Designation: ~~G122 – 96 (Reapproved 2015)ε1~~ G122 – 20

Standard Test Method for Evaluating the Effectiveness of Cleaning Agents and Processes[1]

This standard is issued under the fixed designation G122; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

~~ε1 NOTE—Editorial correction made in October 2015.~~

INTRODUCTION

Many ~~systems~~ products, systems, and manufacturing equipment require a high degree of cleanliness. For example, ~~gaseous and~~ many medical devices must be cleaned (the terms clean, cleaned, or cleaning are used intentionally and do not imply disinfect, disinfecting, or disinfected) of residues that may cause problems when they come in contact with patients. Gaseous and liquid oxygen systems must be clean, particularly of hydrocarbons, to avoid the potential hazard of a reaction and subsequent fire or explosion. ~~Typically, chlorinated solvents~~ Pharmaceutical manufacturing equipment must be cleaned to prevent product cross contamination from residues. Cleaning agents need to be identified and selected based on their effectiveness to achieve cleaning of the system, product, or manufacturing equipment. There may also be other considerations, such as chlorinated solvents that have been used to clean systems and equipment that must be free of hydrocarbons and other ~~contaminants. Environmental~~ contaminants and environmental concerns dictate that suitable replacements are needed. ~~This test method presents a procedure that may be used to evaluate candidate aqueous or non-aqueous cleaning agents.~~

This test method presents a procedure that may be used to evaluate candidate aqueous or non-aqueous cleaning agents for use in cleaning products, systems, or equipment, including medical devices, systems for oxygen service, and drug manufacturing equipment.

1. Scope

1.1 This test method covers a procedure for evaluating the effectiveness and capability of cleaning agents ~~and processes~~ to remove contamination to the desired level. This includes removing drug residues from manufacturing equipment and residues from medical devices (Guide E3106), as well as systems for oxygen service.

1.2 The test ~~coupons~~ coupons/beakers described in this standard provide a ~~relatively rough~~ representative surface to which contamination can ~~easily adhere.~~be applied and tested for the ability of a cleaning agent to remove it.

1.3 ~~The capability~~ This test method is a laboratory scale approximation and the actual effectiveness of a particular cleaning agent depends upon the method ~~by~~ (temperature, agitation, concentration, etc.) in which it is used and the characteristics of the article being cleaned, such as size, shape, and material. Final evaluation of the cleaning agent should include testing of actual products and ~~production process.~~cleaning processes.

[1] This test method is under the jurisdiction of ASTM Committee G04 on Compatibility and Sensitivity of Materials in Oxygen Enriched Atmospheres and is the direct responsibility of Subcommittee G04.01 on Test Methods.

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1.4 *Units*—The values stated in SI units are to be regarded as ~~the~~ standard. The values given in parentheses ~~are for information only.~~after SI units are provided for information only and are not considered standard.

1.5 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate ~~safety~~ safety, health, and ~~health~~environmental practices and determine the ~~applicability of regulatory limitations prior to use.~~safety of each compound on a case-by-case ~~Specific precautionary statements are given in~~ basis.~~Note 2~~.*

1.6 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D1193 Specification for Reagent Water

D6317 Test Method for Low Level Determination of Total Carbon, Inorganic Carbon and Organic Carbon in Water by Ultraviolet, Persulfate Oxidation, and Membrane Conductivity Detection

D6361/D6361M Guide for Selecting Cleaning Agents and Processes

E177 Practice for Use of the Terms Precision and Bias in ASTM Test Methods

E691 Practice for Conducting an Interlaboratory Study to Determine the Precision of a Test Method

~~G94~~E3106 Guide for ~~Evaluating Metals for Oxygen Service~~Science-Based and Risk-Based Cleaning Process Development and Validation

G93/G93M Guide for Cleanliness Levels and Cleaning Methods for Materials and Equipment Used in Oxygen-Enriched Environments

G121 Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents

G127 Guide for the Selection of Cleaning Agents for Oxygen-Enriched Systems

~~2.2 *ANSI Standard:*[3]~~

~~D46.1 Surface Texture (Surface Roughness, Waviness, Lay)~~

3. Terminology

3.1 *Definitions:*

3.1.1 *cleanability, n*—relative difficulty for cleaning a piece of equipment, product, or device.

3.1.2 *cleaning agent, n*—an agent used to support the removal of a contaminant from equipment surfaces or other critical objects (such as a medical device).

