Ethylene oxide sterilization of medical devices: A review

Gisela C. C. Mendes, MD, Teresa R. S. Brandão, PhD, and Cristina L. M. Silva, PhD
Porto, Portugal

Ethylene oxide (EO) is a well-known sterilizing agent. However, only recently has its use significantly emerged, based on its range of applications in the field of new medical device development and sterilization. This paper describes the progress in terms of EO sterilization and concludes that it remains a promising field to explore and develop. The EO action mechanism and toxicity are analyzed, and a critical analysis is made on how it is possible to use EO sterilization for medical devices advantageously, with emphasis on cycle design and validation. One huge challenge is related with the development of mathematical models to integrate lethality to allow a continuous increase of process flexibility, without compromising its safety. The scientific community should also focus on other important issues, such as EO diffusion in different substrates, taking into account different environmental conditions both for sterilization and aeration. (Am J Infect Control 2007;35:574-81.)

The field of medical sterilization has become increasingly complex because of the need to prevent patient exposure to infections caused by organisms on instruments and devices used during their care. Failures in adequate sterilization of medical devices (MDs) result in significant institutional costs related to patient nosocomial infections and mortality/morbidity concerns.[1,2]

The more widely used industrial MDs sterilization technologies are steam, ethylene oxide (EO), and γ and electron beam irradiation. There are other methods under development, such as low-temperature hydrogen peroxide gas plasma, low-temperature peracetic acid gas plasma, vapor-phase hydrogen peroxide, ozone, chlorine dioxide, and high-intensity visible light.[2-5]

EO has emerged as the sterilization method of choice for MDs because of its undeniable advantages compared with other technologies, which will be discussed in more detail. EO is an exceptional sterilizing agent because of its effective bactericidal, sporicidal, and virucidal activity. However, difficulties had to be overcome, mostly related with potential hazards of EO to patients, staff, and environmental, as well as risks associated with handling a flammable gas.[1,2,6-8] EO has allowed and contributed significantly to the advancement and evolution of delicate, complex, and sophisticated MDs that otherwise would not be available because, for sensitive materials, EO is the only acceptable sterilization method.[2,6] EO sterilization has become even more important since the single-use MD market has grown, and, with the purpose of cost saving in health management, there has been a transition to presentation of MDs in customized packs for use in specific medical and surgical procedures. The diversity of developed products, designs, types of materials, and packaging configurations resulted in an exponential growth of EO sterilization and made this method the most widely used MD sterilization technology, with a continuous growth tendency. Today, EO sterilization is described as the most cost-effective, low-temperature sterilization process available, with a recognized history of reliability.[6-11]

The aim of this paper is to summarize the information available on EO sterilization, and to present critical points of view about what has been done and is required, to provide the tools for advancement and optimization of EO sterilization of MDs. The present article provides a 4-part comprehensive review in the context of EO sterilization of MDs. The first part presents an overview of the EO activity mechanisms and inherent toxicity of the sterilizing agent. The second part summarizes the advantages of this sterilization technology over the other 2 industrial sterilization technologies most widely used. The objective is to explain why EO, despite many predictions about its demise as a sterilization alternative, still is a dominant mode of sterilization and continues to be used for increasing volumes of MDs.

The third part outlines the process design and process validation procedures, including the microbiologic validation, which is the most challenging in the context of validation. Finally, the last part addresses the state-of-the-art on optimization of EO sterilization

From the Universidade Católica Portuguesa, Escola Superior de Biotecnologia, Porto, Portugal.

Address correspondence to Cristina L. M. Silva, PhD, Escola Superior de Biotecnologia, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal. E-mail: clsilva@esb.ucp.pt.

conditions. Recently updated and very promising issues, such as parametric release, lethality, and EO diffusion modelling, are discussed.

EO STERILIZATION MECHANISM AND TOXICITY

EO sterilization mechanism

The EO high reactivity, as expressed by the high energy of its exergonic combustion reaction, in combination with its high diffusivity, is of major importance for the inactivation of microorganisms.[12,13] EO is a direct alkylating agent that does not require metabolic activation, and its microbiologic inactivation properties are considered to be the result of its powerful alkylation reaction with cellular constituents of organisms, such as nucleic acid and functional proteins, including enzymes, which leads to consequent denaturation.

