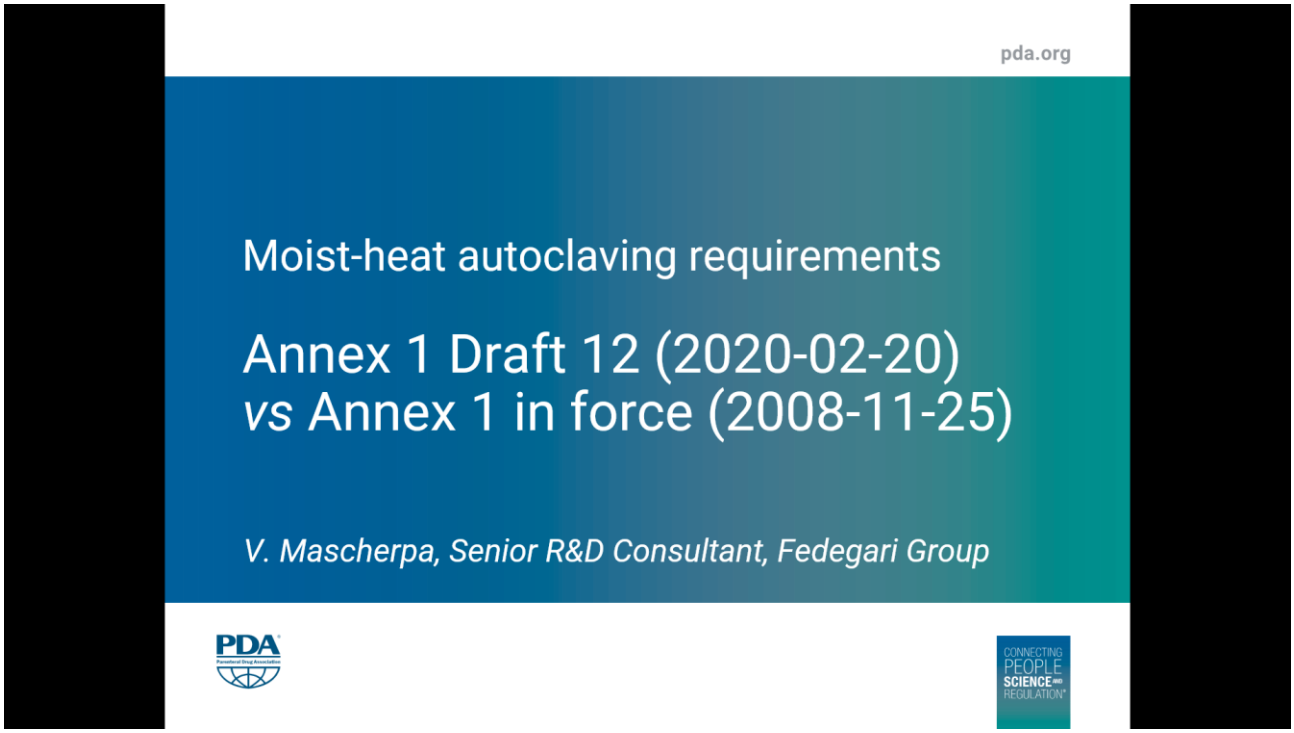
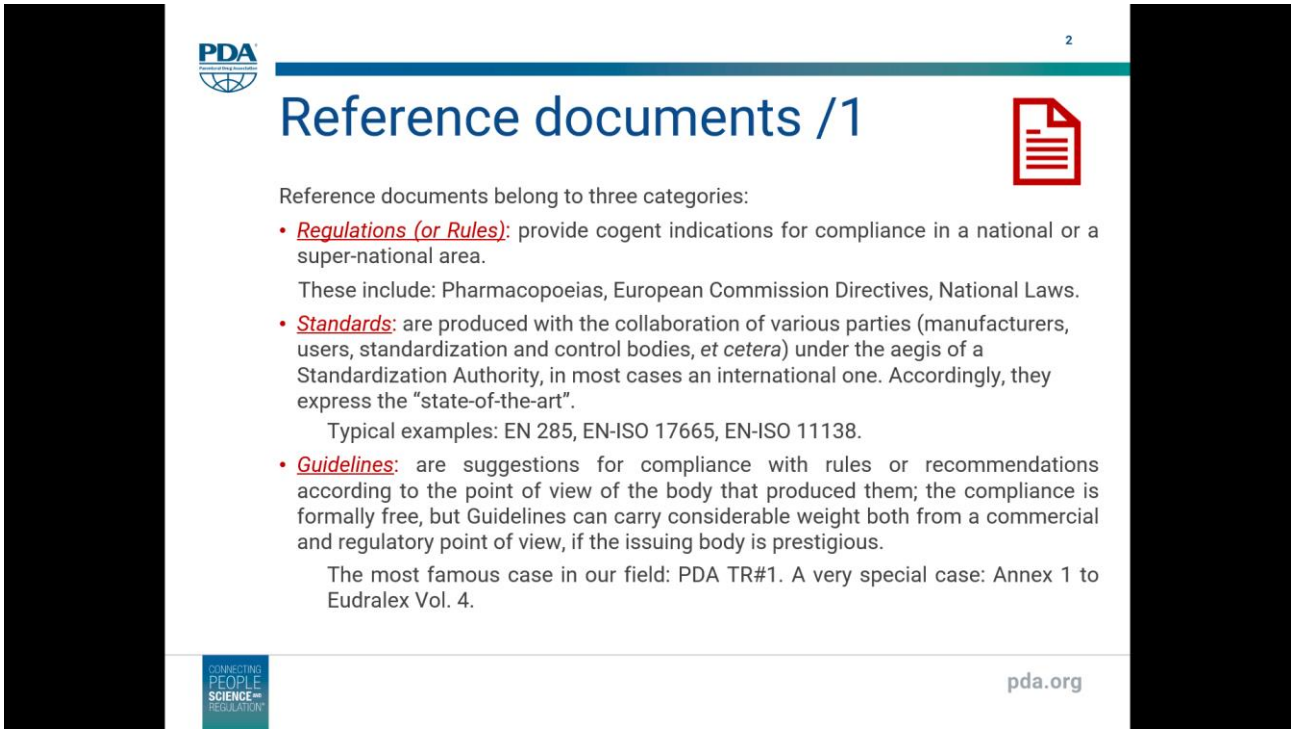
Notes for PDA, June 30th, 2022.

Annex 1 Revision



0:00 (Slide no. 2/51)



I'll start from refreshing some basic concepts on *Reference Documents*.

A document can be a *Rule*, thus being *mandatory* as laws are in a national or super-national area.

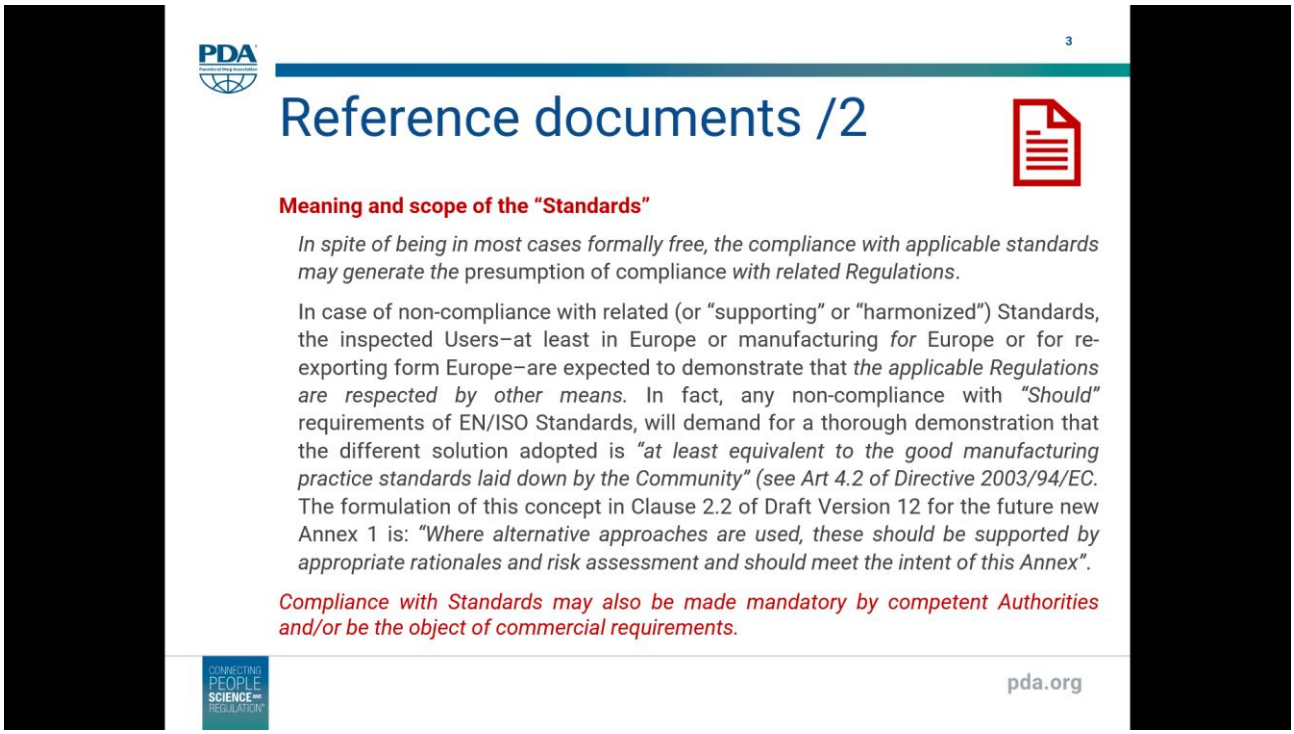
Or can it be a *Standard*, containing technical requirements and testing methods.

Standards are issued by Standardization Authorities, national or super-national again; they represent various parties.

Or can a document be a *Guideline,* intended either to provide guidance to comply with a rule or a standard, or to suggest the best way to do something, according with the point of view of the issuing body.

Compliance with standards and guidelines is *free*… at least formally.

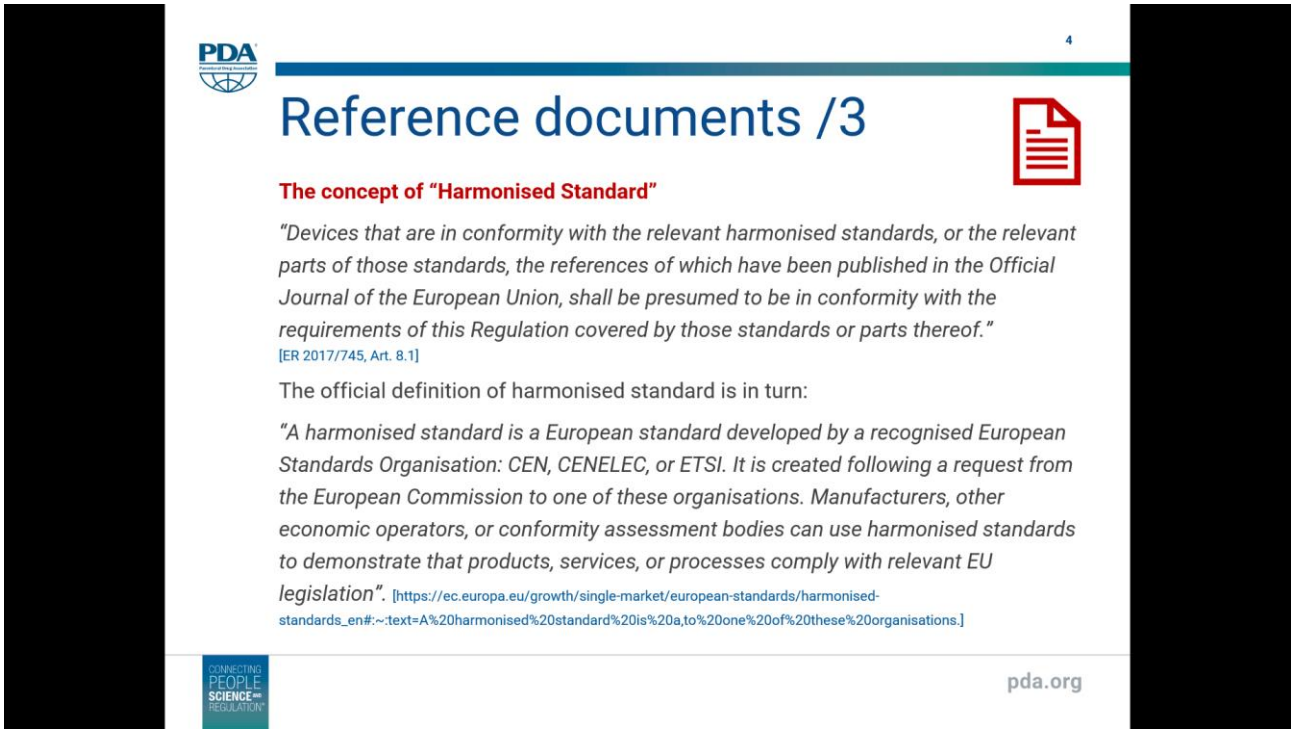
1:00 (Slide no. 3/51)



Usually, technical standards contain approved ways of designing and convened testing methods.

Compliance with standards may be required by Customers and even become object of commercial transactions. More generally, compliance with standards can generate a *presumption of compliance* with a rule or a system of rules.

1:35 (Slide no. 4/51)



This concept is well expressed, for instance, by Article 8.1 of European Regulation 2017/45 on medical devices:

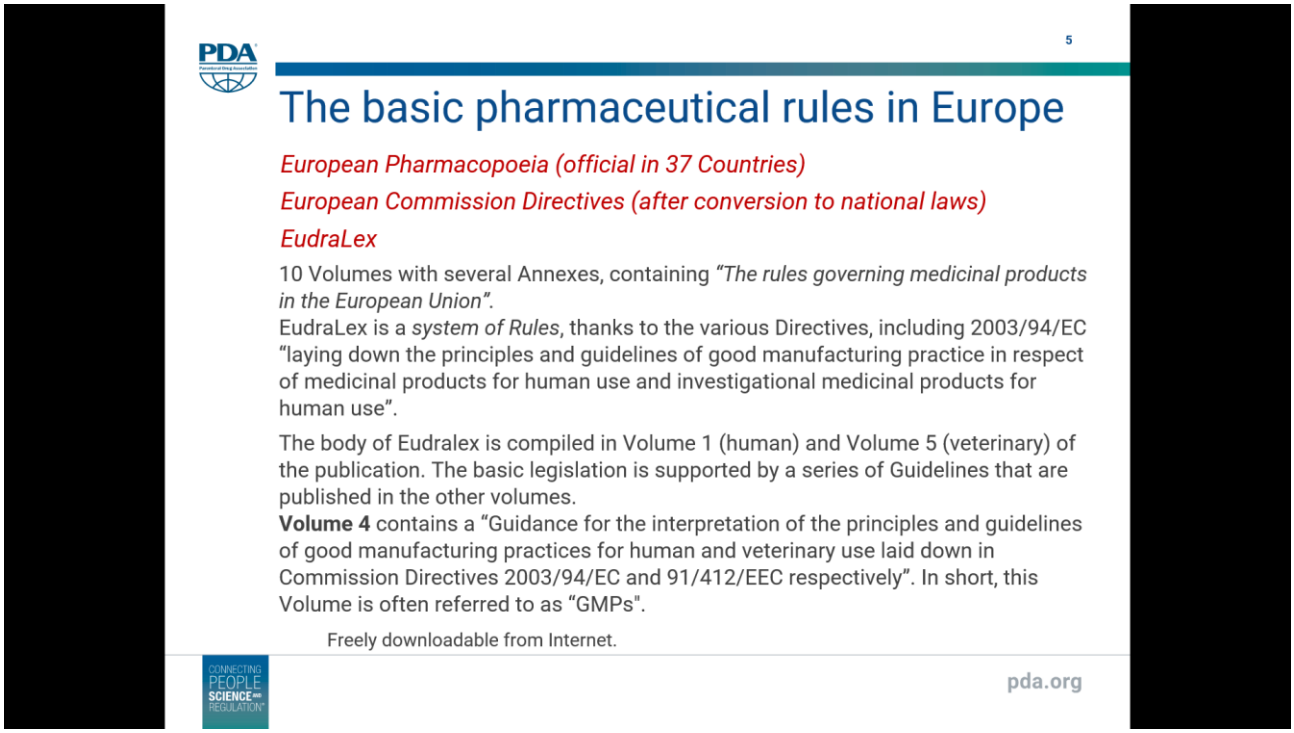
"Devices that are in conformity with the relevant harmonised standards, or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union, shall be presumed to be in conformity with the requirements of this Regulation covered by those standards or parts thereof."

The official definition of *harmonised standard* is in turn: "***A harmonised standard is a European standard developed by a recognised European Standards Organisation: CEN, CENELEC, or ETSI. It is created following a request from the European Commission to one of these organisations.***

Manufacturers, other economic operators, or conformity assessment bodies can use harmonised standards to demonstrate that products, services, or processes** comply with **relevant EU legislation". [https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards_en#:~:text=A%20harmonised%20standard%20is%20a,to%20one%20of%20these%20organisations.]

I suggest you always to remember that the basic concept of those who write standards and guidelines is:
"We are skilled in the art and believe that we have expressed in this standard (or guideline) the right-easiest way to obtain some results. No doubt that you are free to go another way, but in this case, you shall demonstrate that you are… more skilled than we are. Please remember that we will be also your inspectors".

3:55 (Slide no. 5/51)



Basic Pharmaceutical Rules in Europe are:

the European Pharmacopoeia, official in thirty-seven countries,

the Commission Directives, among which is remarkable the 2003/94/E-C, “laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use”,

and the so called EudraLex.

European Pharmacopoeia is the basic pharma rule in thirty-eight Countries where it has the status of a law. These Countries are the European Community and a dozen of other ones in Europe or around it, including U-K.

The European Pharmacopoeia has been elaborated since Nineteen sixty-four and firstly issued Nineteen sixty-nine. At present, it is a mission of E-D-Q-M, the European Directorate for the Quality of Medicines and health care. This directorate is a technical branch of the Council of Europe, a politically non-binding organisation, older and more

extended than European Community. It is worth mentioning that also some non-member States of the Council of Europe participate as observers in E-D-Q-M.

In turn, “European” pharma-inspectors belong to E-M-A, the European Medicines Agency, a technical branch of the European Commission, super-national government of the European Community. At present, UK inspectors, even in their international activity, belong again to M-H-R-A, the Medicines and Healthcare products Regulatory Agency, a technical branch of Her Majesty’s Government.

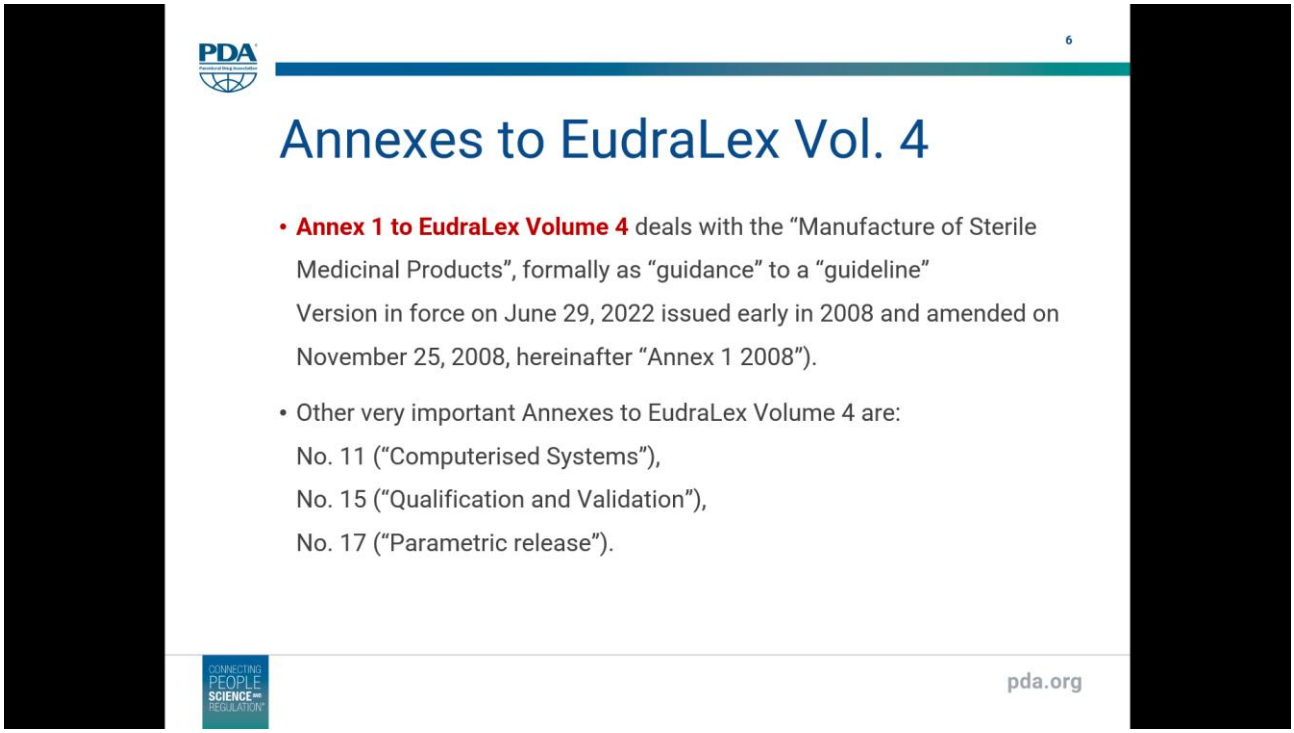
European Pharmacopoeia is divided in monographies. Monography 5.1 of it is titled *General Texts on Microbiology* and contains some “general chapters” in them. Those on microbiology are of the utmost importance in our field and may be regarded as strictly mandatory, even if in many cases the rules are presented as a detailed description of the state-of-the-art.

EudraLex consists out of ten volumes — and almost uncountable annexes. It is relevant both to human and veterinary pharmaceutical products.

Two volumes (nos. 1 and 5) contain legal references; the other ones cover several aspects (application for new products, good manufacturing practices, clinical trials, etc.).

EudraLex is freely downloadable form Internet. Unfortunately, Pharmacopoeias and technical standards are available on sale only.

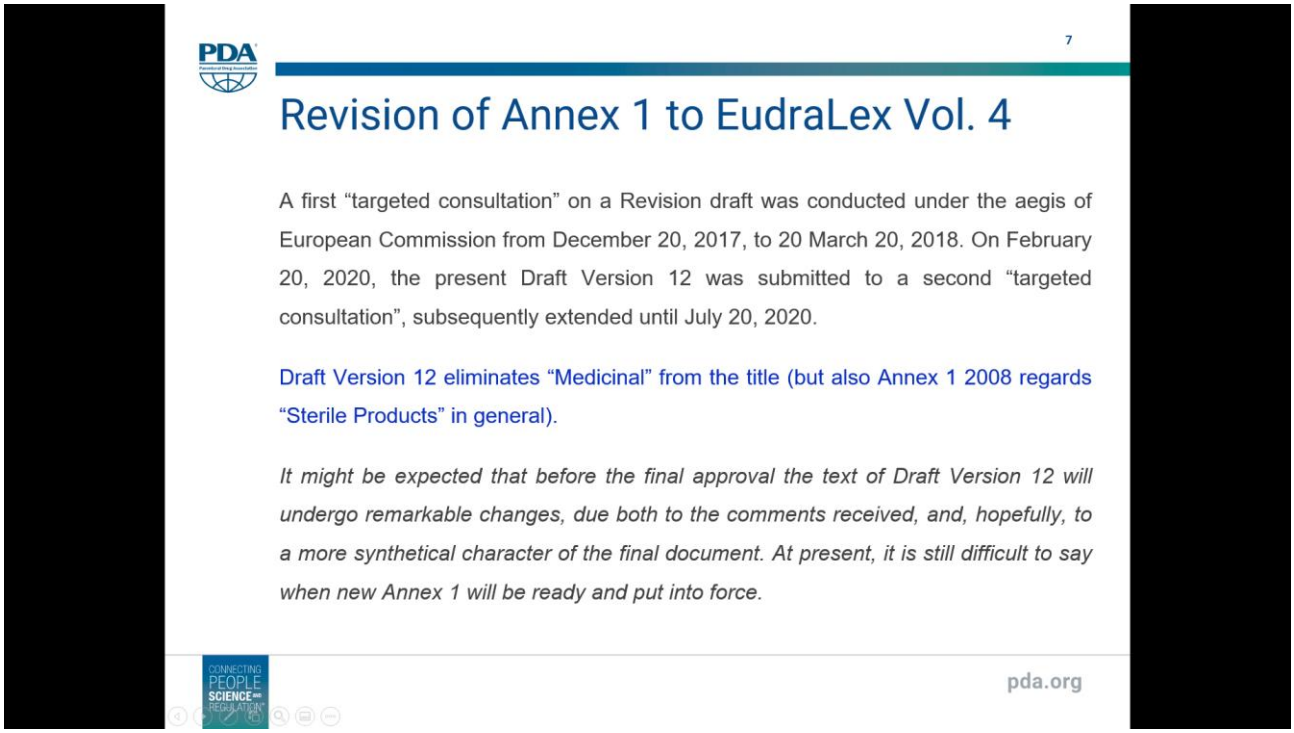
5:15 (Slide no. 6/51)



"Guideline" (or, less properly, "guidance") are defined both the whole of EudraLex Vol. 4 and the European document worldwide known as Annex 1, now dated November 25, 2008.

