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Eu gmp annex 1 pdf 2016

Introduction There are two main, global guidelines for the production of sterile products: the FDA manual, last revised in 2004 (1), and Annex 1 of the EU GMP (2). This is Annex 1, which has recently undergone a major revision, albeit in rough form; it currently contains 269 general provisions (compared to 127 in the latest version). The importance of the new Annex 1 project is that it not only signals changes in the approach of European regulators regarding the safeguards required for the production of sterile products, but also signals a new global direction, given that the FDA has participated in a review of the document under the PIC/S Convention Application 1 EudraLex Rules governing medicines in the European Union is part of Volume 4 of European Guidelines (2). The purpose of the current application and its continuation as a new, modified version, which is expected later in 2018, is to emphasize that the production of sterile products is subject to special requirements. These requirements are necessary to minimize the risks of microbiological contamination of sterile products by particulate matter and piegens; and also to provide guidance as to how sterile products are best protected. This guide includes staff training, equipment qualifications, clean room design and environmental monitoring. The trigger points for the App review included the emergence of new technologies, inadequate root-cause analysis and ineffective CAPA, poor implementation of IR-9, and various points of ambiguity in the interpretation of application 1 requirements. The 1 GMP EU application was first released in 1989 and has not undergone any major changes since 2007 and has changed since 2009 (in 2009 there was a slight clarification on the required classification of air supplies for scuba diving - Class A of Air Supply) (2). The lack of updates over the years has been notable in the context of updates to clean up the technology and the emergence of new types of fast microbiological methods. In 2014, during the rounds of the conference season, it was announced that the app would be reviewed. The project was a lengthy process; signal that the project is imminent was first sent in January 2015 to the released Concept Document (3). There are also a few paragraphs taken from the European Medicines Agency's sterile products guide issued in 2016 (4) (which still remains in the form of the project at the time of writing). The concept paper was continued with a few short messages. The project was finally published through the European Medicines Agency during the third week of December 2017 (5). the protracted release process was undoubtedly due to national disagreements over the revision of some of the technical aspects of the document. The project has four broad areas of change in terms of tone and accent. It's This. at different intervals in the document (often through repeated cases). These areas: Global recognition and implementation of ICH No.9 (quality risk management) and No.10 (Pharmaceutical quality system) is not reflected in the current application. The new draft contains many references, in particular to quality risk management, emphasizing that the CRC should be used as a pre-emptive tool. The new project currently has 92 copies of the word risk, which is more than in the previous version. Progress has been made in sterile manufacturing technology, especially with RABS and insulators. In addition, progress has been made in rapid microbiological methods, as the draft application acknowledges. The current version was ambiguous, and these necessary amendments or clarifications in Annex 1 often went beyond sterile production, including aspects of non-sterile production. The scope of the new project has been modified and expanded to reflect this. There is also a new requirement for an official, holistic pollution control strategy. An official document reflecting the strategy at all sites to minimize pollution control for sterile production is now expected to be prepared. The purpose of this article is to consider the major changes in relation to these broad themes, and to better understand the new paradigm for the production of sterile medicines. This will be useful for those who wish to comment on the project and for those who want to prepare for the final document (expected to be later in 2018), as many key concepts are unlikely to change. The application update process took about three to four years, after the European Medicines Agency announced its intention to begin the renewal process in late 2014. The resulting product has expanded considerably in length, increasing from 15 pages to 50. In addition, there are currently 269 different provisions (in addition to about 100 in the current version, and many of them are expanded). In addition, about 100 provisions have no connection to the status quo. It is also noteworthy that the 14 provisions of the previous version, which are not present in any form in the update, and that only 40 provisions have not actually changed compared to the original version. New sections include one-time technologies; Aseptic operator qualifications; Applying quality risk management to a variety of topics disinfectant qualifications for clean surfaces; water treatment systems, including the production of water systems per year of injections; other