The addition of alkyl groups to proteins, DNA, and RNA in microorganisms by binding to the sulfhydryl and hydroxyl, amino, and carboxyl groups, prevents normal cellular metabolism and ability to reproduce, which render affected microbes nonviable.[1,12,14-17] These chemical moieties are not present in most of the MDs composition; therefore, exposure to EO does not cause them similar structural changes.[5,18]

EO toxicity

Taking into account the previously described EO sterilization action mechanism, it is easy to understand EO toxicity as a chemical agent and potential related problems with employee, patient, and environmental safety.

EO toxicity in the workplace

The ability of a chemical to serve as an alkylating agent, and to cause mutations in a variety of biologic test systems, is widely accepted as an indicator that the chemical may have carcinogenic potential. Both alkylation and mutagenicity potential have been demonstrated for EO.[19,20]

However, nowadays, EO can be used safely, with minimal personal risk of chemical hazardous exposure, by following recommended practices and meeting current Occupational Safety and Health Administration EO regulations.[9] Despite the discussions about EO potential risk, this sterilant is being used with greater frequency, especially because of investments made on equipment that have dramatically improved the efficiency of the process and make it possible to meet concerns over worker exposure. The process equipment of modern plants generally consists of tightly closed, highly automated, and controlled systems.[1,2,7,21]

EO toxicity in sterilized MDs: control of residues

In addition to the problems associated with EO toxicity in the workplace, it is also important to take into consideration the EO and its secondary product residuals and toxicity on sterilized MDs. EO and some of its derivates, such as ethylene chlorohydrin, which appears when chloride ions are present, and ethylene glycol, formed by EO reaction with water, are toxic residues.[14,22-24]

Taking into consideration the diversity of MDs sterilized with EO, and the potential undesirable effect on patient health, residue control is required. The accurate determination of residues is also critical for the development of reliable risk assessment data used by toxicologists, epidemiologists, MD manufacturers, and regulatory bodies.[25]

The series of standards governing the biologic testing of MDs include the International Organization for Standardization (ISO) 10993-7 (Biological Evaluation of MDs—Ethylene Oxide Sterilization Residuals), which specifies the allowable limits of EO and ethylene chlorohydrin by categorization of products based on examination of toxicologic risk of the residue to the patient, according to the length of the time the patient is likely to be exposed to the device.[26]

Just as EO diffusivity has been a well-studied field, so, then, MD design, including the selection of materials that will follow EO sterilization, can be done in a similar logical way. Moreover, investigations about the efficacy of different aeration methods are required.

Different aeration technologies have been reported, such as pulsed vacuums postprocess and heat addition, steam addition, and removal, as well as combinations of different gases and pressure set points and newer developments, such as microwave desorption. Despite the major interest on this issue, there are no recently published studies about efficiency comparisons for the different aeration technologies.[27]

EO STERILIZATION AND ITS SPECIFIC ADVANTAGES

The compatibility of EO with a wide range of materials and its chemical molecule penetration properties in not so aggressive environments, compared with dry heat or steam, made EO sterilization the most suitable process for the majority of heat- and/or moisture-sensitive medical products.[20,28]

The effectiveness of EO sterilization, coupled with the flexibility of the process allowed by the large number of possible control variables, represents some of the advantages of this method.[1,7-10,12,18] Taking into consideration the thermal or moisture sensitivity of the specific material, the parameters of the EO cycle can be adjusted to preserve the integrity of the device.

Steam and γ irradiation sterilization frequently cause polymers degradation and changes in physical or mechanical properties, which can be detrimental for intended performance.[29-31] Many MDs are composed of heat-sensitive materials. Regarding γ irradiation, generation of free radicals through hemolytic bond cleavage occurs because ^{60}Co sources supply 1.17 and 1.33 MeV photon energies, which correspond to 5 orders of magnitude larger than the average energy of a chemical bond.[28,32-36]

The opinion of some sterilization specialists on new developments in the MDs sterilization techniques that use oxidizing agents such as hydrogen peroxide, ozone, peracetic acid, and chlorine dioxide is that limited development will occur because of inherent adverse effects on material properties.[4]

FROM PROCESS DESIGN TO MARKET RELEASE OF EO STERILIZED MD

Process design includes the planning of the physical parameter conditions (such as temperature, humidity, and EO concentration) of a sterilization process, taking into consideration the limitations imposed by the product, the sterile barrier packaging, and the equipment.[37] The efficiency and profitability of the process, the personnel safety, and the equipment integrity as well as the well-being of the end user of EO-sterilized MDs are all directly related to the cycle design. Regarding efficiency, the influence of each of the EO sterilization process parameters on reaction kinetics should be considered when a cycle design is being conducted. Modelling of accumulated lethality and EO diffusion kinetics are 2 important issues that will be further discussed in more detail.