Annex 1 contains "recommendations" on the manufacture of sterile products. But please note that **these "recommendations" are, in practice, mandatory** for sterile products manufactured in the European Community or, without difference, imported into it, even if intended for further re-exportation.

6:00 (Slide no. 7/51)



About *fifty-four months* ago, a first "targeted consultation" on the draft of a revised Annex 1 was launched among representative Bodies including, outside Europe, American PDA and ISPE.

These Bodies are the so called "relevant Stakeholders" in the sterile manufacturing field. Private practitioners could submit remarks and proposals as well, following a different procedure. Eventually, the first "targeted consultation" generated a Draft Version 12, issued on February 20, 2020. The "relevant Stakeholders", in fact sixteen,

- *A3P (Association for Products Propres and Parentals)*
- *AESGP (Association of the European Self-Medication Industry)*
- *AnimalhealthEurope*
- *APIC (Active Pharmaceutical Ingredient Committee)*
- *EAEPC (European Association of Euro-Pharmaceutical Companies)*

- *ECA (European Compliance Academy)*
- *EFPIA (European Federation of Pharmaceutical Industries and Associations)*
- *EGGVP (European Group for Generic Veterinary Products)*
- *EIPG (European Industrial Pharmacists Group)*
- *GIRP (European Healthcare Distribution Association)*
- *ISPE (International Society for Pharmaceutical Engineering)*
- *Medicines for Europe*
- *PDA (Parenteral Drug Association)*
- *PHSS (Pharmaceutical & Healthcare Sciences Society)*
- *EQPA (European Qualified Person Association)*
- *Vaccines Europe*

had *"agreed to receive all the comments of this second consultation from their members, to compile and send the comments to the European Commission"* (Health and Food Safety Directorate General), that means to act as "filters".

New comments and proposals have been expected until July 20, 2020, almost two years ago. P-D-A submitted very detailed comments and proposals. Fortunately–at least from my point of view–those relevant to moist-heat sterilization are not so many and, frankly speaking, not so important.

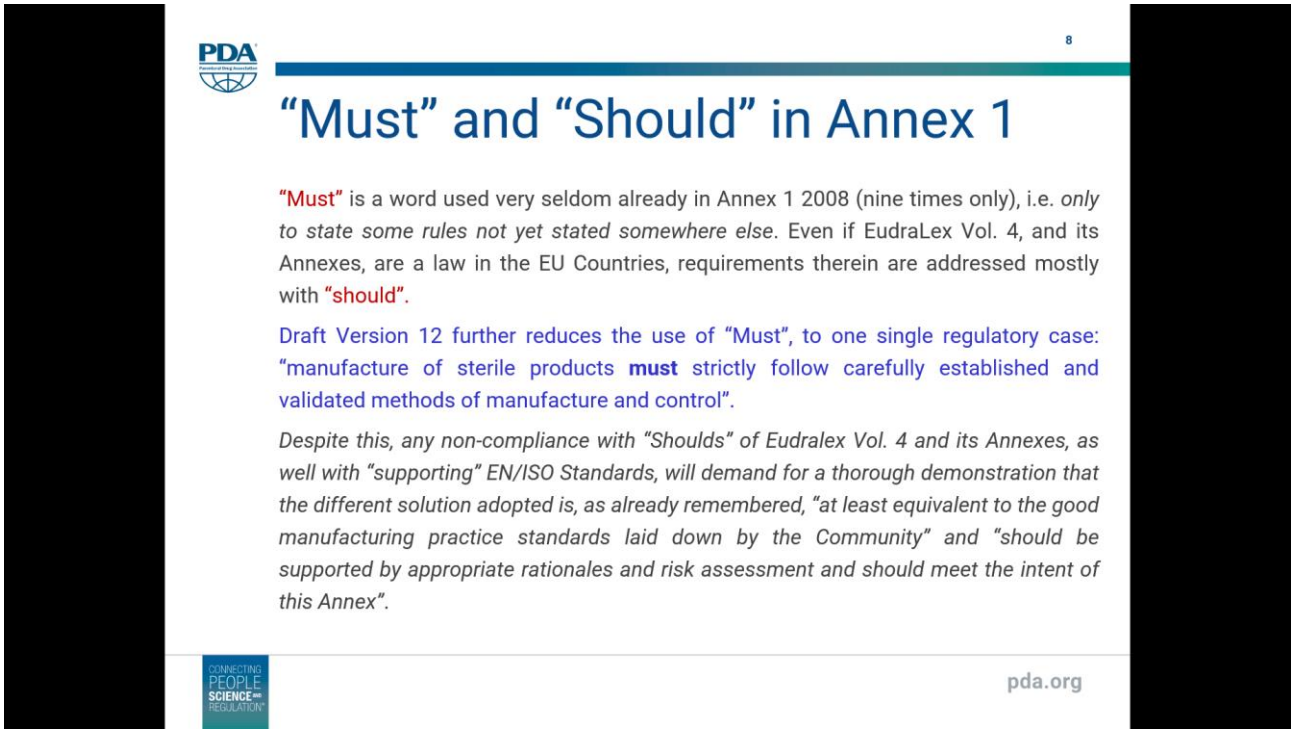
Evaluating and coordinating all the remarks for producing a final draft takes always a rather long time. Thence a final approval is expected by the European Commission (a sort of supranational government).

Officially, nothing new happened on Annex 1 after July 20, 2020, but a lot of meetings on the matter, poking short-terms expectations. You can read in Internet that “a working group consisting of regulators from E-M-A, P-I-C-/-S and World Health Organization endorsed a revised version in mid-February” 2022 and that “the target date is to have a revision in mid-2022”. Legal experts are supposed to be at their work. P-I-C-/-S is the acronym of Pharmaceutical Inspection and Cooperation Scheme, an intergovernmental organization “leading the international development, implementation and maintenance of harmonised G-M-P standards and quality systems of Inspectorates in the field of medicinal products”.

My opinion is that a new Draft will be issued within a few months; I am also convinced that nobody can honestly say when a new Annex 1 will replace the 2008 issue. Informal information on expected coming into force indicates six months **after final approval** by EC Commission for the less innovated parts, but three years after final approval for new requirements.

Probably, the Q-R-M (*Quality Risk Management*) approach is the major innovation in Draft Version 12. In their comments, P-D-A claim several times that the present language of Draft 12 is not so compliant with this branch of current human knowledge.

10:00 (Slide no. 8/51)



Annex 1, both in the actual text and the new expected one, is formally a *guideline* attached to a *code of rules*. For this reason, most requirements–actually all ones but a single one in Draft Version 12–are addressed with "should".

However, as I have already remembered, any different solution has to be recognized *"at least equivalent to the good manufacturing practice standards laid down by the Community".*

Only one *regulatory* "must", and utmost general indeed, is left in Draft Version 12 out of the nine ones of the Annex 1 in force.

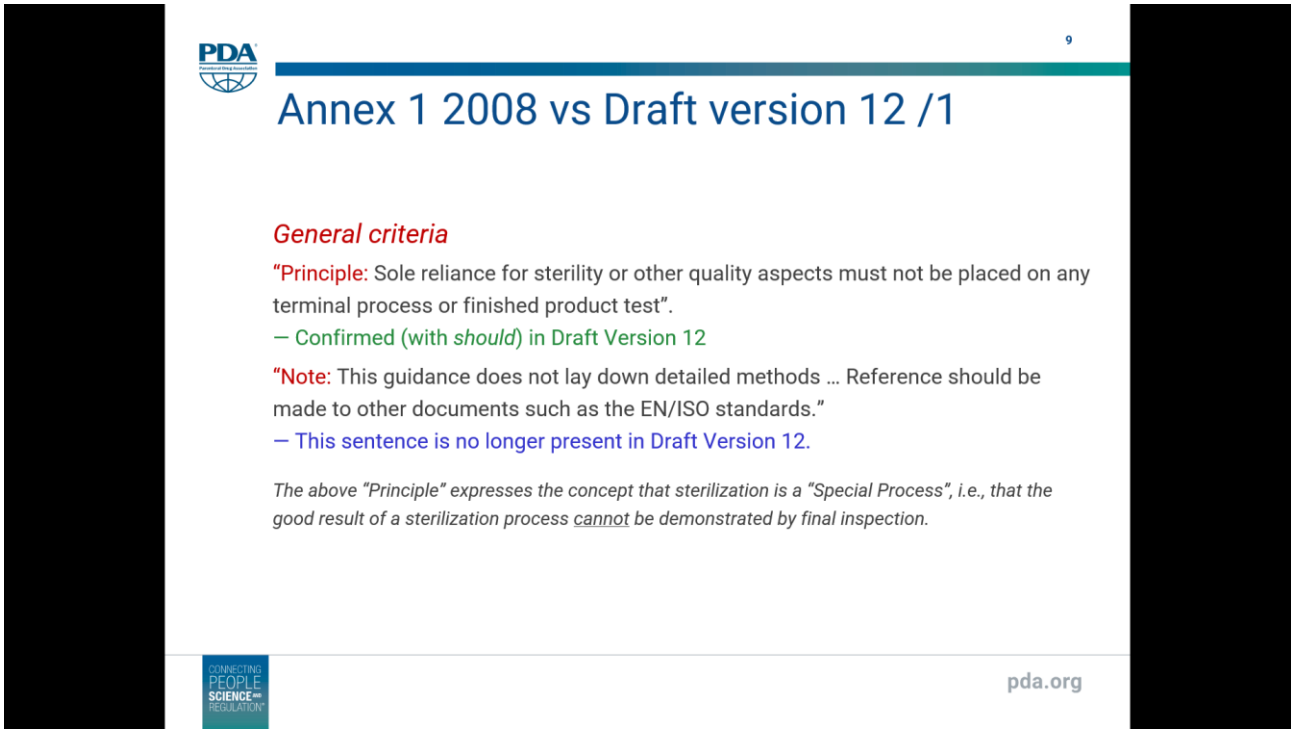
It is: *"manufacture of sterile products **must** strictly follow carefully established and validated methods of manufacture and control"*.

You could find also a second "must" in Draft 12. It is merely descriptive, as relevant to a step necessary in the manufacturing:

“where the product must be held for a long period before sterilisation”, thus generating an unusually high risk of microbial contamination” (Clause 8.1).

This issue of “should” and “must” (as some time ago of “shall”, as well) is so old, as it is evergreen. I remember that all the times I have asked an English-speaking inspector about the meaning of “should” in Standards and Guidelines, she or he has answered: “It is better if you read it exactly as if were written “must”. As we say in Italy: *“Every well-advised man is an already half-rescued one…”* Keep you on the safe side!

12:10 (Slide no. 9/51)



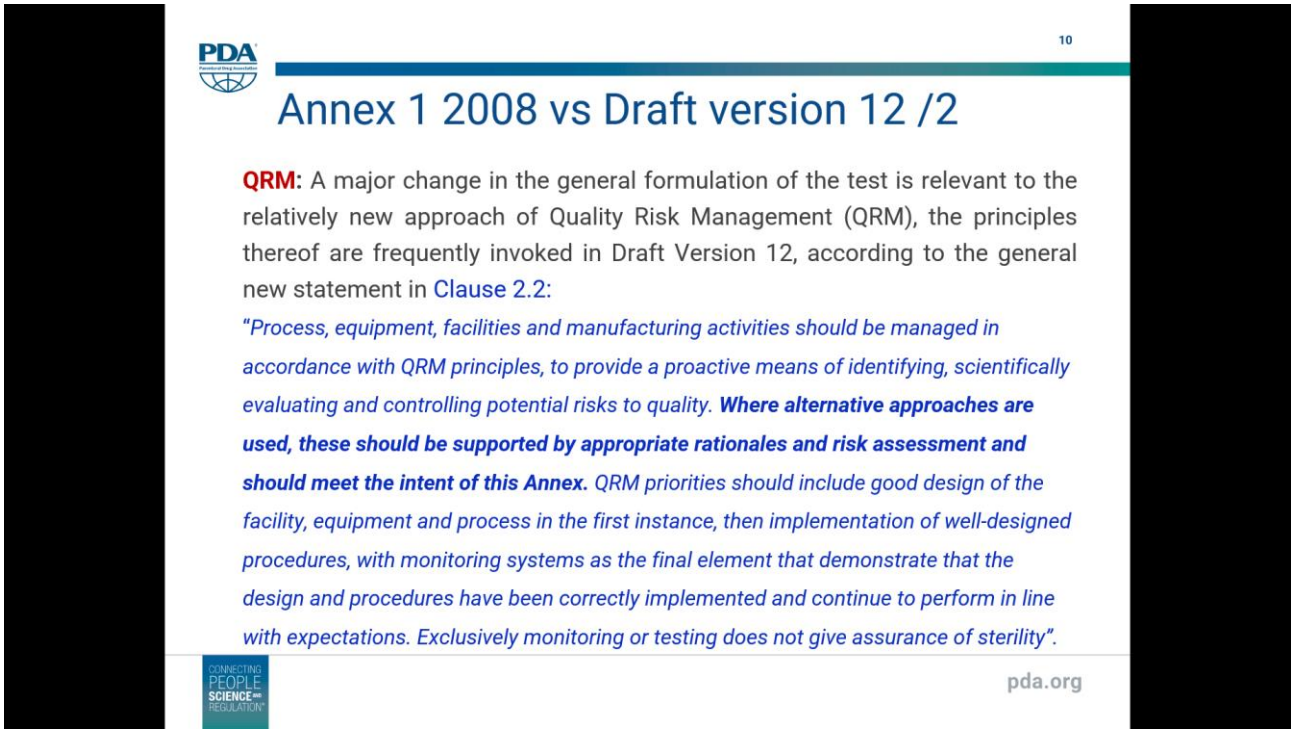
Draft Version 12 is much longer than Annex 1 2008. The dense fifteen pages of the document in force become forty-five in Draft Version 12, but explanations, descriptions, and details, sometimes unnecessary, occupy much more space than completely new requirements.

This approach is unusual in European documents intended for reference. On the other hand, a *law* as the United States Pharmacopeia gives an almost equivalent evidence to *how* to do something and to *why* to go such a way, at least in the Chapters relevant to the sterilization.

I also remember that along the way of revision another U-S primary document, even though it is formally a "private" one — the well-known and very authoritative P-D-A Technical Report No. 1 had

grown up to almost an unbelievable one hundred eighty-five pages. But finally, it has been reduced to the present concise and very good fifty pages, including introduction, glossary, text, and references. So, I expect–and hope, indeed–that the final text of future Annex 1 *Two thousand and question mark* will be remarkably shorter than and, at least in some parts, also different from Draft Version12.

14:00 (Slide no. 10/51)



The importance of the Q-R-M, Quality Risk Management approach is clearly stated at the very beginning of Draft Version 12. The "founding" Clause 2.2 also confirms the concept that Annex 1 should be regarded as a true *rule*: *"Where alternative approaches are used, these should be supported by appropriate rationales and risk assessment and should meet the intent of this Annex"*.

Clause 2.2 emphasizes that quality, and the risk of not obtaining or losing it, are relevant to all the stages of manufacture, from the design of the facilities to that of all stages of process and procedures for them, from their correct implementation to the ongoing monitoring of the production routine.

The last sentence–"*Exclusively monitoring or testing does not give assurance of sterility"*–may also be regarded as a different

formulation of the well-known “Principle” we have already seen: *“Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test”*.

But: what is *risk*? I believe that even a very short attempt to explain what *risk* is and what *risk management* implies would demand a couple of days of a dedicated course — so I limit myself to say that the *extent of a risk* is a combination of two things: the *probability* that an unfavourable event occurs, and the expectable *gravity* of its consequences.

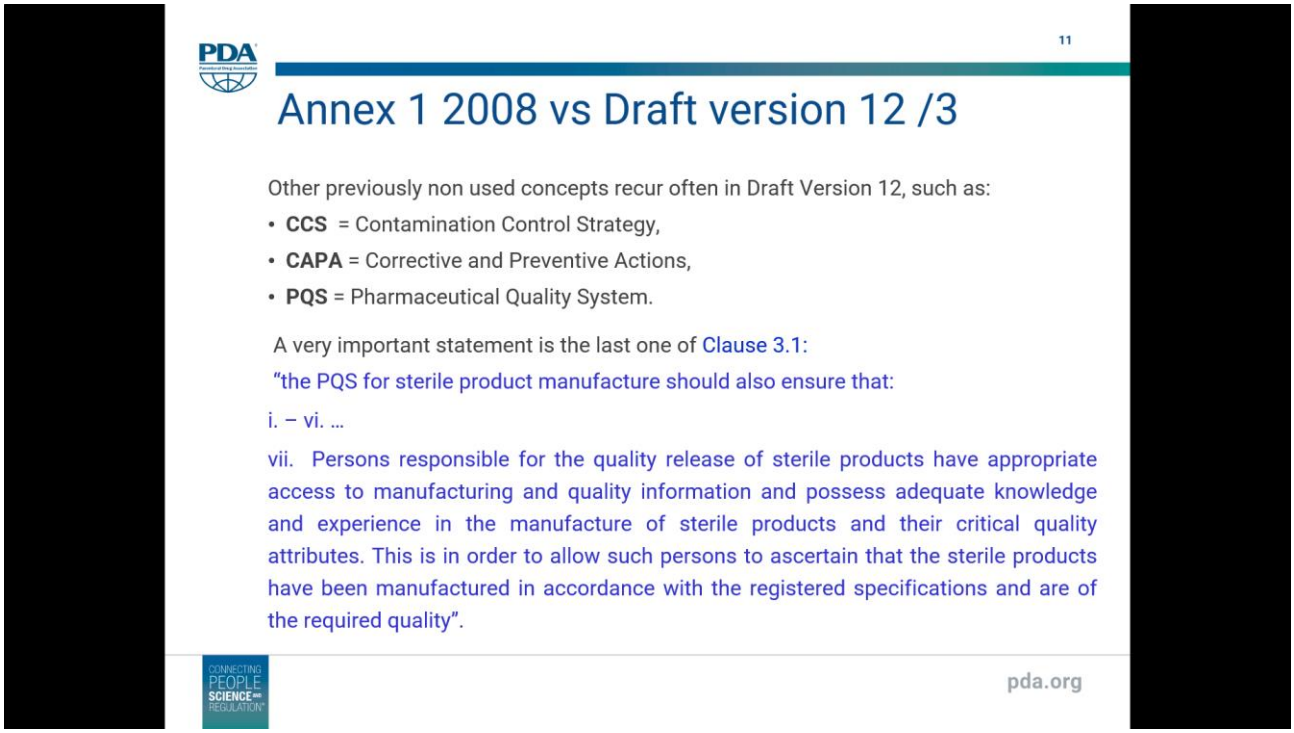
The implementation of a *Quality Risk Management* approach will involve major changes in the mentality of many manufacturers, just as the new concept of *Validation* did almost forty-five years ago.

At that time, validation was something completely new in comparison with the old method of statistical control applied on a small number of items sampled from the production batches. That traditional method had proven not adequately reliable for preventing disasters as the famous Devonport Accident in UK.

Nowadays, Quality Risk Management may be regarded as an attempt to cope with the practical impossibility to validate, at a sustainable cost and in acceptable period time, really *everything* involved in a process.

Hopefully Q-R-M will be no less an occasion of progress than Validation has been.

17:30 (Slide no. 11/51)



In the time we have today, it is apparently impossible to go through all the new concepts used in Draft Version 12. Perhaps, some of them will be object of your questions and discussion.

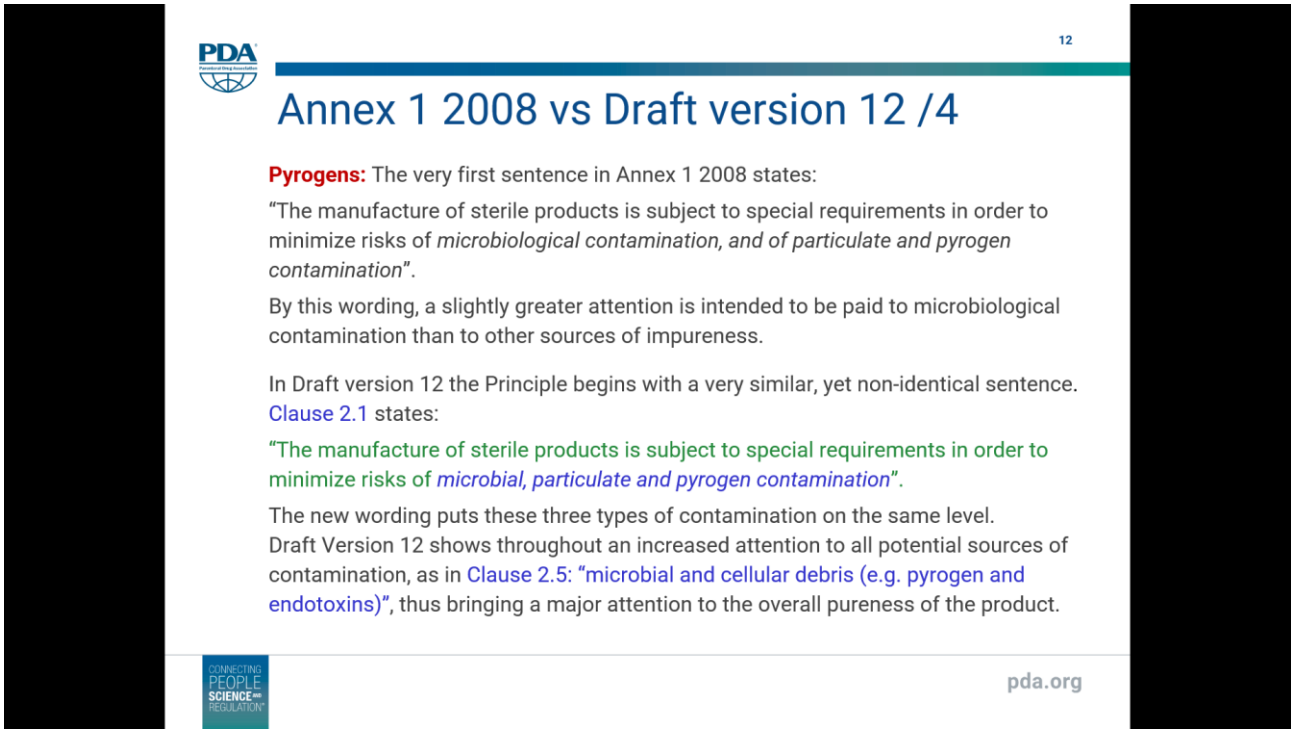
"Elements to be considered within a documented C-C-S" (Contamination Control Strategy) are listed in Clause 2.5.

Corrective and Preventive Actions ("C-A-P-A") are intended as part both of C-C-S and P-Q-S (Pharmaceutical Quality System).

EudraLex Vol. 4, revised 2013 has introduced the concept of P-Q-S, stating some requirements. In addition to them , Draft 12 says that "the P-Q-S- for sterile product manufacture should also ensure that" routine operation are always monitored and reviewed by trained and responsible personnel.

Special attention should be paid to the “persons responsible for the quality release of sterile products”. These ones “should” be widely knowledgeable and experienced also in manufacturing and have “appropriate access” to manufacturing information — I’m afraid that this “appropriate access” could cause troubles in some pharma companies.

