

THE Manufacturing Project

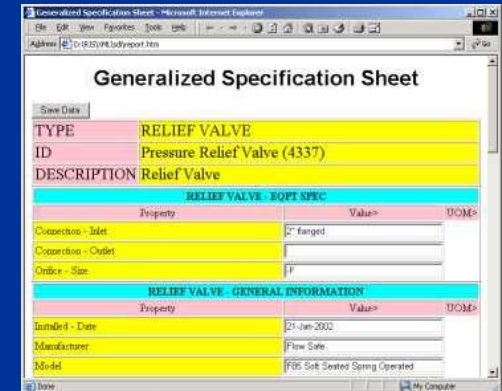
The analytical toolkit for nanopharmaceutical manufacturing



Fully adapted tools

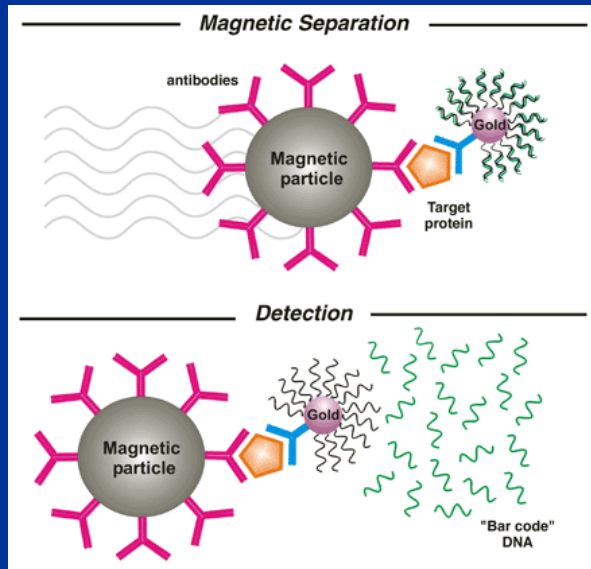
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	3.3V	●	●	●	●	●
	2.5V	●	●	●	●	●
	1.8	●	●	●	●	●
Power CMOS	40V	●	●	●	●	●
	20V	●	●	●	●	●
BCD	12V	●	●	●	●	●
	8V	●	●	●	●	●
BiCMOS	SI 30GHz	●	●	●	●	●
	SiGe 65GHz	●	●	●	●	●
	SiGe 80GHz	●	●	●	●	●
	SiGe 150GHz	●	●	●	●	●
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	VPHP 17GHz	●	●	●	●	●

Roadmap for needs



Specification sheet

Nanopharmaceuticals



HOW BIG?
HOW PURE?
WHAT'S THE SURFACE?
HOW REPRODUCIBLE?

- Very innovative and new production techniques
- Multi-component mixtures
- Conventional analytics for each component often do not work in formulations

Issue to be Solved

- Purity; population distribution (minor components)
- Stability (shelf life)
- Batch-to-batch consistency
- Faster, cheaper leading to on-line measurements
- Validation of methods/reference materials



Need many tools – not a magic bullet
Need to provide information about tools
Need to validate tools
Need to create new tools

Project Description

- This project is divided into three (3) efforts. The aim of these efforts is to enhance decision-making by both the FDA and industry who seek to develop nanopharmaceuticals (NP) for improving patient outcomes. The focus is on creating an analytical toolkit, reflected in a NP specification sheet, with validated methods and widespread acceptance. Provisions for roadmapping needs, refining existing tools and adaptation of other types of methods to this problem area are included