utilities and closed production systems. Many of them are considered, along with others in this article. The introductory sections of the Project App opens with a list of content and is divided into eleven parts, making navigation easier compared to the previous version (which was missing such a guide to the document). This is followed by a section called Sphere (while the current annex enters directly into the declaration of principle, which examines sterile products as a whole). In the new Sphere section, the new project contains a broader definition of sterile products (sterile active substances up to the finished dosage form); changes are noted in terms of the size of batches, packaging materials and the types of technologies used to produce sterile products. This refers to quality risk management (CBPs) to combat microbial pollution. It emphasizes here that the CRM must be active, and this point is repeated several times in the document; RM link aligns the application with ICH No.9 Quality Risk Management (6). From a language point of view, the wording is not always elegant or consistent: there are several references to actions as preventative; here, if the guide is specifically talking about CAPA, in which case it would be customary to use the word preventive. The Sphere section further states that content may be applicable to certain types of non-steroid processing. This applies to microbial, solid and pyrogenic controls where principles can be applied to the development of controlled environments, robes and staff practices. This is probably a reflection of the fact that many non-steroidal product manufacturers are using annex 1 manual to set some internal standards for microbial control. Following the Region, there is a section entitled Principles. This section looks at a number of important areas. The first concerns qualifications and verification. It mentions the equipment used in latrines; Facilities (clean rooms, utilities); and process design. The draft states that users must follow other EU GMP applications, such as Annex 11 (Computerized Systems) and Appendix 15 (qualification and verification). This is the first time that annexes Annex 1 with other parts of the EU GMP. The reference is made to the staff, pointing out early on that people are critical to the processes. Particular attention is paid to the importance of hiring staff, with appropriate skills, training and approaches to protect a sterile product. This applies to production, packaging and distribution in the form of skills, training and relationships. The last two areas are called: packaging and distribution are often excluded from pollution awareness control courses in companies, so attention may need to be paid here. Necessary skills, depending on the function: process, engineering and microbiological. Of interest is the reference to the attitude that puts a greater emphasis on the person's behavior and on the fact that employees are satisfied and motivated by high-quality product. Pollution control strategy Much of the The section is transferred to each object that has a detailed pollution control strategy specific to the object. In order to be effective, it must be an approach that can assess seemingly isolated pollution events holistically and which is able to take appropriate corrective and prevention measures (CAPA) (7). This is designed to sell a new paradigm in terms of pollution control, outweighing the risk review process to a process that assesses the impact of a pollution event in a much broader context. The main elements of this management strategy are: the design of both the plant and the process. Equipment and equipment. Staff. Utilities. Control of raw materials, including control in the process. Containers for products and closures. Supplier approval, such as key component suppliers, sterilization of components and systems of different uses, as well as services. With regard to external services, such as sterilization, the contract provider should be provided with sufficient evidence to ensure that the process works properly. Process risk assessment. Process review. Preventive maintenance - maintenance of equipment and premises (planned and unplanned maintenance) to the standard, which does not add a significant risk of contamination. Cleaning and disinfection. Monitoring systems - including an assessment of the feasibility of implementation by scientifically sound, modern methods of optimizing the detection of pollution. Prevention - Trends, Investigations, Corrective and Preventive Action (CAPA), Identify the root causes and need more reliable investigative tools. Continuous improvement based on information from the above systems. With each of these different elements it is noteworthy that they are not limited to biocontation, as the reference is also made to subcutose particles (classic appearance tests) and the overall appearance of the pharmaceutical product. The draft mentions ISO and other standards that should be reviewed in the development of the monitoring strategy (although not directly triggered, as many commentators had hoped, this would lead to the conclusion that this would be the focus of ISO 14698 Parts 1 and 2) (8). The strategy should also consider modern methods (read by rapid microbiological methods) and the process of continuous improvement. This signals that manufacturers need to constantly survey industry trends in the