Cleaning Validation Checklist

Product Name:_____ Batch Number: _____ Ref No:_____

Date : _____

S. No.	Checks	Yes	No
1.	Reason for cleaning validation		
2.	Is the product manufactured in multiproduct/ dedicated facility?		
3.	If dedicated facility, a risk assessment performed to make sure that there is no potential for degradation and or microbial contamination that may adversely impact the quality of the product?		
4.	In both dedicated and multi-product facilities, the frequency with which the cleaning procedure should be performed is validated to assess risks related to potential degradation and microbiological contamination		
5.	Does all the toxicological / pharmacological data used to identify, assess and characterize risks that are relevant to patient exposure		
6.	Route-to-route extrapolation is possible. Can be used to characterize all the potential exposures?		
7.	A worst-case rating study/Risk assessment done for the product and documented?		
8.	Does the validation program define the quality risk management approach?		
9.	Is the risk assessment done for the HBEL, Equipment & Sampling, Residue Characterization etc.		
10.	Are the cleaning procedures are established outcome of the risk assessment?		
11.	Is the cleaning risk assessment including dirty and cleaning hold time (DHT and CHT)		

Cleaning Validation Checklist

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12.	Does the risk analysis include: • Cleaning process development • Facility/equipment design review • Selection of analytics methods		
13.	The substances are scientifically matrixed by equipment class (train/equipment) and cleaning class (procedure)?		
14.	During a worst-case rating, the results of the investigations are summarised for each substance in each equipment class?		
15.	Are the product solubility studies performed?		
16.	Are the product recovery studies performed?		
17.	Pharmacological or toxicological data available for the product?		
18.	Are the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) values available?		
19.	Threshold of Toxicological Concern (TTC), LD50 and/or general cleaning limits		
20.	Is the MACO calculated? Which method considered to establish the acceptance criteria? Method: Obtained MACO:		
21.	Are the rinse and swab limits established? If yes Limit for Rinse sample: Limit for Swab sample:		
22.	Are the derived Limits being realistic and practical, achievable and verifiable and safe?		
23.	Are the hard to clean parts identified for each equipment and documented and justified?		
24.	Are the swab locations identified? Justified?		
25.	The acceptance criteria for equipment cleanliness are visually clean in dry conditions and an analytical limit		

Cleaning Validation Checklist

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26.	Surface area calculations performed, verified and kept on file for all equipment evaluated?		
27.	Does the cleaning validation programme consider minimum three consecutive runs?		
	Equipment Cleaning Records		
28.	Are the cleaning procedures defined for each individual equipment/ set of equipments?		
29.	Is the cleaning agent/ solvent identified to efficiently remove the residues?		
30.	Are the volumes and or concentrations are defined?		
31.	Reflux or rinse times, and temperatures are clearly defined?		
32.	The sequence of cleaning steps or pre-defined repeats are defined in cleaning records.		
33.	Are the in-process analysis and sample instructions are provided?		
	Analytical Method Validation		
34.	The selection of Analytical Methods for cleaning validation are science and risk based		
35.	Are the analytical methods validated and suitable to quantify at the acceptance criterion level		
36.	The limit of detection is lower than or equal to the acceptance criterion level?		
37.	The methods chosen, detect residuals or contaminants specific for the substance(s) being assayed, at an appropriate level of cleanliness (sensitivity)		
38.	The detection limit for each analytical method is sufficiently sensitive to detect the established acceptable level of the residue or contaminants.		
39.	Are the levels of cleaning identified and defined in procedure		
40.	Cleaning Specification available?		
41.	Cleaning Method of Analysis available?		

