Published in final edited form as:

Vaccine. 2015 April 8; 33(15): 1757–1766. doi:10.1016/j.vaccine.2015.02.003.

Now That You Want to Take Your HIV/AIDS Vaccine/Biological Product Research Concept into the Clinic: What are “cGMP”?

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Abstract

The Division of AIDS Vaccine Research Program funds the discovery and development of HIV/AIDS vaccine candidates. Basic researchers, having discovered a potential vaccine in the laboratory, next want to take that candidate into the clinic to test the concept in humans, to see if it translates. Many of them have heard of “cGMP” and know that they are supposed to make a “GMP product” to take into the clinic, but often they are not very familiar with what “cGMP” means and why these good practices are so important. As members of the Vaccine Translational Research Branch, we frequently get asked “can’t we use the material we made in the lab in the clinic?” or “aren’t Phase 1 studies exempt from cGMP?” Over the years, we have had many experiences where researchers or their selected contract manufacturing organizations have not applied an appropriate degree of compliance with cGMP suitable for the clinical phase of development. We share some of these experiences and the lessons learned, along with explaining the importance of cGMP, just what cGMP means, and what they can assure, in an effort to demystify this subject and facilitate the rapid and safe translational development of HIV vaccines.

Keywords

vaccine; manufacturing; clinical trial; investigational product; Good Manufacturing Practices

Introduction

You and/or your collaborators have been conducting basic research with an aim to translate your research findings into a clinical study that you or your collaborators would conduct. You’ve made great strides and proven that your vaccine concept protects against a pathogen in a relevant animal model and induces the kinds and amounts of immune responses associated with recovery from natural disease in humans (or some other evidence that

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suggests the vaccine candidate could protect from infection or disease). However, as you begin to explore what you might need to do in order to initiate a clinical trial to test your investigational vaccine, you keep hearing the term “GMP product.” What does it mean? Is it necessary? And if so, why? Maybe you heard something like – aren’t Phase 1 studies¹ exempt? Can’t you just take the vaccine material you have made in the lab and used in animals and give it to people? If you’ve ever wondered any of these questions, read on.

In 1901, a historical event occurred that was the lynchpin for the U.S. laws and regulations for vaccines and other biological products [1]. At that time, diphtheria anti-toxin serum was manufactured in horses, and there was no vaccine. In St. Louis, a horse named Jim was used for this purpose. Unfortunately, Jim became infected with tetanus and died, but not before his serum was extracted and used as diphtheria anti-toxin. 13 children died from tetanus from having received the contaminated serum. Not only was there a lack of quality control on the serum, to prevent it from being used before demonstration that it was safe and pure, but some of the serum from the bleed a few days before he died (but after contracting tetanus) were filled into bottles dated from an even earlier bleed when he was tetanus-free. These bottles were misbranded (labeled with the incorrect date), leading to their inappropriate use instead of recall or quarantine. Thus, the concepts that biological products should not be adulterated nor misbranded emerged from this tragedy.

Another point that bears your consideration and understanding is that biologicals are different from drugs in several key aspects. Technically, by FDA definition, they are drugs, in that the same regulations and often, the same guidances apply to them. But, in reality, it’s the difference between mass-producing a mechanical part for a machine and cooking a gourmet meal. Drugs that are made by chemical reactions result in the same end product each time if the right chemicals are added in the right concentrations, right sequence, right temperatures and right pH.² Furthermore, drugs can be extremely well-defined by testing after they are made. Producing biologicals is like cooking. You may follow the same recipe as the guy in the next kitchen and yours will turn out in a manner that leaves your diners begging for more, while his comes out inedible and leaves his diners begging for antacids. The next time you follow the same recipe, you might not have the same outcome you did the first time. Minor differences in oven temperature or cooking time or even the altitude at which you are cooking can have major consequences for flavor and texture. For biologicals, because they cannot be as well characterized after manufacture as small molecule drugs, “the product is the process and the process is the product.”

Think about making a protein (some vaccines are protein subunits). Proteins are folded in a complex manner [2] without which they would not be biologically active. That structure may be held in place by disulfide bonds in the right locations. A mutation in a cysteine might destroy an important disulfide bond. Variation in cell growth/metabolism can lead to

¹Phase 1 studies are small clinical trials in tens of people. Often, they are the first exposure in humans of an investigational product, or so-called “first-in-human” studies.

²Generally, chemical drugs can be sterilized after manufacture, if they need to be sterile. Oral products do not need to be sterile, but need to be controlled for the amount and type of “bioburden” they contain. Parenteral products (injectables), by contrast, must be sterile. Often, you cannot sterilize biologicals after manufacture is completed, without losing the integrity and biological activity of the product (think burning the meal just as it was almost ready to be served).

differential disulfide bonding because many proteins fold while they are being translated and a different rate of translation can cause them to fold differently and then different disulfide bonds form; this happens without any mutation. Or the protein may have N- or O-linked glycosylation. Depending on the cell line (species) in which you produce the protein, different carbohydrates or different structures of those carbohydrates may be used in the glycosylation of the protein. How the protein is glycosylated can also impact its function and the ability of antibodies to bind to it (a critical attribute for a vaccine). Also, differences in the growth rate/metabolism of the same cell type can affect the enzymatic decisions about the final nature of glycosylation; so the same cell could glycosylate a specific protein differently. [3, 4, 5] For all of these reasons, producing biologicals is not as straight-forward as producing chemical drugs. As a consequence, controlling the manufacturing process is all the more important. And this is what complying with “cGMP” permits a manufacturer to do – control the manufacturing process. (see definition of cGMP in next section and in the brief glossary in Appendix 1)

cGMP are intended to minimize those variations in biologicals’ production, even though they cannot be eliminated. By using a biological system for manufacturing, the process is subject to biological variation, and biological variation can be quite broad, so stringent control over those aspects you can control is critical to successfully manufacturing biologicals. It’s just good science. It’s also a way of thinking about the problem scientifically. The problem is assuring consistency. The cGMP are the good science to solve that problem. The FDA states as much in one of their own guidances, in which they state their expectations for manufacturers: “...interpreting and implementing CGMP consistent with good scientific methodology...” [6]

Regulation and Law About cGMP

GMP or Good Manufacturing Practices are regulatory³ and tatutory⁴ requirements for all drug products including those to be used in clinical investigations that are under the jurisdiction of the Food and Drug Administration (FDA) in the U.S. or its equivalent in other countries (e.g., European Medicines Agency in Europe). [7] The purpose of the GMP (or cGMP with “c” standing for “current,” meaning keeping up-to-date as best industry practices evolve) are to document and control your manufacturing process, equipment, personnel, environment, facilities, raw materials, unreleased and released materials, and packaging and labeling to assure that products are safe and pure and not adulterated nor misbranded.