best available technologies to control pollution. The draft also stresses that the pollution control strategy, which should be effective, should be regularly reviewed in terms of its feasibility, as well as in terms of how well CAPA is used. This includes more than just effectiveness of the results of the investigation, but also regular reviews of data on trends. Pharmaceutical quality system The first main section of the project refers to the pharmaceutical system of quality, quality, quality, quality, quality, quality, quality, quality, quality, systems that every manufacturer should have in place. Although general issues are covered in Chapter 1 of the EU GMP, the draft annex mentions specific aspects of sterile production. These include: proactive use of risk management. A regular review of risk assessments. Justifications for considering the different risk categories resulting from risk assessment. Hiring staff with sufficient experience to conduct risk assessments. Using effective root causes and CAPA. Those facing the challenge of producing products should be fully aware of the risks and quality issues. The first two bullet points signal a continuing link to risk management and risk assessment throughout the document. In accordance with previous observations, the risk assessment process is not limited to production, but should extend to packaging (primary and secondary) and distribution of the finished drug product, thus accepting the requirements for good distribution practices. Staff There is a large section in the project dedicated to staff. In this section of personnel data, the content of the draft document has increased significantly. The section begins with a comment about limiting the number of staff allowed to enter the restrooms. The recommendation is that the number of staff, especially in sterile production areas, is minimized on the basis of risk assessment. This confirms that the greatest risk of microbial contamination in clean rooms comes from humans, mainly through shedding and touching critical surfaces (9). In monitoring access to latrines, there is a reference to the importance of inspections, such as the quality checks carried out by the Group, which are carried out outside the restroom. This leads to the conclusion that inspection windows are used or the use of a closed-circuit camera system. Another restriction applies to microbiology staff who deal with microbial cultures, offering some level of internal control so that staff working on the identification bench perform environmental monitoring tasks, as the new supplement indicates that such staff usually should not enter aseptic processing areas. As expected, training plays a significant role in the personnel section. This applies to everyone who enters the restroom, including cleaning and maintenance staff. The minimum basis for the curriculum is set to include: hygiene, clean practice room, pollution control, aseptic methods, and potential consequences for patient safety loss of product sterility and in the basic elements of microbiology. To access higher-grade clean rooms (classes A and B) staff are expected to complete the aseptic qualification process (e.g. through media). An exception is made for service personnel in exceptional circumstances, although it is necessary will be monitored. The core for teaching any person entering a clean room is to score gowning; this should also include staff samples such as the contact plates of their suits and finger fingers (10). This monitoring should also be carried out after each critical activity. In this regard, it is also possible to learn about some of these samples taken independently, such as the staff of the Quality Unit. With gowning, a link to fully closed glasses has been added - in fact it means wearing glasses. This is what the UK MHRA has been pushing for for several years. Other new additions include a poor health reporting system plus periodic health checks; Requiring you to enter a phase into the building to have hand-washing tools; And for employees entering The Class B or C restrooms have undergone initial changes to remove outdoor clothing and don cleanroom 'scrubs' before accessing the final stage of the locker room. Environmental control is under personnel control. A notable change is the removal of references to the established temperature range for clean Class B rooms, with a long-standing temperature range of 18 x 3oC dropped. A reference to humidity has been added, with the phrase: Ambient temperature and humidity must be met to prevent shedding due to operators getting too cold (which leads to excessive movement) or too hot now appearing. In fact, it is a call for further risk assessment. This risk assessment should also include factors such as how much time an operator should spend working in a clean Class B room (the answer here will have to take into account temperature and humidity). Cleanroom Design There are various references to the design and operation of clean spaces in the app. One notable change is the draft application, which currently has the potential intention of a HEPA (or higher) filtering mandate in all classified areas (including Class D). Until now, the D class area could have been, at least in theory, without the need for HEPA filtering. The text as it stood was somewhat ambiguous and could be amended following a period of consultations. Section 3 is added to