PDA Research

PDA Availability of Single-Use-System Components and its Potential Impact on Product Supply Survey Results

November 2021

PDA®
Parenteral Drug Association
Connecting People, Science and Regulation®

PDA SURVEY:

Availability of Single-Use-System Components and its Potential Impact on Product Supply Survey Results

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Introduction

This survey was conducted to gather information on supply chain challenges related to the availability of Single-Use-System components as a result of the pandemic.

The survey was focused on companies that have sterile product manufacturing operations in the European Union, United Kingdom, or United States.

For companies that have operations outside of the European Union, United Kingdom, or United States that wanted to take part in the survey, there was an option to select “Other Countries” in the survey in regard to where the manufacturing operations are located that are impacted.

For this survey Single-Use-Systems were defined as an engineered process equipment solution, most commonly assembled from components made using polymeric materials, which together create a system or unit operation designed for one time or one campaign use (e.g., a single use sterile filling train composed of a set of sterile disposable bags, tubing sets, connectors, and filling needles; a single use bioreactor composed of disposable sterile tank liner bags, tubing sets and connectors, etc.).

This was a blinded survey. The Survey opened on 4 Nov 2021 and closed on 15 Nov 2021.

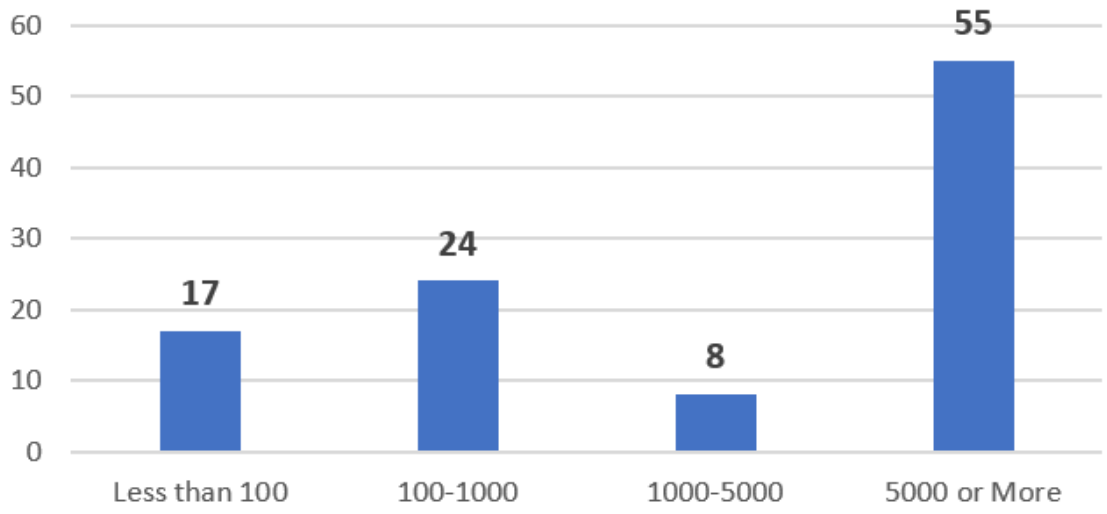
Question 1:

What is the size of your company (number of employees)?

- ○ Less than 100
- ○ 100 - 1,000
- ○ 1,000 - 5,000
- ○ 5,000 or more

Results:

104 Respondents



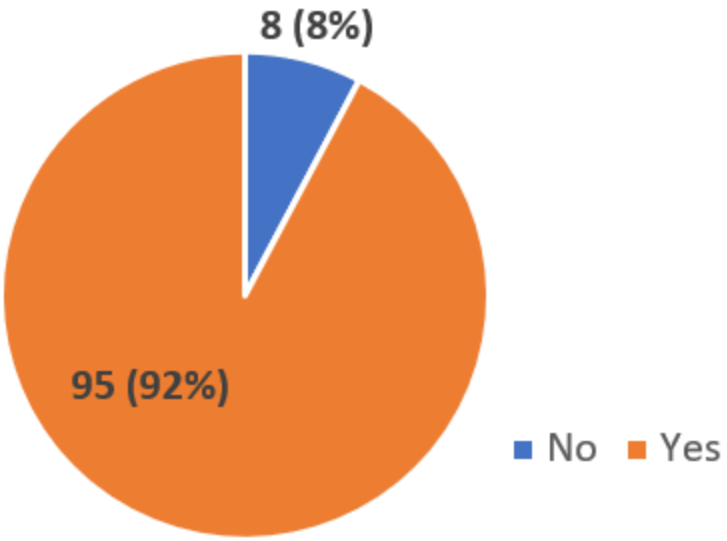
Question 2:

Does your company use Single-Use-System components in its manufacturing of aseptically produced medicines?

- ○ Yes
- ○ No (If "No" End Survey)

Results:

103 Respondents



Question 3:

What types of Single-Use-System components does your company use as part of the manufacturing process?

Results:

68 Respondents

We supply aseptic transfer products (---------*®); Aseptic transfer port (Equipement) and single use aseptic transfer bags for inlet or outlet of sterile components (or contaminated components) to the filling line. **(Brand name removed)*
vials cups and props
Vary. bags, filters, tubings, sensors and assembly of them.
Tubing, reactors, etc.
Tubing, filters, vessels
Tubing, filters, containers (bags), bioreactors
Tubing, connectors, clamps, fittings, filters, films.
Tubing sets, 3D mixers, 3D storage bags, bioreactors
Transfer tubing, Filter Assemblies, Fill bags, sampling assemblies
Through External Manufacturing Partners in Europe (Ireland and Germany), we use single-use mixers, single-use bags, sampling apparatus, tubing, filters, gaskets, and single-use filling systems, including "break tank," fill line tubing and filling needles.
SUS for filling purposes
SUB, SUF, manifolds

SU Bags, Filters, Filling line sets and SU needles
Sterilizing Filters, BPC Bags, syringes, needle, tubes, connection tube gaskets, etc.
sterile filter sets including tubing and connectors, sterile flex bags
sterile bioprocessing bags, tubing, and filters (i.e. ----*) * *(Brand name removed*)
Single-Use Bioreactors, Mixers, Chrom, TFF Skids, Manifolds, Biocontainers, etc.
Single use pumpe tubes conectors, filters and bags (all assemblied)
Single use filtration systems for sterile filtration of drug product. Single use filling systems for aseptic filling. Single use system for up stream processes.
Single use components, Single use materials
single use bioreactors, ultrafiltration devices, filters, and associated components
Single use bioreactors, SUM, Chrom flow kits
Single us bioreactors, Mixers, Bio Process containers , Connectors, Tube sets , Serile filter sets, Flex factories and Roller bottles
Preparation-filtration- filling system
pipette tips
peristaltic pump filling pathways (filling needles included), redundant sterilizing filtration pathways, single use mixing bags, 3D/2D bags, Tubing assemblies, sample bottle assemblies
----------* bags, filters, tank bags, flush bags, connectors, filling stations **(Brand name removed – sampling bags)*
na
multiple. Hoses, steam through connectors, readymate connectors, multiple bags, bottles manifold systems
------* bags, ----* filters, connectors - everything required for formulation **(Brand Name Removed)*
------* *(Brand name removed – brand of bag)*
Mixing bags, Storage bags, Filters (depth and membrane), tubing, hose barbs, Flow kits/Manifolds, Bottles (PETG, PC, Polypropylene, etc)
Mixing and holding bag system, RTU filtration and filling assemblies
many
from simple bags, transfer sets, manifolds to complex mixing systems, filtration kits and Single Use bioreactors
Formulation/pooling bags, Aseptic connections, Filling manifolds, Sampling systems, Filtration devices
Formulation assemblies, single use tanks, filling manifold
Filtration, purification, transfer, bioreactor, mix bags, storage bags, transportation, upstream processed, downstream processes, and drug product
Filters, hoses
Filters, connectors, bags, manifolds, tubing
filters, bags, tubings