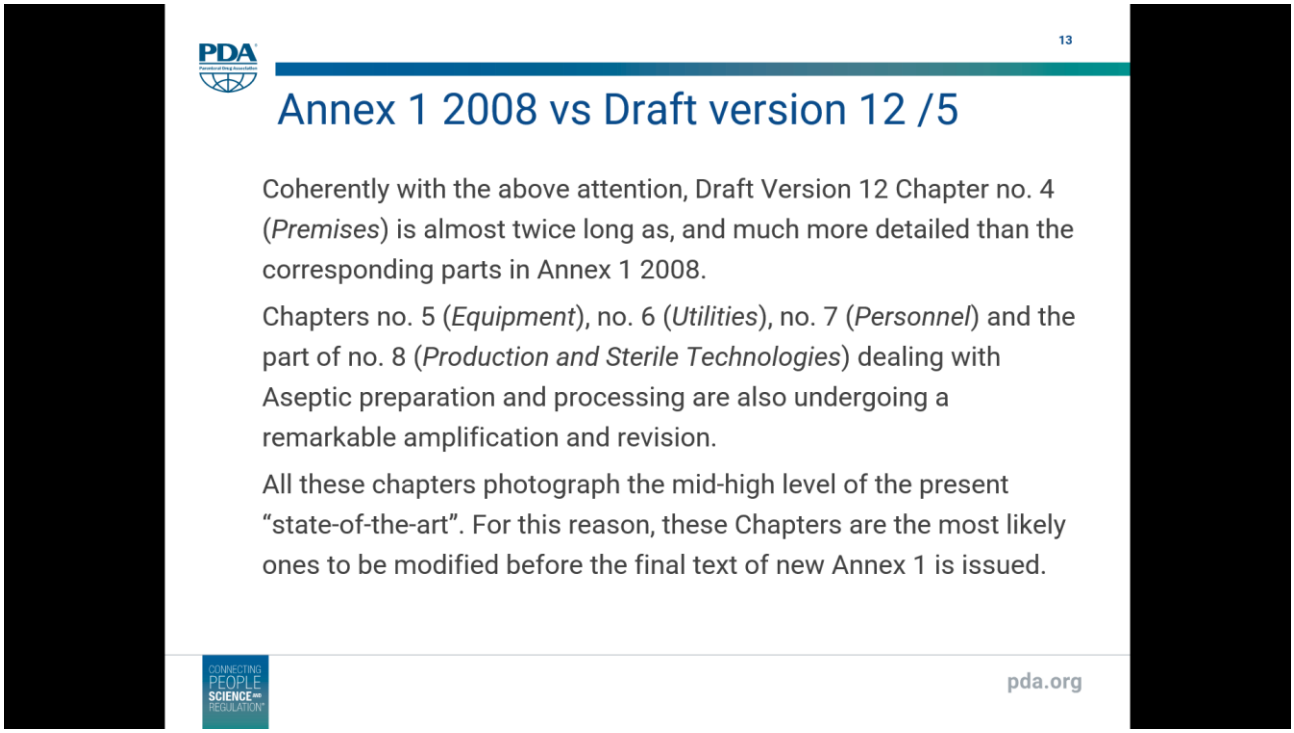
19:10 (Slide no. 12/51)



Let's have a look to a meaningful example to quickly understand the more global approach of Draft Version 12 to C-C-S in comparison with Annex 1 2008. A very slight change in wording, as you can read in the slide, puts particulate and pyrogens contamination on the same level as microbiological contamination. This brings a major attention to the overall pureness of the product.

In general, Draft Version 12 pays more attention to pyrogens than Annex 1 2008.

19:50 (Slide no. 13/51)



Also, in Draft Version 12, much longer and more detailed has become the chapter devoted to premises, particulate contamination, barrier technologies such as Restricted Access Barrier Systems and Isolators.

The clauses on the "grades" of the zones compatible with the different operations for the manufacturing of sterile products have been widely re-written. The same remark applies to chapters devoted to equipment specification, design, operation, and cleaning, to the quality of utilities such as steam, water, gases, vacuum systems, and to the training and management of the personnel involved in sterile manufacturing.

This tendency toward lengthy details affects also the first part of Chapter 8, relevant to "production and Specific Technologies".

Requirements for Sterilization are part of this chapter, starting on Clause 8.33.

All these chapters photograph a mid-high level of the present “state-of-the-art”, P-D-A have extensively commented them, and I believe that they are the most likely ones to be modified before the final text of new Annex 1 is issued.

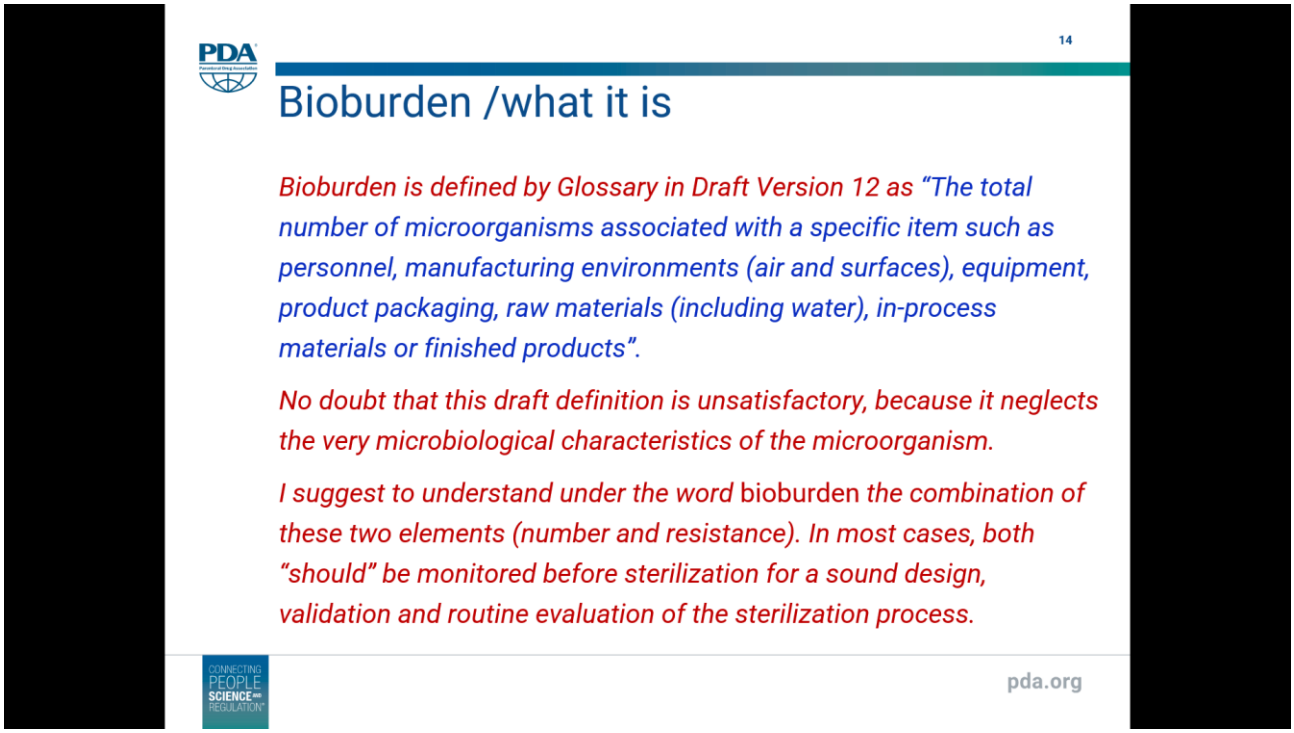
Next slides compare the parts of Annex 1 2008 and of Draft Version 12 relevant to the practice of sterilization. Present clauses will be displayed together with new ones in the draft that correspond to them.

The sentences that remain unchanged will be displayed in green. At a glance, you’ll see that more than eighty percent of Annex 1 2008 passed untouched into Draft Version 12.

But the opposite is not true: Draft Version 12 adds a lot of new sentences, which will be displayed in blue. You’ll see that new sentences, and new wordings as well, are by far more than the fifty percent of the Draft 12 text.

For some of main sterilization topics I’ll display a definition (only when deemed to be necessary), thence the old and new texts, without reading them extensively, to save time, and my comparison, displayed in red. Where applicable, P-D-A observations and proposals will be presented as well.

23:00 (Slide no. 14/51)



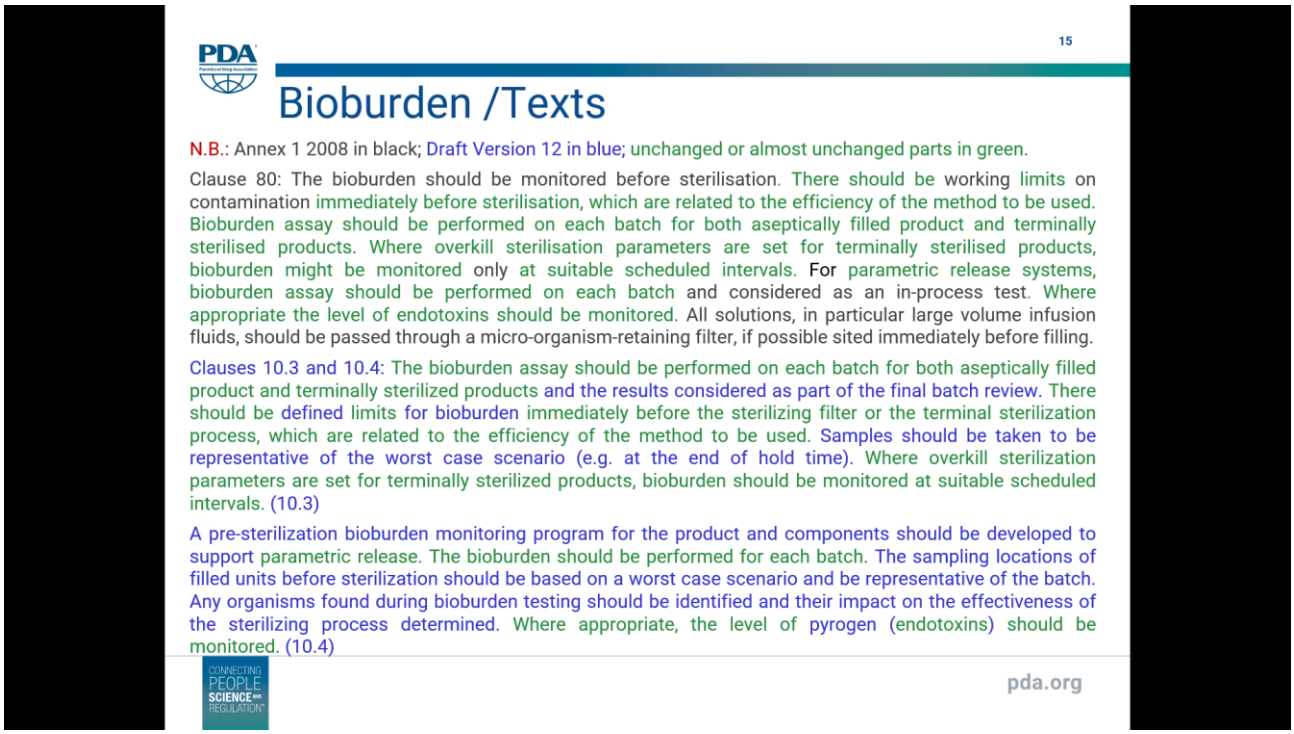
What is it? Glossary in Draft Version 12 gives a definition, perhaps aiming to cover too many aspects. On the contrary, it forgets the biological characteristics of the microorganisms to be inactivated by the sterilization process, which are expressed by parameters as *D*-value and *z*-value

According to the Glossary in Draft 12, *D* is "the value of a parameter of sterilization (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number" — (also forgotten is here something as "under specified conditions").

In turn, *z*-value is not defined in the Glossary: it is the number of degrees of temperature change necessary to change the *D*-value by a factor of 10.

In fact, the same rough amount of initial population may demand a very different temperature and duration of exposure to the same sterilizing agent to reach the same “probability of sterility”.

24:30 (Slide no. 15/51)



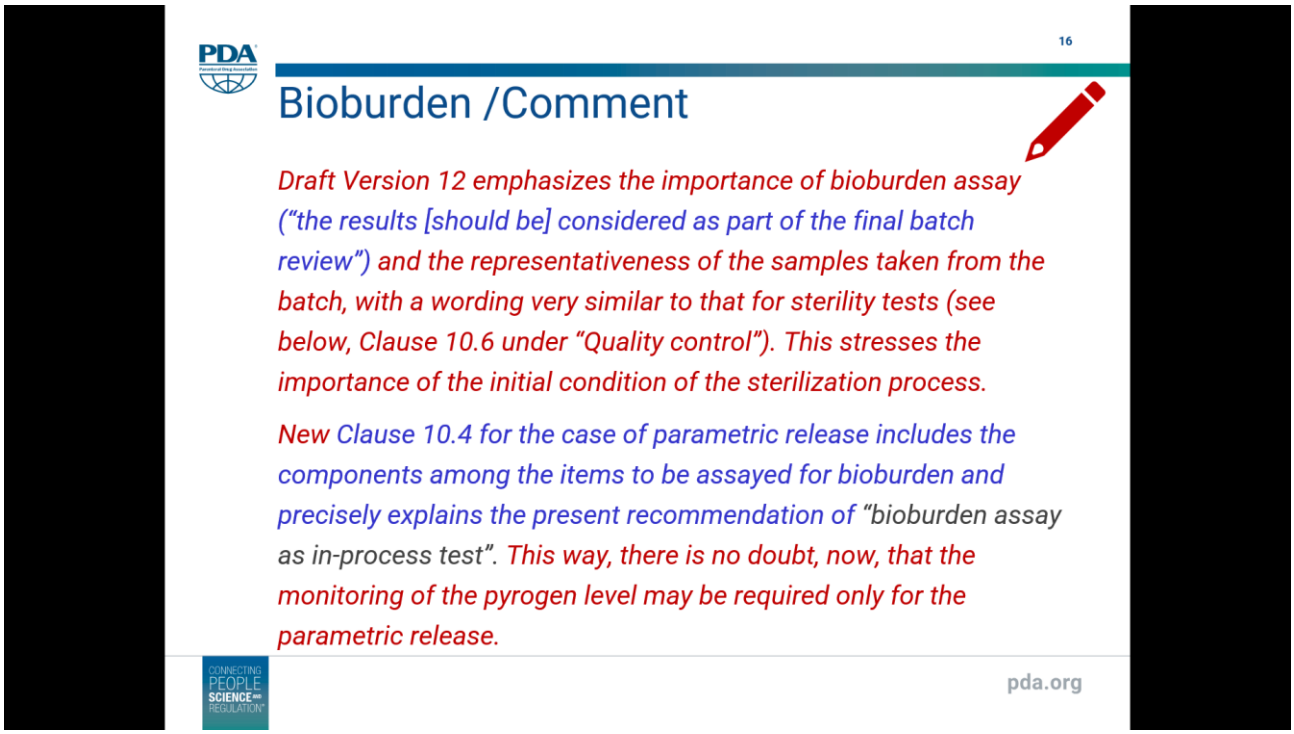
Draft Version 12 doesn’t change substantially the requirement for bioburden assay, already present in Annex 1 2008, which “should” be performed *“at suitable scheduled intervals”* if *“overkill sterilization parameters are set”*. “Overkill” is obviously to be intended in the sense of the E-M-A guidance: equivalent exposure time F_0 higher than 12 minutes, the same as in P-D-A T-R-1.

Draft Version 12 clarifies better than Annex 1 2008 the importance of bioburden assay (*“the results* [should be] *considered as part of the final batch review”*) and underlines the need of taking the samples from all the batch: the wording is very similar to that for

sterility tests This stresses the importance of the initial condition of the sterilization process.

Parametric release–we will meet it again–is defined in Annex 17 as *“one form of RTRT (Real Time Release Testing) based on the review of documentation on process monitoring (e.g. temperature, pressure, time for terminal sterilization), rather than the testing of a sample for a specific attribute”*. In this case, the *components* are to be included among the items to be assayed for bioburden.

26:15 (Slide no. 16/51)

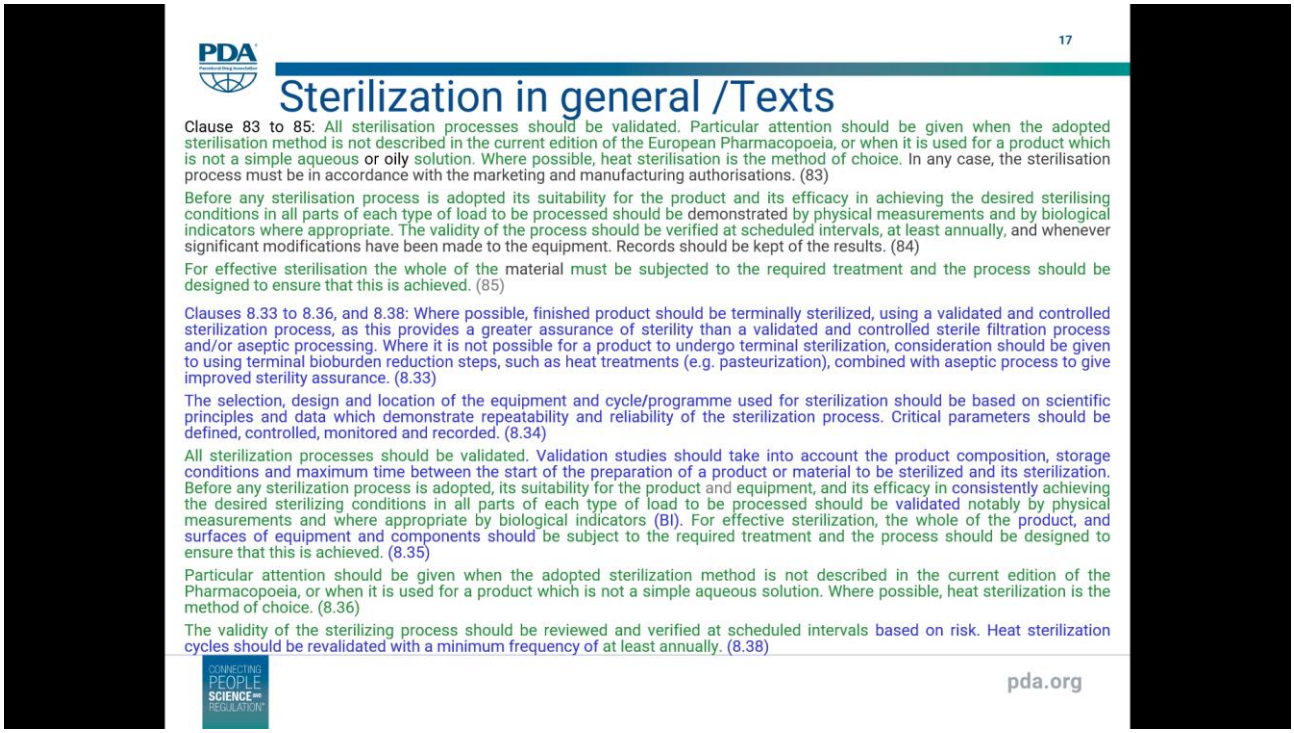


Draft Version 12 precisely explains the recommendation of “bioburden assay as in-process test”, including the identification of the microorganisms, and thus their biological evaluation.

It also seems that the monitoring of the pyrogen level may be required only for the parametric release. In fact, parametric release

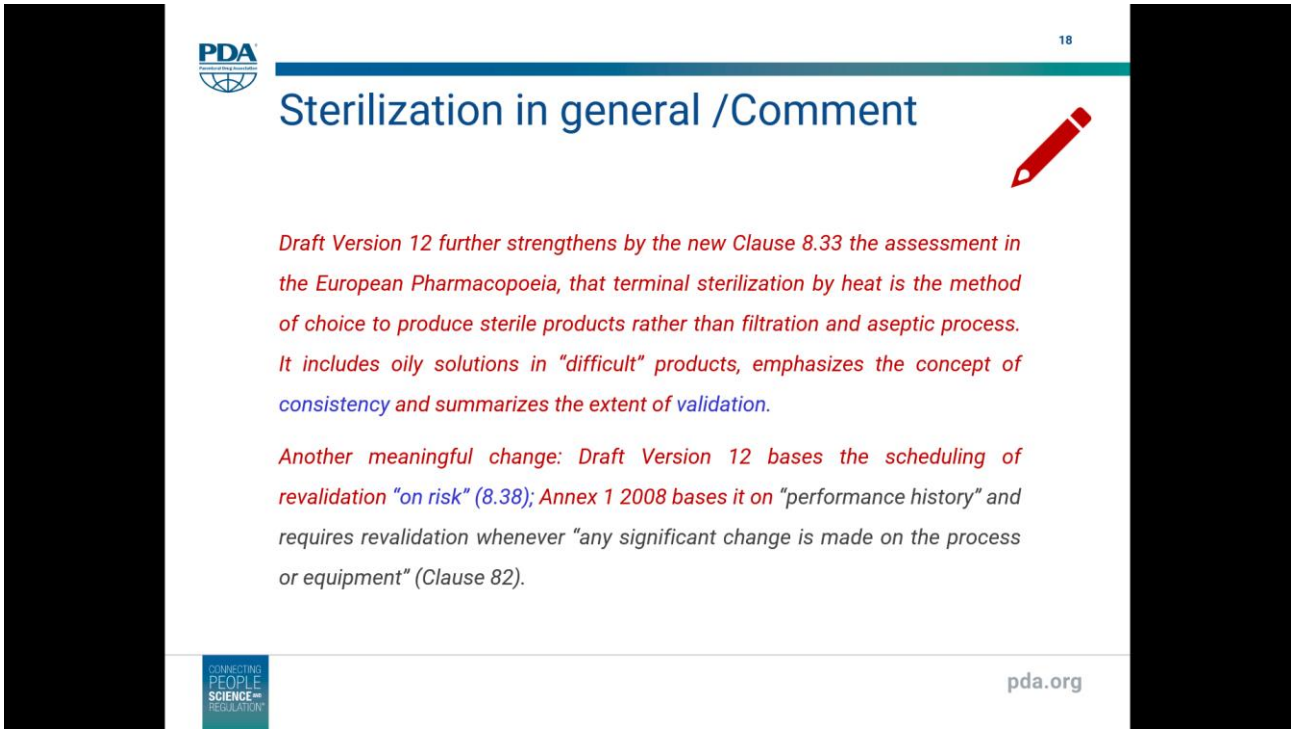
is still far from being a usual approach, and the new demand is only the rather logical and already substantially implicit one, of including *components* in the bioburden assay.

26:55 (Slide no. 17/51)



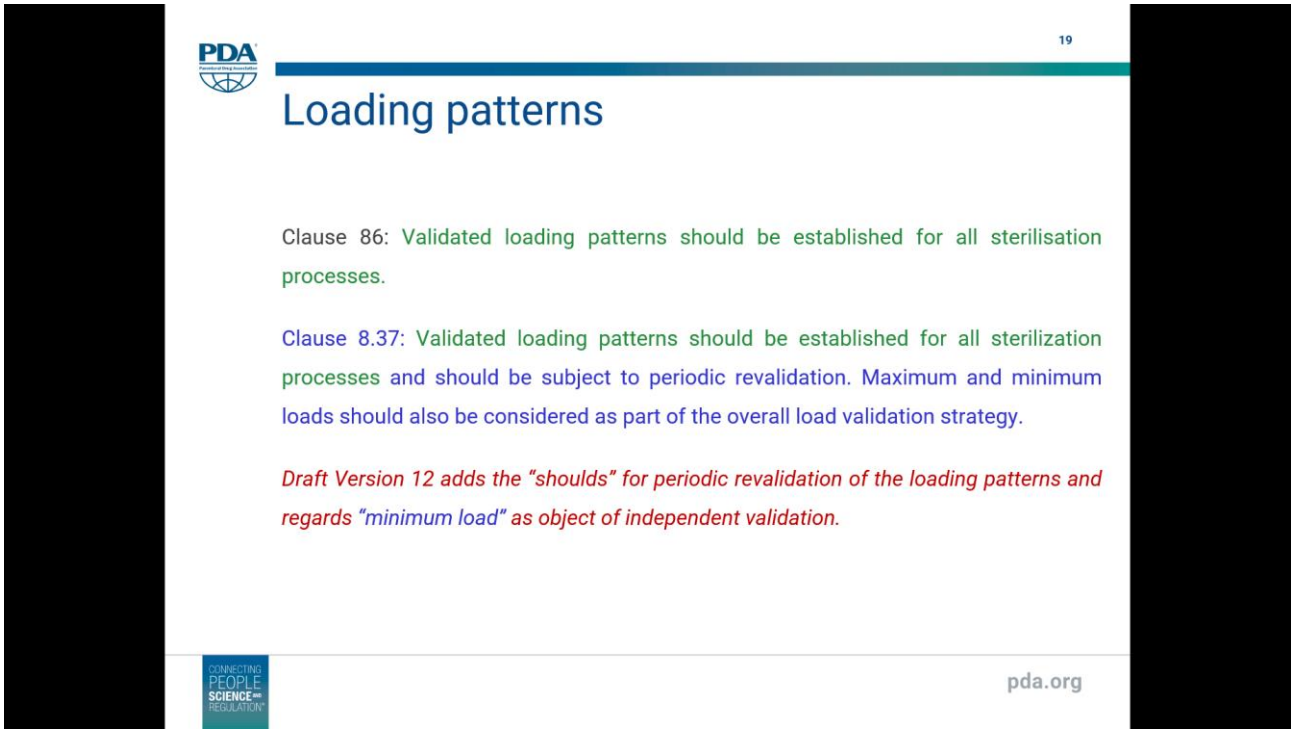
Oily solutions are no longer considered “easy to sterilize”: this is obtained by simply removing a single word in the new Clause 8.36… In fact, they can be an easy case only if the content of water is enough to generate inside containers such an amount of steam that could fill all the volume of the container. We are not talking about a big quantity, as the specific volume of steam under current moist-heat sterilization condition is almost eight hundred ninety times more than of liquid water at ambient temperature.