section 3 requiring each manufacturer to determine conditions in operation and at rest for all clean rooms or latrine sets. This is due to the fact that the facilities are different, although at rest, usually a room complete with all HVAC systems, utilities, functioning and with production equipment installed according to the specified, but without personnel at the facility and production equipment is static and in operation taken for a condition in which the installation functions in a certain mode of operation with the specified number of personnel, It is also proposed that cleaning procedures, rest periods and any other variable conditions should be prescribed in the definition. Unfortunately, with the project There remains some ambiguity around Grade A. This is a transfer from the 2009 update, where the app refers to Class Conditions for Aseptic Processing and Grade A Air for Scuba diving. The requirements for Grade A air supply have had a point of discussion since they appeared, with the consensus being the assessment of Class A at rest. To further complicate things, the new link appears to be on the Class Environment. Although there is currently a glossary at the end of the application, there is still a lack of clarity between the three terms. Further change is due to the maintenance of laminar conditions, which must be demonstrated in open applications compared to insulators/glove boxes where lower conditions are permissible. The continuation of the word laminar, which is mixed with the use of more conventional one-directional, is another reason for ambiguity in the draft. As for the unidirectional air, there is an extension, with paragraph 5.12, from this is the requirement of the Class A environment to include Class B in relation to the clean room used for the RABS home (in particular, not the insulator). This can be challenging for some objects. A constant measure of unidirectional air is to monitor air speed; Here the warning systems should be in place to warn of any decrease in air speed or pressure. With a clean room used to contain the insulator where it is a positive pressure insulator, the app addresses a long-standing debate about the appropriate background environment (about whether a Class C or Class D is appropriate) by settling on a Class D. Further for design, the transfer of manholes without airflow were called as cause for concern. The annex stipulates that the hatches together with the gateways should be effectively washed with filtered air for both personnel and materials. Barrier containment devices receive a number of references in the application from the point of view of RABS (which are described as passive, open or closed) and insulators. Although there is no direct requirement for drug manufacturers to use such devices, the application concludes from the RABS statement, insulators or closed systems in order to reduce the need for Class A intervention and minimize the risk of infection that barrier technology should be adopted. With all forms of RABS, the app requires that research be conducted to demonstrate the lack of air entry. With insulators, there is a reference to the importance of choosing the right glove insulator; those with good mechanical and chemical stability, as well as testing gloves to leak before each batch of production (glove integrity testing). Both with RABS and with insulators requiring that all items transferred to the process, and that these processes will be tested. The cleanroom classification with the cleanroom classification, classification according to ISO 14644-1 mandated and this added to Section 4. In addition, restrictions for non-viable particles in Class A-through D environments are set in class 5 ISO equivalents, which are helpfully included alongside EU GMP estimates; Class D - ISO 8 class equivalence, specified for the first time). In accordance with the changes, ISO 14644 removed the 5.0 micrometer particle monitoring requirement. It is important to note that the exemption of 5.0 euros applies only to classification; continued monitoring of these particles remains a prerequisite for monitoring aseptic processing and other clean-up activities, as established in section 9. It is embarrassing that the classification monitoring and routine monitoring requirements are in different sections and are divided into 25 pages. In addition, the draft application considers additional requirements for the classification of clean spaces (in addition to ISO requirements) in critical areas. This is in terms of adding additional risk-based seats and examples of such cork bowls inside petrol stations are referenced. Portable tube counters are designated as appropriate equipment for classification; this means that the central blocks with long tube length are not acceptable for classification purposes. Although the lengths of the pipes are not specified, this requirement may require investment in new equipment for some manufacturers. Filtering sterile filters is a critical step for aseptically-filled products where products pass through a filter of 0.22 microns, with pressure and time control. A key measure is to evaluate the bio-burden of the product before filtering. Surprisingly, the application does not mention the European CPMP manual for 10 CFU/100mL (11), and instead makes a comment about the requirement to link bio-burdened limitations with filtering efficiency, which seems out