Filters, Bags, asseptic connectors, tubind, flasks, biorreactor bags
filters, sterile to sterile connectors, tubing, pre-assembled tubings and product pathways, flexibles pouches and tanks, sampling bags, or syringes, or tubes
Filters bags etc for dp and ds
filters
filter, bags, tubing, very dependent on single use vs steel
Filling assemblies, aseptic filtration assemblies, compounding bag assemblies
Drug substance and drug product bags, syringes and hoses.
Connector
Bottles, Assemblies, Tubing, Manifolds
Bioreactors, Bioprocess containers, filters, vials, tubing, aseptic connectors etc
Bioreactor
bags, tank liners, tubing, filters
Bags, mixer bags, bioreactor bags, primary packaging material API, filters and TFF cassettes, tubings, pre-assembled tubing sets, connectors, manifolds, sensors, seals
Bags, aseptic connectors, tubing
Bags, Assemblies, Bioreactor bags, sampling devices
Bags and single use tubing and filtration assemblies.
bags
Bags
Bags
assemblies, components, sensors, tubing, bags, bioreactors, purification, filters, etc...
Assemblies, bags, filters
aseptic connectors
All that are usually used: bags, tubings, connectors, filter, etc
all kind of SUS
single bag, mixing bags, filters, connectors
vmhvm

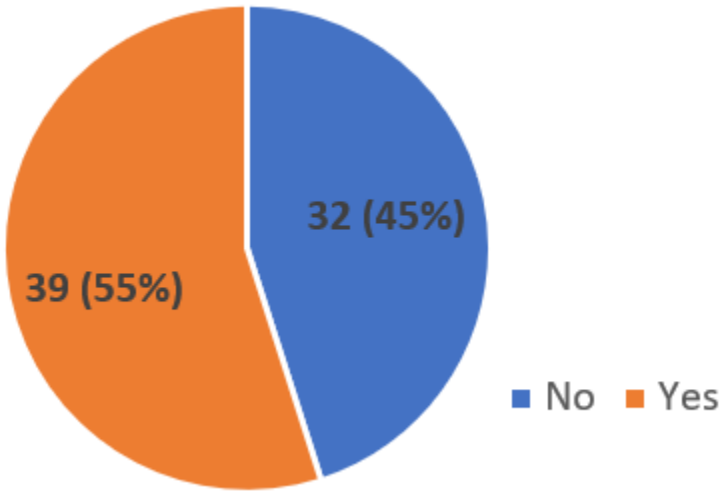
Question 4:

Does your company have contingency plans with approved alternate suppliers in place to address Single-Use-System component shortages?

- ○ Yes
- ○ No

Results:

71 Respondents



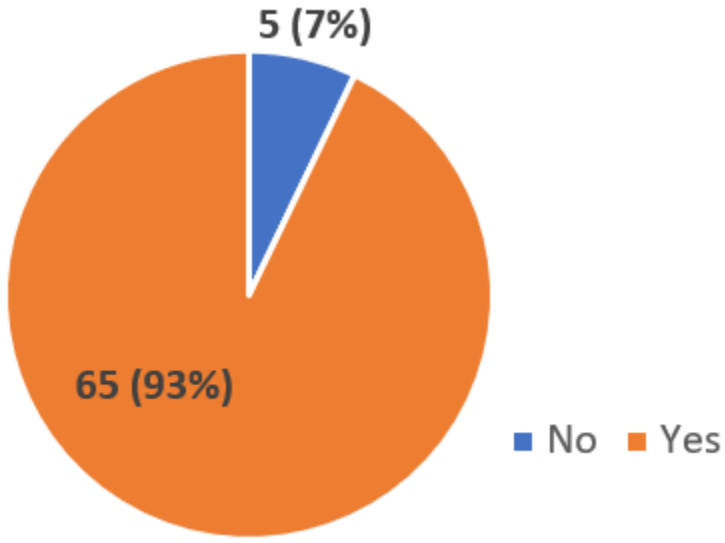
Question 5:

Is your company experiencing shortages of Single-Use-System Components?