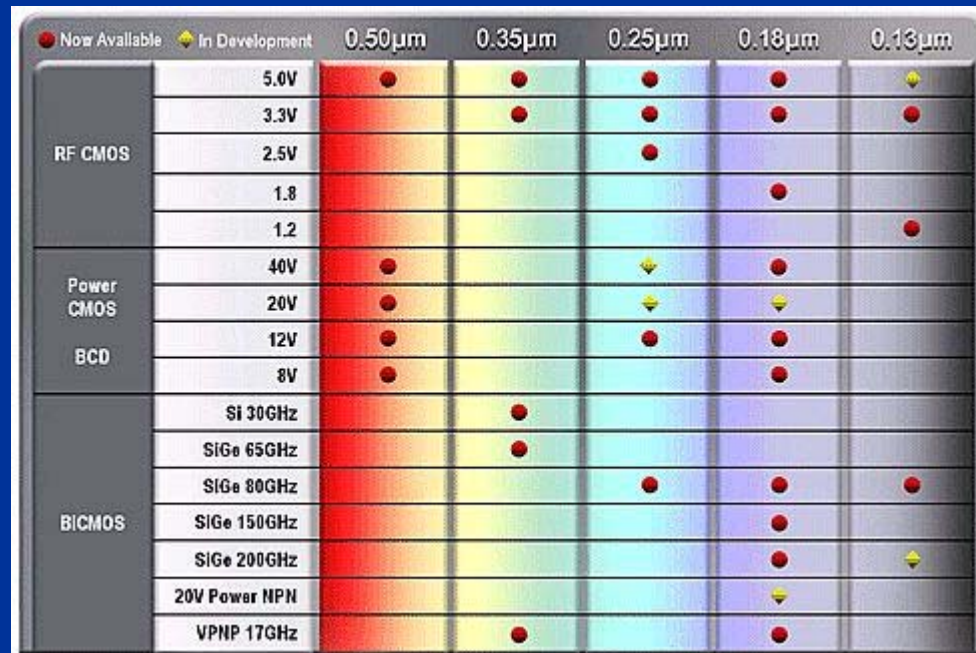
Bird's eye view:

- Effort 1: **PLAN**
 - The roadmap for analytical needs in nanopharmaceutical manufacturing
- Effort 2: The “spec sheet” for nanopharmaceuticals
- Effort 2A: **ADAPT**
 - Adapting related tools to the needs of nanopharmaceutical manufacturing & FDA
 - A) High-throughput B) On-line C) In-vivo
- Effort 2B: **VALIDATE**
 - Validating widely accepted methods so that accuracy and range of applicability is known

Effort 1 Description

- Effort 1: Constructing a 10 year roadmap for developing on-line/high throughput instrumentation for analytical nanoparticle processes. Issues addressed include:
 - Batch to batch consistency
 - Uniformity
 - Purity
 - Stability
 - Basic material properties (size, shape, surface, etc.)
 - Note that emphasis will be on solution-based systems
- Prioritize tools requirements; identify ‘universal’ needs
- Facilitate the development and identification of appropriate reference standards for analytical processes

Roadmapping: What do we mean?



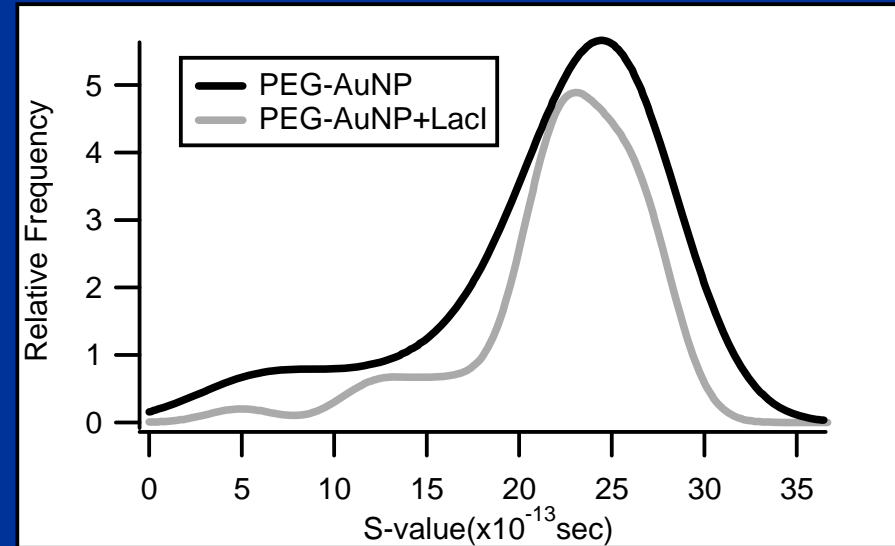
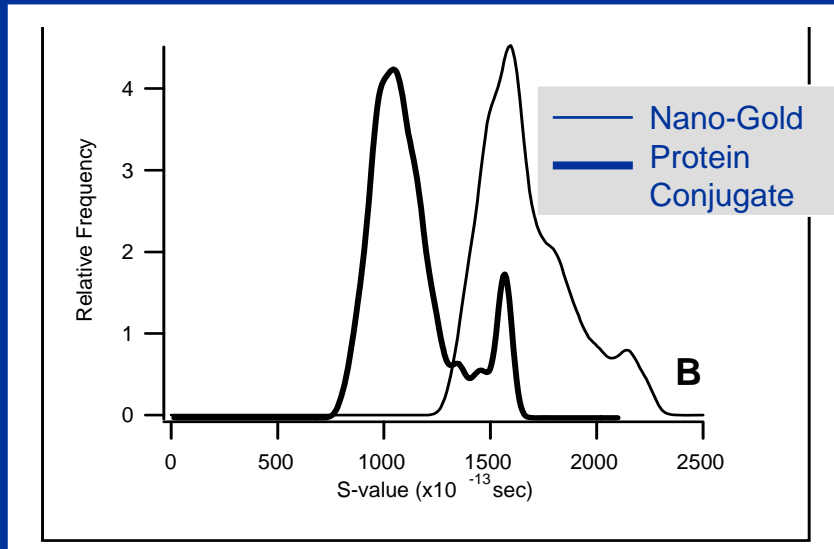
<http://www.microcontroller.com>