of step with most approaches (12). The application also clarifies the need for pre-term integrity testing after sterilization (a filter integrity test performed just before use). This issue was raised by inspectors of the European Medicines Agency before the application project was launched. The sterilization sections have been expanded, with different sterilization processes tailored to subsections. A general comment on the qualification of the sterilizer is made regarding the temperature estimate. This is what temperature probes need to be tested for a second independent temperature probe, located in the same position. For wet thermal sterilization, important verification parameters are set out, namely: equilibrium time, exposure time, pressure and temperature correlation, and maximum Another sterilization dry thermal sterilization, sterilization by radiation and sterilization using ethylene oxide are discussed. Of these, ethylene oxide is presented as a technology that should be chosen only when another method is not suitable. This is due to fears that the remnants of the gas-gas agent may remain. Aseptic treatment of Central sterile products produced, for products that cannot be incurably sterilized, are the controls needed around aseptic processing. Here the days do not use the full barrier technology for aseptic processing, quite rightly seems to have been measured. The pipe project works: RABS, insulators or closed systems should be considered in order to reduce the need for intervention in a Class A environment and minimize the risk of contamination. Although that is RABS (limited access barrier system) and what is not, it could be clarified among the links in the application to closed, open, active and passive RABS. With aseptic processing, there is a new clarification that within Class A, monitoring must be performed for all installations and critical operations. There is another comment that the frequency and size of the sample should be such that all excursions were captured. With sample sizes, there is an explanation for the sampling size requirements, which indicates that sample sizes do not necessarily have to correspond to the full classification. Work time control is discussed in several places, perhaps given that times beyond what is commonly seen can lead to an increased risk of pollution. Time called with: Pre-filling time should be evaluated as part of the media fills. The time required for aseptic assembly Maximum exposure time for sterilized containers and closures before closing. This suggests that the time of overseas swimming should be established. This has an impact on ensuring that the 9C is appropriate (see the discussion on the freeze below). For items sterilized in the home (e.g. by autoclave), they must be stored in Class A or B using appropriately airtight packaging and maximum shelf life must be set. With the previous point (due to the classification of purity), regarding the need to continue monitoring particles measuring 5.0 microns, some information on how to interpret the excursions on particle counting is described in detail. This may be useful in investigating calculations, especially as an operational one on what effects and mitigations can be considered. Disposable systems and technologies are mentioned, and their use is generally encouraged. According to the text, there are some problems with one technology. This is between the product and the contact surface of the product (in particular, adorption, leached and extracted). The app outlines the basic elements of Class A processing, allowing manufacturers to They were put into this author's checklist form, and they: Maintaining a critical processing area. Aseptic assembly of refueling equipment. Aseptic compounds (they should be sterilized by steam in place when possible). Particular attention is paid to aseptic connectivity and mixing. Risks abound in replenishment of sterile product, containers and closures. Fears about removing and cooling items from thermal sterilizers. The production and transportation of sterile components of the primary packaging. Aseptic filling, seal, transmission of open or partially stopper vials, including interventions. Loading and unloading the freeze-off These elements can be cross-transferred back to the pollution control strategy and implied risk assessment. The requirement for particle counting as part of the clean room control operation, which is normally in operation, has been expanded to require the justification of observation sites by risk assessment. Auditors are awaiting an official risk assessment when selecting all locations, including the justification of critical locations. Using classification and previous monitoring data where available should be part of the assessment. The recommendation states that observation sites should not be based on ISO 14644. Requirement for constant monitoring of Class B areas - The new application certainly requires a similar system for continuous monitoring of Class A in Class B areas, however, there is some confusion as to what this actually entails. This probably means that the Class B monitoring system must work with the frequency and size of the sample to detect changes in pollution levels and system deterioration, including alarms. In addition, it can also be concluded that: the sampling frequency may be lower than for Class A systems, the more effective the