- ○ Yes
- ○ No (If "No" End Survey)

Results:

70 Respondents



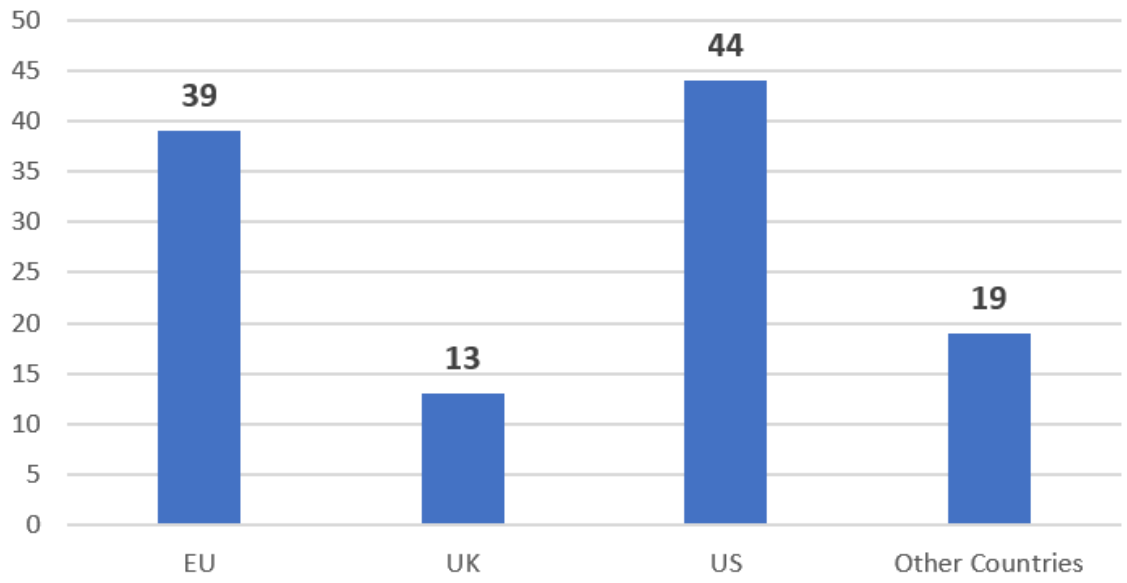
Question 6:

Does this shortage impact manufacturing that is occurring in the European Union, United Kingdom or United States? Select all that apply.

- ☐ European Union
- ☐ United Kingdom
- ☐ United States
- ☐ Other Countries

Results:

62 Respondents



Question 7:

What types of Single-Use-System components is your company experiencing shortages of?

Results:

59 Respondents

We’re experiencing longer leaditmes, but no ongoing shortages. We’ve ordered replacement parts at or beyond our suppliers leadtimes, to avoid shortages.
We are experiencing shortages in all components or delayed delivery dates and from all manufacturers, so contingencies of having alternate supplies is not typically a viable option for us. We have increased inventory rates and our expected delivery times often by as much as 400%
tubing/manifold sets and 3D mixers
tubing, connectors, filters
Tubing, Single-use bags, Single-use mixers
Transfer tubing containing molded components. Filtration assemblies.
tank liners, filters
SUS for product filling purposes
SUB, SUF, manifolds
sterile connectors, bags
Sterile connectors and various tubing types
specific kits for our application
Single use systems for upstream processes. SIngle use systems for filtration of DP. Single use systems for aseptic filling.
Short supply of filters
S2S connector and filters
Preparazione bag, Filtration and filling line
pipette tips
---- * sterile STR bioprocessing bags and Depth Filters **(Brand name removed)*
Needles and sampling assembly
most
Mixing bags, Storage bags, Filters (depth and membrane), tubing, hose barbs, Flow kits/Manifolds, Bottles (PETG, PC, Polypropylene, etc)
Mainly bags, components
Full assemblies and single components (e.g. connectors, filters)
Formulation/Pooling bags, Tubing, Aseptic connectors
filtration sets (sterile filtration -----/-------), flexible bags (-------), ultrafiltration filter sets **(Brand name removed)*
filtration assemblies
Filters, ------ bags, connectors. **(Name brand removed)*
filters, biorreactor bags, connectors
Filters and large bags
Filters and bags
filters
filters