Cleaning Validation Checklist

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	Validation Protocol		
42.	Cleaning Validation Protocol approved?		
43.	Does the protocol define the objective, scope, responsibilities, cleaning procedure, consecutive cleaning runs, sample quantity, sample locations, sampling procedure, acceptance criteria, analytical methods and testing procedure, equipment train, deviations, training and revalidation?		
44.	Are the Sampling Locations identified properly and justified?		
45.	The cleanliness status and validation of cleaning procedures is verified against pre-defined acceptance criteria?		
46.	The cleaning verification made by visual inspection or visual inspection and analytical verification (e.g., swabbing and/or rinsing)?		
47.	The validation of the Dirty Hold Time (DHT) performed and timelines established?		
48.	All cleaning processes for product contact equipment are validated in accordance with Quality Risk Management (QRM) principles		
49.	Non-contact parts from which product may migrate are also considered		
50.	If cleaning process is not capable of consistently producing adequate results, improved cleaning procedures implemented or equipment/facility dedicated.		
51.	Toxicological evaluation is used in setting Health Based Exposure Limits (HBEL) and data is used to determine a safe daily threshold value, such as Permissible Daily Exposure (PDE) or Threshold of Toxicological Concern (TTC)		
52.	PDE or TTC, is used in risk identification and justification of maximum safe carryover limits into the next product		
53.	Is HBEL calculated as an Acceptable Daily Exposure (ADE) or Allowed Daily Exposure (PDE)?		
54.	Is the Maximum Allowable Carryover (MACO) built upon the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE)?		
55.	All potential sources of cross contamination are assessed through a documented		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
	QRM process to confirm that the drug can safely be made on shared equipment		
56.	Measures to prevent cross-contamination and their effectiveness are reviewed periodically		
57.	Cleaning Validation Master Plan is available to outline the general cleaning validation policies at the site		
58.	Cleaning validation studies carried out on all products at the facility or on worst case products only (the product family approach) is addressed in the Cleaning Validation Master Plan		
59.	If a worst-case approach is being used, following are documented: • the methodology/scientific rationale used in determining the worst-case products • the actual worst-case products including a listing of all products deemed to be represented by the identified worst-case products		
60.	Assessment of worst-case products includes the following Factors : ▪ HBEL of the residue ▪ difficulty in cleaning or product cleanability ▪ solubility of residues in cleaning agents and cleaning solvents ▪ physical characteristics of the product, active substance or excipients ▪ past experience (for example during development and with similar products)		
61.	If an equipment grouping approach is being used, following are documented: ▪ the approach/scientific rationale by which equipment were grouped together ▪ the listing of all equipment in each group, identifying the equipment in each group that is considered to be worst case, with proper justification.		
62.	Equivalent cleaning processes are followed if cleaning validation studies are conducted following a worst-case product and/or equipment grouping approach		
63.	Cleaning Validation lifecycle approach involves the following phases: Phase 1 - Cleaning process design and development		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
	Phase 2 - Cleaning process qualification Phase 3 - On-going monitoring		
64.	Cleaning verification studies are conducted in accordance with an established cleaning procedure or a protocol		
65.	Cleaning process qualification study comprised of multiple cleaning verification runs/studies for all equipment involved.		
66.	Appropriate effort and resources like laboratory, material coupon, bench top or pilot scale trials through to commercial scale trials are applied while designing and developing cleaning processes		
67.	Potential issues that could impact the effectiveness and reproducibility of cleaning processes are considered when developing new or revised cleaning processes which includes: a. Understanding the chemical and physical properties of the actives, excipients and by-products or degradants which helps to determine which cleaning agents, solvents and cleaning process parameters would be most appropriate b. Review the design of the equipment considering engineering drawings, experience of maintenance and cleaning personnel, examination of disassembled equipment in the clean and dirty state to establish areas at risk for residue accumulation or migration. Materials of construction for equipment parts, their smoothness, are considered to evaluate any differences these substrates have on residue removal.		
68.	All sampling sites are appropriately identified and justified.		