In the U.S., the cGMP regulations are published in the Code of Federal Regulations in Title 21 (21 CFR 210 and 211).³ [8, 9] The statutes⁴ governing clinical research with investigational products are covered in the Food, Drug, and Cosmetic Act [10], and for biologicals, like vaccines, in the Public Health Service Act [11]. This means that following cGMP is required by the law⁴ and the regulations.³ For the U.S., laws or statutes carry with

³Relevant regulations for GMP are the Title 21 of the Code of Federal Regulations (21 CFR) Parts 210 and 211. Relevant regulations specifically for vaccines are 21 CFR 600’s.

⁴A bill written and passed by Congress and signed into law by the President – in our case, the Food, Drug, and Cosmetic Act (FD&C Act of 1938). Also relevant to vaccines is the Public Health Service Act of 1944, specifically section 351.

them penalties if they are violated, penalties such as disbarment from clinical research, product seizures, injunctions, fines, or federal imprisonment. The FD&C Act contains dozens of “prohibited acts” that can result in such penalties. Regulations are the interpretation of the law and are more specific about how to follow the law. Violations of the regulations can be prosecuted, although there is a due process whereby the violator would be notified and given an opportunity to correct any violations, generally before prosecution would be undertaken. Finally, regulatory guidance consists of recommendations written or spoken by the regulators, which normally reflects their current thinking, although you can choose to propose and gain concurrence for an alternative plan. You aren’t likely to get prosecuted for not following guidance, but you may have your clinical study plans placed on clinical hold.

So, cGMP are required, by law and by regulations. And they are required by science. However, there is a guidance document that suggests that products to be used in Phase 1 clinical studies are exempt from cGMP: “Guidance for Industry: CGMPs for Phase 1 Investigational Drugs.” [6] In the introduction to this guidance, it clarifies that while the cGMP regulations are intended for all stages of manufacture (from early clinical trial phase to marketing lots), that at the time the cGMP regulations were originally published, the FDA’s intent was to provide guidance specific to Phase 1. The reason they wanted to provide such guidance was because certain aspects of the regulations were aimed at “the commercial manufacture of products typically characterized by large, repetitive, commercial batch production (e.g., those regulations that address validation of manufacturing processes [§ 211.110(a)], and warehousing (§ 211.142)); they may not be appropriate to the manufacture of most investigational drugs used for phase 1 clinical trials.” As can be noted from the quote above, certain aspects were deemed inappropriate for Phase 1 products, but not all aspects. Nonetheless, the FDA has published this guidance to exempt investigational products to be studied in Phase 1 trials from the cGMP regulations (not from the statute, but from the specific regulations) and they propose to ensure compliance with the statute through their review of the Chemistry, Manufacturing, and Controls (CMC) section of your Investigational New Drug Application (IND). Thus, they published the above referenced guidance to let you know what they expect you to do. So, does this mean the cGMP are not required? No wonder you’re confused. It sounds like government bureaucratese.

No, you are not exempt from cGMP, but you are exempt from certain provisions of the regulations like those listed in the example from the quote above from the guidance. So, why are cGMP so important that they would exempt you, but not really exempt you? cGMP are required to assure the safety, purity, potency, identity, and quality of the product and thus, ensure that it is not adulterated (nor misbranded). For Phase 1, the most important of these is safety. However, each of the others is critical too. Why?

The Required Attributes of a Product Suitable for Human Use

Purity

If a product is impure, then depending on the impurity, it might be unsafe. Impurities may be process residuals like antibiotics used in the culture medium in which you grew your vaccine organism, and people can be allergic to those antibiotics. Or impurities could be

nonviable or worse yet, viable particulates, like bacteria or fungi that inadvertently contaminated your product because the external environment in which you made it was not adequately controlled or monitored, and these could cause infection or even sepsis in your product recipient.⁵ In the case of vaccines and Phase 1 studies, the product recipients are generally healthy individuals who might not even need your vaccine (e.g., you might start with a low risk population or even already immune individuals in the initial study, the aim of which is simply to show safety, not efficacy). So, putting them at risk from impurities is not appropriate. And how can you assure that your product is free from external contaminants, if you aren't controlling your manufacturing process, raw materials (including water), facilities, environment, and personnel? It is unlikely that you have this level of control in your research laboratory, which is part of why it is not suitable to use materials made in the lab in clinical studies, even those involving a very small number of people.

Potency

So, what is potency? Potency is a measure, such as a bio-assay (assay in animals or cells), that addresses some aspect of the strength and activity of your vaccine. Strength may simply be a measure of content, but potency assesses activity of that content. The official definition [21 CFR 600.3(s)] is: "The word potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." [12] The purpose of measuring potency is to ensure that the product has the level of activity it is expected to have and is a measure of manufacturing consistency and also a bridge, for marketed products, back to clinical lots used in successful efficacy studies. However, Phase 1 clinical trials are the beginning of a bridge forward to future efficacy studies and a means to determine whether what you observed in the research lab is likely to be what you will observe in the clinic. There is no ethical justification to take into the clinic a product that does not have activity of the sort and quantity you intend it to have, because then, there is no prospect for benefit, a necessary ethical justification to conduct a clinical study. And if you get good results in Phase 1, you need to be able to know that you can make that same product again, with the same level of potency, and continue to get good results in further clinical studies. Thus, the potency assay for Phase 1 may be a preliminary assay like a basic quantitation assay (e.g., vector titer), and may be developed into a more sophisticated and more quantitative measure of activity by the time of commercialization, based on a mechanism of action, which may have been elaborated by that time. Nonetheless, some type of assay is needed at Phase 1 to begin to build the bridge forward.