- Focused working group to develop specific timeline for needs
- Categories might be size, surface features, purity etc ...
- Will be a living document – annual updates
- Input into planning for instrument manufacturers

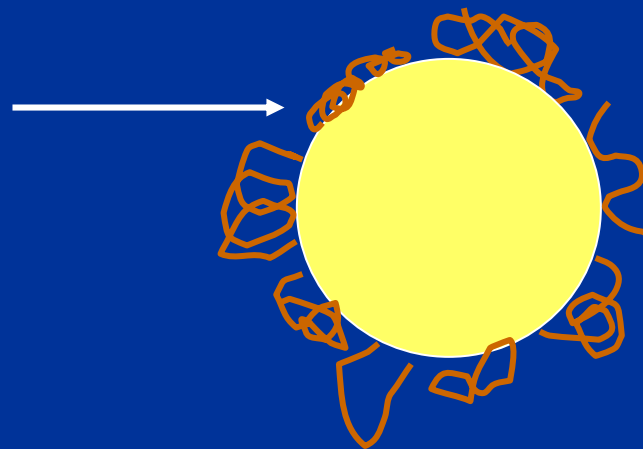
Effort 2 Description

- Effort 2: Adaptation of existing methods for nanoparticle analysis.
- Pursue efforts to make off-line instruments more high-throughput
 - Not all current methods for small molecules may be adaptable to nano characterization
 - Tools might include chromatography, differential mobility analysis, analytical centrifugation, SAXS
 - Multicomponent/complex/combo particles may contain different analytical challenges
 - Density of ligand binding, ligand ratios, order of binding
 - Identify additional techniques that can be adapted for in-line or high-throughput analysis
 - High throughput SEM already on market
- Pursue efforts for in-vivo nanoparticle characterization
 - PK studies/pre-clinical
 - As formulated products

Adaptation: Analytical Centrifugation



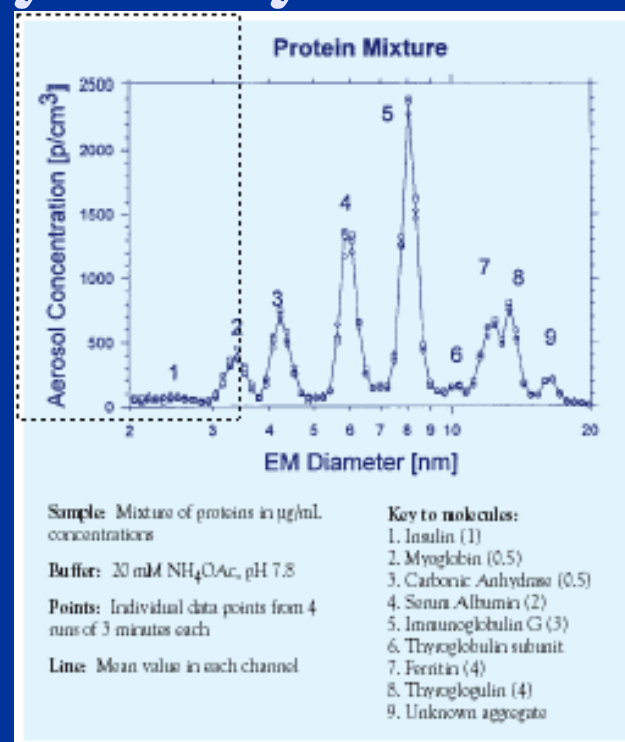
Non-specifically
Adsorbed Proteins



Effort 2 Description Cnt.