27:45 (Slide no. 18/51)



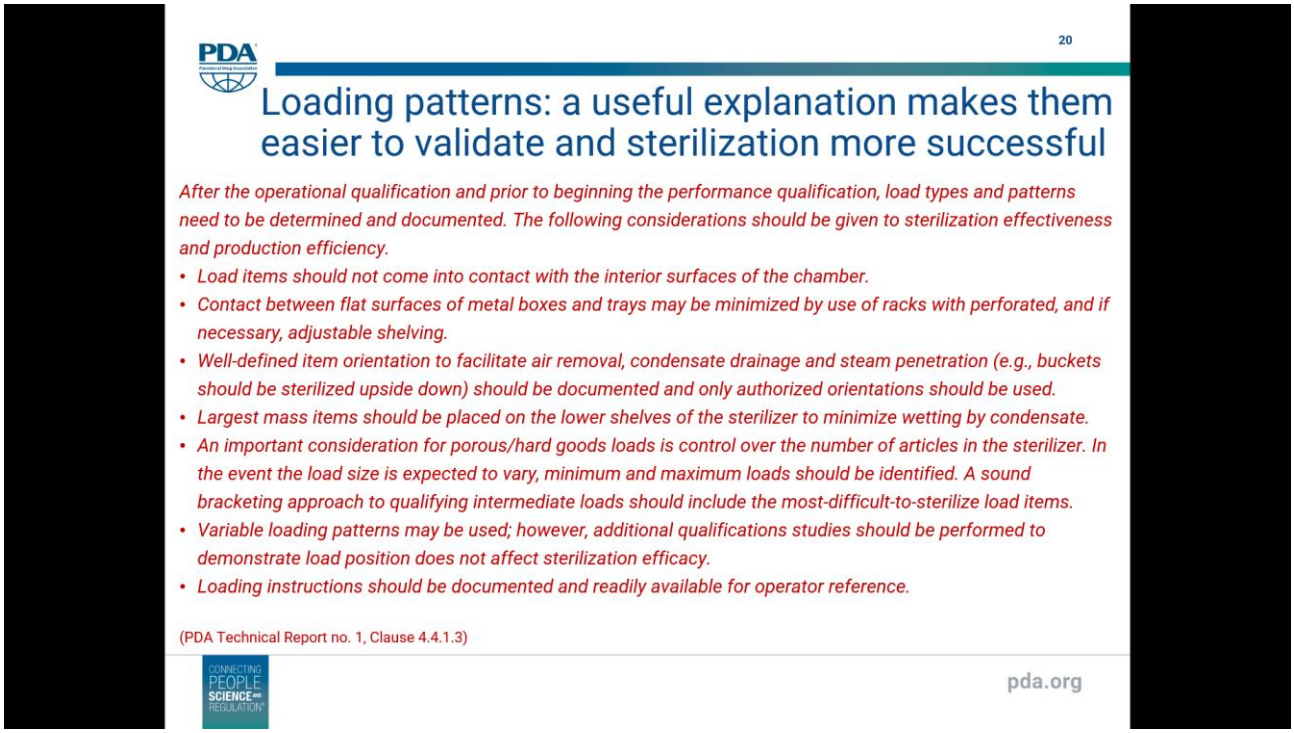
The most important change, in my opinion, regards the replacement of “performance history” and “significant change” with “risk” for scheduling of revalidation.

28:00 (Slide no. 19/51)



In addition to Annex 1 2008, Draft Version 12 requires the periodic revalidation of the loading patterns and regards “minimum load” as an object of independent validation. In fact, the minimum load is quicker to heat up and cool down than maximum load of the same type of items, and usually receives a smaller lethal dose of heat.

28:30 (Slide no. 20/51)



Correct and repeatable loading patterns are of an utmost importance in successful sterilization. This matter is not treated but very shortly in Annex 1, possibly because detailed information in the new Annex 1 would overtake the limits of a general guidance. To understand better what are loading patterns, I suggest referring to Clause 4.4.1.3 of P-D-A T-R-1 Revised 2007. The slide displays useful considerations on the matter.

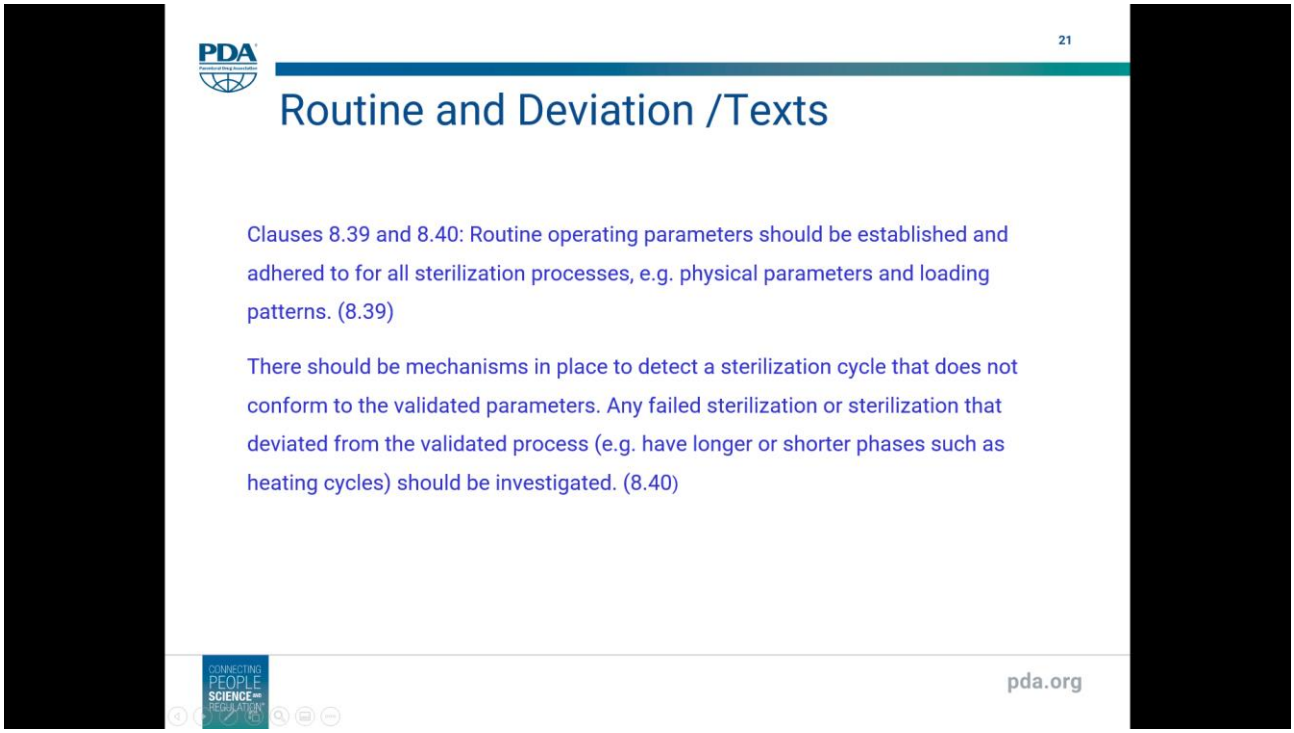
After the operational qualification and prior to beginning the performance qualification, load types and patterns need to be determined and documented. The following considerations should be given to sterilization effectiveness and production efficiency.

- *Load items should not come into contact with the interior surfaces of the chamber.*
- *Contact between flat surfaces of metal boxes and trays may be minimized by use of racks with perforated, and if necessary, adjustable shelving.*

- *Well-defined item orientation to facilitate air removal, condensate drainage and steam penetration (e.g., buckets should be sterilized upside down) should be documented and only authorized orientations should be used.*
- *Largest mass items should be placed on the lower shelves of the sterilizer to minimize wetting by condensate.*
- *An important consideration for porous/hard goods loads is control over the number of articles in the sterilizer. In the event the load size is expected to vary, minimum and maximum loads should be identified. A sound bracketing approach to qualifying intermediate loads should include the most-difficult-to-sterilize load items.*
- *Variable loading patterns may be used; however, additional qualifications studies should be performed to demonstrate load position does not affect sterilization efficacy.*
- *Loading instructions should be documented and readily available for operator reference.*

About forty years ago validated loading patterns were usually referred to as *standard loads*.

29:05 (Slide no. 21/51)



New clauses 8.39 and 8.40 of Draft Version 12 have no direct correspondence in Annex 1 2008 but relate to well established common sterilization practices both in Europe and elsewhere.

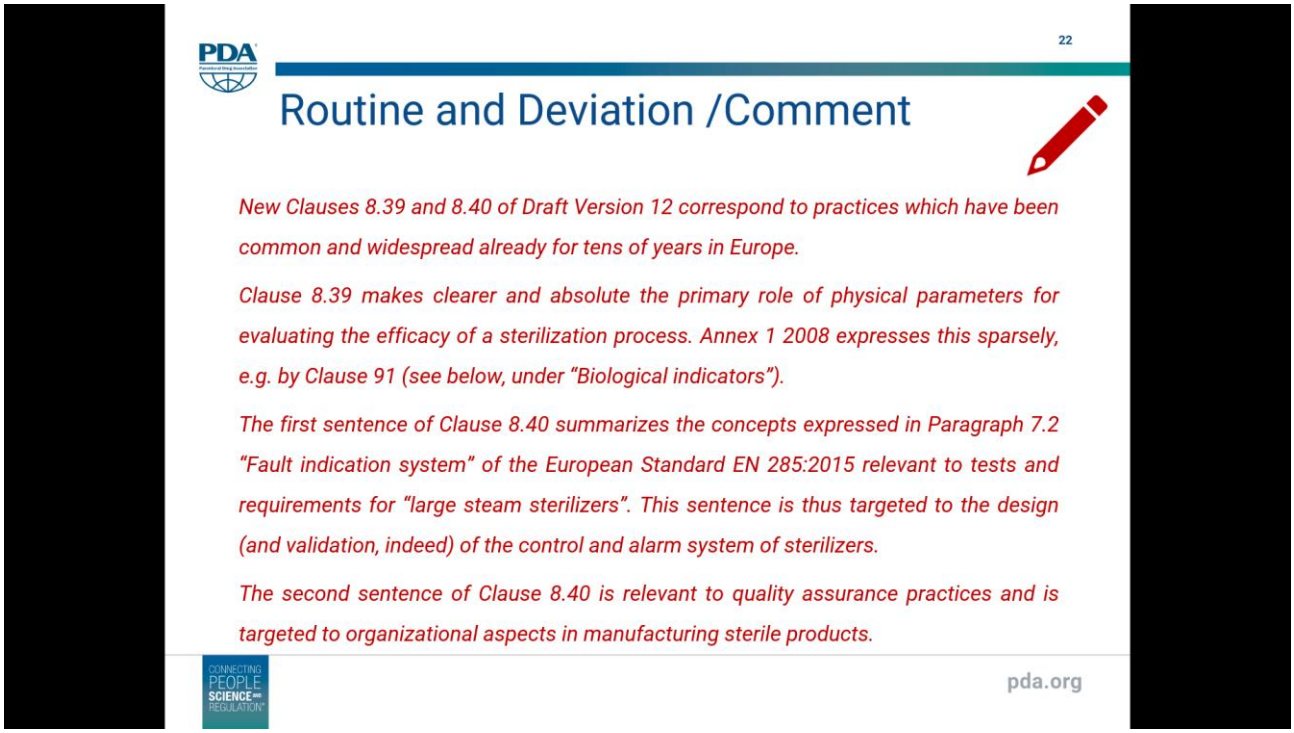
Clause 8.39 also summarizes the primary role of physical parameters for evaluating the efficacy of a sterilization process. Annex 1 2008 expresses the same concept more sparsely, by limiting the role of biological indicators.

Clause 8.40 adopts the concepts expressed in Paragraph 7.2 “Fault indication system” of the European Standard EN 285:2015 relevant to tests and requirements for “large steam sterilizers”. The requirements in it are targeted to design and validation of the control and alarm system of sterilizers. The first one may also be regarded as a “bridge” toward parametric release, asking for an

automatic detection of any deviation. But already Annex 1 2008 (Clause 94) demanded that *“System and cycle faults should be registered by the system”*.

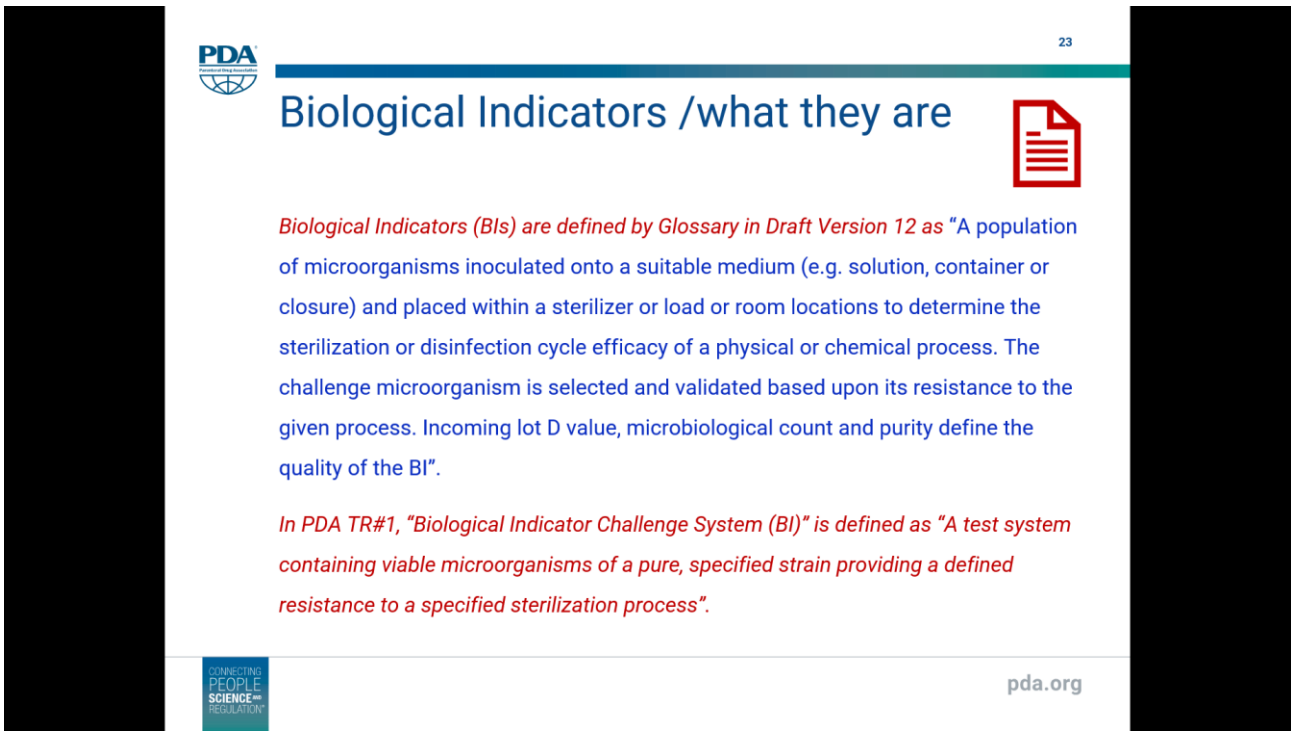
The final sentence of Clause 8.40 is targeted to organizational aspects in manufacturing sterile products. In many pharma companies it has been for tens of years a common practice the definition of “critical” alarms and subsequent thorough investigation of the causes thereof when occurring, in spite of the less demanding relevant Clause 94 in Annex 1 2008.

31:10 (Slide no. 22/51)



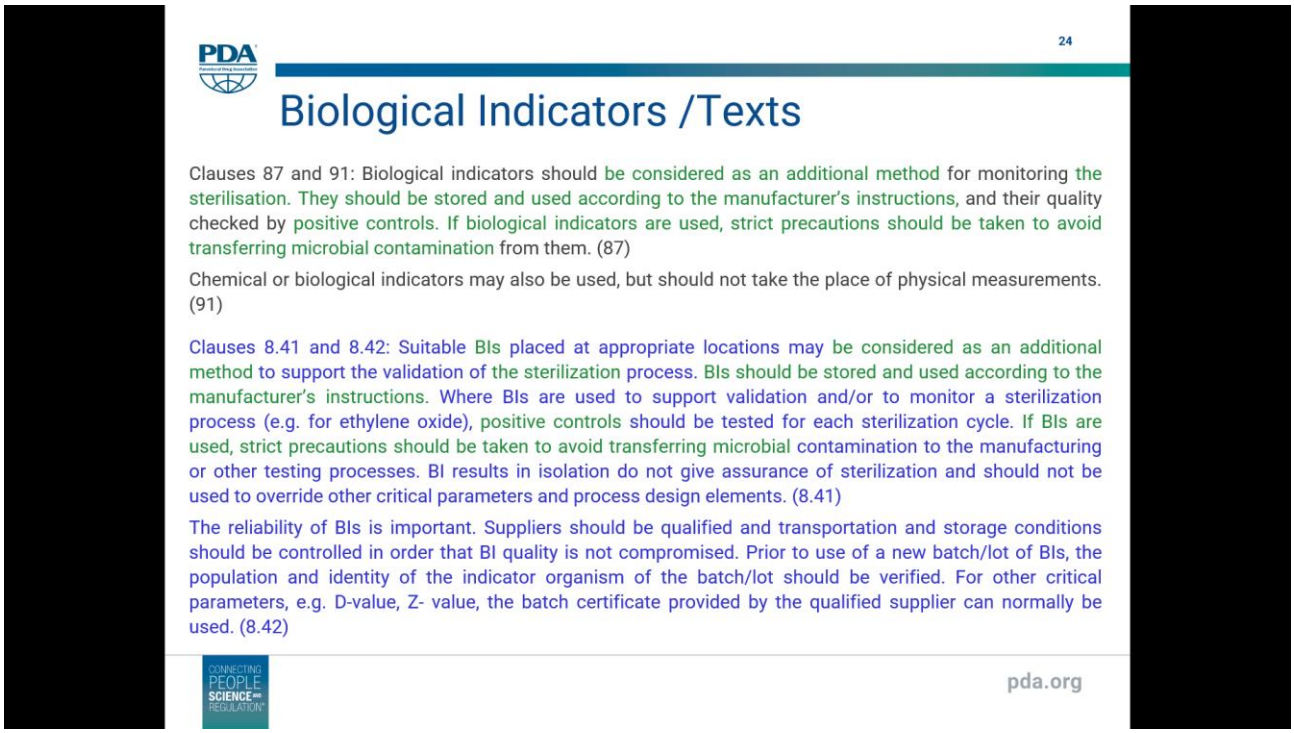
The slide only summarizes my comments, that you have just listen to.

31:15 (Slide no. 23/51)



The “definition” of BIs in Draft Version 12 sounds… as an operating manual. We can refer much better to that in P-D-A T-R-1. The basic concept is that they are test systems for the evaluation of a sterilization process.

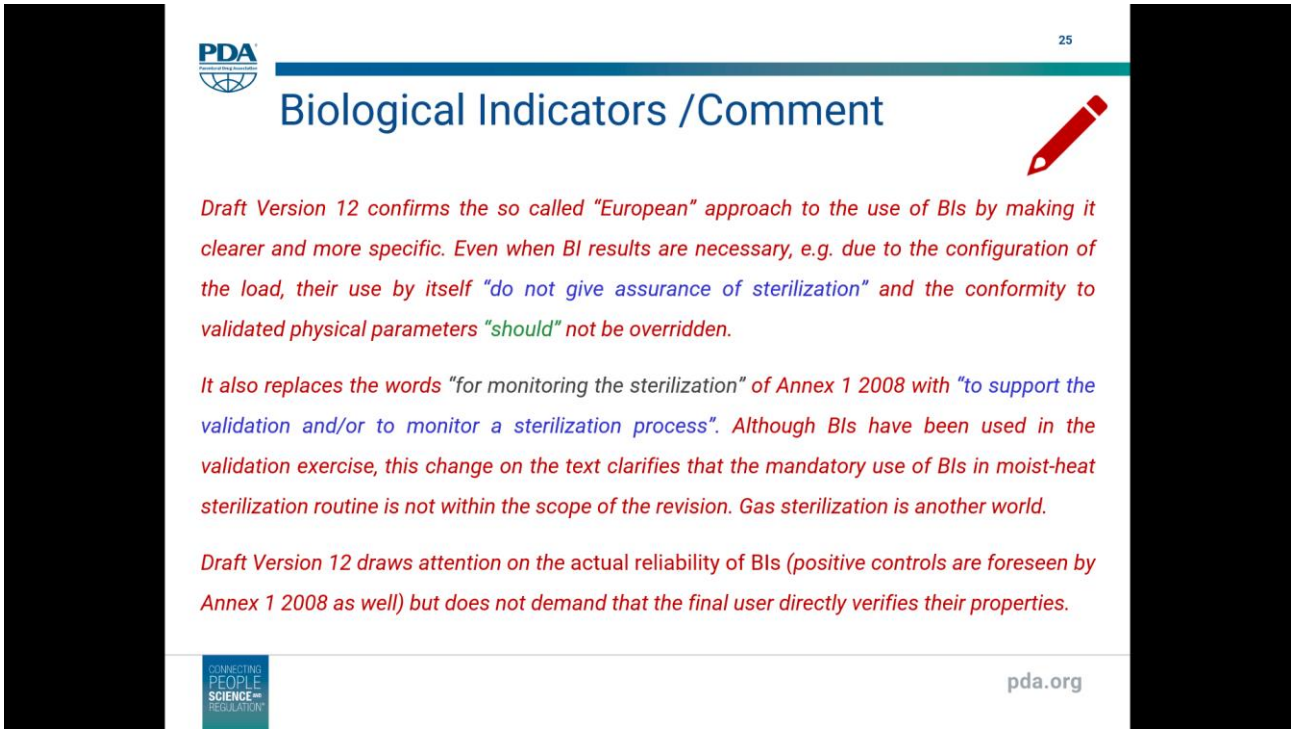
31:35 (Slide no. 24/51)



Draft Version 12 confirms that BIs are neither always necessary, nor sufficient to “give assurance of sterilization”.

The use of BIs in routine for moist-heat sterilization was and remains not necessary even in case that their role has been essential in the validation exercise.