filter
Filling Line stes and SU Reservoir bags
Everything , Subs, SUM, connectors , filter sets , tube sets , etc
BPC bags, Sterilizing Filters, Connection Tubing.
bnmbnmnb
Bioprocess containers, bioreactors, filters, vials, tubing
Bags, mixer bags, bioreactor bags, primary packaging material API, filters and TFF cassettes, tubings, pre-assembled tubing sets, manifolds
bags, filters
Bags including mixer bags, connectors, tubing components, clamps, barblocks,
Bags and tubings
Bags
bags
Bags
bag film which impacts the single use mixing and holding bags, --------* bags (with RTP) impacts the peristaltic pump assemblies, Silicone tubing - braided and unbraided, hose barbs and hosebarb connectors, Band clamps, Sterile disconnects, Stainless steel filling needles, gaskets, specific sample bottle sizes **(Brand name removed)*
assemblies, bags, filters
Aseptic Connectors, Pressure Sensors, Braided Platinum Cured Silicone Tubing, Sanitary Clamps, TPE Tubing
aseptic connectors, filters, single use system assemblies, bags
aseptic connectors
all of them, mostly bags
All of them
All of them
All components: connectors, tubing, clamps, disconnectors, filters, bags, fasteners
All bags and filling set ups.
all
All
Across all items.
- mixing bags, filters, tubing and connectors

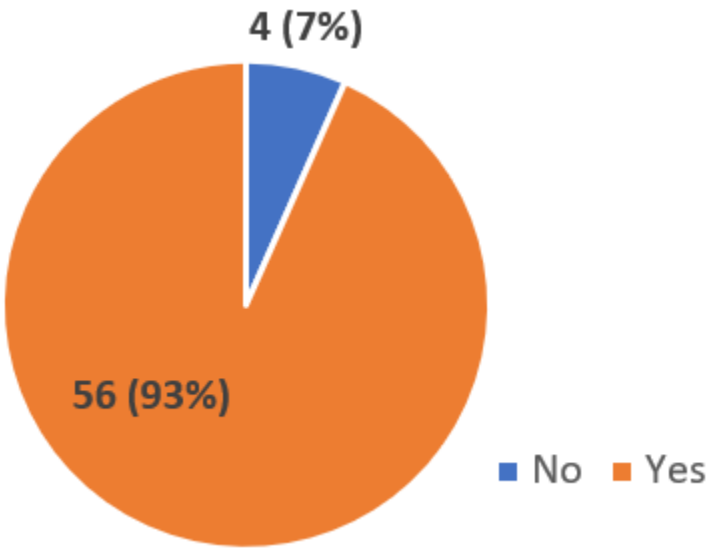
Question 8:

Do these Single-Use-System component shortages have the potential to disrupt manufacturing and the availability of critical aseptically produced medicines?

- ○ Yes
- ○ No (If "No" End Survey)

Results:

60 Respondents



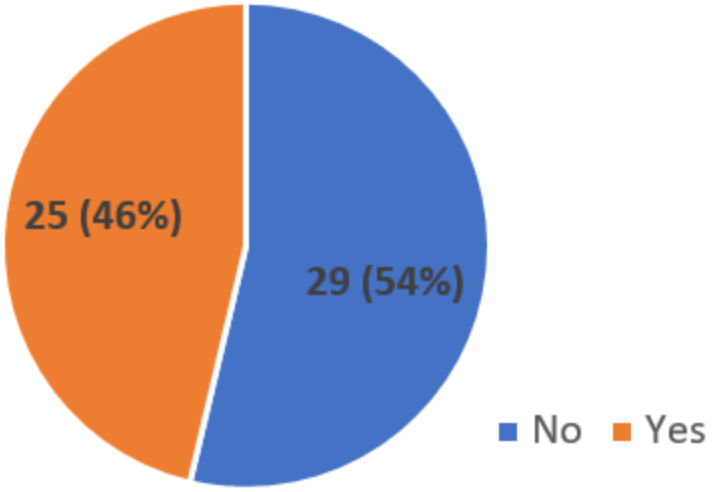
Question 9:

Are there alternatives that could be used by the company even if not currently approved to resolve or substantially mitigate this potential disruption?