segregation between Class A and B zones, the less important the Class B sample becomes. The need to rotate between two different disinfectants remains, although the fact that one of them must be a disposicant agent is new. References are also made to disinfection qualifications for both latrines and disinfection (the act of introducing items into the restrooms or between the latrines of different classes). Not only is the disinfectant performance testing described as an important application concluding that this is the type of testing that needs to be conducted on the facility itself. One reason for this is that different types of surfaces are found in different objects, along with regional variations with microbial flora. During the discussion of disinfectants in section 5 need to evaluate the bio-burden of unsterile non-sterilized and set an expiration date. Freezing drying (lyophilization) and class containment of environmental requirements for partially stoppered freezing drying vials in detail - As a separate requirement, this section is clear; Partially stalled vials should be maintained in Class A conditions until the end, even during the transfer to freeze the drying. However, when viewed with regard to section 34 (which allows transport in airtight containers through a Class B environment), there is some confusion. For vials before freezing, the project requires Class A conditions to be retained. There is a difference from the Class A air supplies required during scuba diving. In light of an earlier point about ambiguity regarding Class A, the change in Class A Terms sees the use of the language used as an aseptic topping. Does this new form of words result in monitoring vials held before abroad? (13) We hope that this issue will be clarified during the consultation period. Section 118 of the project introduces the definition of the integral closure of the container, indicating that it is a cork and a limited bottle. The emphasis on the limited bottle is new; this may have some impact in ensuring that pressing work is appropriate and environmental requirements discussed above. For the freeze process, there is some new information provided to handle vials rejected due to missing/displaced traffic jams. In the case of overseas communications, there is no mention of viable monitoring. However, the new guidance points to the need to study smoke, although this one-way (laminar) stream does not need to be demonstrated. There is another comment that air speed should be justified by the manufacturer. Section 69 of section 69 of media-filling tests contains specific and prescriptive requirements for the permissible limits of refusal to study media filling based on the size of the mileage filling. The official statistical approach of 99.9 per cent with a confidence interval of 95 per cent is no longer applicable to determine acceptable failure limits. Instead, the expectation is zero, regardless of the size of the media filling. This will create tighter restrictions for those manufacturers who have yet to adopt stricter, especially for larger batch sizes. Another point with the media filling glitches is that after investigating and analysing the root causes, the previous proposal to run one media fill has changed to almost the requirement to run three media fills. Some may question this as above and beyond should, say, the reason for the refusal to fill the media be simple operator error. Others may consider the three tracks as the basic principle of re-checking in order to exclude the possibility. Visual inspection and containers of sterile, medicinal pharmaceuticals should be sterile, apirogenic and particleless. This last point relates to visual inspection, inspection, this was not detailed in the app before. Each agency is required to have a list of critical flaws - such as particles, hair and turbidity - and subject operators to regular assessments. The assessment should be carried out in practical conditions, with control of the verification time, line speed and size of the component. To capture operator fatigue, the test must be performed at the end of the shift. There are several references to the integrity of the container. The first is that containers sealed in a vacuum must be checked for vacuum content after an appropriate, predetermined period and during the shelf life (which relates to stability studies). Secondly, the impact of transportation must be taken into account in order to verify the integrity of container closures, which is another reference to such distribution methods. The third point is that microbial entry studies (or alternative methods) should be used to determine the acceptable shift in the height of the cork. Water systems and other utilities During 2017, the European Pharmacopeia has moved into a closer alignment with the Pharmacopeia of the United States in allowing water-for-injection (WFI) to be prepared from purified water using alternative distillation methods (essentially reverse osmosis). Annex 1 recognizes this, although there are several warnings and warnings to manufacturers intending to change the production method of VFI. Much of this focuses on minimizing the risk of biofilm formation and therefore downstream endotoxin control. This appears to be based on an earlier document, the position of the European Medicines Agency (14). The importance of WFI systems in hot water systems remains on the