The sterilization process must consistently assure that all critical process parameters are delivered within the load, to a degree that assures the required sterility assurance level, without causing any deleterious effect on product and its sterile barrier package functionality and safety.[37-39] These activities are part of the process validation, which includes physical and microbiologic performance qualifications.

The release of the MDs to the market is done according to the process specifications defined during validation. There are 2 methodologies for market release of MDs: conventional and parametric. The conventional traditional method of release requires that the process parameters are within the validated tolerance and that the biologic indicators (BIs) exposed to the sterilization process are inactivated. On the other hand, parametric market release relies solely on the recording and evaluation of the process parameters because the equipment potentialities are enough to evaluate the impact of process parameters on microbiologic inactivation.[39] Parametric release is still a very challenging topic and will be further discussed in more detail. A well-structured process design, its rigorous validation, and strict and efficient control of the sterilization cycle parameters are the key principles for the safe and efficacious release of the MDs to the market.

Process design

Investigation of all process variables impact is mandatory for reaching a well-structured EO sterilization process. Furthermore, considerations about product compatibility together with optimization of the sterilization process should be undertaken.

The lethality of EO sterilization depends on the following 4 process parameters: (1) EO concentration, (2) exposure time, (3) temperature, and (4) humidity.[1,10,37,40] The increase of EO concentration within certain limits results in extended microbial inactivation and exposure time decrease.[1,10] Heider et al[40] found a first-order kinetics behavior across the entire concentration range, from 50 to 1200 mg/L. In the past, concentrations of EO up to 1200 mg/L were common, whereas, today, EO concentrations of even less than 300 mg/L are being used.[5,40] A progressive decrease of EO concentration levels have been verified, which results in shorter aeration periods after sterilization and additional environmental, health, and safety benefits.

Temperature is an extremely important parameter affecting microbial lethality.[40,41] Table 1 presents published Q_{10} and related z-values. A consensus seems to have involved a Q_{10} value of 2, which means that a 10°C change would affect lethality by a factor of 2.

Environmental humidity appears to be another critical variable; however, there were always differing opinions about the required optimum relative humidity (RH).[13,42,43] Most of the recent studies indicate that, within the limits of 30% to 90%, the RH does not influence lethality. Sterilization efficacy decreases markedly below 30% and above 90% because RH is critical for the EO diffusivity into devices and microbes.[10,13,41] Heider et al[40] found a correlation between the reaction kinetics rate and the RH in the 10% to 60% range, whereas no further changes were observed at higher levels. According to this, it is recommended to ensure a RH of more than 60% so that the effectiveness of the sterilization process is not compromised. Although, nowadays, it is considered that the RH effect is constant if the parameter is within the limits of 30% to 90%, additional studies should be further performed to assure the true veracity of this information.[10]

Besides the EO sterilization process parameters influence on process design, other variables, such as natural bioburden, device/package properties, load density, and configuration in which the specific MD is

Table 1. Effect of temperature on EO inactivation—Q_{10} and related z-values

Reference	Q_{10}	z-value (°C)*
Ernest[55]	1.8	39.2
Plug et al[56]	1.90	36.0
Bruch[57] and Lui[58]	2.19	29.4
Phillips and Miller[13]	2.21	29.0

*$z = \frac{10°C}{\log Q_{10}}$.

included for sterilization, should be considered. Within the device/package properties, the raw material composition, materials diffusion properties, sensitivity to both negative and positive pressure changes, and maximum allowed heat and moisture as well as chemical tolerance to EO should be analyzed.[10,40,41]