- ○ Yes
- ○ No (If "No" End Survey)

Results:

54 Respondents



Question 10:

What are these alternatives that could be used?

Results:

22 Respondents

We have dialogue with other SUS vendors, who could potentially supply similar systems. However they would need approval and we would need to do assessments (leachable/compatibility) and validation (filter retention studies etc.). These are long lead items.
We can identify alternative offerings in the industry for equivalent connectors, clamps, filters, etc.. However, this activity significantly impacts our customers, and we've historically seem limited desire to adopt multiple sources for critical, fluid/drug contact components.
We are able in some cases to switch to stainless vessels or make our own assemblies vs. purchasing custom. Alternate filters are a bigger challenge based on filter housings and our current process validation. Alternates for bags when stainless isn't an option is also difficult because all single-use manufacturers are experiencing shortages.
Use of approved and validated SS systems.
unapproved suppliers
There are alternate suppliers or technologies that could be implemented and work from a technical perspective. The road blocks would be the qualification, lead times, and registration impact to implement alternatives.
Stainless Steel tanks and manually assembled manifolds/tubing sets that would need to be sterilized onsite and potentially aseptically assembled. Significant validation activities (and API/DS/DP materials) needed to support those options
Stainless steel components

stainless steel
source non-validated comparable products, use glass ware containers instead of flex bags assemble filter sets in house
sometimes 2nd sources are available but not in all cases - so it very much depends If hardware dictates then we cant make changes
Second source programs
other suppliers, alternative design/specification, network with other users
not clear for all
Materials from alternative suppliers. Alternative designs - e.g. use of mechanical components versus molded components
Items from alternative suppliers used in less critical steps of manufacture
Further detail can be provided upon formal request.
different tpe, supplier brand variances - if approved/tested/validated
Components from alternative suppliers
alternative suppliers, alternative material from same supplier, change from pre-assembled tubing sets to in-house assembly, extension of shelf life for materials on stock, postpone production runs until material delivery, material provision by customer (CDMO)
Alternative suppliers of similar components
alternative parts which has comparable functionality are registered.

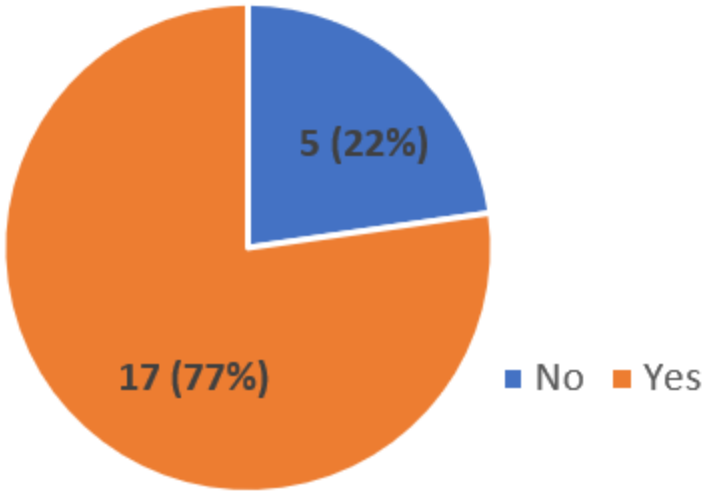
Question 11:

Are these alternatives available even if not currently approved for use (e.g., if the alternative is a different Single-Use-System component, is that component available)?

- ○ Yes
- ○ No

Results:

22 Respondents



For the question above please provide any additional detail you feel would be helpful.