3.1.3 *cleaning effectiveness factor (CEF), n*—the fraction of contaminant ~~removed~~ removed, or remaining, from an initially contaminated test coupon and determined by gravimetric ~~techniques.~~or other analytical techniques (for example, Total Organic Carbon analysis, etc.).

3.1.4 *residual contamination,* R_{eC}*,n*—the absolute mass of contaminant remaining after the cleaning process and expressed in ~~milligrams~~micrograms per square centimetre of area or optionally as milligrams per square foot.

3.1.5 *surface roughness,* R_A*,n*—the arithmetic average deviation of the surface profile from the centerline, normally reported in ~~micrometres.~~micrometers or micro inches.

3.1.6 *test beaker, n*—a variant of a test coupon in that the configuration is similar to a laboratory beaker and the process residue under study is deposited on the inner walls or bottom.

3.1.7 *test coupon, n*—representative surface that is typically a rectangular piece of a material of construction on which a known amount of a compound is deposited to simulate a process residue.

[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

3.1.8 *visual inspection, n*— process of using the human eye, alone or in conjunction with various aids, as the sensing mechanism from which judgments may be made about the condition of the surface to be inspected.

4. Summary of Test ~~Method~~Methods

4.1 ~~This~~These test ~~method provides~~methods provide quantitative results as to the ability of a specific cleaning agent/process for removing selected contaminants from standard coupons. The coupons used for testing are prepared in accordance with Practice G121. ~~Cleaning is~~ To achieve results and data of the highest relevance, the method should be a close model of the cleaning system used that can approximate the conditions (for example, temperature, cleaning agent concentration, agitation, etc.) found during actual cleaning as much as possible. Cleaning may be performed using a cleaning tank with or without ultrasonic agitation, elevated temperature, or other cleaning enhancement features and ~~depends~~ may depend on the ~~manufacturer's instructions.~~ manufacturer's instructions. Cleaning methods may include Immersion models, Cascading Flow models, Clean-In-Place (CIP) models, etc. The effectiveness of the cleaning process is represented as CEF, the cleaning effectiveness factor, ~~that is~~ the fraction of the contaminant removed as determined by gravimetric or other quantitative techniques. A control coupon is used to account for any corrosion or material removal effects due to the cleaning ~~agent/process.~~agent/process, or to account for the normal Loss on Drying due to the contaminant's water or volatile content, unless this has been tested for previously.

5. Significance and Use

5.1 The purpose of ~~this~~these test ~~method~~methods is to define a procedure for evaluating the capability and effectiveness of cleaning agents to ~~clean metallic coupons.~~ remove residues of a compound/product from surrogate surfaces (that is, coupons or beakers) of Materials of Construction. This test method also provides a procedure for determining the compatibility of cleaning agents with the Material of Construction prior to starting tests. Based on the outcome of the testing, suitable cleaning agents may be selected for ~~cleaning in general and for~~further cleaning process development (see Guide D6361/D6361M~~oxygen service in particular.~~).

5.2 The potential critical cleaning parameters ~~can be changed and the test method can be repeated. The usual~~ related to the cleaning agent(s) under study may also be examined using these tests. Potentially critical cleaning parameters include cleaning agent concentration, temperature, ~~and time;~~ time, pH, foaming, type and strength of ultrasonic energy or ~~agitation, if used, and others.~~agitation (if used), and others. These parameters may be varied (for example, using Design of Experiments) to determine their potential optimal settings for actual use.

~~NOTE 1—Usual cleaning parameters are based on the manufacturer's recommendations.~~

6. Apparatus

6.1 *Materials:*

6.1.1 *Test ~~Coupon,~~Coupon/Beaker,* prepared in accordance with Practice G121. ~~The mass of the coupon is approximately 30 to 45 g but will vary significantly for each selected material. Typical materials used in oxygen systems are described in Guide G94.~~

6.1.2 *Control ~~Coupon—~~Coupon/Beaker—*This is uncontaminated and is subjected to the identical cleaning procedure as the contaminated coupons and serves to evaluate corrosion ~~anderosion~~ and erosion of the test coupons.

6.1.3 *Cleaning Agent,* prepared according to the manufacturer's instructions. If the Cleaning Agent is used after dilution with water, Specification D1193 Type ~~II~~ I to IV water shall be used for preparing aqueous ~~solutions.~~ solutions or prepared with water of the purity used in the actual cleaning.

6.2 *Equipment:*

6.2.1 *Cleaning Tank, ~~A vessel~~* of sufficient size to conduct a number of evaluations simultaneously. Testing is enhanced by having automatic temperature and time controls. A cleaning tank with ultrasonics may be used.

