5.1 Introduction

In the early part of this decade the European Commission signaled that it would seek to define a good manufacturing practice (GMP) for the manufacture of cosmetics. Although GMP was already a requirement in the Cosmetics Directive 76/768/EEC and its amendments, there was actually no definition of what that good manufacturing practice should be. By February 2004, a draft document defining the good manufacturing practices had been prepared by the commission (04/ENTR/COS/48). Simultaneously the International Standards Organization (ISO) was also drafting a document with the same scope. Following petitioning from industry, the commission ceased work on its own document and signaled it would make reference to the new ISO standard for GMP for cosmetic manufacturing (ISO 22716). This document was published in November 2007.
The initial commission document for the GMP for cosmetics and the early ISO 22716 drafts indicated that the definition of GMP should be applied as written to the manufacture of cosmetic ingredients as well. Had such a path been followed this would have repeated past mistakes in the pharmaceutical sector, so the European Federation for Cosmetic Ingredients (EFfCI) took the initiative to define a GMP for ingredients. This chapter will explain why it was necessary to separately define a GMP recommendation for cosmetic ingredients rather than accepting the GMP that has been defined for cosmetics or pharmaceutical starting materials and give a brief overview of the key features of the EFfCI guide.

5.2 What is GMP?

First, we should take a look at an often poorly understood term, good manufacturing practice. This is a term in common use across many consumer-orientated industries and is particularly associated with pharmaceuticals and food and is also used in other industries. In the cases of food and pharmaceuticals, governments worldwide have mandated that these products should be manufactured in accordance with GMP. These two industries have a different set of specific rules that define GMP. In this respect, the term may well be in common use but the exact details of what GMP actually is depend strongly on that industry. That noted, GMP is always applied in situations where the final product should do no harm to the end user. All the details in the GMP stem from this simple premise.

EFfCI has chosen to use the following commonly used definition of GMP: The part of Quality Assurance (QA) which is aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use. The key words in this statement are consistently and intended use. Thus, it is not enough to make an occasional good product; there is a strong requirement to make one to the same quality time after time. This is a core principle; users of the product require a high degree of assurance that it is of the same quality with each delivery. Yet quality is also a term that has no specific meaning, but the most general one is appropriate here, "the product should be fit for the intended use." Thus, the use of the product dictates the quality and the extent and detail of GMP required.

This definition is an old fashioned way of stating that the manufacturers should perform a suitable risk assessment regarding the use of their product and identify the controls in manufacture that will assure product quality, in
particular those that will provide a high degree of assurance that the product will not harm the end user. It follows from this view that GMP is a set of rules that can be applied to assure product quality.

This aspect is critical because in the past the food and especially the pharmaceutical GMP have been taken verbatim and applied to their suppliers. This has often met with resistance, usually because the detailed rules are designed to provide control over the manufacturing processes and technology in use in those industries. When their suppliers use different technologies to manufacture their products then the risks posed to the end user by their equipment and operations will be different and so some or many of the detailed controls will be of no value, merely adding cost to the operations. Potentially this is disastrous to the supplier and customer as both would be under the impression that the risks to the end user would be minimized through the implementation of the GMP rules.

Thus, for example, some of the risks to the end user will be different when making and filling 100,000 tubes of moisturizer in comparison with making 20,000 liters of a bulk liquid. In the former, there will often be no opportunity to remove any particulate contamination from the end product as filtration may not be possible without breaking the emulsion that gives the product its beneficial properties. Therefore, a suitable control for this risk could be to apply air filtration to the manufacturing facility. However, the same may not be true of the bulk liquid. If the processing is contained in sealed units and filtration prior to fill off and dispatch can be implemented then this would be an effective GMP control. In this instance, applying air filtration as well would serve only a marginal or even no additional benefit.

Regardless of these differences, it is clear that the same principles are being applied in both cases, namely the avoidance of contamination of the product (moisturizer or bulk ingredient) by particulate contamination. This example illustrates how the common principles of GMP will be applicable in all manufacturing operations and it is from these that the detailed guidance can be built.

What are the key principles of GMP?

- The product should not harm the end user.
- The product should be pure and free from contaminants.
- There should be defined manufacturing procedures that have been proven to be effective in making products of a consistent quality.
There should be records of the manufacturing process which demonstrate that the product has been made in accordance with these planned arrangements.

- Personnel should be competent in the execution of their roles and have sufficient training.
- Manufacturing equipment should be fit for purpose and maintained in that condition.
- You cannot inspect quality in the final product.

The first of these principles is the most fundamental—the product should not harm the end user. All the other principles and indeed detailed rules are aimed at providing assurance that the product is safe to use.