Process validation

The validation of EO sterilization processes, which includes physical and microbiologic performance qualification, is described in detail in ISO[44] 11135 and European Norm (EN)[45] 550. However, none of these norms include guidance for the selection of a sterilization process challenge device to be used as representative worst case matrix. Manufacturing conditions, construction materials, and product design, including materials geometric variability and packaging characteristics, are among the factors that need to be considered. However, the way to relate all these variables is a great challenge for the sterilization specialist. The physical performance qualification allows the verification of the cycle reproducibility, as well as evaluation of the cycle impact on the product, packaging functionality, and safety.[39]

The purpose of microbiologic validation is to assess the microbiologic lethality of the sterilization process.[38,46] The above referred international and European norms provide different approaches for carrying out microbiologic performance qualification and will be described in more detail.[44,45]

Microbiologic validation

There are 3 microbiologic approaches for process definition, which are by decreasing order of utilization:

- Overkill method;
- combined biologic indicator/bioburden method; and
- bioburden method.

The overkill approach uses BI data to assess the microbial inactivation rate for a given process. The process definition based on ''Combined biological indicator (BI)/bioburden method'' defines the treatment extent required to achieve the specified sterility assurance level from knowledge of the BIs inactivation and of the product bioburden population to be sterilized. The ''Bioburden method'' is a process definition based on inactivation of the microbial population in its natural state.[47]

The overkill method is applicable as long as the combination of population (10^6 microorganisms of *Bacillus subtilis niger*, reclassified in 2001 by Fritze and Rudiger[48] as *Bacillus atrophaeus*) and resistance of the BI, expressed as D-value, exceeds that of the product bioburden. The sterilization process definition based on this approach is often conservative because necessary sterilization cycle parameters are significantly higher than those required to kill product bioburden. Cycle lethality determination can be obtained from the half-cycle method, which consists of determining the minimum time of exposure at which there are no survivors from tested BIs. According to this method, at least a 6-log reduction in population of microorganisms is demonstrated for the BI organism in the half cycle. Using the same process parameters, except exposure time, full sterilization cycle achieves at least a 12-log reduction by doubling the half-cycle time. No D-value calculations are performed, and, because of its simplicity, as well to the robust sterility assurance level that is achieved, this is probably the most popular approach.[1,10,38,40,44,45,47-49] The advantage of the other 2 microbiologic approaches, combined BI/bioburden method and bioburden method, is a reduction in cycle exposure time and, consequently, the product exposure to the sterilizing agent is minimized.

The combined BI and bioburden method requires a low population of the product bioburden and the microorganism's resistance to be known, as well as a high level of confidence that the bioburden data are representative of ''worst case conditions.'' The process definition based on the bioburden method requires extensive testing during the development phase and routine processing. It requires a validated bioburden recovery method and identification of the microorganisms that are typically found in or on the routine product, as well as more exigent environmental and manufacturing process control. Furthermore, it is necessary to carry out fractional exposure cycles on a regular basis to support the continued effectiveness of the sterilization process. Despite the extensive work that the bioburden method requires, it may be a requirement if there is a reason to believe that the MD may be contaminated with microorganisms more resistant than the BI.[10,38,39,47,49]

Besides the half-cycle method, there are 2 other commonly used methods for estimating or calculating cycle lethality: the survivor curve method and the fraction-negative method. The survivor curve construction method calculates cycle lethality based on

enumeration of survival microorganisms, and the fraction-negative method uses growth/no growth data from the sterility tests.

The survivor curve construction is performed by counting microbiologic survivors in terms of colony-forming units, recovered after exposing the microbiologic population to sublethal sterilizing cycles of graded exposures of EO, with all other parameters except time remaining constant. The survivor curve construction should include at least 5 points, imposing increasing exposure times to EO, and the resulting data give the EO exposure time required to achieve a particular probability of survival of the test organism.[38,44,50]

The fraction-negative method is also carried out by exposing BIs to sublethal cycles, but the analysis is done to growth/no growth data from the sterility tests.[44,49,50] The exposure time required to achieve a specified survival probability of the test organism is calculated from the D-value, using the limited Spearman-Karber procedure, which is the common reference method for international standards. However, there are other commonly used statistical methods, such as the Holcomb-Spearman-Karber procedure, the Stumbo-Murphy-Cochran procedure, or the limited Stumbo-Murphy-Cochran procedure, which can be used under particular conditions,[38,50] although an ISO meeting suggested that the Stumbo-Murphy-Cochran procedure was less accurate than the limited Spearman-Karber procedure, and the ISO recommended abandoning the Stumbo-Murphy-Cochran procedure. However, according to Shintani et al,[51] the Stumbo-Murphy-Cochran procedure is not less accurate than the limited Spearman-Karber procedure. In fact, the Stumbo-Murphy-Cochran procedure seems superior to the limited Spearman-Karber procedure with the proposed restriction (ie, $n \geq 50$, $r \geq 1$, $r/n < 0.9$, where n is the number of BIs and r the number of negative BIs).

