TECHNICAL BRIEF

Guidelines for Scale-Up with CUNO Zeta Plus® Depth Filter Products

A Review of Scale-up Parameters for Bioprocessing, Biological & Pharmaceutical Manufacturers

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Introduction

Zeta Plus filtration media are widely accepted as the depth filters that meet more criteria of excellence than any comparable product. Their extensive use is a reflection of their versatility and consistent filtration performance. *Hundreds of CUNO Zeta Plus process systems are in operation worldwide, providing reliable, cost-effective filtration performance at pharmaceutical, biotechnology, vaccine, veterinary, diagnostic, and other process facilities.*

Scale-Up

Process development engineers are responsible for developing scale-up strategies for efficient and cost-effective manufacture of pharmaceutical, biological, and bioprocess-derived products at bench scale, at pilot plant scale, and at manufacturing scale.

Scale-up:

Design process in which the data of an experimental scale operation is used for the design of a large unit, usually of commercial scale.

(From McGraw Hill Dictionary of Scientific & Technical Terms)

A Range of Zeta Plus Products for Lab-Scale, Pilot-Scale, and Manufacturing-Scale Operations

CUNO offers a range of completely encapsulated Zeta Plus disposable capsules, the Bio-Cap™ Series, for laboratory-scale filtration, for process development scale-up work, and for small lot production runs. (Request product literature LITZPBC1.0197). BioCap disposable Zeta Plus capsules are ideal for scaleup evaluations as working process volumes move from laboratory or bench-scale through pilot plant scale to full manufacturing scale operations. Numerous pharmaceutical and biotechnology companies worldwide have scaled-up reliably and predictably to high area 12-inch and 16-inch diameter cartridge systems using small surface area Zeta Plus benchtop development kits which included BioCap disposable assemblies. For instance, studies by Singhvi *et al.*[*] have confirmed that small scale Zeta Plus data can accurately predict large-scale Zeta Plus filter system requirements.

Guidelines for Scale-Up

This document is intended to provide guidelines for scale-up using Zeta Plus filtration products. If additional information is required, please contact CUNO Incorporated, Scientific Applications Support Services (SASS), 400 Research Parkway, Meriden, CT 06450, Telephone (203) 237-5541.

Guidelines for Scale-Up with Zeta Plus

CHOICE OF BIOCAP® FILTERS

A series of one or two small-scale filters (bench-scale and/or pilot-scale) is often studied when attempting to define production-scale filtration requirements. Capsule data should first be generated using the Zeta Plus Biocap System, Biocap 30, and/or Biocap 1000/2000. In critical applications, both Biocap 30 and Biocap 1000/2000 data should be generated. After collection of the data, production-scale filtration area requirements can then be safely estimated.

* Singhvi, R., Schorr, C., O'Hara, C., Xie, L., and Wang, D.I.C. (1996). "Clarification of Animal Cell Culture Process Fluids Using Depth Micro filtration," *BioPharm*, **9** (4), 35 - 41.

MEASUREMENT ACCURACY

Volumes and flow rates should be accurately measured. (Do not assume that positive displacement pumps or calibrated flow meters are performing properly, especially when processing debris-laden suspensions.) Effective filtration areas rather than nominal filtration areas should be used in all throughput and scale-up calculations. For the BioCap series of disposable Zeta Plus capsules, use the following effective filtration areas for scale-up calculations:

BioCap 30 Capsule	24 cm^2
BioCap 1000 Capsule	650 cm^2
BioCap 2000 Capsule	1300 cm^2

REPRODUCIBILITY

Filtration processes may not be highly reproducible, especially when biological fluids are involved. Therefore, all important experiments should be repeated, usually in triplicate. Filter performance is also affected by upstream processing variables. Therefore, a representative range of incoming samples should be tested.

FLUX SELECTION & THROUGHPUT OPTIMIZATION

Depth filtration is scaled up using a fixed value of filter flux (fluid flow rate per unit of effective filtration area, in milliliters per minute per cm^2). Once identified, this flux will be held constant - irrespective of operating scale. Determination of maximum reasonable flux, typically 0.2 - 1.0 ml/min/cm^2 (120 - 600 LMH or 0.05 - 0.25 gpm/ft^2), is based upon the filter's ability to deliver filtrates of minimum acceptable quality. The volume of fluid filtered per unit of filtration area, or throughput (milliliters per cm^2, liters per m^2, or gallons per ft^2), affects operational cost and overall process economy. Reductions in flux relative to maximum achievable values usually give rise to increased throughput. Thus, flux and throughput should be studied at the bench-scale until reasonable filtrate throughputs are produced. Optimized throughput is then used to project large-scale Zeta Plus filtration area requirements.

PRESSURE DROP SELECTION

A batch filtration operation is typically terminated at a predetermined pressure drop such as one-half of the filter's maximum rated pressure drop (20 psid for Zeta Plus filter media).