⁵You may recall the recent cases of fungal meningitis caused by a compounding pharmacy that was not clearly under FDA's jurisdiction, because they were repackaging drugs that they did not manufacture, so they were not regularly inspected. However, they managed to contaminate the drugs they repackaged with bacteria and fungi, resulting in the death of several people. This has led Congress to reconsider giving FDA the clear authority and responsibility to inspect such facilities. <http://www.fda.gov/drugs/drugsafety/fungalmeningitis/default.htm> (accessed March 29, 2013) http://vitals.nbcnews.com/_news/2012/11/15/15193199-fda-to-congress-fungal-meningitis-outbreak-could-happen-again?lite (accessed 22, 2014)

Identity

What about identity – obviously, you know what product you are making, right? Well, have you ever gotten a research reagent from a colleague and then you couldn't get the result you expected, e.g., you get a plasmid that is supposed to contain a kanamycin resistance gene but no colonies grew from your transfections in the presence of kanamycin? After some investigation, you determine that that plasmid had ampicillin resistance, not kanamycin. This kind of mix-up is not so uncommon. Obviously, you cannot have such a situation arise when you inject material into humans. So, identity is critical too. Even from Phase 1. Some physical or chemical characteristic of starting materials, raw materials, or the vaccine itself should be assessed to distinguish the material from anything else that could be present in the manufacturing environment. It is unlikely that you do this in your research lab. If you receive a container of NaCl, you accept that it is NaCl, without testing it to prove it. However, cGMP require you to test to verify the identity of raw materials, instead of accepting everything on faith. This prevents failures from reasons of simple mix-ups.

Quality

What about quality? Have you ever looked at the fine print when you purchase research reagents? Like restriction enzymes you might have used for cloning a gene-of-interest into your vector? Or the polymerase or PCR mix you used to amplify a gene-of-interest or insert point mutations to manipulate that gene to express what you want? They probably all say "NOT FOR HUMAN USE" – for research use only. Why would they say that? Well, for one thing, they were probably not manufactured in accordance with cGMP, so their quality and suitability for human use cannot be assured. If your experiment fails, you get a new reagent lot and start over, but if your clinical trial fails because of poor quality material, you may actually harm someone. At the very least you have put human subjects at risk for no justifiable reason. So, quality matters too at Phase 1 and should be assured all the way from raw materials to fill and finish. Quality attributes can include many product attributes including measures such as pH and osmolality, both of which, if not controlled, can result in undesirable reactogenicity in the clinic.

Stability

Another aspect that the regulators will be concerned about with the material you will use in your clinical study is whether or not it will remain stable throughout its use in the clinical study. For example, if your Phase 1 clinical trial involves three inoculations over several months, but your product is only stable for one or two months in the manner in which you are storing it, then, many or even most subjects will not have received as many inoculations of vaccine as you think they did. There is a specific guidance document for how regulators expect you to demonstrate stability [13]. They will expect "real-time" stability data, initially from every single lot of vaccine you make for the clinic. Whatever the storage conditions you will use for your product, a stability program should be established under those conditions to gain data that shows your material is not degrading or in some other manner, losing integrity (e.g., container/closure failures) upon storage.

How cGMP Assures the Required Attributes

Pretty much everything that cGMP help to assure is something that is critical for Phase 1 studies. But, there are some exceptions and that's exactly what the phase 1 cGMP guidance document⁶ is all about. This guidance discusses which regulations you can disregard in Phase 1 and which you can't. Some flexibility is described for products that might be used in sick and dying patients for whom the risk/benefit balance is quite different, as opposed to your product that you'll be using in a healthy population that you will be studying in your Phase 1 vaccine study.

Now perhaps you are asking, but I've heard people talk about manufacturing their products in GMP-like or GMP-lite conditions or even GLP⁷ (Good Laboratory Practices) conditions. Isn't that okay? No, it isn't. There is no such thing as GMP-like or GMP-lite. And GLP applies to nonclinical studies, i.e., the conditions under which toxicology and other animal studies to enable IND applications are to be performed [14]. They do not apply to manufacturing clinical trial materials. So, they are not the appropriate regulations to follow to manufacture your product. What is appropriate is a graded scale of cGMP compliance and manufacturing with the appropriate elements of the cGMP regulations in place at your manufacturing facility, as relevant and appropriate for the Phase of clinical study. This assures a safe, pure, potent, correct identity, high quality product that can be manufactured again and remain stable for the time it takes to conduct your clinical trial successfully.

So, hopefully by now we have convinced you why cGMP are necessary and answered some of the questions with which you started when you began reading this article. Now, we will explain more specifically what the cGMP are, so you can comply with them.

What are cGMP?

Have you ever set up an incubation and at the end, you get nothing? Maybe you forgot to add something? You can't quite remember. You were setting it up from your memory of what was needed and not precisely following a protocol, or maybe you followed the protocol, but you didn't check off each component as you added it. Or maybe you've run a successful experiment previously, but you can't seem to repeat it and you can't quite remember what you did the first time? Perhaps none of these things has ever happened to you, but they have to many. As a successful scientist, you have already learned about good documentation practices. But, cGMP takes good documentation practices to a whole new level. So much so that the mantra of cGMP is "document, document, document – if it was not written down, it did not happen." You should document what you are going to do (standard operating procedures and master batch production records) and get a quality assurance unit (QA) approval before you do it.⁸ Then, you should document what you are

⁶Guidance for Industry: CGMPs for Phase 1 Investigational Drugs; something to keep in mind about this guidance document is that it not only applies to chemical drugs and complex biologicals, but it also applies to investigational products like autologous cell therapies – things that really are always made at small-scale and customized lot-by-lot and sometimes intended for people for whom death is impending. So, you can't just blindly follow the guidance document either. You have to know which parts are relevant to which product types and situations. The FDA's "case-by-case basis."

⁷GLP regulations (21 CFR 58) cover the conditions in which preclinical or nonclinical studies in support of product development are performed, and cover aspects of animal facilities, study directors, quality unit for the animal facility, etc. Although 21 CFR 58 Subpart F discusses the test articles that can be used in animal studies, this is not applicable to clinical trial material.

doing as you are doing it (like checking off the components of a reaction as you add them) and you should have a second verifier documenting that you did what you are documenting you did (in batch production records or “BPR”). And finally, you have QA review what you did to ensure that you have documented everything properly – and they do this by reviewing objective information such as documented equipment read-outs (what time does the machine say you started it and is that consistent with what you said in your documentation?). Maybe this seems like overkill to you, but when you are talking about a million dollars’ (or more) worth of product being made in a lot and people’s lives and safety at risk, it really isn’t.⁹ It is how you design quality into a product and it assures that your contract manufacturing organization (CMO) does what you wanted them to do. And if anything goes awry, it should have been documented in the BPR, so that the CMO can investigate such deviations to determine a root cause for them. Additionally, this allows the CMO to identify any potential Corrective Actions (for this time) and Preventive Actions (for next time – a process of continual improvement) or CAPAs. The deviations, investigations, CAPAs, and the objective information that QA reviewed should accompany the BPR, along with analytical data for the product (including in-process control testing and batch or lot release tests).

