REGISTRATION OF ALTERNATE FILTERS DURING RAW MATERIAL SHORTAGES

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CHALLENGES IN SOURCING RAW MATERIALS DUE TO THE COVID PANDEMIC

- Supply of critical filters and single use components has been strained by the development and manufacturing of COVID-19 vaccines and monoclonal antibodies.
- Under the Defense Protection Act, COVID-19 related therapeutic developers can place rated orders.
- Amgen has experienced delays in delivery confirmation as raw materials have been diverted from non-COVID related products to raw material purchase orders associated with COVID therapies.
- Amgen along with other companies have had to mitigate these supply challenges.

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EXAMPLES OF MITIGATION STRATEGIES

- **Reduce filter usage**
  - Increase the load amount within the characterized range (minor change)
  - FDA feedback: May be acceptable to report in annual report with appropriate characterization data
- **Register alternate filters**
  - Major, moderate, or minor change depends on the proposed alternate filter characteristic (how closely matched to current) and type of filter/impact on product quality, safety and efficacy
  - Examples:
    - Minor: Non-product contacting filter used to filter media/buffer or product contacting depth filter
    - Major: Alternate pre-filter and virus filter for viral filtration step or drug product sterilizing-grade filter

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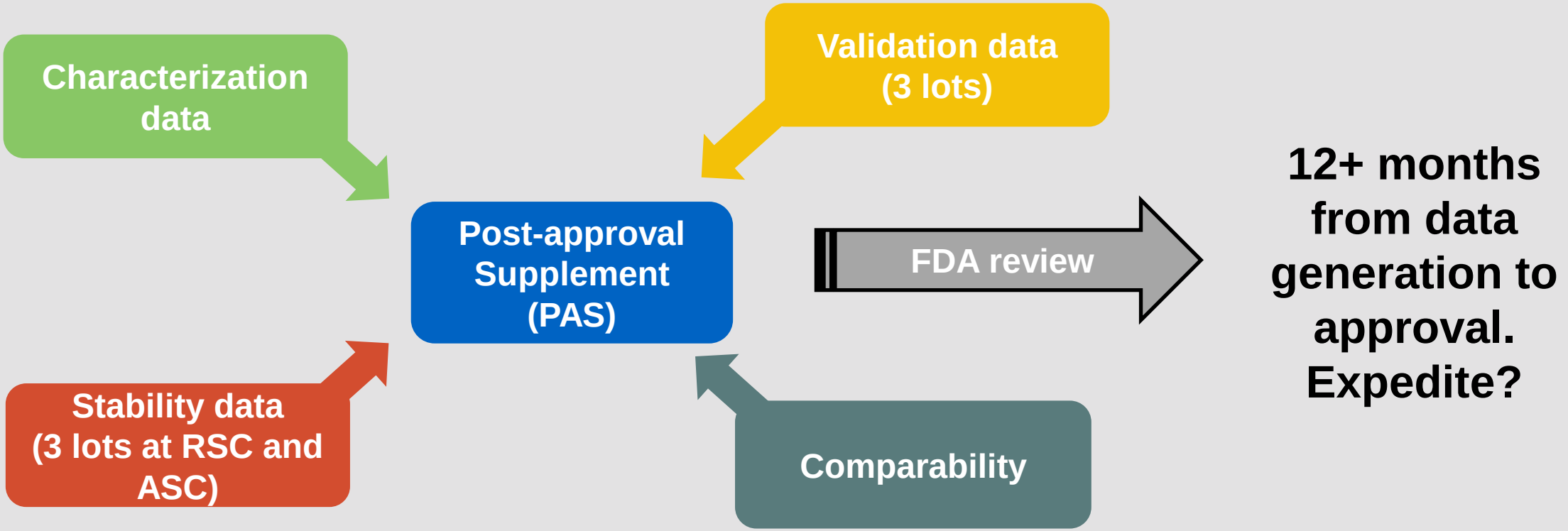
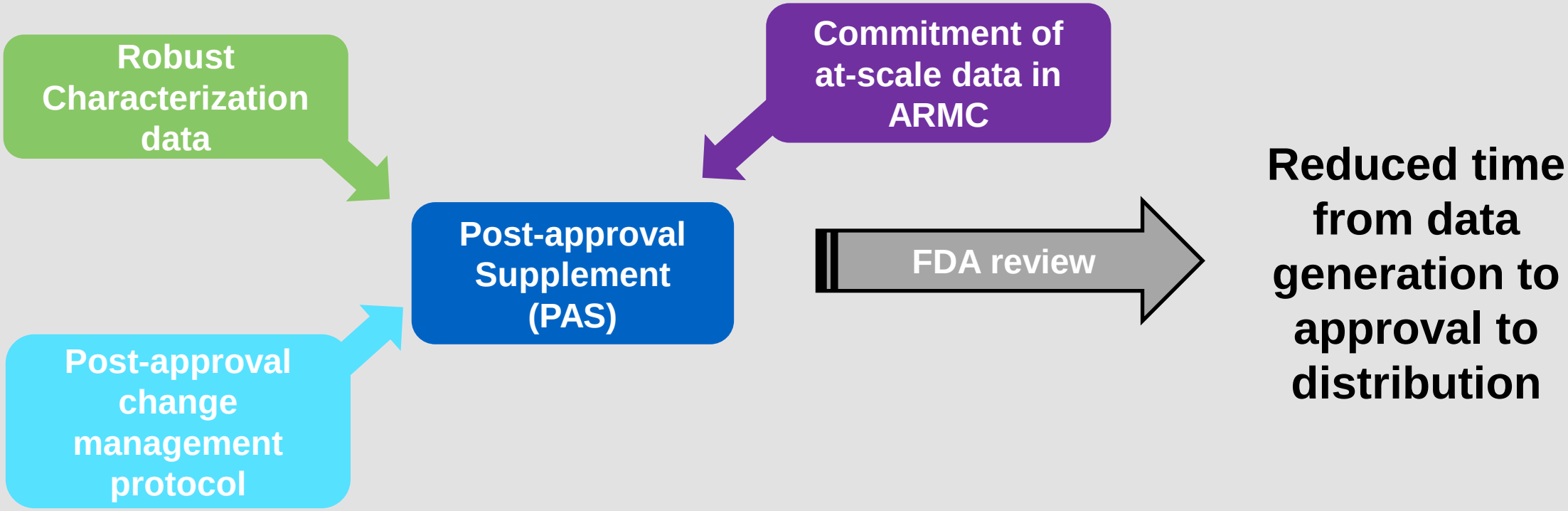
TYPICAL PATHWAY FOR FDA FILING ALTERNATE FILTERS WITH MAJOR POTENTIAL IMPACT TO PQ AND SAFETY

