 17 α Estradiol (45,793)
2. 17 β [redacted])
3. 17 α [redacted] 9,650)
4. 17 α [redacted] 78,230)
5. Estr[redacted]
6. Estr[redacted]
7. Equ[redacted]
8. Lev[redacted] 5)
9. Trin[redacted])
10. Estradiol Valerate (24,779)



C_o = measured (GC/MS) starting concentrations.

35

Results Summary

- **Dynamic Study:** overall 99.9% removal of all compounds was observed using 3 columns in series with and EBCT of 10 min each at neutral pH and ambient temperature.

Example 2: Ultrasound Technology

Example 3: Evaluation of Antibiotic Treatability using Respirometers

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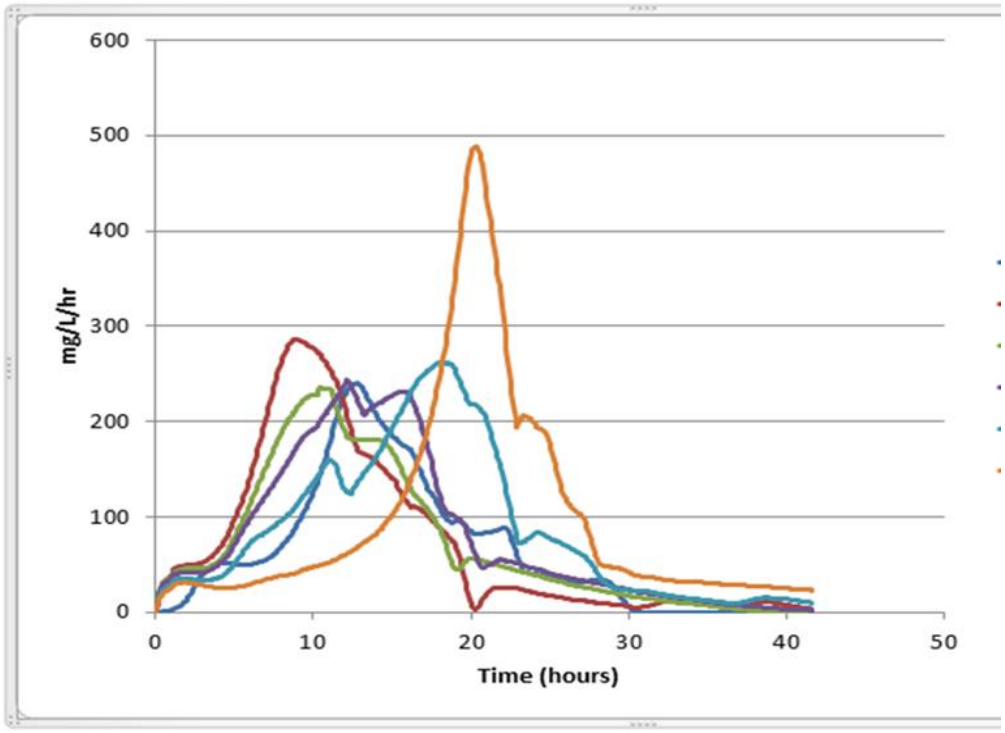
Figure 2. Oxygen Uptake Rate



As this family of curves indicates the increasing concentration of antibiotics appears to cause a lag in substrate utilization and peak respiration. In view of data obtained using the Microtox® assay that involves a single bioluminescent organism where toxicity is inferred based on ATP and changes in light output the Microtox® appears to grossly over-estimate the threshold of inhibition for the mixed culture.

These curves are for compounds that interfere with Chemiosmosis; specifically the transport of monovalent cations across cell membranes; primarily sodium and potassium. Initial Microtox® assays indicated EC_{50} of 40 and 75 mg/l for the compounds in the wastewater matrix.

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Example 3: Fermentation/Antibiotic Waste Stream Options Analysis

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Options Comparison

	A	B	C	D	E
	EQ N[illegible] + [illegible]lids Separation	EQ Aerate + Solids Separation	EQ Aerate + Solids Separation + Bio	EQ Aerate + Waste Diversion + Direct Bio	EQ A[illegible] + Solids Separation + Bio to River
CAPEX ($M)	10.5	11.4	13.8	9.8	12.7
Operating Costs ($M / YR)	1.9	1.8	1.7	1.7	1.0
NPV					
Intangibles Score	-31	10	28	52	23
Process Uncertainty	>95% Confident	>95% Confident	>95% Confident	>65% Confident	50% Confident
Disposal Location	Land Application / Landfill	Land Application / Landfill	Land Application / Landfill	Land Application	River / Landfill

Option A – Eliminated due to low intangibles score (high odor, worker exposure)

Option B – Eliminated due to process uncertainty and strong desire by EHS to avoid going to river)