Now it is time for a few words about testing. In cGMP, testing is a matter of verification. You should not be trying to test quality into a product, you should have designed it in there in the first place. A product cannot be tested into regulatory compliance with lot release specifications. Testing a portion of the product lot simply verifies that you actually achieved your prospectively defined quality attributes or release criteria. Yes, everything needs to be prospectively defined and documented. While you may not have enough manufacturing experience to set tight specifications for each quality attribute at Phase 1, you should set provisional specifications and appropriate ones for parameters that assess safety, particularly. You may set some as TBD (to be determined) or “report result,” but those attributes should not be critical ones, and should not be more than one or two of the tests. However, some FDA reviewers may not accept any release specifications to be undetermined even at Phase 1. An example of a provisional specification may be that you may not know what level of potency you need to achieve success in the clinic, but you should have a specification for strength so you know how much you are giving. The provisional specifications can be a little wide and often reflect to some degree the variability of the assay method being used. For example, if you are measuring titer by doing a series of 1 log dilutions, then the variability of that assay is likely to be ± 0.5 log (or a 1 log interval). Other provisional specifications may reflect your uncertainty about what you will experience during manufacturing, e.g., pH can be measured quite precisely, but you might set a specification with a range of 0.5 of a pH unit because you just don’t know how your product’s pH might vary at the scale of manufacturing and with the formulation you will need for Phase 1, until you gain more manufacturing experience.

⁸For Phase 1, it may be acceptable to have a second verifier approve, rather than a QA unit – though this exception is generally in the case of cell therapies that are made in small-scale batches and individualized by trial subject. Generally, such an exception would not apply for prophylactic vaccines against infectious diseases.

⁹If you hope that you have a successful Phase 1 study that will lead to further clinical development and ultimate licensure, then you must be able to document that you have reproduced the product throughout the development cycle – that what you use in Phase 1 is related to what you used in research, and that what you use in Phase 2 and 3 is related to what you used in Phase 1, and what you will license is essentially identical to what you used in Phase 3.

Whatever specifications you set, you must accept the results you get or justify why not. You can't simply re-test because you didn't like the result. You have to have just cause. For example, upon investigating why your product fell outside its pH specification, you find that the operator who performed the testing failed to verify that the calibration of the pH meter was in date. Once the pH meter was calibrated (which should have been done prospectively, if cGMP were being followed), a new result is obtained that meets the specification. That might be a suitable justification (although you would have to retrain the operator to always prospectively calibrate the pH meter and probably update the SOP for the test to make sure that the calibration is required before testing!). But, if the pH meter was properly calibrated and you decide to just test it again anyway – there is no real justification to do that. You have to live with your prospectively defined criteria.

Analytical methods used in testing for release of clinical trial materials need to be developed, alongside development of manufacturing processes. At Phase 1, many analytical methods will not be fully developed in the manner they would be used for a licensed product, comparable to the discussion above for the specifications. Nonetheless, those analytical methods used to establish safety of the product should be validated [15]. Other analytical methods should be qualified (a term used variously, but generally taken to mean that analytical performance parameters are established and understood, if not formally validated, and that the method has been shown to be suitable for its intended use – scientific validity). Systems suitability criteria, e.g., specifications for results from positive controls, may be particularly important at this stage, to assure adequate performance of the as-yet-unvalidated methods.

So, now that we've described some of the principles behind the cGMP, just what do they cover? They cover the need for qualified and trained personnel; an autonomous and accountable quality unit; appropriate facility design (e.g., unidirectional flow of materials, personnel, and waste, adequate air handling, suitable quality water, etc.); calibrated, validated, and clean equipment; control of components (including raw materials, biological starting materials, and intermediates) and of containers and closures; manufacturing procedures and records (document, document, document); laboratory controls (analytics) for release and for stability testing; packaging, labeling, and storage; and record-keeping.

The Phase 1 guidance mentioned previously covers some special topics, e.g., multi-use facilities (high degree of risk for cross-contamination); general concerns about biologicals, e.g., risk of adventitious agents or aspects unique to cell therapies, and sterile or aseptically processed products (vaccines to be injected must be sterile). Some of the flexibility they describe in the guidance is because it covers all types of products, including cell therapies that are almost always made at small-scale and often, are individualized. Some of this flexibility in the guidance would not apply to prophylactic vaccines, particularly those made in a contract manufacturer's multi-use facilities.

Case Studies

In case we haven't yet convinced you why you need to go to all this effort just to do a Phase 1 study (we acknowledge that it's expensive, time-consuming, may require expertise you

don't have, and so forth), we'd like to share with you some real-life examples that our Vaccine Translational Research Branch at NIH/NIAID/DAIDS has confronted over the years in our quest to facilitate the development of safe and effective HIV/AIDS vaccines.

Case Study A: What Can Possibly Go Wrong with a DNA Plasmid Vaccine?