69.	Any risk for endotoxin contamination or microbial proliferation in susceptible products through incoming materials, usage, handling, hold times and storage has been evaluated		
70.	Whether any variation in raw materials might affect cleanability is determined		
71.	All cleaning process elements, parameters and controls such as cleaning agents, solvents, critical cleaning parameters (time, temperature, pressures, and action such as scrubbing, soaking, circulating or reflex) are scientifically established		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
72.	Manual cleaning procedures have detailed instructions and establish range/value of the applicable critical process parameters: • detailed disassembly instructions • sequence of the cleaning steps • cleaning agent to be used and its concentration • cleaning agent application means (e.g., soaking or scrubbing) • contact time • temperature of the cleaning solutions or rinses • rinsing techniques (i.e., pre-rinses, soaking, flushing, times and pressures) • method of drying		
73.	Operators are trained and training records available		
74.	Calibrated measuring devices such as timers, temperature probes, dosing pumps and flow meters, are used if required		
75.	**Clean-In-Place** Adequately detailed procedures describing the automated cleaning process, controls and requirements such as equipment preparation or disassembly, and loading patterns are in place		
76.	Frequency is defined for emptying and cleaning bulk CIP tanks		
77.	Cleaning equipment and cleaning protective clothing are visually distinctive and stored separately.		
78.	Equipment used for such cleaning is Qualified		
79.	Circuits are designed so that employees cannot manually advance or skip CIP cycles or steps		
80.	If CIP circuits are stopped for any reason, the cycle is reset and not skipped. The flow rate, temperature, chemical concentration (conductivity) and time are reset to meet the CIP parameters		
81.	Scavenger pumps are operated to ensure no build up of cleaning chemicals in the vessels		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
82.	All parts of the product circuit, including divert valves, buffer tanks, mobile tanks, etc. are included in the CIP circuit		
83.	Tools for measuring conductivity, temperature, flow rates, and time are validated		
84.	All product contact surface areas are being appropriately contacted by the cleaning/rinsing agents has been verified		
85.	Appropriate calibration and maintenance programs are established and maintained		
86.	Cleaning sequences including all temperatures, concentrations, valve openings, spray rates, pressures and volumes are defined		
87.	Critical control points and parameters with appropriate sensors and alarms are monitored to ensure the process is highly controlled		
88.	Critical alarms are identified and regularly checked or verified		
89.	Steps to be taken in response to such alarms are addressed in the procedure		
90.	Cleaning sequences and data, including alarms, are appropriately controlled and reviewed		
91.	Cleaning process qualification studies carried out for all products, or worst case products if a product family approach is used		
92.	QRM principles has been used to determine the extent and scope of cleaning process qualification requirements a. number of cleans to be assessed using a documented risk assessment is determined b. critical process parameter limits are verified during qualification studies c. challenge testing includes ✓ minimum detergent contact time, ✓ minimum or maximum temperatures and ✓ minimum rinse time/volume/pressure d. Operator variability is assessed, particularly when manual cleaning processes are being used		
93.	Cleaning process qualification protocol includes: a. objective and scope of the cleaning qualification exercise		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
	b. responsibilities for performing and approving the qualification study c. description of the equipment to be used for the process and for cleaning d. references and descriptions of the cleaning procedures and parameters to be used, with a description of all critical parameters e. any worst case challenges to be evaluated in the study f. the number of cleaning cycles to be performed g. sampling procedures h. clearly defined sampling locations, with rationale for their selection i. validated analytical methods, that are appropriate for the residue limits under consideration and data on recovery studies j. the acceptance criteria, including the rationale for setting the specific limits Protocol refers other documents which has details of Rationale and data to support approaches taken		
94.	Data is available to demonstrate that the following variables do not impact cleaning effectiveness: a. The length of time between the completion of manufacturing and start of cleaning (dirty hold time). b. The maximum allowable number of batches of the same product manufactured prior to full cleaning, specifying maximum campaign lengths in days and/or number of batches.		
95.	Any cleaning failure is investigated as per quality system requirements		
96.	Final qualification report is available		
97.	Ongoing monitoring requirements have been established which includes a		