PRODUCTION-SCALE FILTRATION AREA DETERMINATION (BATCH PROCESSING TIME FLEXIBLE)

For a batch of known volume, choice of throughput **T** (ml/cm^2) and flux **f** (ml/min/cm^2) predetermines batch processing time **P** (min):

$$P = T / f$$

When an acceptable **P** is established, constant filter throughput **T** is then used as the scaling factor for determination of production-scale filtration area. During scale-up, the following relationship usually holds:

$$T_{bench} = T_{pilot} = T_{production}$$

Since throughput **T** equals the ratio of batch volume **V** (ml) to filtration area **A** (cm^2) at each scale (T = V/A), calculation of production-scale filtration area is based upon solving either of the following equations for $\mathbf{A_{production}}$:

$$[V / A]_{bench} = [V / A]_{production}$$

or

$$[V / A]_{pilot} = [V / A]_{production}$$

PRODUCTION-SCALE FILTRATION AREA DETERMINATION (BATCH PROCESSING TIME CRITICAL)

In applications where further minimization of batch processing time is important, selection of filtration area $\mathbf{A}_{\mathbf{production}}$ is based upon one's ability to process a batch of volume **V** at flux **f** in batch processing time $\mathbf{P}_{\mathbf{max,\ production}}$:

$$P_{max,\ production} = [\ 1 / f\ ]\ [\ V / A\ ]_{production}$$

This equation is solved for $\mathbf{A}_{\mathbf{production}}$, and $\mathbf{P}_{\mathbf{max}}$ is used as a constant scaling factor throughout experimentation:

$$P_{max,\ bench} = P_{max,\ pilot} = P_{max,\ production}$$

The following relationship should hold during scale-up, and it is used to select batch volumes to be studied at each scale:

$$[\ 1 / f\ ]\ [\ V / A\ ]_{bench} = P_{max,\ production}$$

$$[\ 1 / f\ ]\ [\ V / A\ ]_{pilot} = P_{max,\ production}$$

NON-CONSTANT SCALING FACTORS

In those cases where throughputs or batch processing times unexpectedly differ with scale, the most conservative value of throughput (lowest) or the most conservative value of batch processing time (highest) should be used when estimating $\mathbf{A}_{\mathbf{production}}$. When large differences between $\mathbf{T}_{\mathbf{bench}}$ and $\mathbf{T}_{\mathbf{pilot}}$ or between $\mathbf{P}_{\mathbf{bench}}$ and $\mathbf{P}_{\mathbf{pilot}}$ have been observed, the details of the experiments should be carefully scrutinized to determine the source of the unexpected scaling behavior. Typical problems include systems which naturally exhibit high degrees of non-reproducible filterability, poor operational technique, etc. Only robust, reproducible filtration solutions should be incorporated into actual pilot or manufacturing scale operations. When uncertain as to how to proceed, contact an applications specialist at CUNO, Inc., Scientific Applications Support Services in Meriden, Connecticut, at 203-237-5541.

ENGINEERING SAFETY FACTOR

Initial estimation of $\mathbf{A}_{\mathbf{production}}$, the production-scale filtration area, should be made using conservative, non-inflated numbers. Increasing the calculated filtration area by an engineering safety factor of 20 to 50% should be considered as the final calculation step. Choice of engineering safety factor is in part governed by real world constraints such as standard housing sizes, consistency of feed solution and cartridge area options.

EXAMPLE OF SCALE-UP

Using Zeta Plus 60LA filter media, select a cartridge filter and housing system capable of filtering 1,400 liters of suspension in approximately 2 hours.

Process Variable	Units	BioCap 30	BioCap 1000	Calculated Production Requirement	Recommended System	Safety Factor
Area	ft^2	0.026	0.70	26	32.8	26%
Flux	LPM/ft^2	0.46	0.46	0.46	0.46	—
Throughput	liters/ft2	57	54	54	43	—
Volume	liters	1.5	38	1,400	1,400	—
Time	minutes	120	118	118	93	—

1. BioCap 30 Disposable Capsule - Initial Evaluation

   a. Throughput was optimized up to 57 liters/ft^2 by reducing the flux from a maximum value of 1.0 ml/cm^2/min to 0.5ml/cm^2/min (0.46 LPM/ft^2).

   b. Constant flux was studied thereafter.

   c. 1.7 liters of suspension was processed in 120 minutes to a final pressure drop of 15 psid.

2. BioCap 1000 Disposable Capsule Study - Confirmation of BioCap 30 Process Data

   a. 48.5 liters of suspension was processed in 115 minutes to a final pressure drop of 15 psid.

   b. A throughput 5% less than the BioCap 30 result was achieved at this scale. This slight difference was not considered significant.

3. Calculation of Production-Scale Requirement

   a. A throughput of 56 liters/ft^2 was conservatively projected for the production scale.

   b. A filtration area requirement at scale was calculated to be 25 square feet.

4. System Sizing and Recommendation

   a. Selection of a two-high, 12-inch diameter Zeta Plus sanitary design housing (model 12ZPC2 or 12ZPB2) containing two (2) 12-inch diameter 60LA filter cartridges (16 cells per cartridge) provides 32.8 ft^2 of filter area, 26% more than the calculated requirement.

   b. Thus, the recommended system would operate at a reduced throughput and would therefore process the 1,400 liter batch in less than 120 minutes.

CUNO SCIENTIFIC APPLICATIONS SUPPORT SERVICES (SASS)

The cornerstone of CUNO's philosophy is service to customers, not only in product quality and prompt delivery, but also in applications and validation support and in the sharing of scientific information.

CUNO is ready to support your on-site testing needs. CUNO's Scientific Applications Support Services (SASS) group works closely with pharmaceutical and biological manufacturers to solve difficult separation problems and to recommend the most efficient, economical filter systems. SASS specialists are skilled in performing scale-up evaluations with actual process fluids and in relating test results to full manufacturing-scale operations.

CUNO's SASS group is comprised of highly qualified scientists and engineers, supported by state-of-the-art laboratory facilities. Located worldwide, SASS teams provide prompt on-site response to your filtration needs.

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