- Effort 2: Adaptation of existing methods for nanoparticle analysis.
- Develop on-line instruments for nano-characterization
 - Develop specific protocols for batch to batch consistency
 - QC for product/manufacturing development for pre-clinical and early clinical batches
 - QC for production lots; control and batch to batch consistency would also benefit
 - In accordance with regulatory initiatives (PAT, QbD) and regulations (GMP) with in line
 - To determine what level of characterization is required when changes occur
 - Manufacturing procedures, suppliers, excipient changes, location changes

Differential Mobility Analysis



- 1) Analyte is nebulized into ultrafine droplets via electrospray
- 2) Droplets evaporate and lose charge in an ionized atmosphere:
 - Both neutral and singly charged species
- 3) Charged species go through the mobility analyzer (DMA)
- 4) They are counted by a condensation particle counter (CPC)

Effort 3 Description

- Effort 3: Validation of instrumentation prioritized in the roadmap (effort 1)
- Tools that are widely accepted
 - Tiered approaches/decision trees/flow charts for specific characterization
 - 5 tools for phase I/ 5 tools for phase II
 - Characterization in the as-formulated media
 - Example: particles in solution (DLS + EM)

Expected Results (applicability)

- **Output**
 - **Commercially available tools**
 - **Spec sheet for developer**
 - **Decision tree/guidance**
 - **New tools development capable of meeting criteria**
- **How the outputs will address the issue**
 - **The characterization criteria will be specifically covered by methods. We need a broader group to completely develop this.**

The output: a 'spec sheet'

Nanopharmaceutical

Composition

Core (1,2,3 ...)

Surface

Purity

Size

Hydrodynamic

Grain size

Surface area

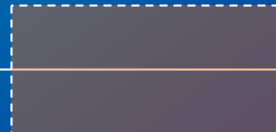
Surface charge

Click to methods/wiki link

Click to tutorial

Click to guidance

Click to decision tree



Cost effectiveness

- **How widely useful are the outputs?**
 - Go-no-go sponsor decisions on specific designs
 - Go-no-go decisions on manufacturing batches
 - Input to FDA guidance development
- **What benefit value of the project?**
 - Direct effect on cost of goods sold
 - Reduction of development time

Critical Study Design Elements and Data Output Elements and

- **Design**

- Well characterized reference material libraries for analytical methods development
- Harmonized methods – agreed to by the community – at least as a starting point
- Provisions for data sharing and round robin type activities

- **Output**

- **Material spec sheet**
- **Description of method and its limitations**

Timeline/ Level of Effort

- **Timeline** (roughly: initiation to completion)
 - Effort 1 (roadmap)
 - Prioritize tools requirements; identify ‘universal’ needs
 - 12 months-24 months
 - Effort 2 (Adaptation of existing methods from other areas)
 - 3 YEARS per method
 - Effort 3 (validation)
 - 5 methods in phase 1 and 5 methods in phase 2
 - 18-24 months/5 methods
- **Level of effort** (low, medium, high)
 - High

Cost effectiveness

- **How widely useful are the outputs?**
 - **Very generalizable project**
 - **Drugs, devices, biologics, combination products**
 - **Will benefit complete production process from pre-clinical to launch**

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The NanoPharma Toolkit

Year

Year

Year

1: Roadmap



2A: Adapt



2B: Validate



Efforts are linked tightly – that is why they are in same project
Can be scaled based on funding and interest
True partnerships with industry and integration with others

Summary

- Critical and focused need for manufacturing
- Analytical toolkit fits PPP criteria
 - Not so pie in the sky
 - Needs collaboration from industry-govt-academia
 - Provides tangible outcomes that have value
 - No other clear way to do this
- It's doable, interesting and it's very, very important