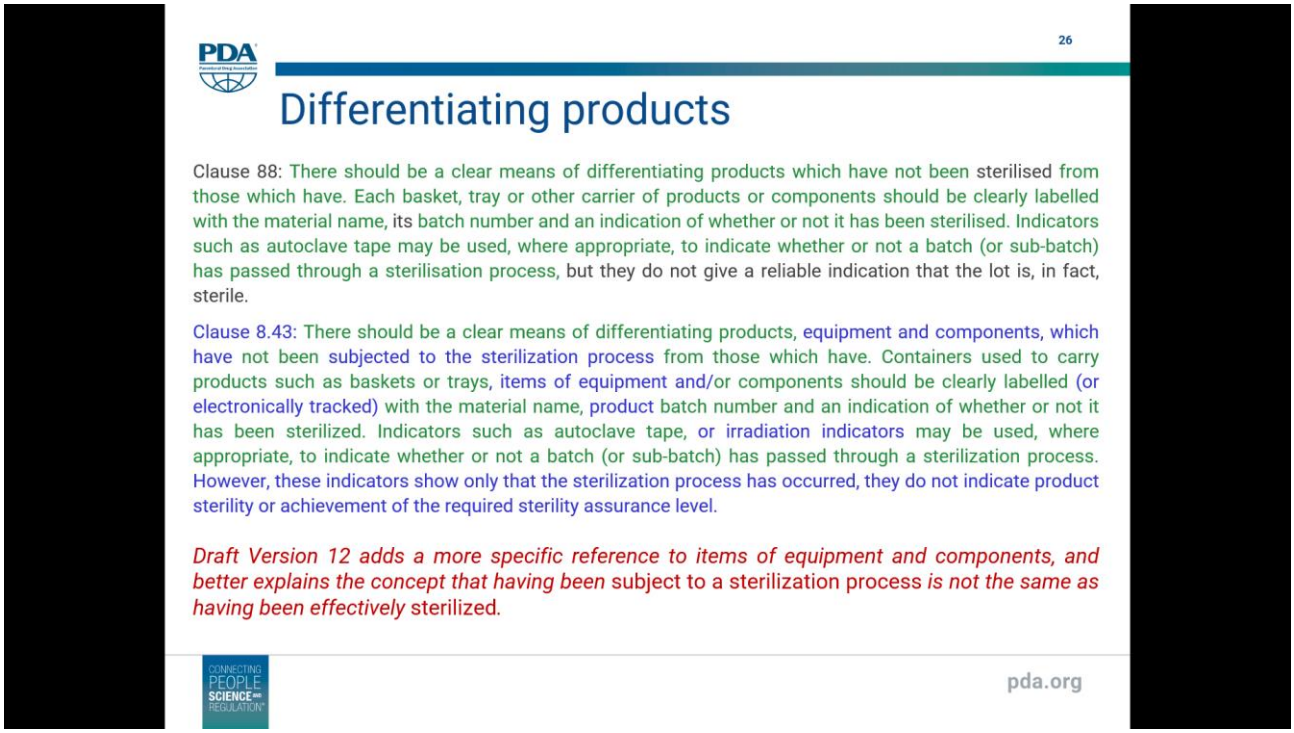
32:10 (Slide no. 25/51)



The potentially ambiguous words *"for monitoring the sterilization"* are replaced with a very clear *"to support validation"*.

Nor it is deemed necessary that the final user directly verifies the actual properties of the BIs she or he uses. Only a verification of reliability is required; in fact, the so called "positive controls" were already required by Annex 1 2008.

32:50 (Slide no. 26/51)



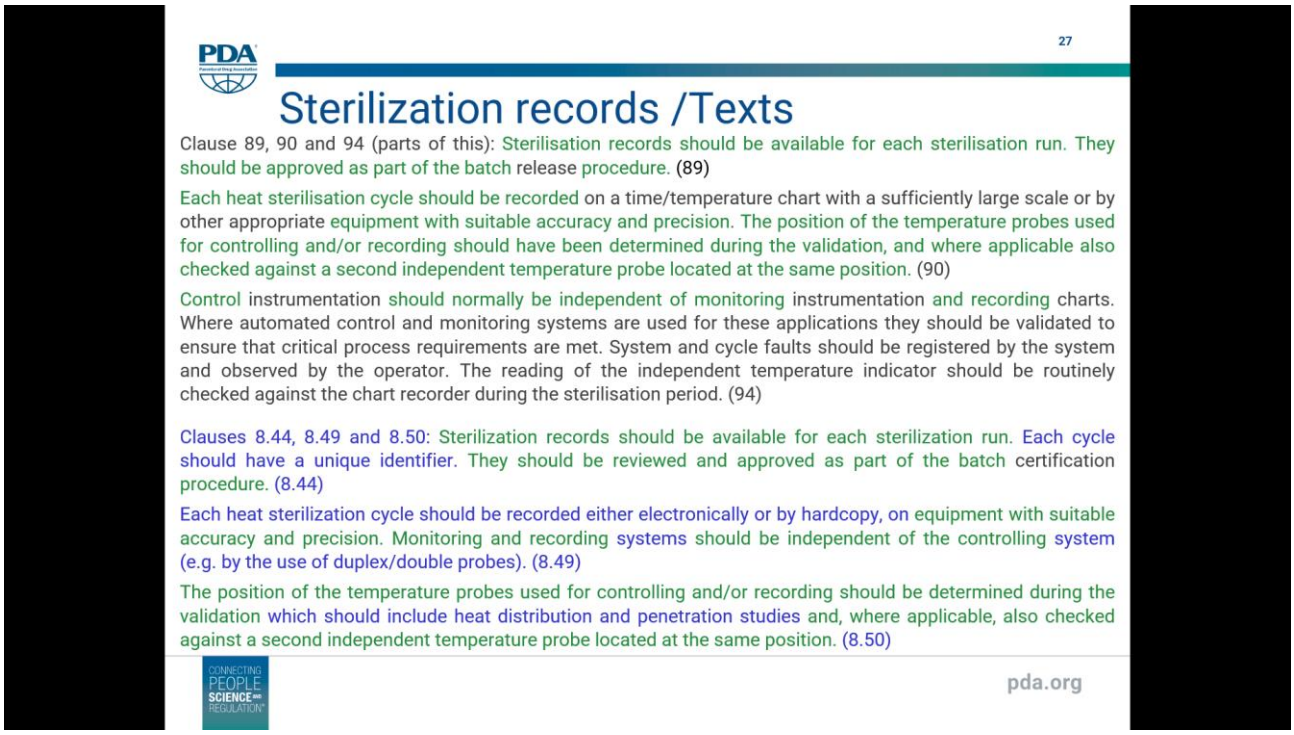
As already noted for the bioburden assay, Draft Version 12 brings attention to equipment and components as well as to the product itself, and *better underlines the difference between having been subjected to a sterilization process and having been sterilized*.

Due to the technological evolution, labelling autoclave loads may be now replaced with electronic *tracking*. I regard as implicit that this should also allow tracing, if necessary. I suppose that this is an opportunity to precise the concept.

In fact, “to *track* an object, you follow the path forwards from the starting point to wherever the object currently is; whereas, to *trace* an object, you follow the path backwards from its current point to where it began”.

From the point of view of the final user of a pharma product or medical device, it is obvious that the interest is *traceability*, but Draft 12 says *tracking* because it deals with manufacturing, not with use.

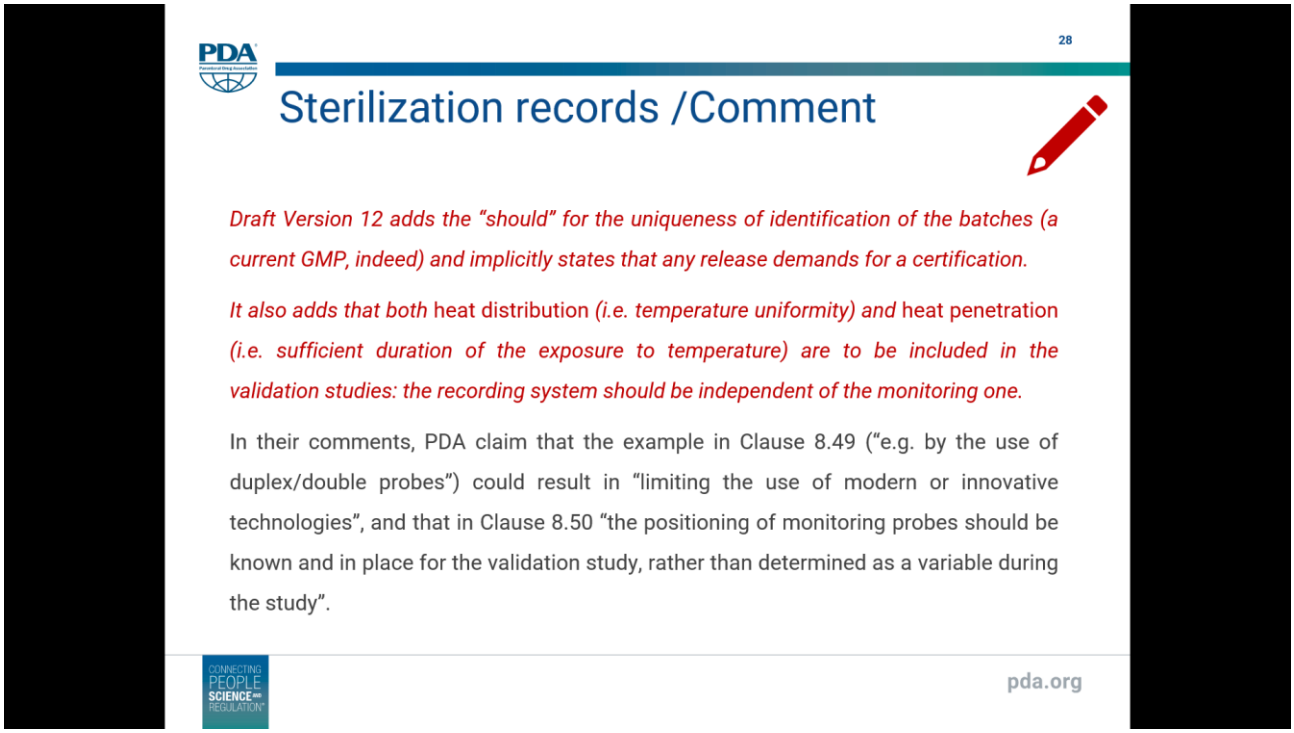
34:00 (Slide no. 27/51)



Drafts Version 12 demands the uniqueness of batch identification (which has been already for many years a common Good Manufacturing Practice) and implicitly states that any release requires a certification.

Clause 8.50 identifies the two main tasks in the validation exercise: *heat distribution* and *heat penetration*. Both these have been for tens the core of the *thermal validation.*

34:35 (Slide no. 28/51)



These clauses seem very clear and sound, at least to me.

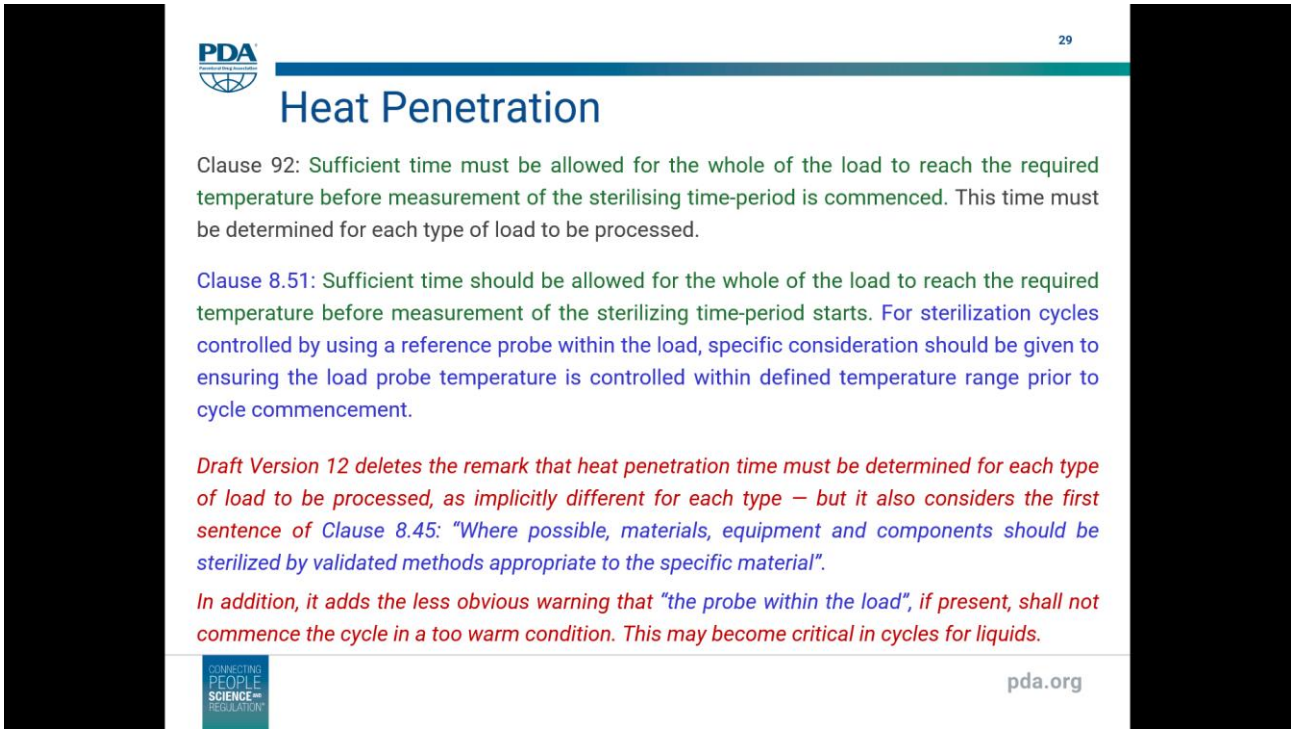
I take therefore the liberty to consider very curious the comments submitted by P-D-A to Clauses 8.49 and 8.50. They propose to replace the example in Clause 8.49 with the alternative requirement of *"safeguards and/or redundancy to detect a cycle not confirming to validate cycle parameters requirement and abort of fail the cycle"*. This requirement could be in alternative to the independence of monitoring and recording systems.

I believe that this proposal of P-D-A repeats, on the one hand, the requirement of Clause 8.40 we have already seen, namely that of "mechanisms in place to detect a sterilization cycle that does not conform to the validated parameters".

On the other hand, the text proposed by P-D-A eliminates the essential requirement of using separate systems for controlling the process and monitoring/recording it.

On the question when or while the position of the temperature probes for controlling and/or recording should be determined, I find hard to understand how this position should be finally known and fixed but properly thanks to the validation exercise. To determine the methods and instruments of control is part of the Process Definition, one of the historical pillars of the Validation, the other being Instrument Calibration and Personnel Training.

36:45 (Slide no. 29/51)



In their comments, P-D-A propose to restrict to porous/hard good loads the requirement *"Sufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period starts"*. P-D-A comment claims that *"load equilibration is only applicable to porous hard goods loads"* and names "lag in temperature" the considerable heating delay of liquid loads "behind the temperature in the sterilizer". The comment also invokes the fact that the physical lethality delivered to liquid loads is currently measured by the equivalent time F_0, so that "temperature equilibration prior to the start of the sterilizing phase is not applicable for liquid loads".

In my opinion, the point may easily become confusing.

First, it useful to distinguish between the *concept* of equilibration time and the *requirements* on maximum equilibration time.
According to the international standard E-N I-S-O 17665, definition 3.13, equilibration time is the ***"period which elapses between the attainment of the sterilization temperature at the reference measurement point and at all points within the load."***
These words indicate a delay, without prejudice of the causes of it, either poor air removal, as in the case of porous/hard goods, or a remarkable thermal inertia, as in the cases of six-liter liquid volumes invoked by P-D-A.

There is no doubt that with most liquid loads "temperature lags of the loads behind the sterilizer" cannot be shortened down to tens of seconds.

There is also no doubt that the concept of equilibration time is not mentioned at all in this clause of Draft 12. We'll see in short that the only occurrence of the words "equilibration time" in the entire document is explicitly relevant to moist-heat sterilization and to the so called "porous cycle".

On the contrary, Clause 8.51, to which P-D-A refer in this comment of theirs, is under a general section "Sterilization by heat", not in the subsection for moist-heat, and it is hard to understand why the statement in argument would not apply to all loads.

Draft 12 doesn't mention here any sterilization phase, but a most generic sterilizing time-period.

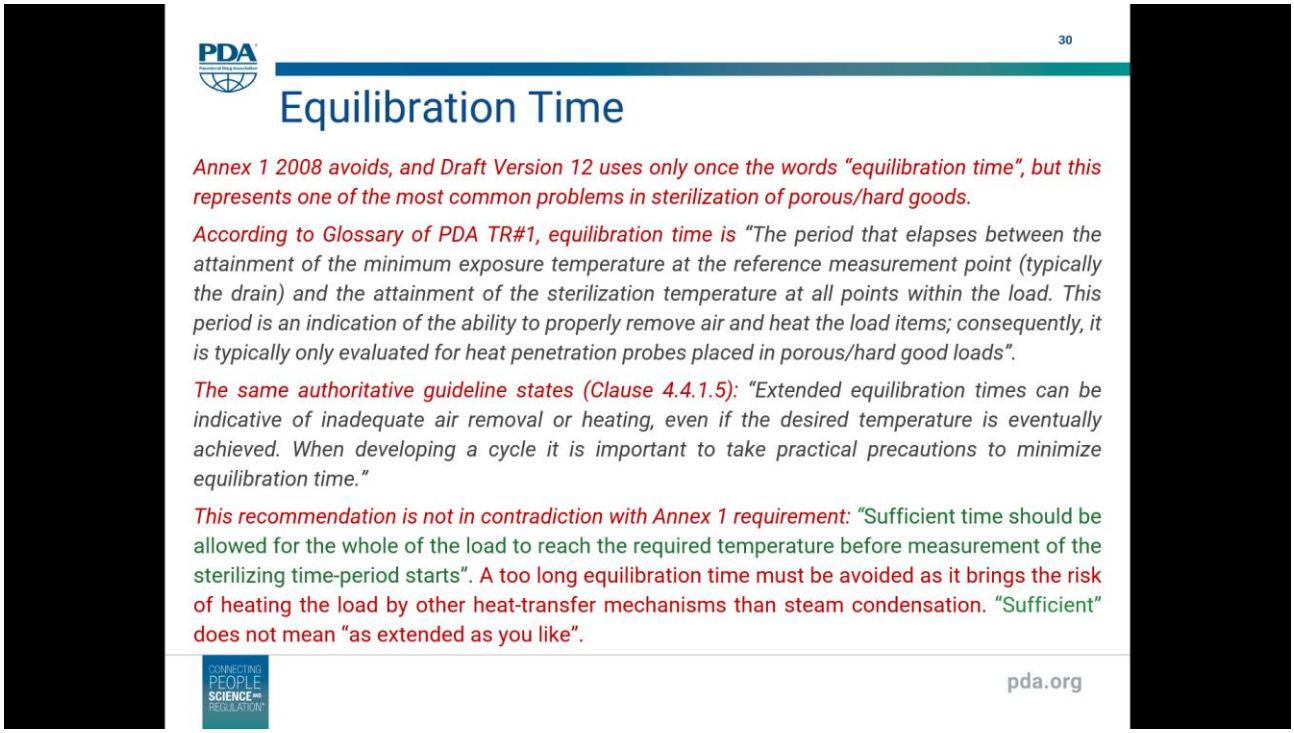
Please note the remark that has been added in Draft Version 12: if a “probe within the load” is present, this shall not commence the cycle in too warm a condition.

This typically applies to cycles for liquids. In fact, if you load a batch of bottles containing liquid at 20 °C, bur the “reference probe” is within a bottle cooled down only to 50 °C at the end of the previous run, the new run will be monitored by a temperature that doesn’t correspond with the real load.

Regardless to any non-applicable or not meaningful equilibration time, the physical calculation of lethality delivered to the liquid loads, or equivalent time F_0, would be wrong if sufficient time has not been allowed for the whole of the load to reach the required measurement temperature.

I wish to add that proper location and handling of the *“reference probe within the load”* are typically belonging to the validation exercise, cannot be “set prior to” it, as another comment suggests.

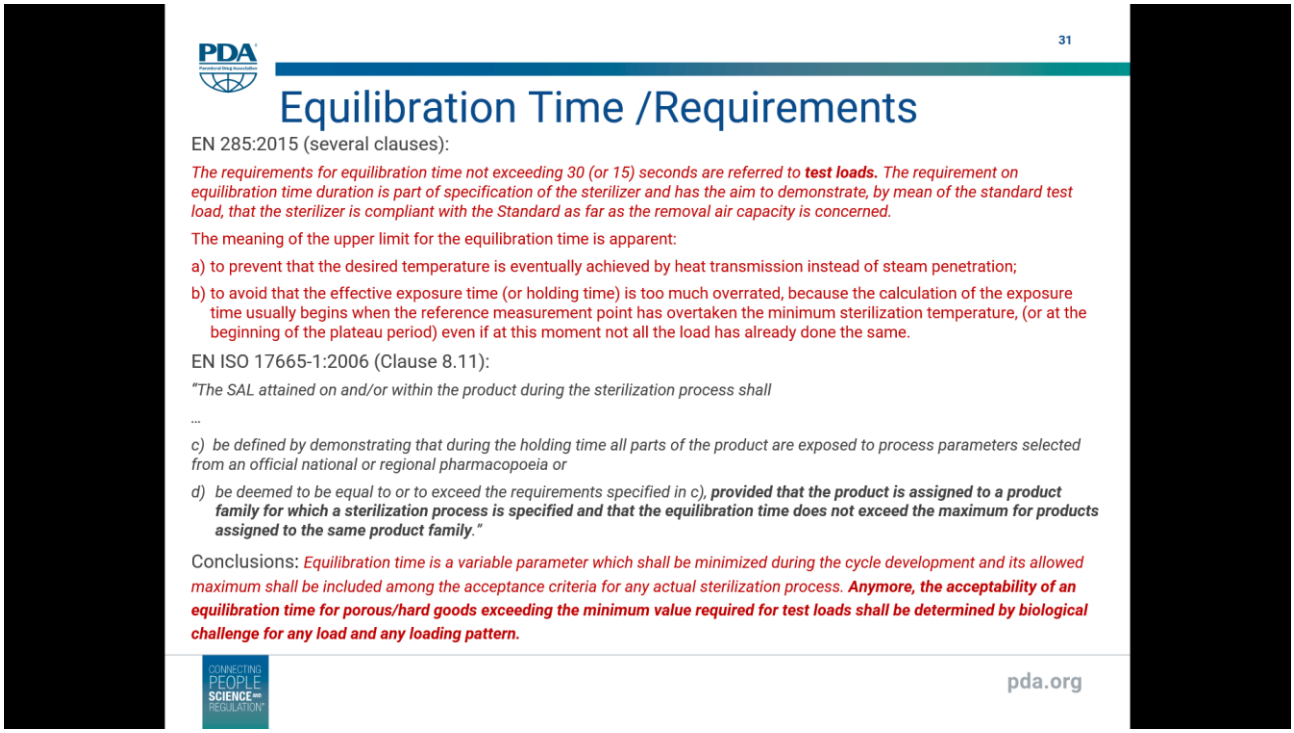
41:40 (Slide no. 30/51)



It's noteworthy that neither Annex 1 2008 nor Draft Version enter with details the rather difficult issue of the so called "equilibration time".