DNA plasmids are about as close to a well-characterized biological product as vaccines get. They are closed circular molecules of DNA of a defined sequence. Anyone can prepare plasmids in their lab. What's so hard about that? We worked with a collaborator for whom we were supporting the development of a viral vector intended to be used as a boost to a DNA plasmid that they were manufacturing under their own funding (from another source) at a CMO that they chose after getting advice from noted experts in the HIV/AIDS vaccine field. Part of our support to these collaborators was the regulatory support: to conduct preclinical safety studies (toxicology and biodistribution) and to prepare the regulatory filings. The FDA-required biodistribution study entailed determining where in the body of animals the vaccine would go and how long and to what level it persisted (or was cleared), and the study involved a placebo control arm. The CMO of the collaborator who made the DNA plasmid vaccine also made the placebo that was used in the biodistribution study. In the process of conducting the biodistribution study, we obtained results that suggested that the placebo animals were vaccinated with plasmid. These results initiated an investigation at the animal facility. In addition, the CMO shipped vials of placebo directly to a 3rd party vendor who would perform PCR to determine whether there were vaccine sequences in the placebo. These vials had never been in the animal facility. In this way, it could be determined if the contamination problem occurred with the placebo vials or at the animal facility. To our amazement, the placebo vials were, in fact, contaminated with vaccine plasmid. So, then we were left scratching our heads over whether the vaccine was contaminated with any other plasmids that the CMO may have made in their facility, prior to making the vaccine. The CMO was unwilling to test the vaccine product for other products they made. Despite the evidence of contamination of the placebo with vaccine plasmids, we were assured that there was no common-use equipment, only disposables were used. Consequently, they claimed that there was no need to validate the cleaning of the equipment and no possibility of product cross-contamination. After all, they were only making Phase 1 products, so they didn't need to validate their manufacturing procedures, right? Then, on further questioning, we received a 5-page list of common-use equipment that the manufacturer used for this project. So, with no way to ensure that the vaccine was not also contaminated and knowing that the manufacturer's practices were capable of contamination, we could not justify risking human subjects by giving them material that was potentially adulterated. That mistake cost our collaborators years before they could get their research concept into the clinic. They had to start from scratch with a new plasmid backbone and a new manufacturer, and they had to obtain the additional funding to do this. Had we, rather than our collaborators, selected the CMO, we would have audited them before manufacturing and thus, likely determined that they didn't have the proper practices and validation before initiating the manufacturing.

Case Study B: What Can Possibly Go Wrong with Filling Liquid Into Vials and Storing Them Frozen?

In this case, a biotech company with whom our grantee was collaborating was using a CMO for filling their bulk product into vials and finishing them (i.e., labeling and packaging). Another Division of NIAID was collaborating with this same biotech company on another project. One lot of product made for that project was noted to have visible particles at a high frequency, resulting in rejection of the vials containing visible particles during the lot release process. The manufacturer (biotech company) and their CMO's quality agreement did not prospectively define the rejection rate that was acceptable and the rejection rate exceeded 10% of the filled vials (yes, that's unacceptably high!). Nor did the quality agreement define in detail the methods required for inspection for visible particles. As the IND sponsor, our sister Division rejected the lot from clinical use. Unfortunately, we did not learn about this until about a year later, when we were experiencing a similar problem. In our situation, the visible particles were only noted upon stability testing and not at the time of release. The product was already being used in clinical studies by our grantee. The initial investigation by the manufacturer was not sufficiently thorough, was confined to only one affected product lot and was not a global (comprehensive, as opposed to specific) investigation of the problem, did not identify a specific root cause, and did not thoroughly document the product impact. FDA put our IND on hold, as well as others, because they saw the global (far-reaching) nature of the problem as a consequence of having several INDs under their review for products vialled by this CMO for this biotech company. In this case, proper audits were done by the biotech company for their CMO, but a proper investigation was not initially performed by the biotech company to thwart an identified problem before it expanded to involve several lots of several different products. Further, their quality agreement did not contain sufficient detail to prevent such a problem. This manufacturer did eventually conduct a thorough investigation and provided sufficient assurances to the FDA that the FDA removed the clinical holds from various INDs. The products under those INDs were allowed to be used in the clinic, with very specific agreements and appropriate CAPAs being implemented. Although the problem was eventually resolved, this case illustrates that even something as simple as aliquoting into vials can go wrong. It also illustrates the importance by a manufacturer of taking a global approach to quality and to have sufficient detail in their quality agreements. Visible and sub-visible particles are a known problem for products filled in glass vials,¹⁰ so perhaps the manufacturer did not initially take the issue too seriously. But, once INDs were put on clinical hold, the situation got quite serious. This highlights a question about which you might ask your selected CMO – have any of the products they

¹⁰Many biotech and biological products are liquids filled into glass vials or syringes. Glass is essentially a non-homogenous conglomerate of various materials such as sand (silica) and ash, which has been formed and milled into the appropriate shape. It can contain process residuals like silica and powders. It can also contain fine bits of glass that are not integral to the glass vial or syringe, e.g., glass dust. Further, plastics from stoppers or plastic bags used to autoclave them, threads from sterile wipes, and other debris from filling line equipment, environment, or personnel can be imparted into the liquid, during the filling process, resulting in visible and sub-visible foreign particles. This is a recognized problem in the biotech industry. Thus, visual inspection of appearance is performed to identify and remove vials with visible foreign particles during the lot release process. Visual inspection of appearance should also be performed as part of the stability program. Visual inspectors must be adequately trained on the normal appearance of the product, especially so when it is somewhat particulate in nature itself, in order to be able to distinguish foreign particles from the expected appearance of the product, even if these inspectors are from a CMO and may not have previously seen the product in development.

manufactured been subject to an FDA clinical hold. It also highlights the importance of considerable detail built into a quality agreement, which we'll discuss further below.

Case Study C: What Can Possibly Go Wrong When You Passed Your Sterility Test?

A researcher with whom we were collaborating had chosen a CMO based on recommendations from other researchers at his institution. He was making a viral vector and wanted to perform a dose escalation in the initial Phase 1 study with this vector and this construct. Not an unusual plan. So, the CMO made a single batch of vaccine and then filled some of it at the highest concentration in vials in a hood using a semi-automated method, then diluted the rest, and filled more, and so on for a dilution series of 5 vaccine lots. Each lot was tested for sterility, as required for lot release. The middle batch (filled 3rd of the 5) failed sterility but the other 4 passed the test. Were they sterile? And how could we prove that they were? The normal sterility test involves 20 vials. So, we asked one of our statisticians to determine how many vials would need to be tested and found sterile for us to have 95% confidence that each of the other whole lots was sterile. Then, we tested more vials to get to the number the statistician advised for each lot. When more vials were tested, all of the lots were shown to be contaminated, and thus, not suitable for human use. This mistake cost the researcher the first entry into the clinic with this vector approach. While new lots were being made, other researchers proceeded into Phase 1 before him. In this case, we began to work with his chosen CMO on another project and when we audited the CMO, we found substantial deviations from cGMP, including inadequate facility design to assure sterility, which caused us to stop working with that company. Our auditors even found holiday decorations and other non-GMP materials stored in the same storage room with the cGMP-controlled raw materials used in manufacturing. They also found drip lines in that same storage room, because it had previously been used as an animal room. The manufacturer could provide no evidence that the water had been turned off to prevent bacterial growth in the drip lines, a potential source of contamination for released cGMP raw materials. Had a proper audit been done by the collaborator in the first place, he might have chosen not to work with that CMO despite the advice he had been given.