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Example 4: State-of-the-Art Pharmaceutical WWTP

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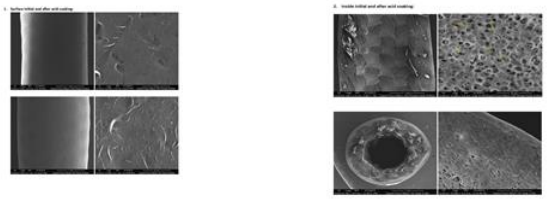
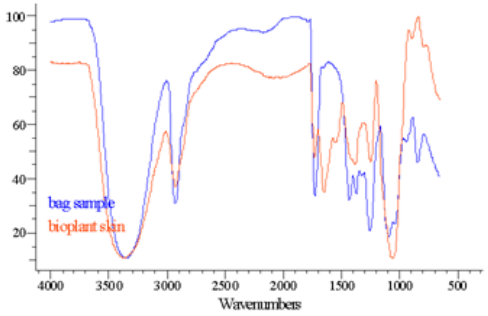
Advanced Biological Treatment-MBRs

Don’t clog the spaghetti!

Scanning Electron Microscope (SEM) results
Pre and post acid cleaning



Fourier Transform Inferred Spectrometry (FTIR) Spectrum of PVA Bag vs Skin (fouling) on membrane fiber



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50,000 Hours is a lot of wastewater treatment system experience……do you have it?

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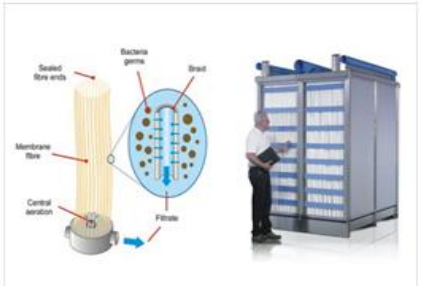
Hollow Fiber Membrane Filtration System- KOCH-



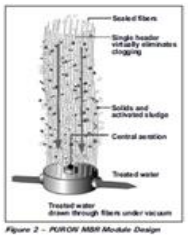
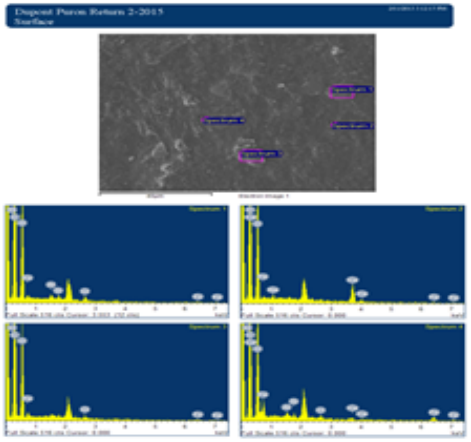
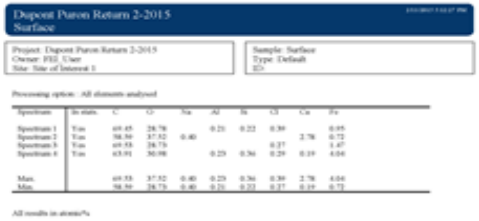


Figure 2 – PORON MBR Module Design

Energy Dispersive X-Ray Spectroscopy (EDX) analysis of fouled membrane





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The power of ozone-lightning in a can!

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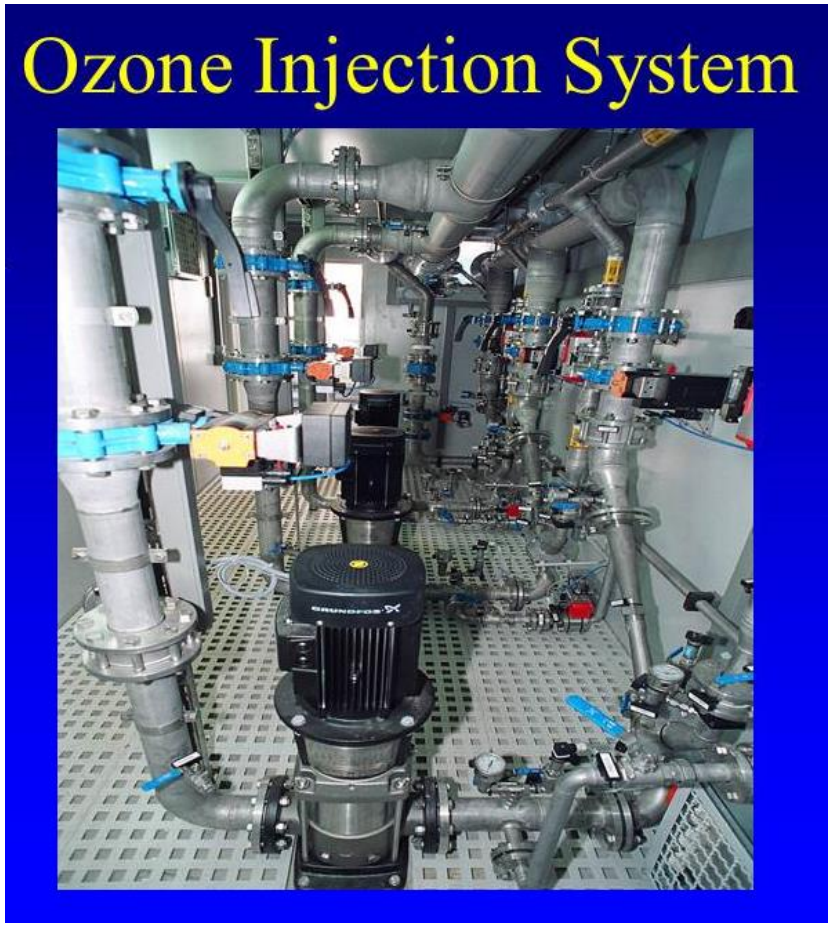
The complexity of Mass Transfer