condition that WFI should be distributed at temperatures of 70oC. One part of the water monitoring section has somewhat ambiguous wording. It is a requirement that the sample is taken from the worst place in the water system process every time the system is used for production. As it states this requirement is unrealistic, although it is probably a reflection of the phraseology used. Given that some systems can be used multiple times a day, it is instead assumed that the application means sampling at a high enough frequency to assess the pollution problem, but not at every time of use. Few microbiological laboratories have handled the workload. The statement refers to the trending data that the draft application applies to all utilities: Results on high-risk utility critical parameters should be regularly analyzed in trends so that the system's capabilities remain appropriate. This can create problems for facilities where cleanliness monitoring monitoring, as pressure differentials, remains based on sound alarms and without electronic data collection tools. With other utilities, compressed gases are called microbial contamination. As in other parts of the pharmaceutical manufacturing process that require filtration, the integrity of the filters used to supply compressed gases has received attention. There is an additional requirement to include filter verification data in the batches with the proposal: Confirmation of the integrity of the final gas sterilization filter should be part of the batch release process. Class C and D monitoring requirements for regular Class C and D monitoring are detailed in the draft application. In this regard, there is a requirement to use risk management techniques to justify the location, number and frequency of samples for regular monitoring of Class C and D areas, both in terms of particle count and for monitoring viable calculations (15). Unlike the production of aseptic products class A and B, monitoring should not be continuous, monitoring episodes should be more frequent than retraining. It is important to note that risk assessment should justify frequency. With lower-class cleanrooms the way that such a clean room interface with other areas is called in terms of gateways and transfer hatches. There is also a link made, for the first time, to controlled but not classified areas. Here, the movement of materials from controlled but not class-class C-classified should be based on the principles of the CRM, and the cleaning and disinfection are commensurate with the level of risk assessed. For the first time, the project (section 9 for environmental monitoring and Section 10 for end product testing, such as infertility testing) mentions rapid microbiological rapid response methods for the first time. While it is disappointing that more information is not provided, references to rapid microbiological methods at least pave the way for real-time consideration of alternatives such as spectrophotometric counters. The application emphasizes that these methods should be considered only after verification and until they are agreed to be at least equivalent to the established Reporting methodology and the integrity of the data Surprising omission from the application any link to the records or integrity of the data. This can be concluded by cross-referencing other chapters and applications in the project. However, given the importance that regulators bring to the integrity of data, and especially given the vagaries of how data integrity principles are best applied in microbiological laboratories (16), some mention could at least be expected. The summary of the application project 1 signals a lot of changes that manufacturers should consider. This article attempts to generalize and, where appropriate, comments on the most significant changes. It is impossible, or even necessarily productive, for one article to go through each of the provisions of paragraph by point. It is important to reiterate that the document document and that its contents may change after receiving comments from government and professional bodies. However, for those who prefer to plan ahead, it is unlikely that many of the basic principles will change, and so many of the paragraphs referred to in this article are likely to appear in the finished document. Consultations on draft annex 1 end on March 20, 2018. Any parties interested in contributing to the consultation process should provide feedback directly to the European Commission on: Sante-Pharmaceuticals-B4@ec.europa.eu, with the title: Targeted Public Consultation - Review of Annex 1 of the EU GMP Guidelines. Links 1. Fda. Guide to Industrial Sterile Drugs Produced by Aseptic Treatment - Current Good Manufacturing Practices, U.S. Department of Health and Human Services, Food and Drug Administration, Bethesda, MD, U.S., 2004 2. Eudralex Rules governing medicines in the European Union, Volume 4 Es Guidelines for good manufacturing practices of drugs for humans and veterinary use. Appendix 1 The production of sterile medicines, European Commission, Brussels, Belgium, 2009: ... 3. EMA. The concept paper on the revision of annex 1 guidelines on good industrial practice - the production of sterile medicines, EMA/INS/GMP/735037/2014, issued jointly by the European Medicines Agency and the Convention on Pharmaceutical Inspection: ... 4. EMA. 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