6.2.2 *Balance,* accuracy to 0.1 mg. However, 0.01 mg accuracy is desirable to detect contamination levels ~~of~~ of 10 mg ~~10 mg/m~~/m^2 ~~(1~~ (1 mg ~~mg/ft~~/ft^2) or less.

6.2.3 *Beaker Holder*—A device to support beakers in the ultrasonic cleaner tank such that the beakers do not contact the bottom and sides of the tank.

7. Test Procedure

7.1 Prepare a minimum of six test coupons by Practice G121.

7.2 Indicate the masses of coupons in grams as *MXy* where *X* is the coupon designation (number, letter, or name) and $y = 1$ indicates a clean coupon, $y = 2$ indicates a contaminated coupon and $y = 3$ indicates a coupon after cleaning.

7.3 Designate one coupon as the control coupon to undergo cleaning without contamination.

7.4 Measure the mass of the control and test coupons (recording them as *MX*1 as previously defined).

7.5 Contaminate five test coupons in accordance with Practice G121.

7.6 Measure the mass of all contaminated test coupons (recording them as *MX*2 as previously defined).

7.7 Process the control coupon in the test cleaning solution separately from the contaminated test coupons.

7.8 The contaminated test coupons can be processed in independent beakers held in the cleaning tank or as a batch in a single beaker.

7.9 Clean the test and control coupons in the candidate cleaning agent by the manufacturer's procedure or selected procedure.

7.9.1 Prepare the cleaning agent in accordance with the manufacturer's recommendations.

7.9.2 Select beakers of suitable size to accommodate the test coupons and fit the beaker holder.

7.9.3 Wash the beakers thoroughly with a solution of liquid, surface-active cleaning agent in hot water and rinse with type II water.

7.9.4 Fill the beakers with the cleaning agent solution to a level that will ensure the test coupons are submerged.

7.9.5 Fill the cleaning tank to its operating level with the transfer fluid and preheat to desired test temperature.

7.9.6 Place the beakers in the beaker holder in the tank so that the liquid levels in the tank and beakers are approximately equal.

7.9.7 Allow the temperatures of the tank fluid and cleaning agent in the beakers to equilibrate at the desired temperature.

7.9.8 Suspend the test coupons and control coupon in the cleaning agent, using a wire hook of the same material as the coupon or a compatible material. Position the coupons such that they do not touch the beaker or one another.

7.9.9 Begin agitation or sonication in the cleaning process and start the timer.

7.9.10 Upon completing the required cleaning time, discontinue the agitation or sonication, and remove the coupons from the cleaning agent.

7.9.11 Rinse the test coupon in accordance with the manufacturer's recommendations.

7.9.12 Allow the suspended coupons to dry overnight or in a forced convection oven for one hour.

NOTE 2—**Warning:** Do not place test coupons directly in the oven after application of the solution containing the contaminant. A fire may result if the solvent is flammable or rapid evaporation of the solvent may cause spattering of the contaminant thereby reducing the amount of contaminant on the test coupon. It is recommended that the test coupons be air dried until no traces of a liquid phase are visible.

7.9.13 Determine the final mass of each test coupon (recording them as *MX*3 as previously defined), including the control coupon.

7. Material Compatibility Testing

7.1 *Initial Determination of Material Compatibility*—The first step in using this guide is to determine the compatability of the material, or materials of the parts, being cleaned with the cleaning agent(s) (see Guide G127). This will provide material compatibility test data required to ensure the cleaner will not damage the parts being cleaned. It is important to note that alloys behave differently than pure metals and different alloys behave differently than other alloys; therefore, specific alloys must be utilized when conducting these compatibility tests. Non-metallic materials (for example, plastics) may also have compatibility issues with cleaners and this should be considered as well. If data are not available on a specific alloy with a specific cleaner, these data must be developed prior to the use of the cleaner. This can be performed by exposing the Coupon/Beaker of different Materials of Construction to the cleaning agent(s) to determine their compatibility prior to running any cleaning agent studies.

7.2 *Validation of Procedure*—Examine the control coupons to determine whether they lost mass (such as might occur if there was corrosion, incompatibility or oxidation occurring, if the coupons were dissolving, or if the standard cleaning procedure used prior to contamination had left residue on the coupons); gained mass (such as might occur if the solution was plating a material on their surfaces, or was depositing contaminant rather than removing it); or exhibited the same mass. The simplest valid test procedure is one in which there is no change in the control coupon's mass to within the measurement error of the balance. Controls for the contaminant's normal Loss on Drying (LOD) due to the contaminant containing water or other volatiles must be also be used. A control coupon should be coated with the contaminant and dried. Any loss on drying should be noted and used to adjust the weights of the contaminant applied to the test coupons to avoid the loss on drying being confounded with removal due to the cleaning agent.