Case Study D: What Can Possibly Go Wrong When Your Master Virus Seed Appears Free From Cross-Contamination?

Neither the FDA regulations nor the guidances state that cGMP need to be followed in the research and development laboratory where pre-seed constructs are made, although the cell substrate guidance from OVRP does suggest this need be considered. [16] We also advise you to follow some concepts of cGMP even in the early stages of vaccine development based on the following experience. Although researchers do follow many good documentation practices and do document what, when and how their experiments are conducted, other principles of cGMP could well save you time and resources in the long run. In two separate cases, a "fragment of another vector" was found during the in-process testing of cGMP materials intended for the clinic. All the raw materials and Master Virus Seeds (MVS) for the products were released under cGMP conditions, and should not have been the source of contamination. The MVS were demonstrated to be pure to the limits of detection. However, in both cases, the investigation led to discovering that the contamination occurred at the pre-seed level in the development lab where the scientists

were working on multiple vectors during the same period of time. The low-level contaminations were only revealed after sufficient rounds of passage and amplification had occurred, from the pre-seed to the MVS to the clinical lot. Due to good documentation practices in the R&D settings, the root causes in each case were identified. However, because of these independent experiences in two separate biotech companies, the corrective actions taken independently by the firms were to bring in some cGMP aspects of “Cleaning/Change Over” practices to their research labs, to prevent cross-contamination for future constructs. In each case, the contaminations not only caused the clinical trial material to be unusable, but they had to “go back to square one” to re-make the constructs and both lost more than a year’s time until getting into the clinic.

Lessons Learned and Our Advice

What should you do to prevent these kinds of problems from happening to you? You don’t want your entry into the clinic stalled, but you certainly do not want to harm anyone. Nor do you want to be placed on clinical hold.

The first step is a proper due diligence audit of your proposed contract manufacturing organization. Despite what other people have done, if something goes wrong, you cannot just say “Well, Dr. John Doe used this CMO and FDA let him get into the clinic. So, what’s the problem with me using them?” The IND sponsor is the party responsible to assure the FDA that the investigational product has the correct identity and strength/potency and is of suitable quality, purity, and safety [17]. The CMO is responsible to their client, not to the FDA. And if you are not the sponsor of your own IND, but you are the clinical investigator, you have an obligation to assure your clinical trial volunteers’ rights are not violated and they are not put in harm’s way. Thus, it’s your obligation to know that the CMO you are using has a facility that is adequately designed, with proper equipment and trained personnel, with written documentation of their general and specific procedures, as well as what they have actually done, and with written documentation of test results verifying that everything went according to plan. Additionally, if any deviations occurred, it’s your obligation to know that they were thoroughly investigated with the aim of identifying a root cause, that proper CAPAs were taken, and what was the “product impact” of the deviation. While you may trust your CMO, it’s your responsibility to verify that this trust is well-placed. As the sponsor of the IND, you must sign a form (FDA 1571) that indicates you are the legally responsible person for initiating a clinical investigation [17]. This obligates you to assure the FDA of the identity, potency/strength, purity, quality, and safety of the product you plan to use in your proposed clinical investigation [21 CFR 312.23(a)(7)(i)]. See Appendix 2 for how to go about a quality audit of a CMO.

Two points that bear emphasis in regards to using a CMO, which should be verified in a quality audit, are as a result of the fact that CMOs are multi-use facilities. As such, absolute attention should be paid to cleaning validation, carry-over, and change-over procedures and to aseptic processing. The CMO will give you little or no information about the products made in the facility prior to yours, so you cannot test for carry-over. Thus, it is crucial that they have thorough cleaning validation of common use equipment and the suite(s) in which process steps occur to not only assure low and acceptable bioburden, but also that there is no

product carry-over. They should also have procedures (SOPs) in place to prevent use of a suite that is not cleaned adequately, i.e., an SOP for change-over procedures. Also, if your product requires aseptic processing, absolute attention to validation and proper monitoring is essential for this purpose. Aseptic filling is an area where the most attention is required as this is generally the last process step and thus, most proximal to human subjects. Qualification of the filling process by media fills is essential to assuring aseptic processing is adequate, as you cannot test all vials of a product lot for sterility, whereas you can and do so for media fill qualification.

What next? Next is the quality agreement. Again, trust but verify. Manage expectations. Like any contractual arrangement, where each party's expectations should be outlined in writing to prevent misunderstandings and disagreements, a quality agreement should detail what you will provide to the CMO (e.g., starting materials, tech transfer or knowledge and know-how) and what they should provide to you, including assurances, timelines, materials, documents, and any other expectations you have of how they will make your product. It is YOUR product and YOU are responsible, so you need a quality agreement that will help you assure that the product meets your expectations. Some of the corrective actions from audit observations can be very specific to your product/process and it may not make sense to change the CMO's normal operating procedures/processes, so these changes and the management of those changes can be part of the quality agreement. If the CMO deviates from your quality agreement, you may have recourse, e.g., they may be obliged to re-manufacture the lot (if that was part of your contractual agreements). The FDA expects you to have a quality agreement and if you or your CMO ever get inspected by the FDA, this will be one of the documents they will ask to see. [18, 19, 20, 21] A quality agreement is a documented expectation of cGMP.

OK, so now you have your CMO selected and a quality agreement in place, surely that's enough, isn't it? Well, no, now you need to manage the project. You should consider hiring a project manager if you don't have sufficient time or experience managing this kind of project. A project manager can develop timelines and help you identify what things are parts of the "critical path" to getting into the clinic. Then, you can focus your attention most closely on those critical path items to ensure they go smoothly and that there are no delays to your timeline. A project manager can also help identify resources you may not have realized you might need and even manage the budget. They can work with the CMO to ensure they are meeting your timelines and your budget and to resolve problems as they arise. You and/or your project manager should have weekly or bi-weekly calls with your CMO to assess where things stand and what problems have arisen (and what is the impact on the product and the timelines). Again, this falls in the category of trust, but verify.