Because of its major simplicity, the half-cycle method is more popular than the fraction-negative method, and the least popular is the construction of the survivor curve. However, according to the present regulatory remarks, the microbiologic qualification of a parametric release sterilization, which will be explained later in more detail, should not use the half-cycle method because of the fact that it does not provide sufficient information on lethality kinetics.[44]

EO STERILIZATION PROCESS OPTIMIZATION

Optimization of EO sterilization processes is a challenge because of the fact that the global competition market requires cost-effectiveness, flexibility, and inherent reduction of overall sterilization process time while continuing to comply with regulatory requirements and product quality.[8,9,11] Traditionally, most of the EO sterilization production time is taken up with 2 operations, which are when products are held waiting for the microbiologic test results and/or for the validated aeration time to ensure residues levels in compliance with the requirements of ISO 10993-7.[26] Implementation of parametric release simply eliminates the microbiologic test phase from routine.[8,9,11,44,45,52] Validation of not only sterilization but also the aeration process, with consequent assessment of EO residues in compliance with the requirements of ISO 10993-7,[26] has allowed a reduction in processing time. Furthermore, to get a reduction on EO residuals after sterilization, research in the field of EO diffusion is required. Investigations about comparative efficiencies among different ways of carrying aeration are also lacking.[8,9,11]

To shorten production time, a joint study involving sterilization and aeration processes limits shall be performed. Direct measurement of key process variables, as well as improvements in process design achieved through scientific modelling and experimental evidence, allows development of each process phase and consequent reduction in an overall sterilization process time. EO sterilization process optimization will be explained below in more detail under 3 main topics: parametric release, lethality modelling, and EO diffusion modelling.

Parametric market release

Parametric market release is the declaration of product sterilization adequacy based solely on measurement and evaluation of physical process parameters compliant with previously validated parameters.[8,39,44,45] The main difference between parametric and conventional release is the number of process parameters directly measured. According to ISO[44] 11135 and EN[45] 550 requirements, for conventional release compliance, the parameters that should be directly measured are the time of each phase, the pressure throughout the process, and the headspace temperature. The remaining two critical parameters, humidity and EO concentration, can be quantified indirectly by thermodynamic calculation based on pressure rise and temperature. Acceptance of the 2 indirectly measured parameters is supported by the negative growth of the exposed BIs. According to conventional release procedure, the BIs data integrate and confirm that appropriate levels of heat, water vapor, and EO concentrations have been delivered to the load, as demonstrated during microbiologic validation of the process.[11,44,45]

The philosophy of parametric release is that once a cycle is validated, using direct analysis of all critical

process parameters and distribution of microbiologic indicators, the resulting data can be used to define scientifically the approved physical limits of each of the process parameters.[44,45] Parametric release is, from a scientific point of view as well as from a strategic production standpoint, the preferred choice. In comparison with conventional release, the more thoroughly monitored process parameters give further understanding and stricter sterilization process control, simultaneously reducing costs and bringing a significant flexibility to the process.[8,11,44,45,52]

Lethality modelling

The scientific modelling of the EO sterilization cycle allows the definition of optimal microbiologic inactivation conditions. The prediction of accurate D-values and process times, necessary to achieve the target sterility assurance level, allows to reduce cycle times and/or EO concentration and the comparison of effectiveness and equivalency of different sterilization processes. Furthermore, the lethality modelling contributes to the process efficiency and flexibility, and the industrial movement toward parametric release is much more scientifically supported.[10,40,53]

To integrate mathematically the dynamic temperature and concentration conditions effects on inactivation, Rodriguez et al[42] developed the following model for BI spores of *Bacillus subtilis niger*:

$$N(t) = \frac{N(t=0)}{e^{\left[k_{T_R}\int_0^t C(t)^n * 10^{\frac{T(t)-T_R}{z}} dt\right]}} \tag{1}$$

where *C*, EO concentration; *C(t)*, EO concentration as a function of time; *k*, rate constant; *N*, number of survivors; *N(t)*, number of survivors as function of time; *t*, time; *T*, temperature; *T(t)*, temperature as a function of time; T_R, reference temperature; *n*, exponent; and *z*, temperature increase required to reduce the decimal reduction time (D-value) by 90%.