7.2.1 If the control coupon is designated MC, and if | MC3 – MC1 | is less than the balance error, then the method is valid. Proceed to perform the chosen test method.

7.2.2 If | MC3 – MC1 | is greater than the balance error, the test may be considered to be suspect and the reason for the mass change should be investigated. If found to be a result of the cleaning agent, then this cleaning agent is not acceptable for use.

7.2.3 If necessary, additional material compatibility evaluations can be performed as outlined in Guide G127.

8. Cleaning Effectiveness Test Procedure

8.1 Prepare a set of test coupons/beakers following Practice G121. For oxygen service, this should be a minimum of 6 coupons (5 plus 1 control); however, the number of coupons/beakers depends on the requirements of the study and the number of coupons can be changed if justified. An additional "Control Coupon/Beaker" should be prepared and added to the study if MOC compatibility or the contaminant's normal Loss on Drying has not already been determined as described above or unless prior testing indicates this is unnecessary.

NOTE 1—Due to pharmaceutical regulations, all Materials of Construction must be "non-reactive and non-additive" for use in drug manufacture and have typically already been approved for use.

8.2 Indicate the masses of coupons in grams as MXy where X is the coupon designation (number, letter, or name) and y = 1 indicates a clean coupon, y = 2 indicates a contaminated coupon, and y = 3 indicates a coupon after cleaning.

8.3 Designate one coupon/beaker as the control to undergo cleaning without contamination (if used).

8.4 Measure the mass of the control and test coupons/beakers (recording them as MX1 as previously defined).

8.5 Contaminate the test coupons in accordance with Practice G121.

8.6 Measure the mass of all contaminated test coupons (recording them as MX2 as previously defined).

8.7 Process the control coupon in the test cleaning solution separately from the contaminated test coupons.

8.8 The contaminated test coupons can be processed in independent beakers held in the cleaning tank or as a batch in a single beaker.

8.9 Clean the test and control coupons in the candidate cleaning agent following Guide G93/G93M, or by the manufacturer's procedure or selected procedure.

NOTE 2—There are many procedures in use, some of which are proprietary and some which have been published, including some automated procedures.[3,4,5,6]

8.9.1 Prepare the cleaning agent in accordance with the manufacturer's recommendations.

8.9.2 Select beakers of suitable size to accommodate the test coupons and fit the beaker holder.

8.9.3 Wash the beakers thoroughly with a solution of liquid, surface-active cleaning agent in hot water and rinse with Type I or II water.

8.9.4 Fill the beakers with the cleaning agent solution to a level high enough that will ensure that the test coupons are submerged and low enough that spillage or cross contamination does not occur.

8.9.5 Fill the cleaning tank to its operating level with the transfer fluid and preheat to the desired test temperature.

8.9.6 Place the beakers in the beaker holder in the tank so that the liquid levels in the tank and beakers are approximately equal.

8.9.7 Allow the temperatures of the tank fluid and cleaning agent in the beakers to equilibrate at the desired temperature.

8.9.8 Suspend the test coupons and control coupon in the cleaning agent, using a wire hook of the same material as the coupon or a compatible material. Position the coupons such that they do not touch the beaker or one another.

8.9.9 Begin agitation or sonication in the cleaning process and start the timer.

8.9.10 Upon completing the required cleaning time, discontinue the agitation or sonication, and remove the coupons from the cleaning agent.

8.9.11 Rinse the test coupon in accordance with the manufacturer's recommendations.

8.9.12 Allow the suspended coupons to dry overnight or in a forced convection oven for 1 h at a temperature that will not affect the residues (melting, evaporation, etc.). Companies should establish temperature ranges that are acceptable and not to be exceeded during testing.

NOTE 3—**Warning—**Do not place test coupons directly in the oven after application of the solution containing the contaminant. A fire may result if the solvent is flammable or rapid evaporation of the solvent may cause spattering of the contaminant, thereby reducing the amount of contaminant on the test coupon. It is recommended that the test coupons be air dried until no traces of a liquid phase are visible.

8.9.13 Determine the final mass of each test coupon, including the control coupon, recording them as MX3.

9. ~~Calculation~~Calculations

9.1 *Validation of Procedure*—Examine the control coupons to determine whether they lost mass (such as might occur if there was corrosion occurring, if the coupons were dissolving, or if the standard cleaning procedure used prior to contamination had left residue on the coupons); gained mass (such as might occur if the solution was plating a material on their ~~surfaces,~~ surfaces through solvent swelling or was depositing contaminant rather than removing ~~it)~~it); or exhibited the same mass. The simplest valid test procedure is one in which there is no change in the control-coupon's mass to within the measurement error of the balance.