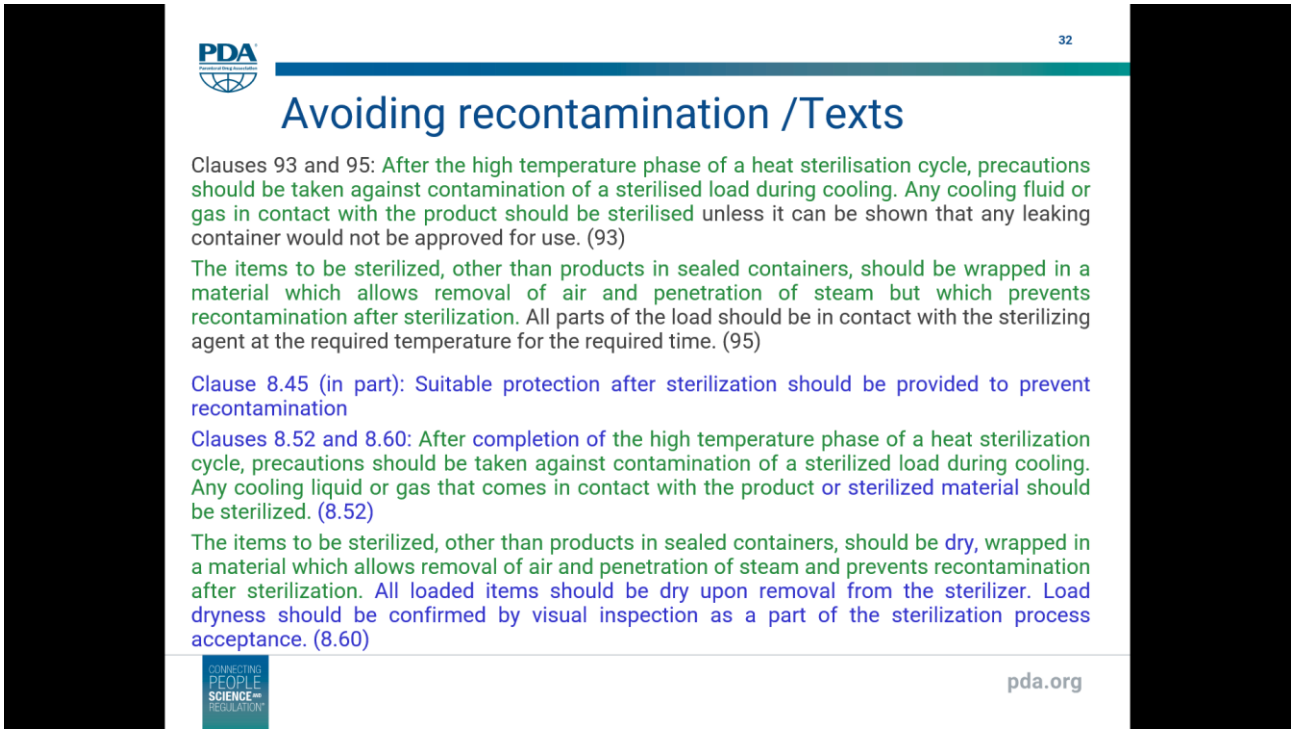
This slide and the next one refresh the remarks we have seen yesterday when speaking on the matter…

42:05 (Slide no. 31/51)



…so, I believe that today we can skip them.

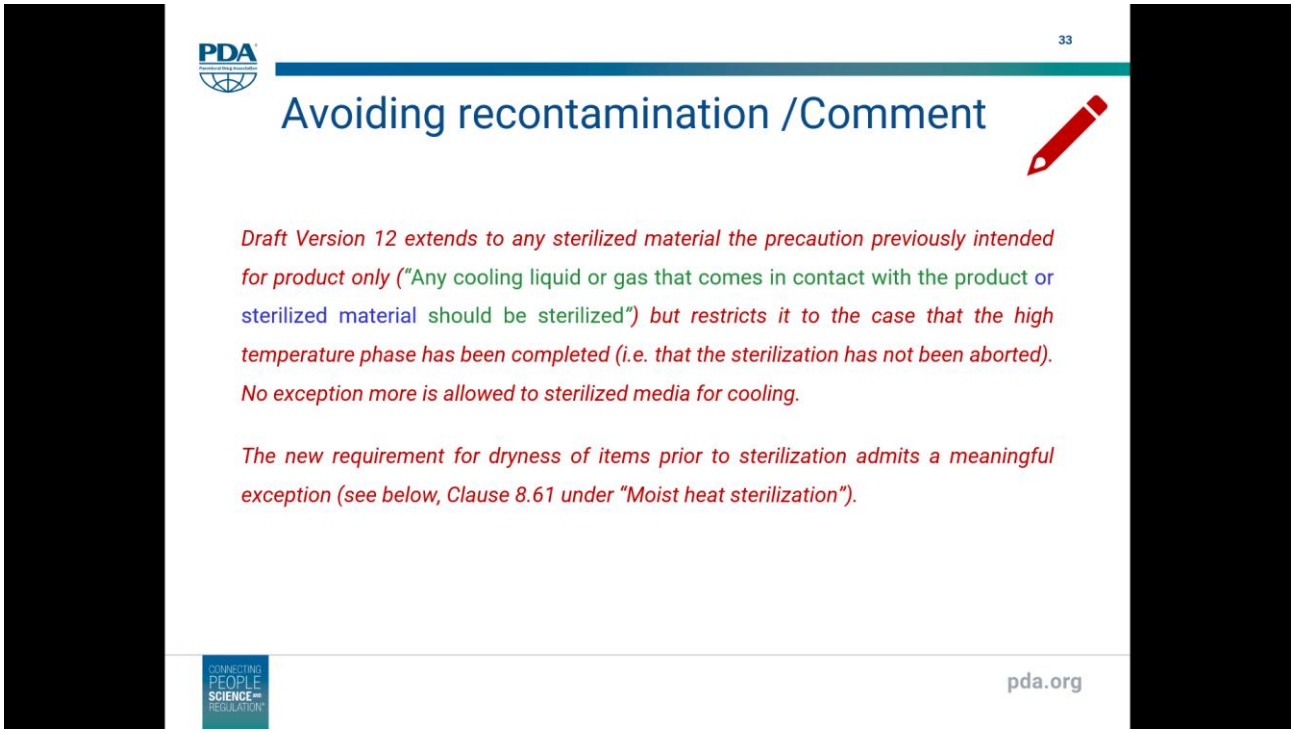
42:10 (Slide no. 32/51)



In the worst case, recontamination may occur while the load is still inside the sterilizer. Cooling media and vacuum-break-air are the most frequent causes of this “internal” recontamination. Draft Version 12 removes any exception for the sterility of *“any cooling liquid or gas”* coming in contact with the product or any other material present in the sterilizer after the sterilization has been completed.

In Annex 1 2008 this exception is: *“unless it can be shown that any leaking container would not be approved for use”*. All of us know that it is rather unrealistic. Anymore, Draft Version 12 is written in such a way that if the sterilization has not been completed, the cooling liquid or gas can be non-sterile.

43:10 (Slide no. 33/51)



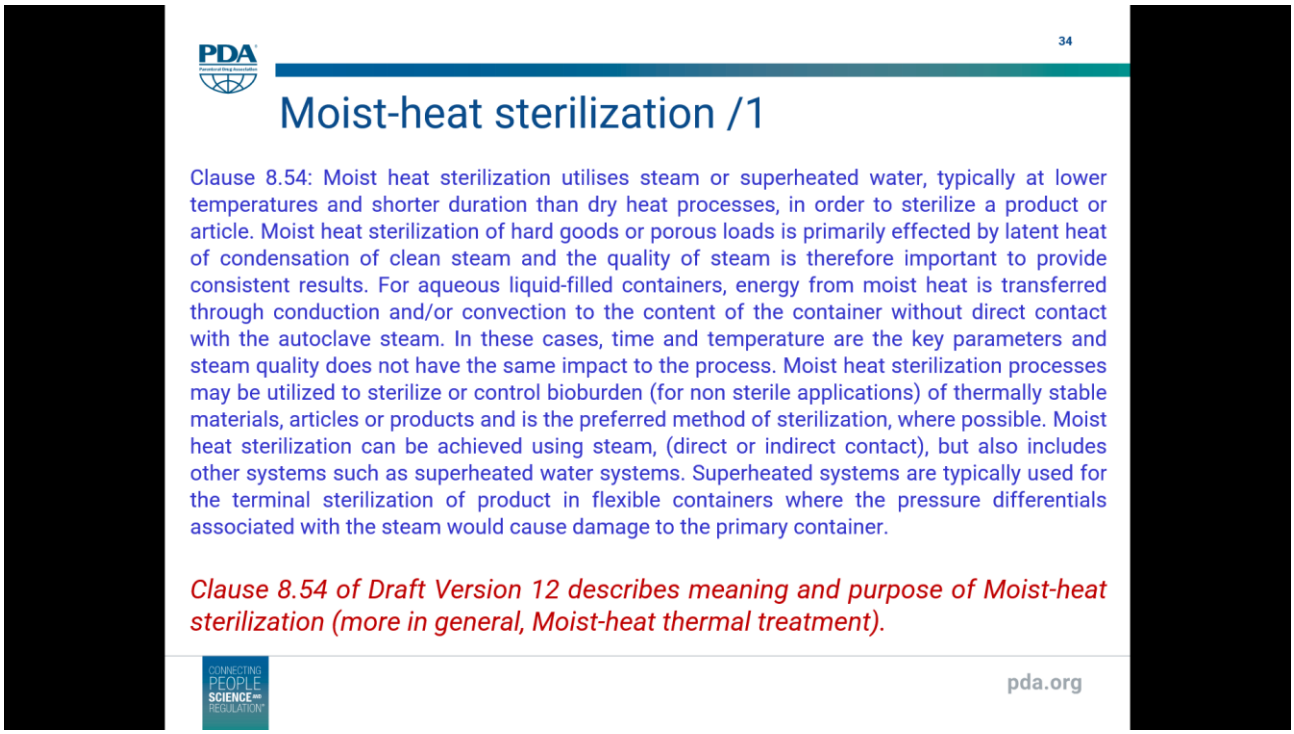
The recontamination may also occur after removing the product from the autoclave. Preventing this demand, for porous/hard loads, a satisfactory level of dryness after sterilization. Technical standard EN 285 deals with requirements and testing methods which refer mostly to hospital practice, but the dryness of steam pervious membranes is essential for maintaining the sterility, for instance, of blisters or “Tyvex bags”.

The post-sterilization dryness requires, in most cases, a pre-sterilization dryness. But there is an important exception that we’ll see in short.

In most cases intake gases are sterilized by filtration (with all the complications due to the sterilization and integrity test of the filter, or filters). On the contrary, sterilizing filtration of cooling water has

always been very unusual: it has always been easier and much safer to sterilize it by heat.

44:30 (Slide no. 34/51)

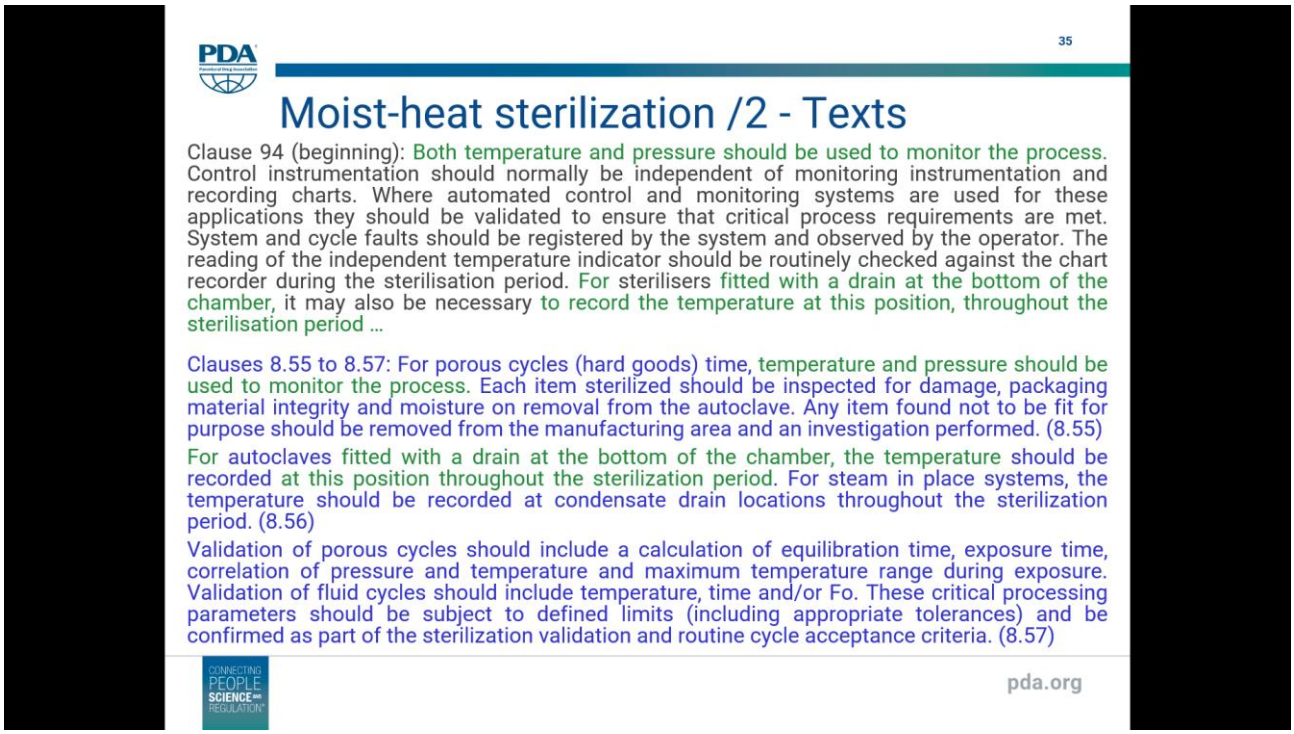


The completely new clause 8.54 is a merely descriptive one. This does not mean it is useless. The distinction is important between direct and indirect use of steam, for heating and sterilizing by contact, or for heating only.

The words *"superheated systems"* occur also in another clause of the Draft. It is not clear, at least for me, whether they only refer to superheated water autoclaves, or the so-called air-over-steam as well. At least in this case, the scope of the treatment could include air-over-steam. More difficult is the case, for instance, of blistered or bagged containers: the intermediate space is currently expected to be sterile, and the surfaces of it can be sterilized only by direct

contact, but a lot of non-condensable gas is necessarily present together with steam.

41:15 (Slides no. 35/51)



Clause 8.55 of Draft Version 12 confirms, with a more precise wording, the importance of monitoring pressure in “porous cycles” and adds the *“shoulds”* for inspecting the items *“on removal from the autoclave”* and rejecting them immediately if no longer *“fit for purpose”*.

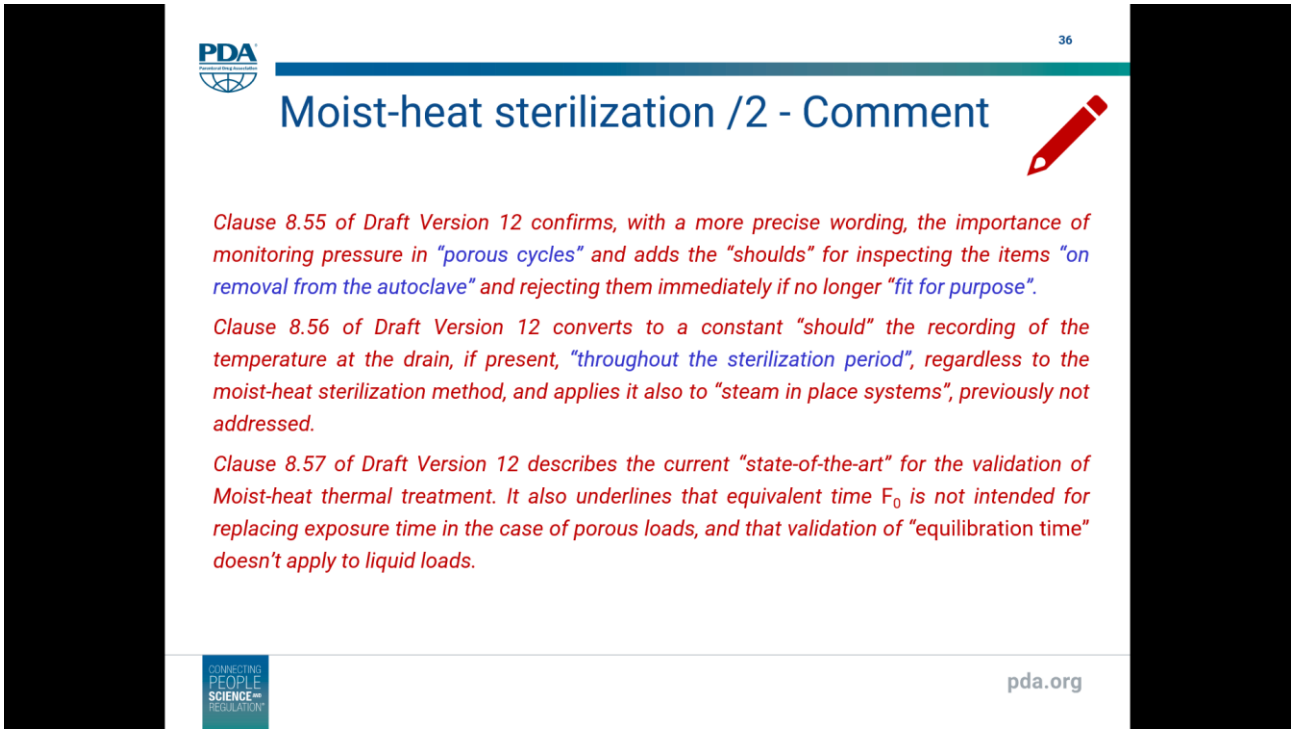
Clause 8.56 converts to a constant *“should”* the recording of the temperature at the drain, if present, *“throughout the sterilization period”*, regardless to the moist-heat sterilization method, and applies it also to *“steam in place systems”*, previously not addressed.

Clause 8.57 depicts the current “state-of-the-art” for the validation of moist-heat thermal treatment. It also underlines that equivalent time F_0 is not intended for replacing exposure time in the case of porous loads, and that “equilibration time” doesn’t apply to liquid loads. I believe that this is a very important remark, because F_0 as equivalent time is meaningful only if the product under sterilization is in contact with condensing saturated steam.

This is always true for aqueous liquids in sealed containers; on the contrary, for porous/hard loads we expect this only during the so called “holding time” — that means, by definition, the period for which both the temperature at the reference measurement point and those at all points within the load are continuously within the sterilization temperature band.

A sound remark of P-D-A’s suggests specifying better to which “critical processing parameters” does refer the requirement in Clause 8.57, as the case of the so-called porous cycles” is intrinsically different form the that of “fluid cycles” — some listed parameters are not applicable in both cases.

43:50 (Slide no. 36/51)



Another comment by P-D-A regards Clause 8.56. They suggest restricting the requirement of recording the drain temperature during the sterilization period only to autoclaves ”capable of performing prevacuum sterilization cycles”, so to exclude superheated water autoclaves.

Undeniably, the text of Draft 12 is a little ambiguous.

Other documents use the words “active drain” to indicate a drain *essential to the operation* of the autoclave, and this wording would make the point easier, including autoclaves as well, that remove air by displacement of air. Perhaps P-D-A have forgotten them, perhaps not, perhaps even included in *“steam in place systems”*. I can’t know…

There is no doubt that bottom outlet of superheated water autoclaves is no active drain during a sterilization cycle. This notwithstanding, it is usually the coldest point of the chamber during the plateau period.

Different is the case of the air-over-steam sterilizers. Some of them are also capable of performing prevacuum, some others are not.

Air-over-steam autoclaves usually drain condense from the bottom, and this makes the drain “active”. Both condense and air flow through this drain.

In practice, it is not easy to maintain the temperature of the drain within the sterilization temperature band for the entire plateau period.

This obviously depend on the amplitude of the sterilization temperature band and on the difference between the control temperature and the minimum of the band.

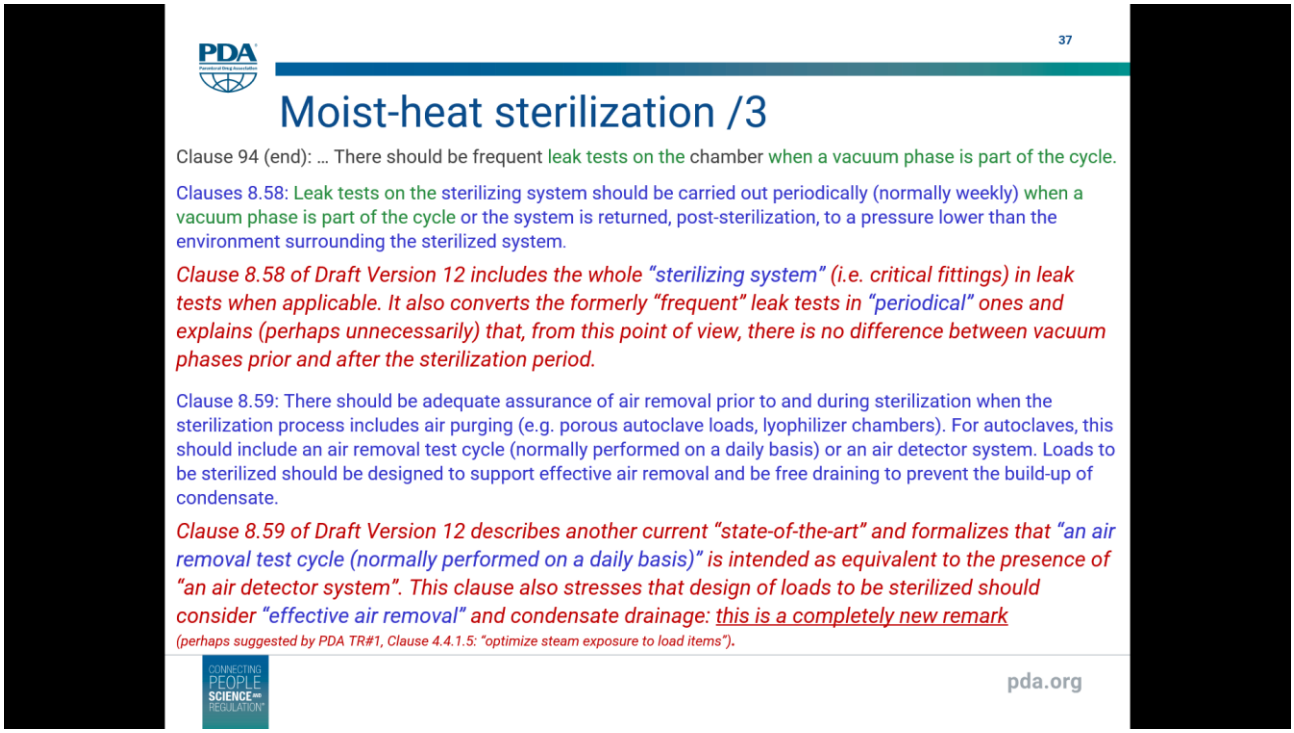
A slightly lower temperature in the drain of an air-over-steam autoclave doesn’t usually hinder sterilization of the load but could be incompatible, for instance, with the final opening of the autoclave to a sterile area.

Anymore, air-over-steam autoclave are often used also for contact sterilization of the internal parts of a blister containing, for instance, a prefilled syringe. It is hard to suppose that in these cases the drain temperature would not be object of the validation study, even if the autoclave were not equipped with a vacuum pump.

In any case, if the temperature gap between chamber and drain becomes bigger, this indicates that something is going wrong in the drain of condense.

So, personally, I am convinced that the allowable minimum of this temperature should be validated and monitored in routine through the “sterilization period” also in most autoclaves not capable of performing prevacuum. But the requirement should be expressed in a better way than the present one.

47:15 (Slide no. 37/51)



It is a common experience that vacuum leaks very seldom occur because the autoclave chamber itself leaks. By far the most leakages are due to connections, pipes, and valves. These are becoming more and more complex — you may know how many valves and pipes and connections are necessary for an automatic test of air intake sterilizing filter, so very logical is the change from *"testing the chamber"* of Annex 1 2008 to *"testing the sterilizing system"* of Draft Version 12.

On the leak test P-D-A have remarked that *"a weekly frequency may be not necessary for modern well. maintained prevacuum sterilizers, while a frequency greater than weekly could be necessary for older sterilizers"*, so that *"the specified weekly*

frequency" for the leak test is excessively prescriptive". They invoke Q-R-M principles and tailoring to each specific sterilizer.