Cleaning Validation Checklist

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	number of different activities such as: a. data analysis (such as data generated from automated processes) b. additional cleaning verification studies c. rinse sample analysis		
98.	On-going monitoring, includes (areas of special concern): a. products with low HBEL values which are generally more hazardous products b. products for which visual inspection cannot be used to estimate cleanliness of the equipment, meaning HBEL derived residue levels cannot be visually detected c. equipment and products with a history of failure or highly variable testing results during verification and qualification testing d. manual cleaning processes e. locations or surfaces that are difficult to access or clean f. equipment which cannot be appropriately visually inspected		
99.	Appropriate and timely action is taken if there are any signs that cleaning processes are inadequately controlled. Eg, a. statistical evaluation of data generated through cleaning verifications and/or any data generated from routine cleaning process itself. b. review of traditional quality indicators such as complaints, deviations and lab failures.		
100.	Cleaning process data and quality indicators are regularly reviewed for any trends or failures that may indicate the need for a review of technical		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
	or operational measures.		
101.	Change control system is in place to assess and document all changes that might impact the cleaning process for eg.; a. new products b. changes to the cleaning process c. changes in the formulation and/or process of products d. raw material changes (e.g. change in impurity profile or physical properties) e. new cleaning agents and/or changes in cleaning agent formulation f. significant equipment changes or new equipment g. lot size or campaign length changes h. changes in analytical procedures or sampling method or materials i. changes to cleaning limits, which might happen upon periodic review of the data which form the basis of the HBEL		
102.	All new product introductions are reviewed through the QRM process and change control to determine whether the existing technical and organizational controls are sufficient or need to be modified. Following points are considered: • The HBEL of the new product and evaluating the suitability of the product in the facility and whether dedicated facilities/equipment or other additional controls are required. • The ease of cleaning the equipment used to make the new product whether the new product is a new worst case product. If existing cleaning processes are adequate or if		

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S. No.	Checks	Yes	No
	a new or revised process is required is determined. If additional development of the cleaning process is required, Phase 1 - Cleaning process design and development has been followed. • Any new equipment and/or equipment modification that may impact cleanability.		
103.	Verification studies are conducted in commercial equipment to demonstrate equipment has been adequately cleaned following production of the new product (development, technology transfer or clinical trial batches).		
104.	Analytical methods used to measure residue and contaminants on equipment (for example, product active drug or degradants and cleaning agent residue) are validated.		
105.	Limits of quantification and detection to ensure the sensitivity of the analytical method is appropriate for the residue levels under consideration is determined		
106.	Whether the selectivity of the analytical method needs to be established in relation to potential degradants such as those formed during the cleaning process has been evaluated.		
107.	Recovery studies conducted for all sampling methods used with analytical methods to: a. Ensure the sampling method used in the laboratory is equivalent to the method used in manufacturing. b. Conduct recovery studies for all applicable product contact materials of construction to be sampled in the equipment. c. Establish percent recovery for each surface/material of construction and use this in the calculation of residual contaminants. d. Low or variable recovery of standard concentrations of		

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S. No.	Checks	Yes	No
	residue during recovery studies may not be acceptable as it is indicative of an inadequate sampling or extraction technique.		
108.	Non-specific analytical methods, for example total organic carbon (TOC) and conductivity, used with appropriate justification		
109.	Effectiveness of non-specific method is established to detect the target residue		
110.	Visual inspections are conducted after all cleans and before conducting any cleaning verification/qualification/on-going monitoring sampling activities. Results are documented		
111.	Procedures for conducting visual inspections is in place which include clear instructions with respect to: • ensuring equipment is dry • disassembly instructions • use of an appropriate light source and lighting conditions • how to assess difficult areas, such as the bottom of mixing blades		
112.	Visual inspection is conducted by trained personnel only		
113.	Any visual inspection failures are Investigated through the applicable quality system.		
114.	Equipment sampling is conducted by direct surface sampling (swab/wipe method), rinse sampling or a combination of the two		
115.	Swab sampling is carried out by wiping an equipment surface with a specified material wetted with solvent to recover residue from the surface		
116.	Swab/wipe sampling is conducted on areas determined during the risk assessment and specifically on identified hardest to clean areas Hardest to clean areas is specified clearly in relevant protocols		

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S. No.	Checks	Yes	No
	Choice of swabbing locations are justified with appropriate supporting data		
117.	Following points are considered while determining hardest to clean areas: a) accessibility b) equipment geometry c) potential for residue accumulation d) material of construction		
118.	Material to be used for swabbing and the sampling medium or solvent is specified in the protocol		
119.	Production equipment is sampled in the same way as sampled during recovery studies in the laboratory		
120.	Measures to ensure consistency during equipment sampling includes: detailed procedures qualification/certification of swabbing personnel to demonstrate suitable recovery on the job training and supervision of swabbing personnel when swabbing manufacturing equipment		
121.	Placebo sampling evaluations are conducted to complement swab and/or rinsing studies		
122.	Risk management principles being used for determining maximum allowable carryover calculations for residues of concern, and limits are based on toxicological evaluation		
123.	Alert limits established in the event that HBEL derived cleaning limits are significantly higher than historic cleaning limits (for example, 1/1000th of a dose and 10 PPM)		
124.	Calculated cleaning acceptance criteria accounting for the cumulative impact of residue from multiple shared equipment is established		
125.	HBELs are periodically re-evaluated and the impact of any changes on the overall cleaning validation program is assessed and documented		
126.	Equipment and facility design, operation, cleaning and maintenance appropriately controls microbiological bioburden		