[3] ~~Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.~~Canhoto, A. J., Azadan, R. J., Putnam, J., Kreuze, M., and Williams, B. E., "A Semi-Quantitative Matrix for Selecting an Appropriate Cleaning Validation "WorstCase" Challenge Soiling Solution," *Journal of Validation Technology*, Vol 11, No. 1, November 2004.

[4] Rathore, N., Qi, W., Chen, C., Ji, W., "Bench-Scale Characterization of Cleaning Process Design Space for Biopharmaceuticals," *Biopharm International*, March 2009.

[5] Song, R., Canhoto, A. and Walsh, A., "Cleaning Process Development: Cleanability Testing and "Hardest-To-Clean" Pharmaceutical Products," *Pharmaceutical Online*, January 2019.

[6] Sharnez, R., Lathia, J., Kahlenberg, D., Prabhu, S., and Dekleva, M. "In Situ Monitoring of Soil Dissolution Dynamics: A Rapid and Simple Method for Determining Worst-case Soils for Cleaning Validation," *PDA Journal of Pharmaceutical Science and Technology*, Vol 58, No. 4, July–August 2004.

9.1.1 If the control coupon is designated MC, and, if and if | MC3 – MC1 | MCis3 – MC1 | < less than the balance error, then the experiment is valid. Proceed to calculate a cleaning effectiveness factor.Cleaning Effectiveness Factor.

9.1.2 If | MCMC33 – MC1 – MC1 | is greater than the balance error, the test may be considered to be suspect and the reason for the mass change should be investigated. Controls for the contaminant's normal Loss on Drying due to the contaminant containing water or other volatiles must be also be used. A control coupon should be coated with the contaminant and dried. Any loss on drying should be noted and used to adjust the weights of the contaminant applied to the test coupons to avoid the loss on drying being confounded with removal due to the cleaning agent.

9.2 *Cleaning Effectiveness Factor (CEF):*

9.2.1 The cleaning effectiveness factorCleaning Effectiveness Factor indicates the fractional contaminant that was removed during cleaning (for example, CEF = 0.9 = 0.9 indicates that 90 % of the contaminant was removed). Note: the CEF may be also calculated to indicate the fractional contaminant remaining instead. To measure contaminant removed:

$$\bullet CEF = \frac{MX2 - MX3}{MX2 - MX1} \quad (1)$$

$$CEF = \frac{MX2 - MX3}{MX2 - MX1} \quad (1)$$

where:

MX2 – MX3 = the mass of contaminant removed, and
MX2 – MX1 = the mass of contaminant applied.

9.2.2 Calculate the CEF for each test coupon.coupon (adjusted for volatiles if necessary).

9.2.3 Calculate the average CEF by arithmetic mean.mean, standard deviation, and confidence intervals.

9.3 *Residual Contamination (RC):(R_C):*

9.3.1 A cleaning agent does not necessarily remove a fixed fraction of the contamination on a given surface. In some cases, it cleans a surface to a constant residual cleanliness level. For example, sometimes the cleaned surface will exhibit a layer of organic material that has remained after a fluid vehicle has dried, and a constantIn many cases, it is more important to know if the cleaning has achieved a required limit for residues and a calculation RCof for varying initial contamination levels suggests this may be happening.how much contaminant is remaining after cleaning is more informative. These data can also be used as outputs of a Design of Experiment to help design a cleaning process.

9.3.2 Calculate the contaminated area ((S)S) of each coupon in square centimeters.

9.3.3 Calculate the residual contamination that is ((MX3MX3 – MX1) – MX1) in grams.

9.3.4 Using the equationTo measure contaminant remaining, use the equation:

$$R_C = \frac{MX3 - MX1}{S} \quad (2)$$

RC = (CalculateMX3 – MX1)/S, calculate the value of RCR_C for each coupon (milligrams/centimetre^2).

9.3.5 Determine an average RCR_C in(mg/cm^2 mg/cmor mcg/cm^2.), standard deviation, and confidence interval.

9.3.6 As an option, RCR_C can be calculated in mg/ftmg/in^2.

9.3.6.1 For coupons where the R_C is not measurable gravimetrically, analytical methods such as Total Organic Carbon analysis may be used to determine low levels of residues (see Test Method D6317).