- Viral filtration filters (DS)
- Sterilizing-grade filters (DP)



PROPOSED EXPEDITED FDA FILING PATHWAY

- Viral filtration filters (DS)
- Sterilizing filters (DP)



FDA FEEDBACK AND KEY MESSAGES

- **FDA feedback: Well-written, clear, actionable, and straightforward with thoughtful considerations and comments**
- **Key messages:**
  - Robust characterization package should demonstrate interchangeability
  - At-scale data required to confirm no impact to IPCs and specifications
  - Consider updating old methods with current ones during product testing
  - Consider placing the 1st post-change DP lot on stability as an ad hoc lot
  - Consider long-term leachable study and toxicology evaluation if increase in risk to patient safety from toxicological perspective

CONSIDERATIONS FOR CHOOSING ALTERNATE FILTERS

- **Filter media, pore size, material of construction**
- **Viral filtration**

	Pre-filter		Virus Filter	
	Filter media		Filter Media	Nominal Pore Size
Approved Filter	Cellulose, inorganic filter aid		Polyethersulfone	20 nM
Proposed Alternate	Polyethersulfone		Polyethersulfone	20 nM

- **DP sterilizing-grade filter**

	Membrane material	Pore Size	Microbial removal rating	Sterilization method	Filtration Time	Filtration temp	Max filtration pressure
Approved Filter	PVDF	0.22 um	>10^7 CFU/cm^2 B. Dimunutae	Autoclave or ɣ-irradiatable	≤ 72 hours	2°C to 30°C	15 psig
Proposed Alternate	PVDF	0.22 um	>10^7 CFU/cm^2 B. Dimunutae	Autoclave or ɣ-irradiatable	≤ 72 hours	2°C to 30°C	15 psig

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PROPOSED CHARACTERIZATION DATA TO SUPPORT ALTERNATE FILTERS

Characterization Study	Study Description
Filterability	Scale-down study using alternate filters to • Confirm no practical change in filterability of the product. • Confirm the appropriate filter membrane area needed
Product quality impact from filtration and filter contact	• Scale-down study using alternate filter to demonstrate no product quality impact due to filtration • For DP sterilizing-grade filter, contact for the maximum validated filtration time
Viral Clearance (VF only)	Small-scale study to demonstrate effective virus removal. Overall viral clearance will be recalculated and excess clearance to be confirmed.
Extractables	Vendor data, operational details, and downstream clearance of extractables to be performed via risk assessment