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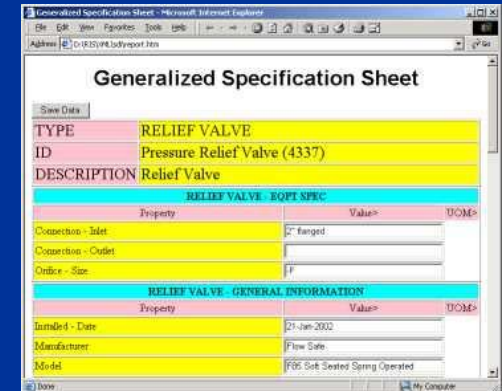
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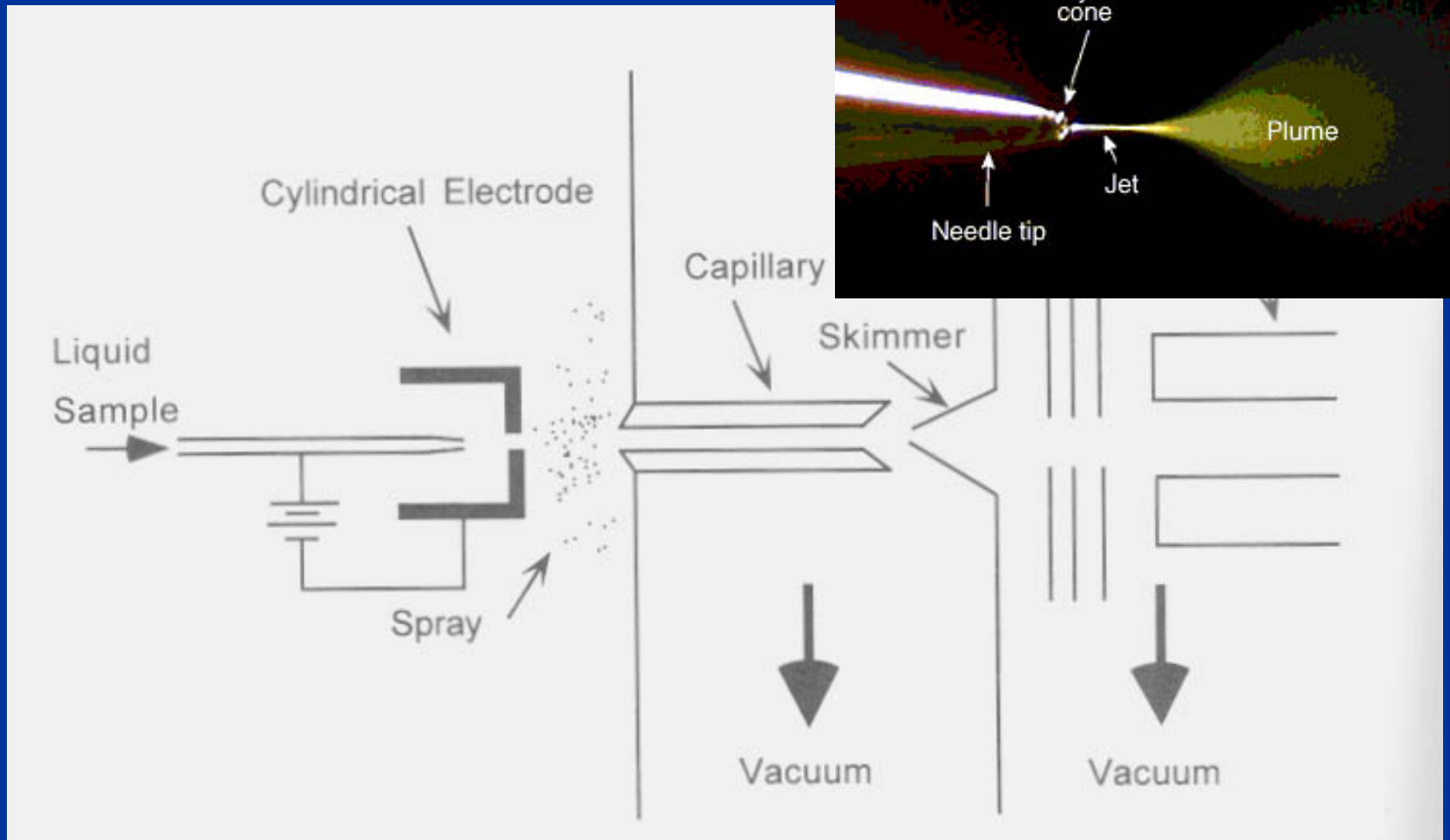