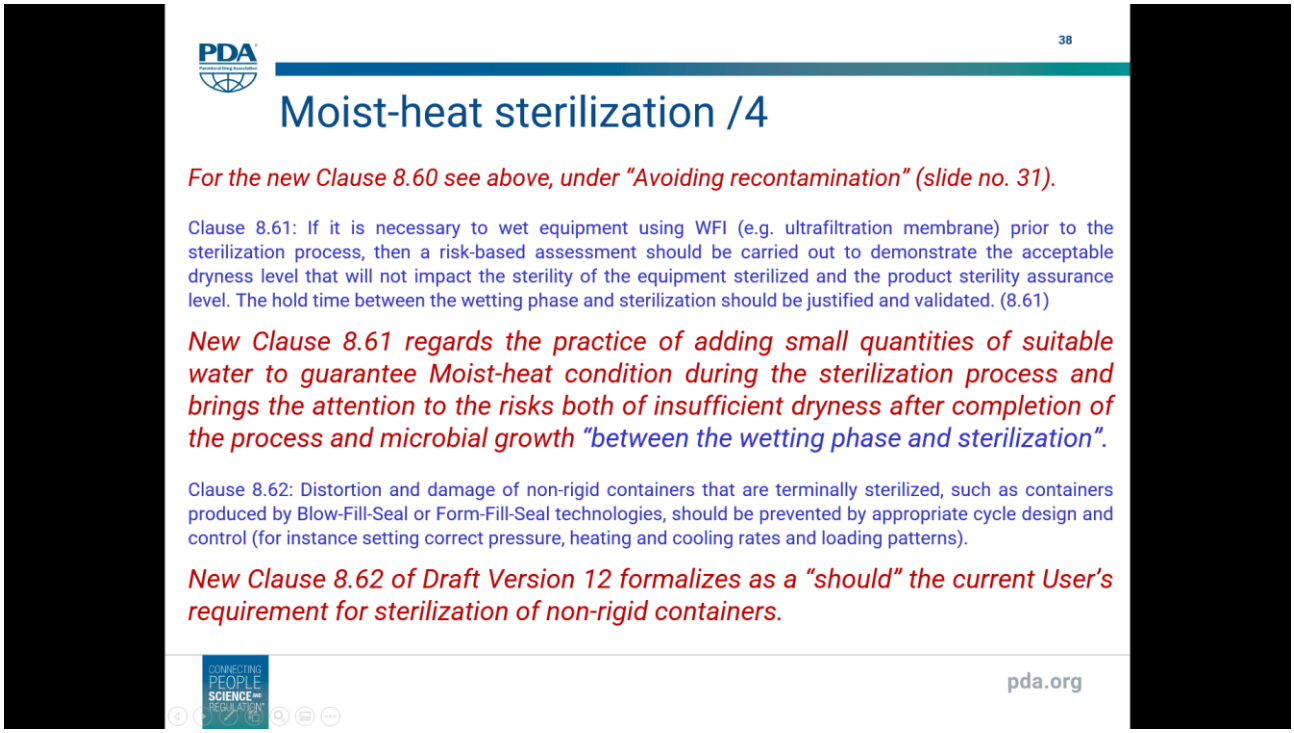
The true point, in my opinion, is how shall be managed the period between the last successful test and the failed one. This is relevant not only to the leak test.

New Clause 8.59 of Draft Version 12 requires a daily testing of air removal capacity of the autoclaves, or, as an alternative, the presence of an air detector system. In my opinion, the two things are not equivalent, because an air detector system provides information only till the moment it is connected from the autoclave chamber, that means before the completion of the heating phase.

On the air-removal test, P-D-A suggest clarifying better the field of application and repeat the remarks on the frequency they have done for the leak test. Quality Risk Management could provide a more suitable frequency.

In my opinion, without testing it could be hard to define the threshold between *purported* good maintenance and *effective* good maintenance.

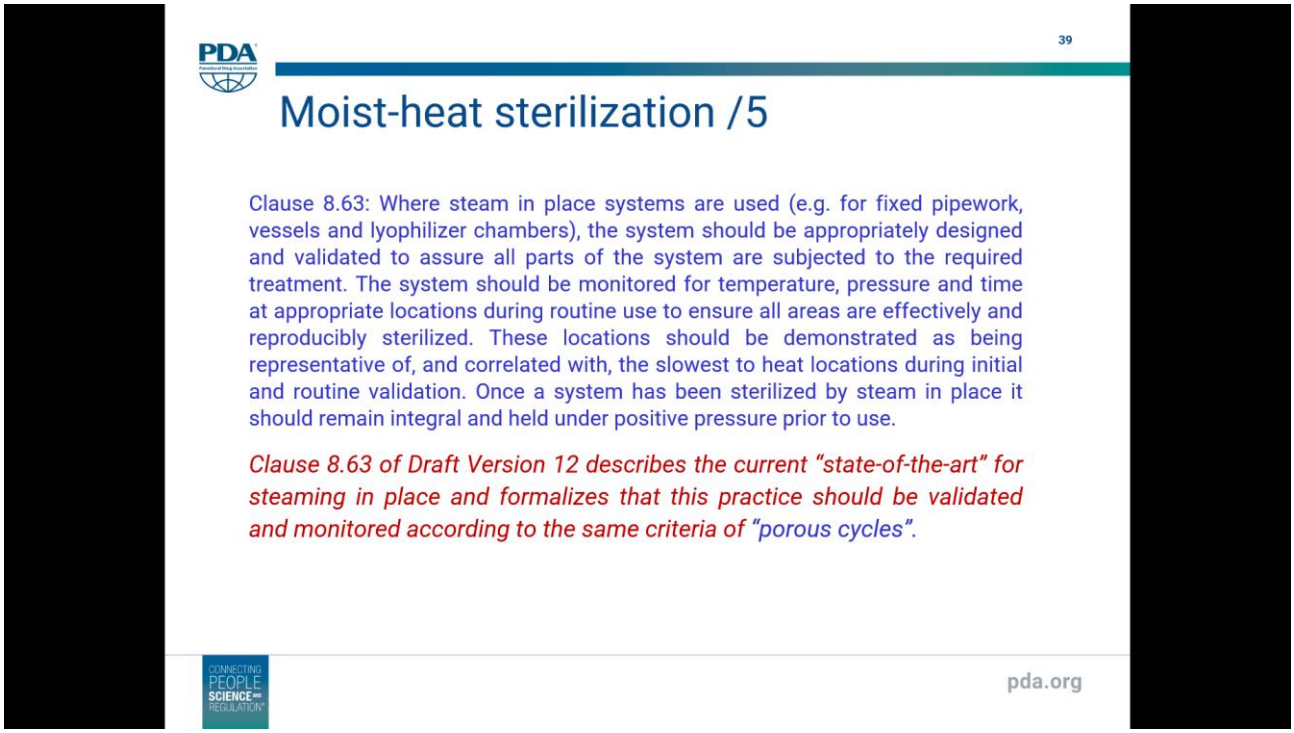
49:30 (Slide no. 38/51)



New Clause 8.61 of Draft Version 12 regards the practice of adding small quantities of suitable water to guarantee Moist-heat condition during the sterilization process and brings the attention to the risks both of insufficient dryness after completion of the process and microbial growth “between the wetting phase and sterilization”.

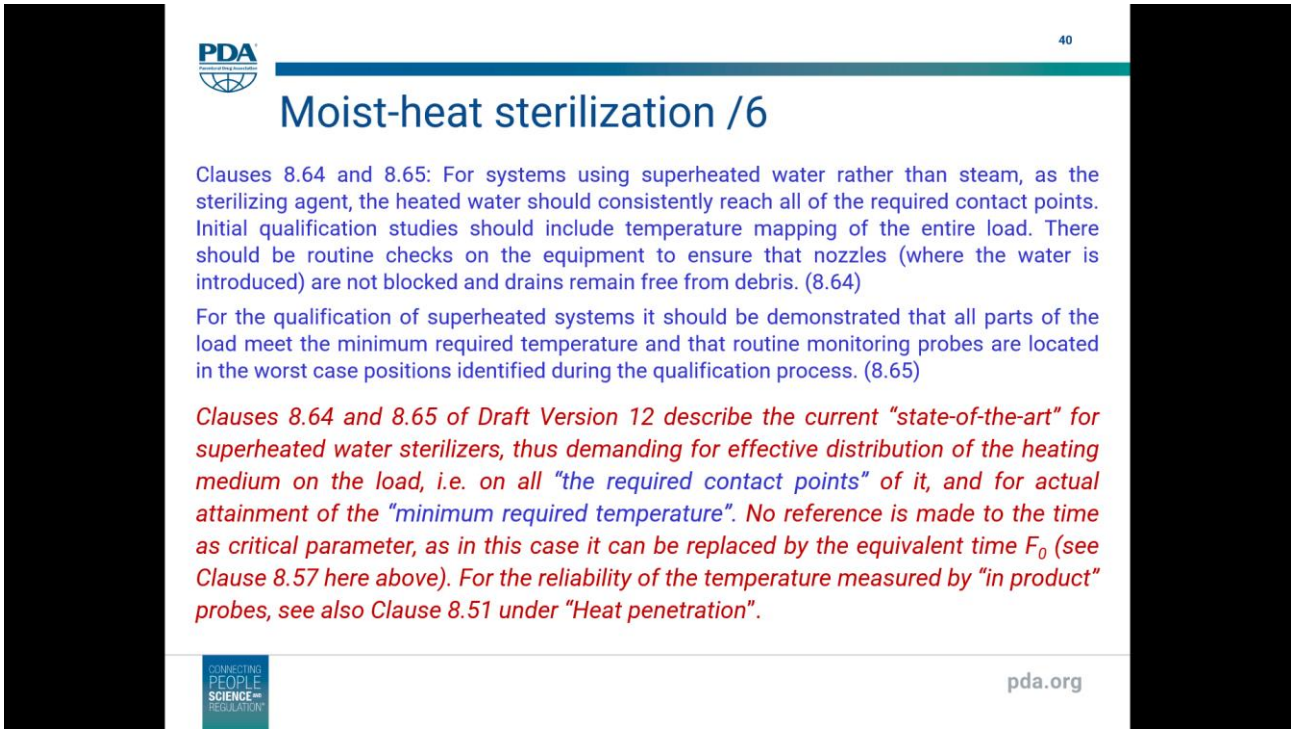
New Clause 8.62 formalizes as a *“should”* the current User’s requirement for sterilization of non-rigid containers. A sterilization process which distorts, or damages containers has always been rejected commercially.

50:10 (Slide no. 39/51)



Clause 8.63 of Draft Version 12 describes the current “state-of-the-art” for steaming in place and formalizes that this practice should be validated and monitored according to the same criteria of “porous cycles”.

50:30 (Slide no. 40/51)

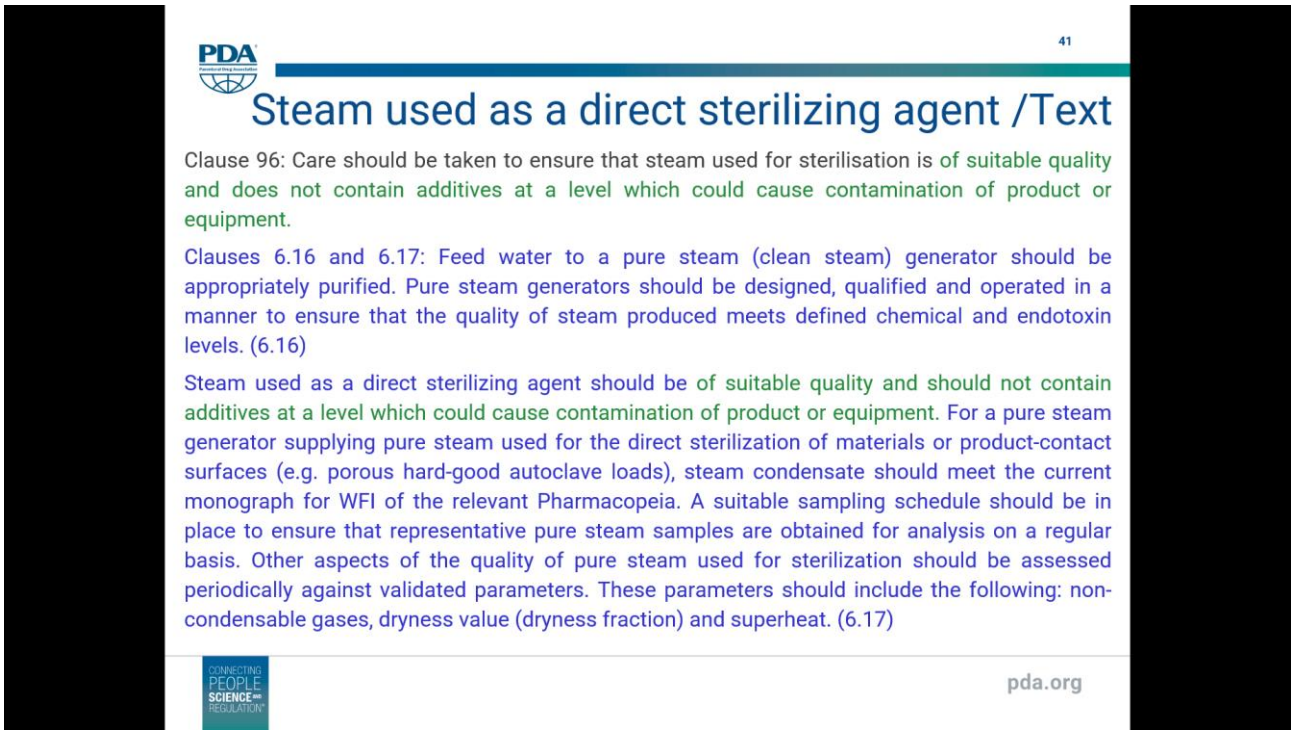


Clauses 8.64 and 8.65 describe the current “state-of-the-art” for superheated water sterilizers, thus demanding for effective distribution of the heating medium on the load, i.e. on all *“the required contact points”* of it, and for actual attainment of the *“minimum required temperature”*. No reference is made to the time as critical parameter, as in this case it can be replaced by the equivalent time F_0.

Rather obviously, the requirement on attainment of the minimum required temperature is in addition to those of Clause 8.57: *“Validation of fluid cycles should include temperature, time and/or F_0”*. In fact, for European rules, the minimum specified temperature shall always be attained, and the simple attainment of the target F_0 is not accepted.

P-D-A comment to this clause attacks the requirement of the attainment of a minimum temperature, so it seems to suggest that a European guideline should ignore European laws.

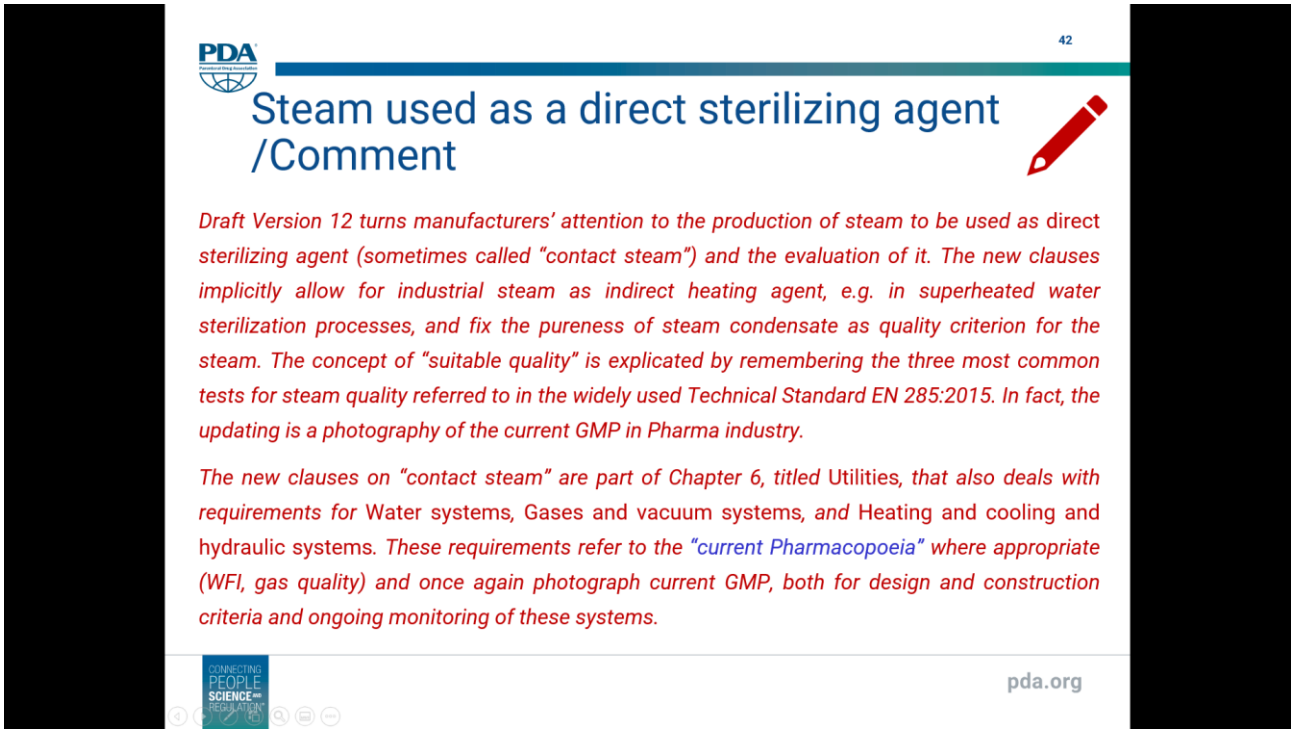
51:45 (Slides nos. 41/51)



The new clauses on “contact steam” are part of Chapter 6, titled *Utilities*, that also deals with requirements for Water systems, Gases and vacuum systems, and Heating and cooling and hydraulic systems. These requirements refer to the “current Pharmacopoeia” where appropriate (WFI, gas quality) and once again photograph current GMP, both for design and construction criteria and ongoing monitoring of these systems.

Clause 6.17 formalizes the long-established definition of “clean steam” by the quality of its condensate meeting the requirements of Water for Injections.

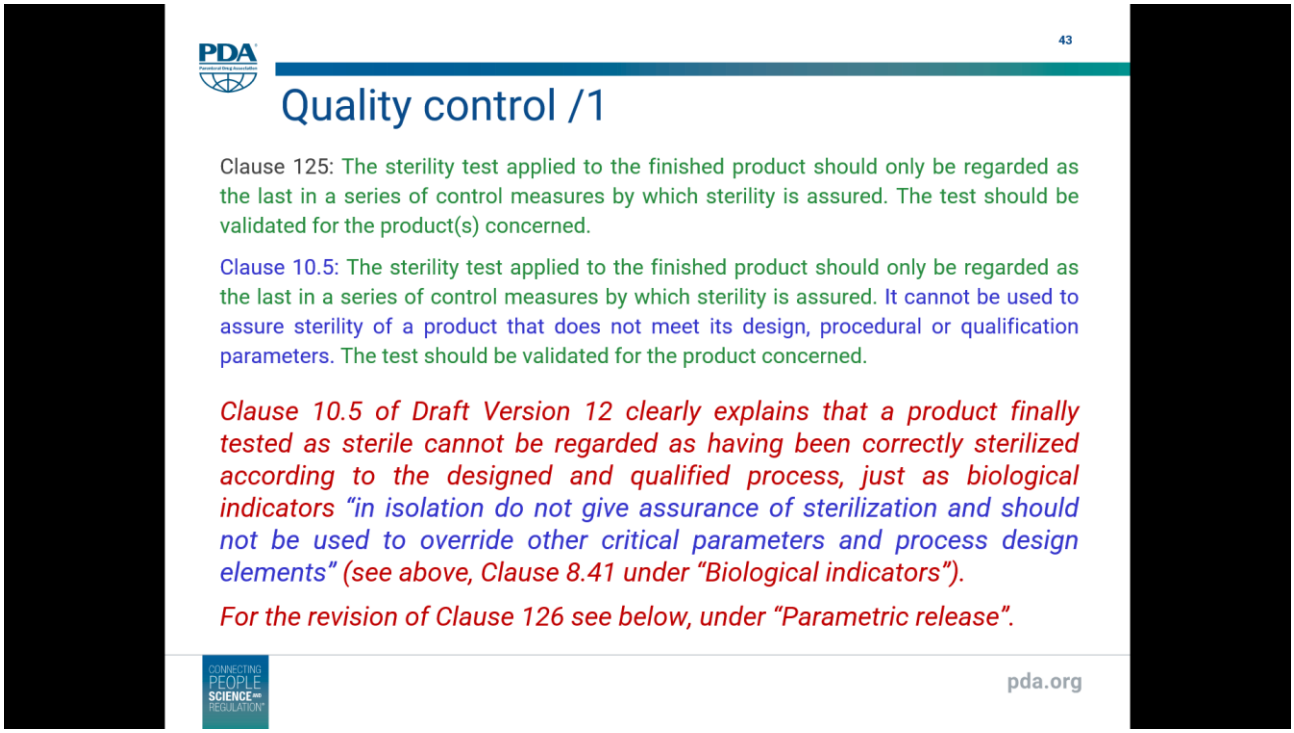
52:40 (Slide nos. 42/51)



Draft Version 12 brings manufacturers' attention to the production of steam to be used as direct sterilizing agent (sometimes called "contact steam") and the evaluation of it. The new clauses implicitly allow for industrial steam as indirect heating agent, as it happens in superheated water sterilization processes, and fix the pureness of steam condensate as quality criterion for the steam. The concept of *"suitable quality"* is explicated by remembering the three most common tests for steam quality referred to in the widely used Technical Standard EN 285.

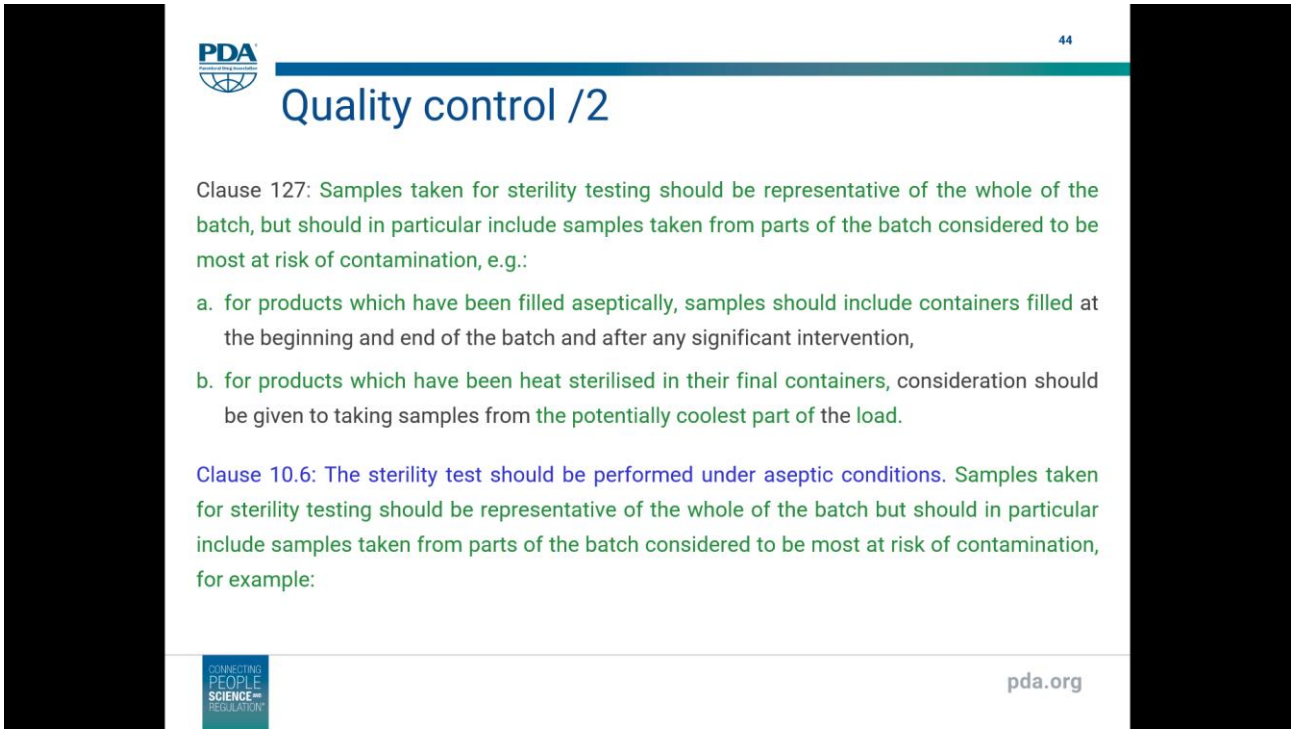
In fact, the updating is a photography of the current GMP in Pharma industry.

53:30 (Slide no. 43/51)



Clause 10.5 of Draft Version 12 clearly explains that a product finally tested as sterile cannot be regarded as having been correctly sterilized according to the designed and qualified process, just as biological indicators *"in isolation do not give assurance of sterilization and should not be used to override other critical parameters and process design elements"* (see above, Clause 8.41 under "Biological indicators").