The model was validated under the following conditions: 15% to 90% RH, 200 to 1200 mg/L of EO gas, and z-value of 29, 4°C.[42] The same authors also deduced an expression for determining the accumulated lethality (equivalent process time) of an EO sterilization process[42]:

$$F_{T_R,C_R,z} = \frac{1}{C_R^n}\int_0^t C(t)^n 10^{\frac{T(t)-T_R}{z}} dt \tag{2}$$

where C_R, reference EO concentration; *F*, exposure time at T_R and C_R that would cause the same lethal effect as the *T(t)* and *C(t)* temperature regimes—equivalent process time.

Mosley et al[10] criticized equation 2, referring that, although it is mathematically correct, it is unusable in the given format because of the fact that EO concentrations cannot be defined by any reasonable equation. Although an n = 1 was suggested, no solution for *n* was proposed.

Mosley et al[10] enlarged the scientific modelling of EO sterilization by deducing another mathematical approach that allows the calculation of equivalent time, based on reference values for EO concentration (C_R) and temperature (T_R), for different EO concentration and/or temperature conditions:

$$F_{C_R,T_R} = \left(10^{\log t_{T_R}}\right)\frac{C}{C_R}$$

and,

$$\log t_{T_R} = \log t_T + \frac{(T-T_R)}{z} \tag{3}$$

where t_T, time at a given constant temperature *T*; and t_{T_R}, time at reference temperature. The same investigators also developed another equation to determine accumulated equivalent time, where conditions are changing for EO concentration and/or temperature:

$$F_{C_R,T_R} = \sum_{i=1}^{n} F_i = \sum_{i=1}^{n}\left(10^{\left[\log t_{T_i} + \frac{1}{z}(T_i - T_R)\right]}\right)\frac{C_i}{C_R} \tag{4}$$

where *i*, process step, for which the EO concentration and temperature are constant; and *n*, total number of process steps.

According to Mosley et al,[54] greater errors can be associated with calculated integrated lethalities for steam processes because z-values are lower and more variable under steam sterilization.

The mathematical models above presented are essential for designing EO sterilization processes. Optimization and validation of the different methodologies are a requirement.

EO diffusion modelling

The study of EO diffusion from the sterilizer headspace to the articles and through the articles is a challenge matter. Once well understood and defined, efficiency comparison among different aeration methodologies, and prediction of the dynamic distribution of EO concentration within the load, with the purpose to define the specific relationship between EO concentration and process lethality as well as to diminish EO residuals after sterilization, will be possible. However, despite the interest of this kind of studies, investigations in this field are almost inexistent. Once the modelling of accumulated lethality, as well as the modelling

of EO diffusion according to different matrices, is fully comprehended, then new approaches for design, validation, and routine control of the EO sterilization processes will occur.

FINAL REMARKS

EO sterilization is a key issue for current medical device designs, and a considerable amount of work concerning this topic has been published. Experimental evidence and scientific modelling have allowed significant improvements on each process phase, resulting in overall reduction of sterilization process time, without compromising the delivery of sterile and safe products to the market.

Further developments are needed in terms of understanding the microbiologic inactivation kinetics under EO sterilization process conditions. In parallel, there is much to be done to understand EO diffusion behavior on different materials. The ability to predict the dynamic distribution of EO concentration within the load being sterilized would allow the estimation of theoretical sterilizing EO concentrations.

Comparison of effectiveness and equivalency of different aeration methodologies are also required. In the same context, it is also critical that the development of reliable risk-assessment analysis for EO and related residuals mature.

In terms of speed to the market and despite the great advances already achieved, EO sterilization and its unique capabilities are still in progress. Regarding newer and future developments on MD sterilization methodologies, it is essential to compare them against the characteristics of an ideal low-temperature ($<60^{\circ}C$) sterilant, which includes high efficacy, rapid activity, strong penetrability, material compatibility, nontoxicity, adaptability, ability to withstand an organic load, monitoring capability, and cost-effectiveness.

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