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S. No.	Checks	Yes	No
127.	QRM principles are used to determine: a. the need for including microbiological and/or endotoxin contamination evaluation as part of verification/qualification and on-going monitoring assessments b. sampling locations in equipment, which should consider those locations or materials that might be more prone to microbial growth c. the type, nature and scope of an ongoing environmental monitoring program.		
128.	Maximum period of time that cleaned equipment can be held before use without re-cleaning or re-sanitization (commonly referred to as clean hold time) has been established.		
129.	Microbiological assessments are considered, as per risk management principles, when assessing maximum campaign lengths(may not be applicable for some API products).		
130.	Procedures are available for the appropriate handling of hoses.		
131.	Microbiological limits are scientifically justified		
132.	All processing equipment is designed to facilitate cleaning and permit visual inspection (where possible)		
133.	Equipment have smooth surfaces and made of non-reactive materials		
134.	Piping of the equipment is sloped continuously to ensure adequate drain ability of the lines. Dead legs are avoided		
135.	Special consideration given to long transfer lines as appropriate cleaning processes involves flooding the entire pipe to ensure contact with all surfaces		
136.	Removable sections are considered, where appropriate for the process, to evaluate the efficacy of the cleaning process by visual, swab testing and/or rinse sample		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
137.	Cleaning agents whose composition is known are selected, preferably whose components have favourable toxicological profiles and limits		
138.	Any changes in composition of the cleaning agent is notified		
139.	Cleaning agents are easily removable		
140.	Water quality attributes (chemical, microbiological and endotoxin) is appropriate to perform the last rinse (i.e. Equivalent to or better than the grade and standard of water being used at that stage of the process)		
141.	If a solvent as the last rinse, the quality of the solvent is appropriate.		
142.	Parts of equipment which are particularly difficult to assess or clean (e.g. filter bags, gaskets or screens) are dedicated.		
143.	Cleaning validation requirements are determined for using dedicated equipment or facilities considering following areas of concern: • microbiological considerations • cleaning agent removal • potential product degradants and process impurities		
144.	Cleaning control and evaluation requirements for the final API production processes is equivalent to those required for finished dosage form manufacture. For example: a. relevant cleaning processes are validated in accordance with a lifecycle approach b. equipment is designed in accordance with the same concepts as used for finished drug products		
145.	If solvents are used for API cleaning processes following are taken care : a. API is soluble in the agent being used for cleaning and rinse recovery studies b. solvents used for the cleaning process, including the final rinse, are of appropriate quality c. consider reflux or boil-out steps		

Cleaning Validation Checklist

S. No.	Checks	Yes	No
146.	A reflux or boil-out step is included when collecting a rinse sample for qualification, verification, or monitoring activities.		
Additional checks for cleaning validation of biotechnology processes			
147.	Removal of a large number of substances such as media, proteins, acids, bases, salts etc. is considered in cleaning development programs		
148.	Cleaning validation requirements includes a microbiological and endotoxin assessment		
149.	Validation of the cleaning of shared product-contact equipment is evaluated for each product and process		
150.	Bracketing for similar products or equipment is adopted with appropriate justification that is based on sound and scientific rationale for eg. a. cleaning of fermenters of the same design but with different vessel capacity, used for the same type of recombinant proteins expressed in the same or similar cell lines and cultivated in closely related growth media b. for multi-antigen vaccines, use of a representative antigen (or combinations of them) when validating the same or similar equipment.		
151.	QRM principles is used in setting appropriate limits for carry over taking into account the manufacturing process and the stage of manufacture		