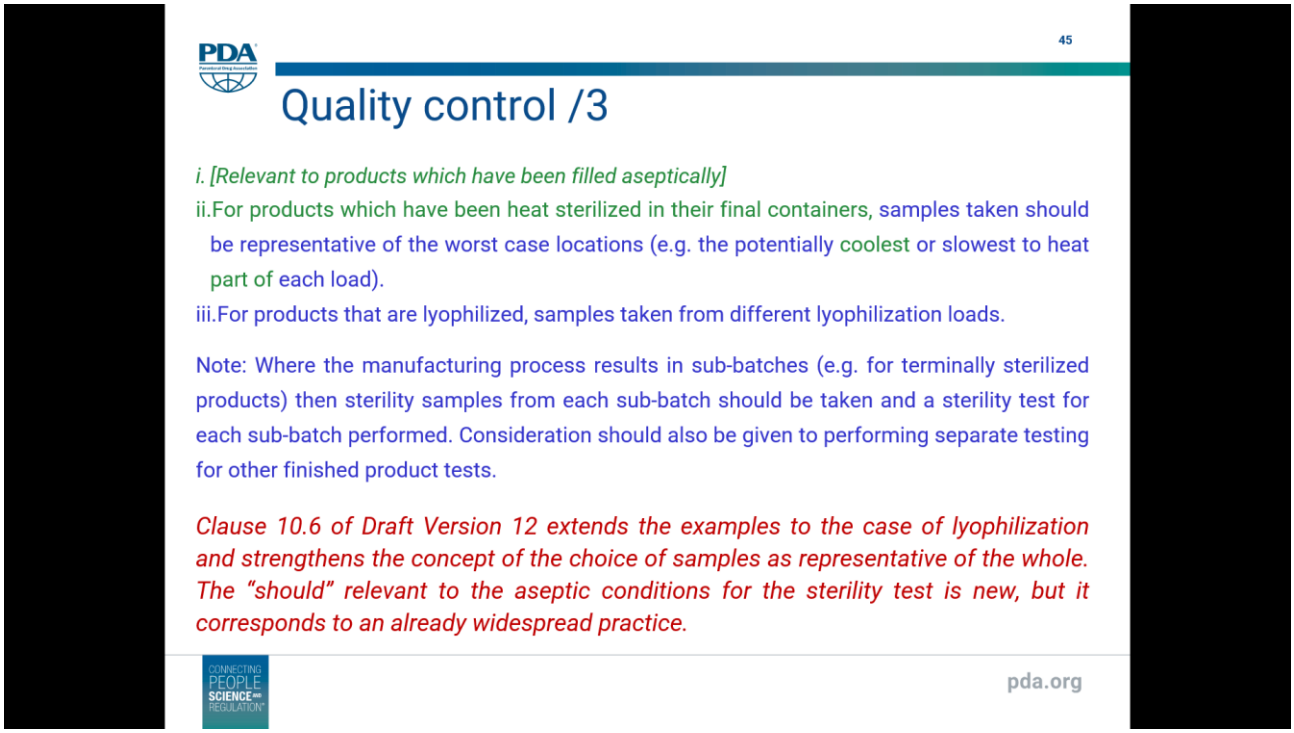
54:10 (Slide no. 44/51)



The concept remains unaltered, that the choice of samples be representative “of the whole of the batch”.

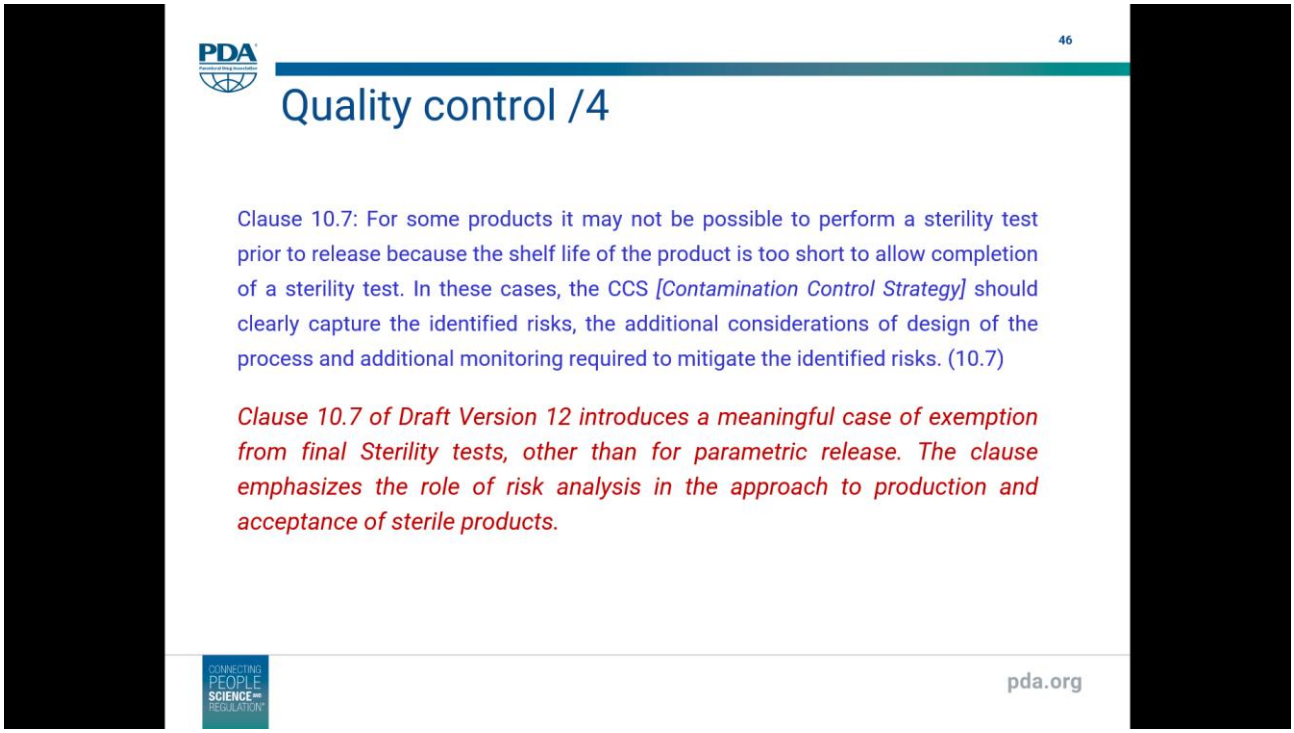
In spite of being new, the *“should”* relevant to the aseptic conditions for the sterility test corresponds to an already widespread practice.

54:20 (Slide no. 45/51)



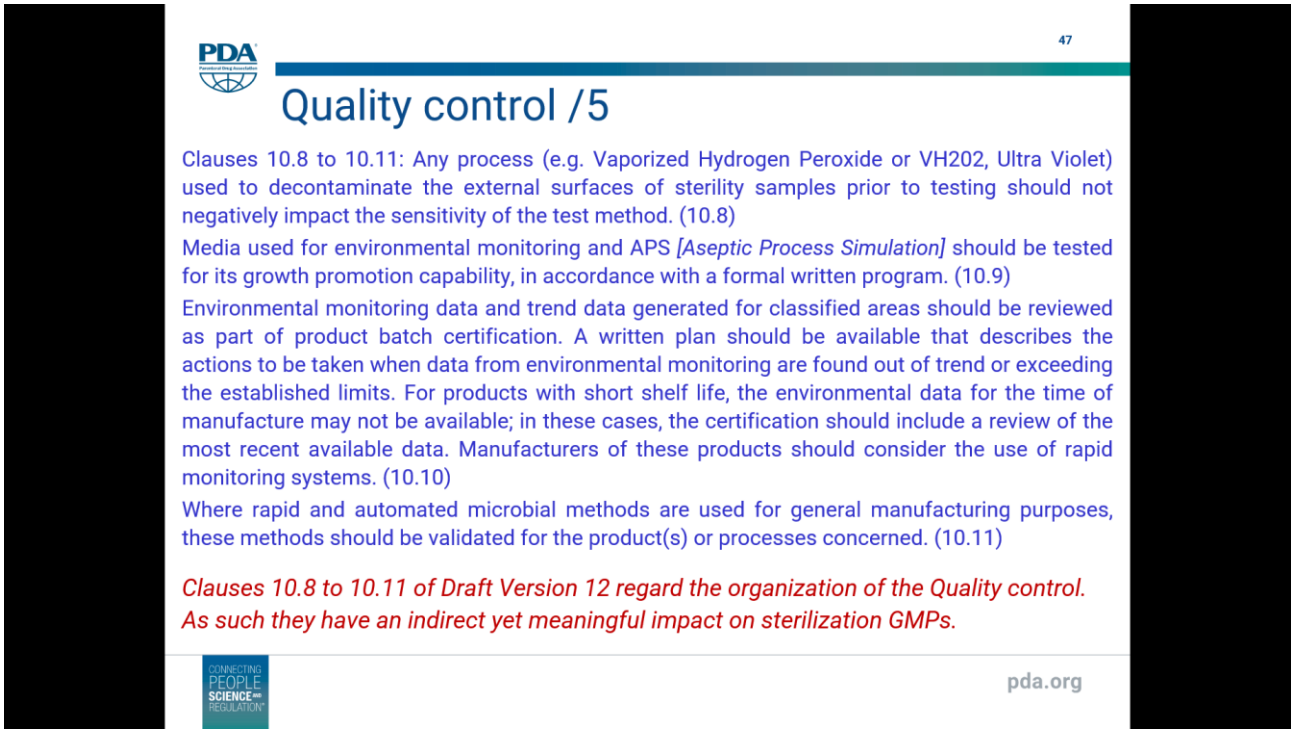
Clause 10.6 extends the examples to the case of lyophilization and finally strengthens the concept of the choice of samples as fully representative by introducing the case of sub-batches, that in our field can correspond to the output of any sterilization run.

54:40 (Slide no. 46/51)



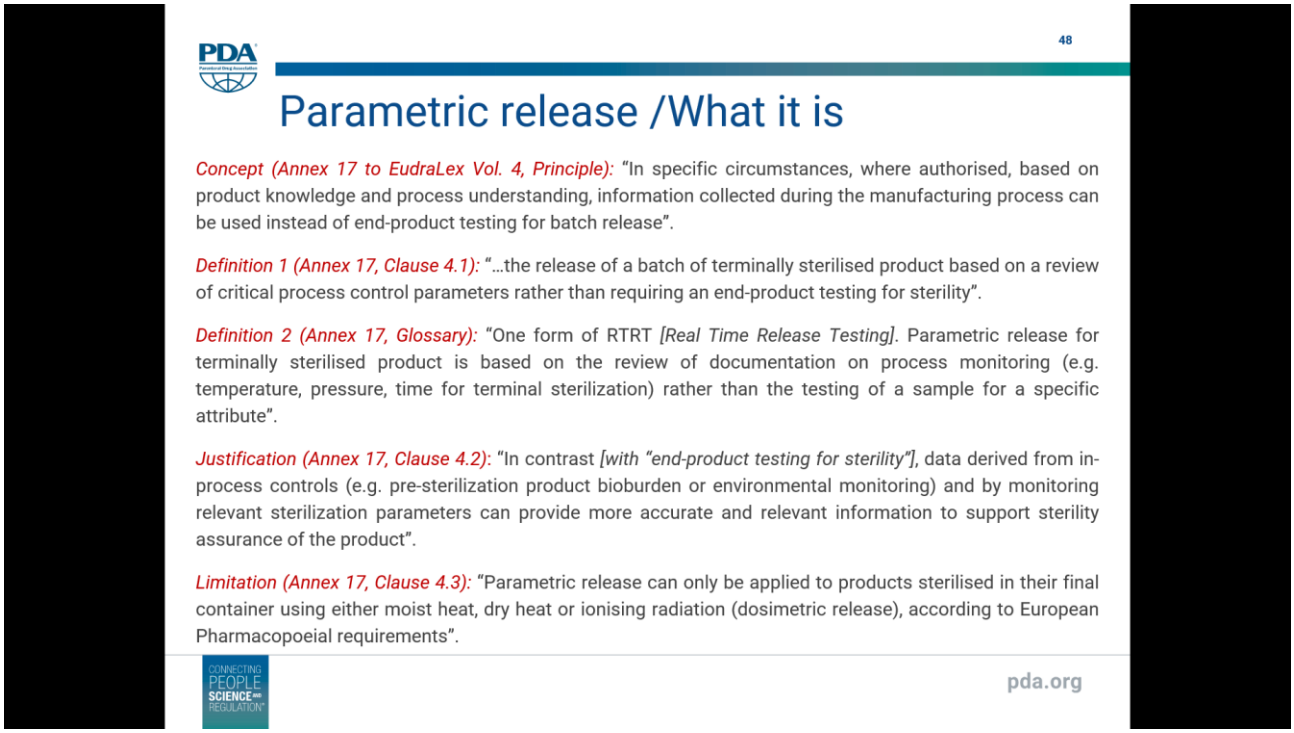
Clause 10.7 introduces a meaningful case of exemption from final Sterility tests, other than for parametric release. The clause emphasizes the role of risk analysis in the approach to production and acceptance of sterile products.

54:40 (Slide no. 47/51)



Clause 10.10 requires that environmental monitoring data become part of product batch specification. These data assume a positive role in assuring the quality of the product; until now they were only regarded as a possible cause of failure.

55:20 (Slide nos. 48/51)



European Pharmacopoeia is, as any other pharmacopoeia, is a prescriptive document. In Chapter 5.1.1 it states: *"When a fully validated terminal sterilisation method by steam (moist heat), dry heat or ionising sterilisation is used, parametric release (i.e. the release of a batch of sterilised items based on process data rather than submission of a sample of the items to sterility testing) may be carried out, subject to the approval of the competent authority."*

The reason why is explained in Chapter 5.1.9: *"In the case of terminally sterilised products, physical proofs, biologically based and automatically documented, showing correct treatment throughout the batch during sterilisation are of grater assurance than the sterility test"*.

“For the purpose of this text a batch is defined as a homogeneous collection of sealed containers prepared in such a manner that the risk of contamination is the same for each of the units contained therein”

In the slide you can see some meaningful sentences from Annex 17 to EudraLex Vol 4, which is in force since December 26, 2018. Apparently, these sentences are an application of the pharmacopeial concepts I have just read.

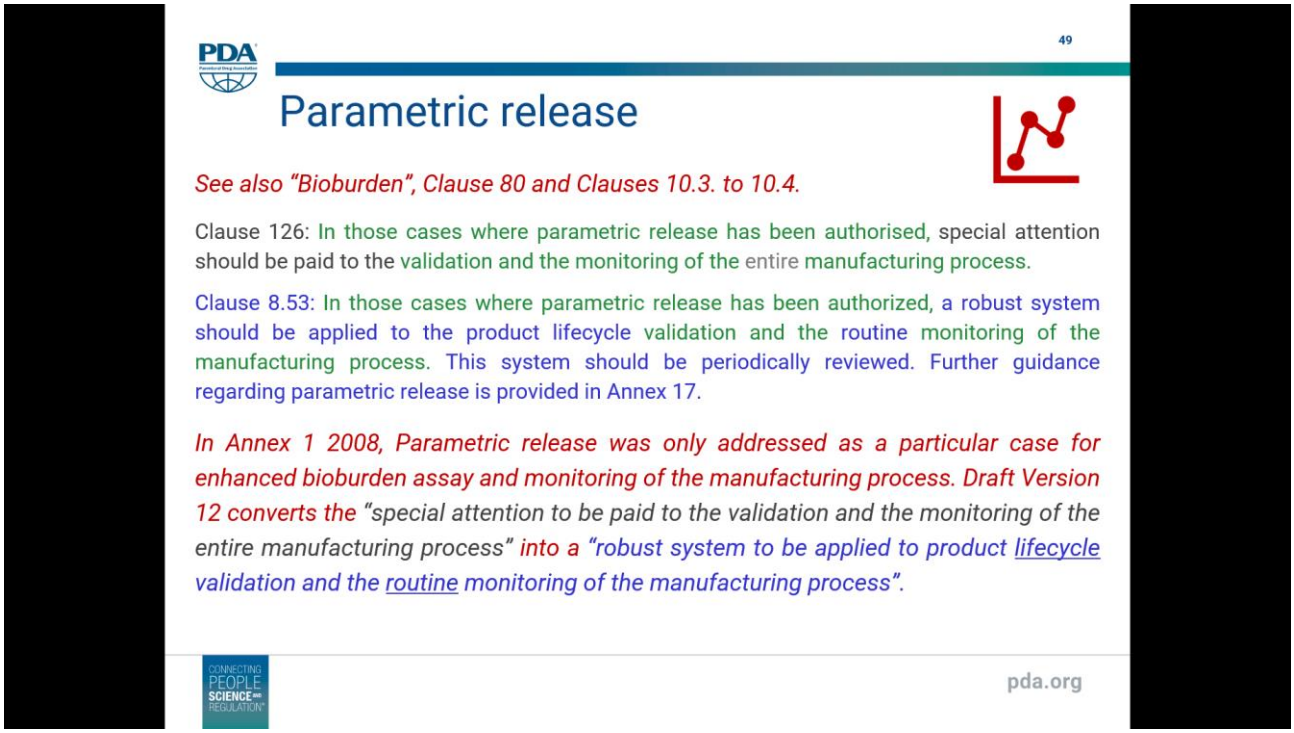
Logically, Draft Version 12 of Annex 1 refers to Annex 17 as a general guidance on the matter.

No doubt that parametric release, if approved, is preferred because it overcomes the shortcomings of end-product testing for sterility.

According to Annex 17 Clause 4.2, *“only provides an opportunity to detect major failures in the sterility assurance system (i.e. a failure that results in contamination of a large number of product units and/or that result in contamination by the specific microorganisms whose growth is supported by the prescribed media).*

In contrast” with this you can read the following of Clause 4.2: The release based on review of documentation only is restricted to *“products sterilised in their final container”*. This is clearly stated by the European Pharmacopoeia.

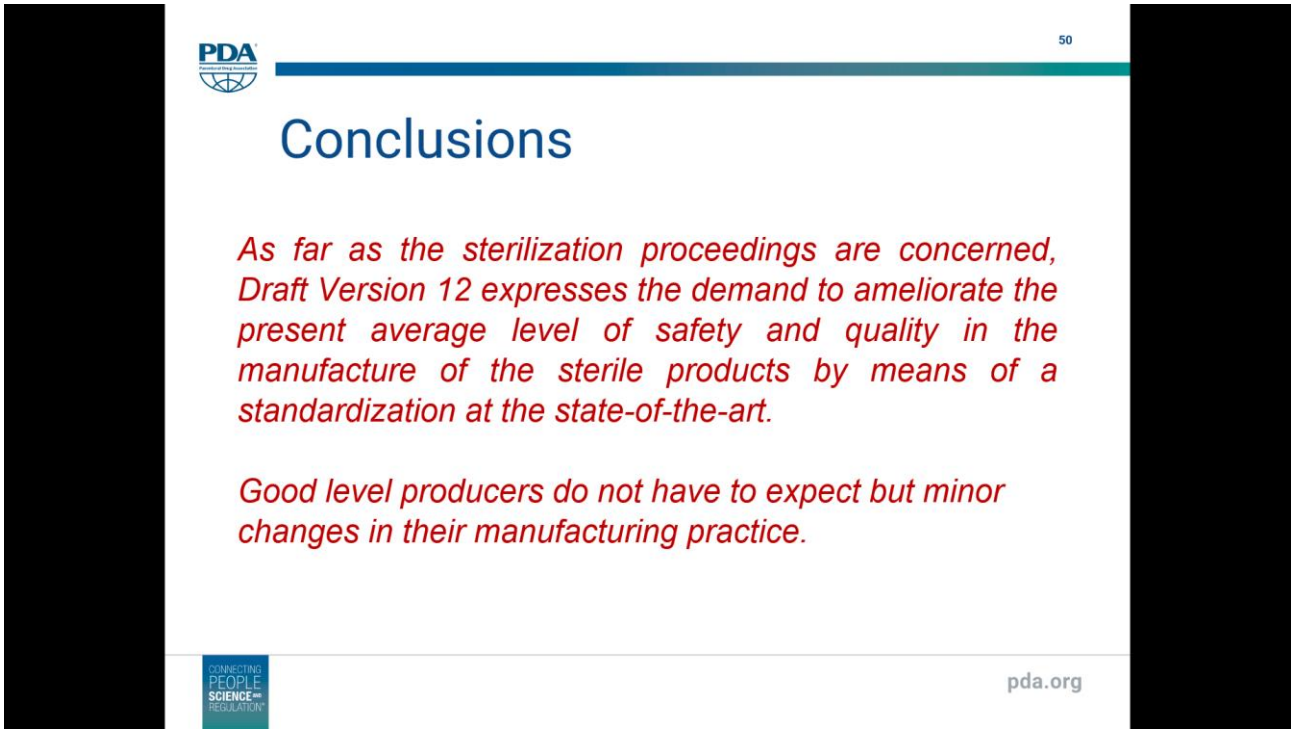
58:15 (Slide no. 49/51)



In Annex 1 2008, Parametric release was only addressed as a special case for enhanced bioburden assay and monitoring of the manufacturing process. Draft Version 12 changes the *"special attention to be paid to the validation and the monitoring of the entire manufacturing process"* into a *"robust system to be applied to product lifecycle validation and the routine monitoring of the manufacturing process".*

In my opinion, this sentence provides inspecting Agencies a wide margin of freedom for authorize or not parametric release: on a side this is encouraged, on the other side it is made rather difficult.

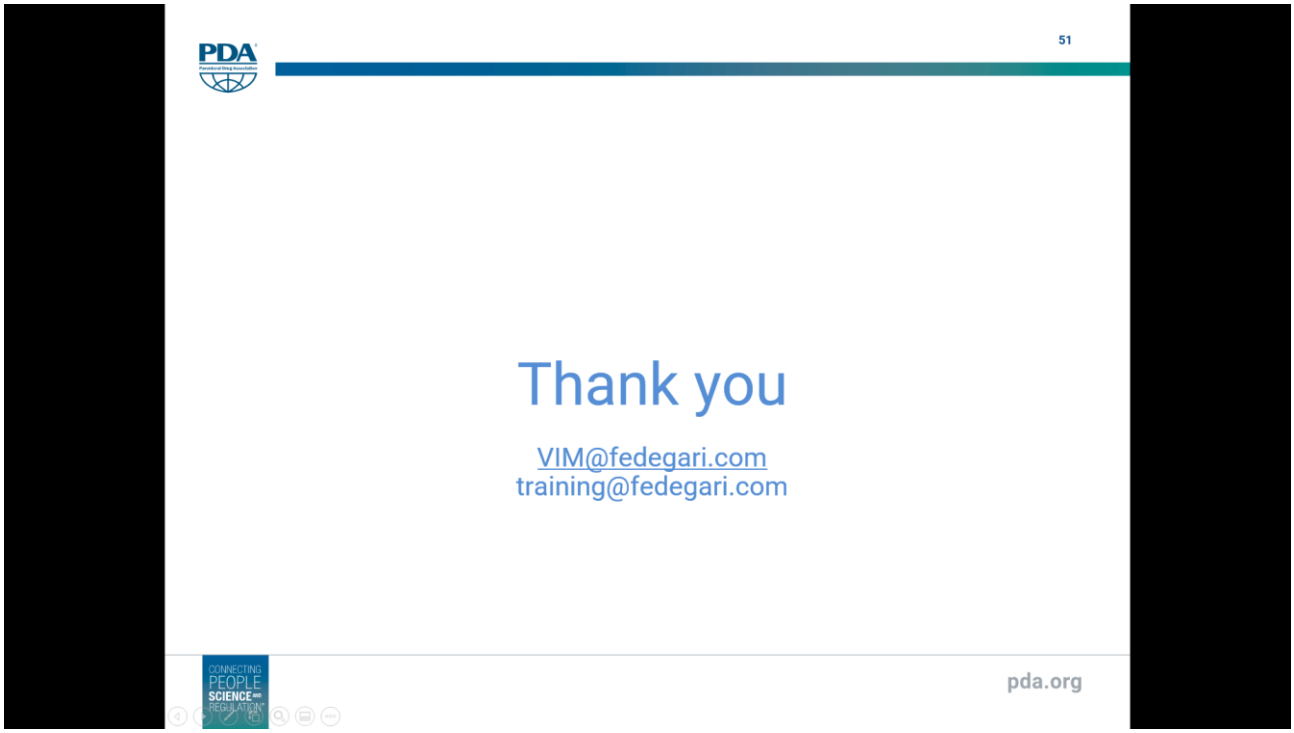
59:00 (Slide no. 50/51)



As far as the sterilization proceedings are concerned, Draft Version 12 expresses the demand to ameliorate the present average level of safety and quality in the manufacture of the sterile products by means of a standardization at the state-of-the-art.

Good level producers do not have to expect but minor changes in their manufacturing practice.

59:30 (Slide no. 51/51)



Thank you very much for your attention. We have spared some time and any question of yours we'll be welcome