Issues may arise for which you may not have the proper expertise or sufficient experience to address. While your CMO may have the necessary expertise, they will expect you to know how you want your product made. They can tell you what they generally do, but since your product is unique, they will not have every answer. In these instances, it's important for you to consult experts. There are a variety of consulting services, ranging from individual, independent consultants to large contract research organizations with consultants on staff. Yes, they are expensive, but avoid being penny-wise and pound-foolish. Certain aspects like

formulation, validation of analytics, and regulatory strategy may not be your bailiwick but are critical to the success of your product getting to the clinic. Formulation is critical to the stability of your product upon storage, as well as safety and tolerability in the clinic. Regulatory strategy ranges from decisions about what cell line to use to manufacture your product that the regulators will accept to whether to request a pre-IND meeting and about what to ask FDA for concurrence [22]. (Yes, you should request a pre-IND meeting!¹¹) Sometimes, you may even want to consult an independent expert to determine whether your CMO is giving you the best advice or advising you on the basis of their own strengths and weaknesses and not necessarily the best course of action. Again, trust but verify. If you are funded by NIH, you should consult with your program officer or contracting officer's representative, because they have likely been through similar experiences with similar product concepts and may be able to identify potential collaborators who might be useful in, e.g., identifying the best choice for formulation (but please understand that as Government employees they are not permitted to direct business to specific CMOs or consultants).

A point that bears repeating is that in the end, the IND sponsor is responsible for the safety, purity, identity, potency, and quality of the investigational product, not your CMO. FDA has made public presentations about how overwhelming the number of facility inspections is that they are responsible for yearly. Because they cannot inspect every facility, they have to choose their inspection program on a risk-basis [23]. Facilities making investigational products for Phase 1 are not prioritized to be as high-risk to the public health and the consumer as facilities making licensed products (being used by millions of people). Thus, quality oversight for the investigational product is the job of the sponsor, not FDA. You may be surprised to know that FDA does not routinely inspect facilities that manufacture Phase 1 clinical trial materials. Often, the first time FDA steps foot in a manufacturing establishment is towards the end of the licensure process (well after phase 3 studies and after the Biologics License Application has been submitted; just before a licensure decision is imminent), when they conduct a pre-approval inspection (aka "PAI"). Given that the typical development time for a vaccine is 10-15 years and clinical trial material may have been given to tens of thousands of individuals over that time, it should be clear that the IND sponsor is the one responsible for ensuring that during the investigational phase, the product has been safe and suitable for human use. During that same time, FDA has been conducting paper reviews only. They have to trust that the IND sponsor has been giving them accurate and complete information to assess risks to clinical trial subjects and that the IND sponsor has taken their responsibilities seriously, by virtue of signing the Form 1571. They will generally only go into a manufacturing facility for an inspection at Phase 1 if they have a cause to do so, i.e., a so-called "directed" inspection or "for-cause" inspection. This might occur if they find that the IND proposes unsafe procedures, the IND sponsor reports some inappropriate practices by their manufacturer, or they have received complaints from the public, a clinical trial participant, an investigator, or a whistleblower. Even though your CMO may have never been inspected by FDA, as a part of your due diligence audit, you should request to be informed about your CMO's inspectional history. Ask what regulators have inspected them,

¹¹A good orientation to FDA pre-IND meetings, and regulatory thinking in general, is Shapiro SZ. "The HIV/AIDS vaccine researchers' orientation to the process of preparing a US FDA application for an investigational new drug (IND): what it is all about and how you start by preparing for your pre-IND meeting." *Vaccine* 2002; 20: 1261-1280.

if any. Ask if FDA or another regulator has inspected them in the past, was there a “483” (the FDA form used to document objectionable or potentially violative observations made during the inspection) or similar from other regulators. Was there a warning letter issued (which only occurs if observations were deemed sufficiently violative to warrant regulatory action)? What was the facility’s reply or response to any 483 observations to the FDA (or similar for other regulators’ inspections)? In Europe, manufacturing facilities have to be cGMP-certified, and there is a similar process in the state of California. You may ask to receive a copy of your CMO’s cGMP certificate. Even if they are certified, this does not guarantee they are suitable for your needs and you still need a due diligence audit to verify. Their certificate does not obviate you from your sponsor’s responsibilities. Need we say again, trust, but verify?

Finally, you may wish to consider, if it is your lab that is making the constructs that will serve as the pre-seed for vaccine production, implementing some aspects of cGMP even in your own laboratory to prevent cross-contaminations and mix-ups that could lead to delays to the clinic. The principles behind the Good Manufacturing Practices are valid even in the R&D setting, when the material is planned ultimately to be used in human subjects. It makes good business sense not to have to re-derive your viral seed, especially if positive attributes may be altered when doing so, but also given time delays and materials and resources needed. It’s just good science as well.

Summary

Now that you are ready to take your long-sought vaccine concept into the clinic, so that the world may benefit from your hard work, you need to ensure that what goes into the clinic is safe and suitable for human use. Your laboratory is highly unlikely to be the place where a safe and suitable-for-human-use product can be manufactured and you will likely need to seek a corporate partner or a CMO. They must manufacture your Phase 1 clinical trial material in compliance with statutory requirements for current Good Manufacturing Practices. These practices are meant to minimize risks to the manufacturing process and to the product, and thus, to the recipient. They are also meant to document what should have happened, what did happen, and what the quality attributes of the resulting product are, as well as whether they met prospectively defined criteria. Your responsibilities include ensuring that the CMO you chose is meeting cGMP standards, suitable for clinical trial material for the phase of clinical trial that will be conducted and which is likely to go into healthy individuals (eventually even into toddlers or infants, if your vaccine is for a disease for which children are susceptible). It must be safe, pure, potent, of correct identity, and suitable quality. To ensure this, you should conduct a due diligence audit of your selected CMO, address any audit findings before you proceed to manufacture, complete a quality agreement prior to manufacture, consider hiring a project manager to shepherd the process along successfully and keep to timelines, and consult with experts, as needed. You should also consider introducing some aspect of cGMPs into the research and development lab that will make the initial vaccine constructs (vectors, expression cell lines, etc.) With these facets in mind, cGMP should be easier for you now.