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The Importance of Experience
Degassing is matters!

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Ozone Contacting and Degas

Recirculation is from degas internal overflow to injector skid with forward flow from permeate holding tanks

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The importance of experience and process safety

Figure 2. Results from a foaming problem and operator error that led to catastrophic implosion of an ozone contactor.
Photo by Edward G. Helmig.

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Understand the fate before you go full scale… the value of bench and pilot studies

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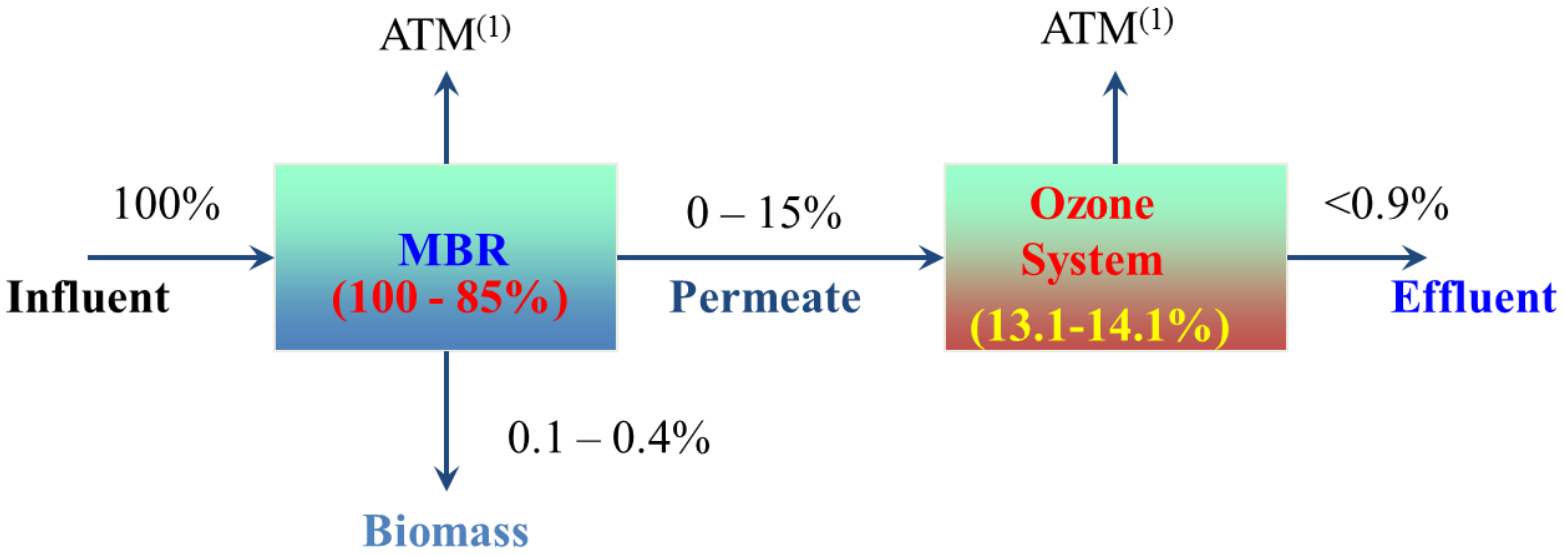