Characterization studies to confirm no product impact as the result of proposed use of alternate filters

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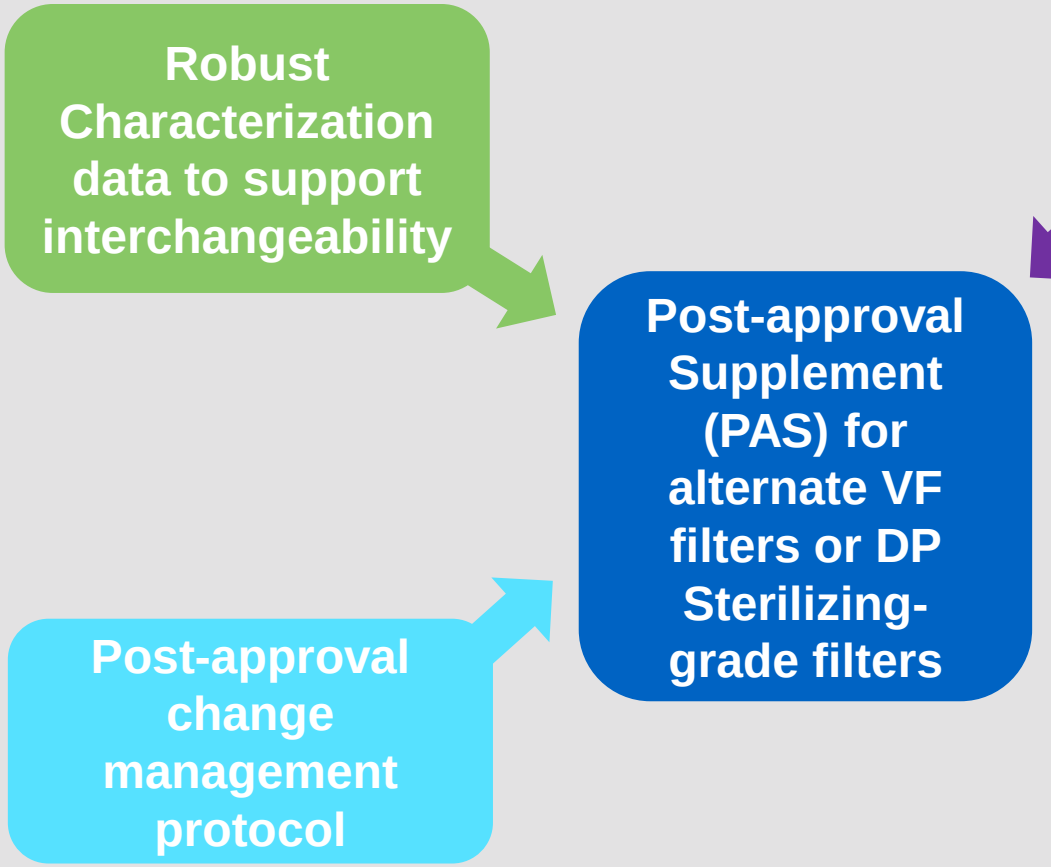
ADDITIONAL CHARACTERIZATION DATA TO SUPPORT ALTERNATE DP STERILIZING-GRADE FILTER

Characterization Study	Study Description
Surfactant/protein binding to filter	Small-scale study to evaluate surfactant and protein adsorption on the alternate filters and to assess any changes to the filter flushing procedure at the start of filling
Filter rinse volume for post-use FIT using water as wetting agent	At-scale characterization study to determine filter rinse volume for effective removal of drug product from filter
Filter integrity tests	At-scale characterization study to confirm filter integrity testing process and acceptance criteria for proposed alternate filters
Microbial retention	Scale-down study using alternate filter to mimic worst-case processing condition for filters
Filter membrane compatibility	Scale-down study using the alternate filter to be subjected to commercial representative filtration process conditions
Filter extractables	Filter extractable study for both sterilization methods, autoclave and gamma irradiation separate

PROPOSED EXPEDITED FDA FILING PATHWAY



- Upon approval, can distribute post-change material
- Changes can be initiated earlier into commercial manufacturing

FDA feedback: Amgen proposed submission strategy may be acceptable, however….