Results:

15 Respondents

There are different suppliers providing the same type of needed components but these new components have to be internally integrated and validated, however, the risks increase due to additional manipulations.
studies needed
some are and others aren't, the current issues are constraints in component shortage supplier expansions has increased mfg/integration
not sure
It really depends on the component, for examples different tubing might be able to be used but all tubing is on long lead times but a bioreactor bag from one company only fits in one suppliers bioreactor tank so alternate not available
It is common to be aware of a good technical alternative, but that alternative also has lead times that are too long for implementation. There are still instances where a technical alternative could be provided in the timeline required.
In some cases alternative components have been identified and are available
I selected yes, but really, it depends. In some cases, supply is short across the total industry and certain sizes of bags are unable to be obtained or have long lead times that won't help our manufacturing schedule in the near term.
glass ware is available, non-sterile materials are available but these need to be assembled and sterilized. Validation takes much efforts and costs so difficult to consider. Also impact on stability should normally be investigated before introduction which could make thongs prohibitive.

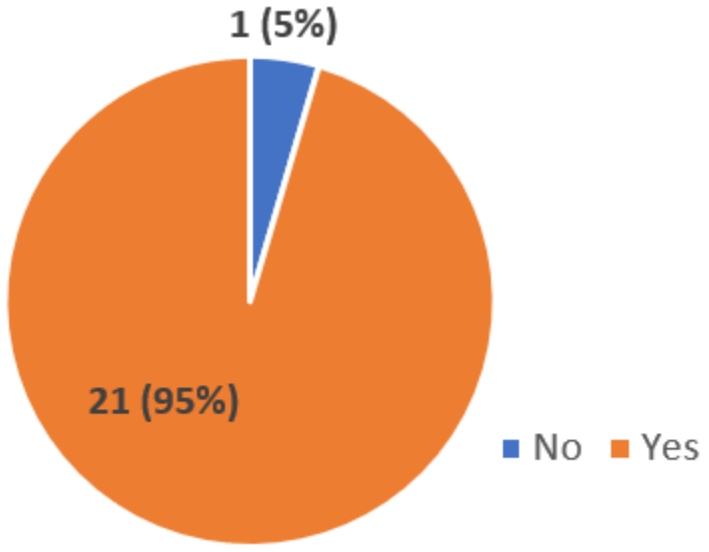
We assume that alternative filters (for sterile production or TFF) can be found but not with the full validation package. So, a pragmatic approach on the qualification should be introduced, minimizing risks but accepting some.
concurrent validation to allow material release prior to normal stability and approval timelines.
But most would likely have significantly long lead times.
before to proceed we need to perform a gap evalutaion and impact assessment (including on the process validation, material compatibility, L&E, etc)
approval of change control is needed at the minimum. Critical items are defined in dossier so immediate change is not allowed
alternative components available in most but not all cases
According to the initial talks, some of the alternative vendors claim, they can provide alternatives with shorter lead times. However they are not readily available as the alternative vendors also experience longer lead times on sourcing of components for the single use systems.

Question 12:

Is the risk involved with the use of these alternatives considered acceptable, and if so would their use outweigh the risk of creating a potential shortage or delaying availability of a critical medicine?

Results:

22 Respondents



For the previous question on risk between the use of alternatives and creating a potential shortage of a critical medicine, please provide any additional detail you feel would be helpful.

Results:

16 Respondents

We would conduct supporting validation testing, and exractables testing; but most cases would require a supporting assessment by our customers.
We perform a risk assessment prior to introducing an alternate into the process. We believe the process we have in place would demonstrate to regulators the due diligence we are performing to balance a compliant process with our patient's needs.
Validation of these new processes depends on the know-how of the manufacturing facility. Direct communication with regulatory agencies to receive feedback on plans would be helpful.
Use material at business risks waiting for compatibilities studies results
The implementation of alternatives is managed through the quality change control process where all required assessments are conducted
Setting alterative suppliers are very difficult in some cases such as single use for specific equipment or item determined in dossier.
Our internal teams do not want to risk the material needed to pursue an alternate without confidence that the strategy will be allowed. Therefore, i think ability to discuss the alternates and the strategy to use/approve with a regulatory agency to ensure that if the runs meet all expectations, the material will be allowed for release to market.
Only E&L risks exist
none
It would be helpful to have a guidance on equivalency of materials and components so they could be used interchangeability if they meet the same functional requirements and CQAs.
It will be easier if a risk mitigation rational is created
difficult as there are many
Depends on application and if alternate contacts product or not
Creating more flexibility by allowing extra in process and final product controls for the first production batches instead of necessity of a full validation prior to commercial or clinical production would be helpful. Potential extra analytical testing should be performed using scientifically sound methods.
Changing a filter membrane type for sterile filtration of drug product, typically has regulatory impact, and therefore has a very long leadtime. With proper validation, i personally, think that it would be acceptable to prevent drug shortage, without prior approval from the authorities. We are looking into dual sourcing of all components and single use systems, as well as increasing our safety stock levels (just like the rest of the industry i presume). So the general shortage on SUS will probably last for a while due to this.

Any alternative bears risks which have to be evaluated in detailed risk assessments. So far, this risk has been rated acceptable for all changes

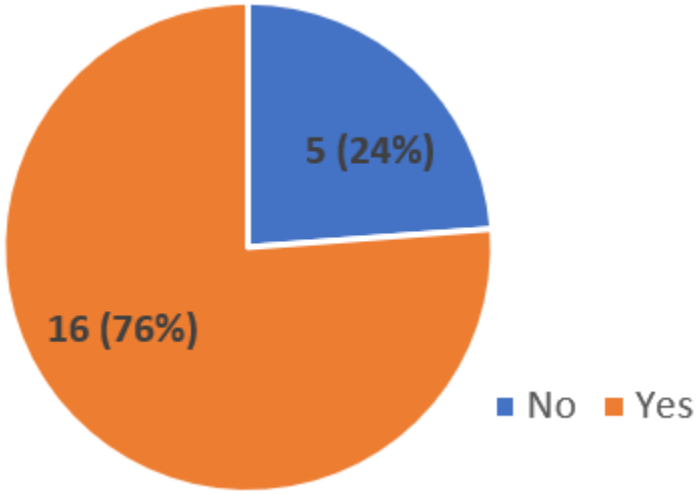
Question 13:

Could the use of these alternatives be implemented in a manner that would be a minimal deviation (departure) from normal requirements (process)?

- ○ Yes
- ○ No

Results:

21 Respondents



For the question above please provide any additional detail you feel would be helpful.

Results:

Respondents 9

We could act with minimal deviation in the case of non-fluid contact components; but any fluid contact component requires an assessment and validation period. Typically a minimum of one to two quarters (best case).
We are not looking into reducing requirements from a process perspective.
Only that case is allowed to use.
It depends on the position a regulator could take when inspecting or reviewing these deviations/changes. Some inspectors may consider these deviations to be well justified and adequately risk managed while others, the ones who are "to the letter" can consider these to be "critical changes" because affect the product, and risk assessments may not matter to them classifying these as critical changes. Critical findings can lead to Warning letters...
for the mixing or storage in SS, the interactions with SS is minimal, the cleaning validation could be overly robust pending results. So implementing SS tanks on risk is low. the manually assembled tubing sets/manifold are of equivalent construction and path lengths. aggressive overkill cycles for autoclaving, leveraging previous parts and understanding of aseptic techniques can allow rapid implementation of alternates.
Based on change control and also on risk mitigation
Again, if certain components are deemed interchangeable up front for functionality and CQAs, then the implementation time would be expedited and have lower impact on supply continuity.
again depends on application - alot of work could be invovled
After extensive trouble-shooting, the processes could be handled with minimal deviation from normal process requirements. The alternatives were/are implemented via change management. The amount of related work to e.g. risk assessments was high. The trouble-shooting included research for alternatives, negotiations with alternative suppliers, supplier delivery date tracking, release and testing of new materials and was time-consuming

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