Schedule- real world time line for $22M end-of-pipe API removal WWTP

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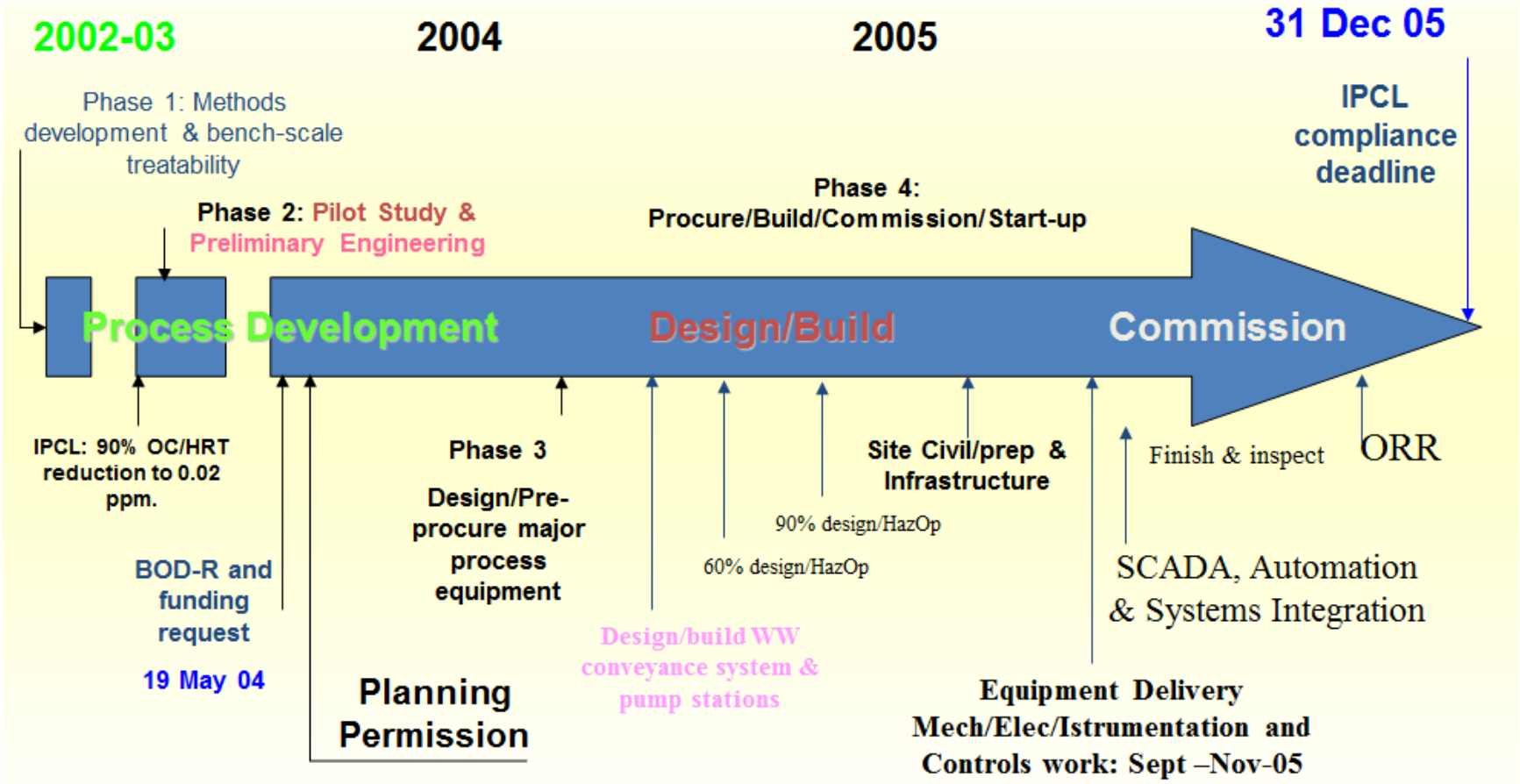

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Final Words on Project Delivery

Key Recommendations:

1. **Partners:** only partner with a highly experienced consultant who has either ***done*** this or something very similar before. ***Done*** means ***built and verified/proven*** full-scale performance. Its all about people, trust and relationships. You want a wastewater subject matter expert (SME) with at least 50,000 hours of experience.
2. **Short Cuts:** don't take short cuts. Do the hard work of performing the alternatives analysis, visiting other benchmark sites, and conducting bench and pilot scale treatability testing. Start by developing a solid, engineering Basis for Design and document it carefully.
3. **Risk Mitigation**: identify project risks up-front and have a plan to mitigate those risks. This also means doing a system Hazards and Operability Assessment (HAZOP) and Operational Readiness Review (ORR).
4. **Vendor Engineered Systems:** stay away from testimonials, magic bullets, snake oil, and vendor engineered solutions and systems. Don't let an amateur pound square pegs into round holes at your site. ***You will likely need a very custom and professionally engineered system and anything less is a prescription for failure!***
5. **Value Engineering**: don't be beaten back by the procurement team. Value engineering can save or destroy a project. Procurement and accountants are not known for their engineering acumen. Know the critical components and stand your ground.

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Questions

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