ADDITIONAL CONSIDERATIONS FOR BOTH ALTERNATE VF AND DP STERILIZING-GRADE FILTERS

- **May be feasible to perform generic/modular studies that can apply to multiple products, taking into consideration the similarity of process parameters among different products**
  - FDA recommends virus filter validation stud(ies) run under worst-case conditions for each product or each generic modular study
  - If modular studies are conducted, provide a comparison of parameters used in scale-down model to the operating parameters used for the product
  - For DP sterilizing filters, max filtration times and other performance parameters should be consistent with microbial retention study results
  - Max filtration time may not be solely supported by existing media fill studies
- **Acceptability of the proposed product characterization may depend on the specific product.**
  - If analytical methods and IPCS controls for older products have not been updated to reflect current methods
- **Commit to place the first post-change drug product lot on stability as ad hoc lot, in addition to current annual stability commitments. If DS is frozen, no need for ad hoc DS lot**
- **Long-term leachable study and toxicology evaluation, If changes in extractables that increase the risk of patient safety from the toxicology perspective**

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FOR DP STERILIZING-GRADE FILTERS, ALSO CONSIDER….

- **Product-specific microbial retention validation data required**
- **Media fill validation studies should support any significant changes to aseptic operations associated with the use of an alternate filter**

ANNUAL REPORTABLE MITIGATION STRATEGIES

AMGEN PROPOSED SEVERAL EXAMPLES OF ANNUAL REPORTING FOR SUS OR FILTER CHANGES

- **Changing filter load ranges within characterized ranges**
- **Final DS filter and other product contacting filter changes**
  - Interchangeable based on filter capacity and performance, hold-up volume, filter extractables
  - Established bioburden limits prior to any filtration step should remain the same
- **DP bioburden filter changes**
  - Characterization studies performed prior to implementation
  - Established bioburden limits prior to bioburden reduction filter and prior to sterilizing filter should remain the same
- **Purification process pool hold bags**
  - At-scale data confirming established microbial control criteria during pool hold time can be reported in the ARMC
  - To ensure continued microbial control, recommend that acceptance criteria for alternate bags include sterilization method and acceptance criteria (eg gamma sterilization)
  - Impact of any change in the configuration of an inline filter should be considered with respect to microbial control

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THANK YOU!

ALTERNATE UF/DF FILTER USED DURING DRUG SUBSTANCE MANUFACTURING

ULTRAFILTRATION/DIAFILTRATION

- **UF/DF step is designed to exchange the viral filtered pool into the formulation buffer and concentrate to the target concentration for DS**
- **UF/DF filter retains the product protein and allows smaller buffer components to pass through**

CONSIDERATIONS FOR CHOOSING AN ALTERNATE UF/DF FILTER

- **Filter media, molecular weight cut off**
- **Technical assessment of physical characteristics to show current and proposed alternate are comparable**
  - No expected impact on product quality

	Virus Filter	
	Filter Media	**MW cut off**
Approved Filter	Regenerated cellulose	30 kDa
Proposed Alternate	Regenerated cellulose	30 kDa

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PROPOSED SUBMISSION PACKAGE FOR ALTERNATE UF/DF FILTERS

- **File post-approval change management protocol via post-approval supplement (PAS)**
- **Provide characterization data package to support change**
- **Commit to provide at-scale data in subsequent Annual Report of Minor Changes to demonstrate no impact to IPC or product specification tests**
- **Upon PAS approval, Amgen will consider the proposed changes as approved**
  - Changes can be initiated into commercial manufacturing

FDA feedback: Amgen proposed submission strategy may be acceptable.

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PROPOSED CHARACTERIZATION DATA TO SUPPORT ALTERNATE UF/DF FILTERS

Characterization Study	Study Description
Filterability	Scale-down study using alternate filter to confirm no practical change in sizing, loading, osmolality, transmembrane pressure as compared to original UF/DF filter
Product quality impact from filtration and filter contact	Scale-down study using the alternate filter to demonstrate no product quality impact to filtration and contact with alternate filters
Cleaning and Lifetime	Small-scale study to demonstrate alternate filter will support cleaning and reuse up to an established maximum. Characterization of cycles will assess normalized water permeability and protein carryover.
Extractables	Vendor data, operational details, and downstream clearance of extractables to be performed via risk assessment

Characterization studies to ensure UF/DF step meets the desired expectations of buffer exchange and concentration of the protein and no product impact throughout the life of the study

ADDITIONAL CONSIDERATIONS PRESENTED BY FDA

- **Confirmatory cleaning study at scale should include microbial tests for bioburden and endotoxin**
  - Criteria for use of UF/DF membrane after storage and prior to sanitization should include criteria for bioburden and endotoxin
- **Commit to place the first post-change drug product lot on stability as ad hoc lot, in addition to current annual stability commitments. If DS is frozen, no need to put post-change lot on stability**
- **If there are changes in extractables that increase the risk of patient safety from the toxicology perspective, a long-term leachable study and toxicology evaluation will be needed.**