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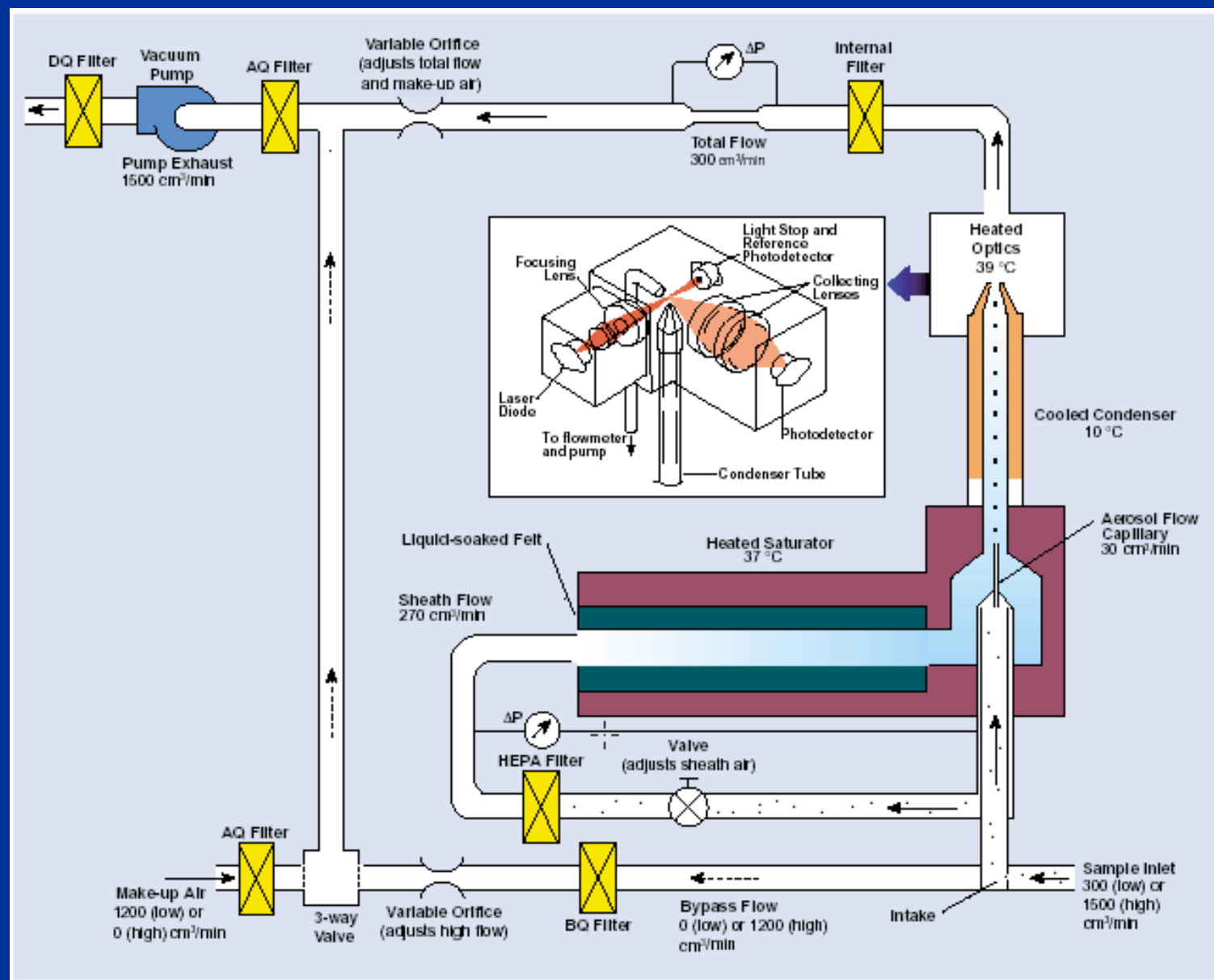


Specification sheet

Electrospray



Condensation particle counter



DMA Example