We hope that we have de-mystified the process of cGMP and armed you with knowledge that will permit you to successfully translate your research concept into a product suitable for human use, so that you can conduct safe and ethical clinical research and develop a successful vaccine that will promote and protect the public health.

Acknowledgements

We would like to acknowledge the contributions to discussions and problem-solving by our fellow colleagues in the Vaccine Translational Research Branch, Jack Hill and Ronelle Lucas. We would also like to acknowledge the thoughtful and critical review of the manuscript by our colleagues, Drs. James Bradac, Que Dang, and Kevin Ryan.

We also wish to acknowledge our other experiences, too numerous to count, that we could not share with you, but which have contributed to our experience base, which helps frame our thinking and understanding on this topic, and which we wish to share with our grantees and contractors and others in the field of HIV vaccine development, specifically, and biological products development, in general.

Appendix 1: Brief Glossary of Terms

Audit	A due diligence site visit to a facility that will be contracted and used to perform some aspect of an IND sponsor's obligations, e.g., a CMO that will make Phase 1 clinical trial materials to be used in a trial under IND. The purpose of an audit is generally to assure the facility is adequate for the intended use and procedures and practices are in place to assure suitable compliance with applicable laws and regulations.
CAPA	Corrective actions and preventive actions are formed as the outcome of an investigation into a deviation or failure. They are the actions you will take to correct the situation, if the situation can be corrected, or to prevent the same situation from happening in the future.
cGMP	Current Good Manufacturing Practices: the expectations of regulators of medicinal products that manufacturers, including CMOs, should meet to assure that investigational or licensed products meet appropriate standards that assure safety, purity, potency/strength, quality, identity, and stability. The cGMPs cover aspects of qualified and trained personnel; an autonomous and accountable quality unit; appropriate facility design; calibrated, validated, and clean equipment; control of components and of containers and closures; manufacturing procedures and records; laboratory controls for release and for stability testing; packaging, labeling, and storage; and record-keeping. They should represent current best industry practices. Regulators have a sliding scale of expectations from Phase 1 to post-marketing. There is a specific guidance to outline their expectations for Phase 1, which is distinguished from the expectation of full compliance from Phase 2 and throughout the product life-cycle.
CMO	Contract Manufacturing Organization – a manufacturing facility for hire to produce investigational and/or licensed medicinal products. By their nature,

they are multi-use facilities, which require a higher level of oversight and validation than a dedicated facility might.

Deviation	Any change (planned or unplanned) from a protocol, SOP, procedure, method, or an unanticipated outcome of any of those (e.g., failure to meet a specification).
IND	An investigational new drug application is required by the Food and Drug Administration for review when an unapproved new drug (investigational product, like an unlicensed vaccine) will be investigated in a clinical trial. There are exemptions to submission of an IND, and these are listed in the IND regulations – 21 CFR 312; most situations are not exempt and FDA now has a presumption of interstate commerce.
Root cause	The fundamental underlying basis for a deviation or failure. The cause that lies at the root of the deviation. For example, a pH measurement that has fallen out of specification may be because the pH meter was not adequately calibrated, as a result of use of an out-of-date pH buffer. The root cause is use of a pH buffer that was out-of-date to calibrate the pH meter.
Specification	Essential quality attributes required; e.g., a pH of 7.2-7.4
SOP	Standard Operating Procedures – prospectively written instructions to be precisely followed for a given process step, analytical method, or other facility procedure (e.g., cleaning procedures). SOPs must be reviewed and signed as approved by QA. Operators must be trained on SOPs they will use in the performance of their duties.
QA	Quality Assurance – all the planned and systematic activities implemented within the quality system that can be demonstrated to provide confidence that a product or service will fulfill requirements for quality. (Definition from the American Society for Quality ¹²)
QC	Quality Control – the operational techniques and activities used to fulfill requirements for quality. (Definition from the American Society for Quality)

Appendix 2: Quality Audit

How do you go about an audit of a CMO? Our advice is to hire professional auditors, thoroughly versed in cGMP and with biologics experience, to conduct the audit, and to have a product expert (such as yourself) accompany them to ensure that any procedures are appropriate for the type of product you will be making. Prior to the audit, in addition to

¹²<http://asq.org/glossary/q.html>; accessed 10/22/2014

deciding when and who will go to the facility, and confirming this with your chosen CMO, you should plan what the focus of the audit will be and what documents should be reviewed. You also need to decide who will be on the audit team and who will be the lead auditor, arrange any confidentiality disclosure agreements needed, establish an agenda for the audit, and manage expectations on the part of each party involved. Expectations include logistics like hours of the audit, arrangements for lunch, timing of facility tours, and organization of de-briefings. You may not want to conduct a full six systems quality audit,¹³ but focus on the aspects most critical to your Phase 1 production. This should be communicated before the audit to the audit team and the CMO staff. During the audit, the lead auditor is in charge and any disagreements that the other members of the audit team may have among themselves should be discussed in private, and generally after hours, if possible. At the end of each day of the audit, a brief de-briefing (e.g., ~1/2 hour) should occur that informs the CMO staff of any potential problems that have already been identified, makes them aware of what the auditors plan to do the next day, and identifies any documents requested during the day that were not delivered for review, so that they can be found and provided the following day. If people who are not at the audit will be attending the de-briefing by phone, then arrangements for this should be made in advance so that the CMO can obtain proper confidentiality disclosure agreements, if needed. At the end of the audit, a more comprehensive de-briefing should occur to identify any unsatisfactory findings. A typical facility audit is three days, but depending on the complexity of your manufacturing and the focus of the audit, it could last less time or more. After the audit, the professional auditors should prepare an audit report to be delivered to you. This audit report should cover what rooms were toured, which personnel were interviewed, what observations were made and what the severity of those observations was deemed to be (critical, major, minor are the usual classifications, though others may be pertinent). The audit report should be shared by you with the CMO. If you decide that the audit findings can be adequately addressed to your satisfaction, an opportunity for the CMO to reply to the audit findings should be given. Then, when the critical observations are adequately addressed and corrective and preventive actions implemented for those, and a plan that you find acceptable is provided for the timing and manner of addressing the major and minor findings, you have found yourself a CMO!

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¹³The key systems are: Quality System (which overarches the other 5), Facilities & Equipment System, Materials System, Production System, Laboratory & Control System, Packaging & Labeling System <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pdf> These are what Team Biologics from FDA will inspect.

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