Historically, GMP grew up as a result of the fact that you cannot perform 100% inspection when making many small components, for example, tablets or tins of food. In such cases, the testing can destroy the item in question! The only way to have confidence that the end product is safe to use is to apply controls throughout the manufacturing process. In this regard GMP is aligned with statistical process control techniques that have widespread application today in the engineering manufacturing industry. However, GMP is based on a softer definition and control of manufacturing, and to a degree it is easier to implement over a wider range of operational activities. But it is this fundamental basis of GMP that also limits its application to other industries, particularly those where you can perform 100% inspection, such as taking a representative sample from 20,000 liters of liquid and testing it. Yes, the liquid has to be homogeneous to ensure that the sample test results apply to the whole of the batch, but in this instance it can be argued that quality can be assured through inspection alone.

Yet such an approach highlights another critical aspect that is central to GMP: the problem of only knowing what you know. That is, you only test for characteristics that are part of the product specification. If something has gone wrong in manufacturing the material, which causes some new harmful impurity to be formed, then testing to specification would not look for it and so you could be misled into thinking that the material is suitable when it is not. It is here that the other principles and derived rules in GMP come into play, as they will ensure suitable controls are put in place to manage just this kind of risk.

Now, until relatively recently the only definitions of GMP have been for finished pharmaceuticals and food. Several organizations have drafted and
prepared their own interpretation of GMP to ensure that the key principles are adopted and applied in their particular industry, most notably for pharmaceutical excipients and pharmaceutical active ingredients. These materials are often made by chemical synthesis or biotechnology and so have many similarities in terms of the technology used to make cosmetic ingredients. The main reason these industry specific definitions of GMP were prepared was to ensure the best practices match the risks to end user safety posed by the manufacturing technologies in each sector.

5.3 Why Should GMP Be Applied to Cosmetic Ingredients?

Given the key principles of GMP, surely the questions should be why has GMP not previously been applied to the manufacture of Cosmetic Ingredients? There is a risk to the user that the cosmetic may cause them harm, particularly if it is contaminated in some manner. So from a moral position, if an organization is serious and wants to be credible in supplying cosmetic ingredients, then it should be applying the principles of GMP to its manufacturing operations.

Legally, in Europe at least, there is no specific legislation that mandates GMP for the preparation of cosmetic ingredients. However, there are two specific updates to the Cosmetics Directive, 76/768/EEC, which do mention GMP for the preparation of cosmetics. These are:

  

  1. Without prejudice to their general obligations deriving from Article 2, Member States shall prohibit the marketing of cosmetic products containing: (a) substances listed in Annex II … .
  2. The presence of traces of the substances listed in Annex II shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms to Article 2. Annex II lists substances that are harmful to health and so should not be included in cosmetics above certain limits that have been shown to reduce or eliminate the risk to health. Article 2 of the same directive requires that the fundamental principle of GMP
be applied to cosmetic products: A cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use . . . .


The manufacturer or his agent or the person to whose order a cosmetic product is manufactured or the person responsible for placing an imported cosmetic product on the Community market shall for control purposes keep the following information readily accessible to the competent authorities of the Member State concerned at the address specified on the label in accordance with Article 6(1)(a): the method of manufacture complying with the good manufacturing practice laid down by Community law or, failing that, laid down by the law of the Member State concerned; the person responsible for manufacture or first importation into the Community must possess an appropriate level of professional qualification or experience in accordance with the legislation and practice of the Member State which is the place of manufacture or first importation Initiatives from DG Enterprise.

Thus, the cosmetics directive requires cosmetic manufacturers to apply GMP in their operations. In directive 82/368/EEC, Article 4.2 can be interpreted to apply not only to finished cosmetics but also their ingredients. In this regard there is now an implication that GMP should apply to cosmetic ingredients. Directive 95/35/EEC requires GMP for the manufacture of cosmetics but provides no further clues as to what it should be. It was this article that prompted the EU to begin work on a suitable definition of GMP for cosmetics so that there would be no technical barriers to trade within the community as some member states had signaled that in the absence of a community definition they would introduce their own set of rules.

The initial drafts of the “Guidelines on Good Manufacturing Practices for Cosmetic Products” included some 45 references to cosmetic ingredients including the specific application of the GMP to the manufacture of those materials in the scope. This was amended later in the drafting process to make the connection less explicit but it was hard for a cosmetic ingredient manufacturer to demonstrate compliance with the rules and so comply with the GMP themselves, unless they also had them applied by their suppliers.
Thus, there was no mandate for cosmetic ingredient suppliers to apply GMP to their operations other than those that their customers demanded. The danger in this situation was that the GMP rules would be those designed for the manufacture of cosmetics, which for the most part do not use the technology to be found in the chemical and biological synthesis of the ingredients. Thus, the controls would add little value in assuring end user safety and could result in a false sense of security for both parties.

It was against this backdrop that EFfCI seized the imitative and began to develop its own GMP for the manufacture of cosmetic ingredients.

### 5.4 What GMP Should Be Applied?

EFfCI noted that a new GMP Guide for the manufacture of pharmaceutical excipients was being prepared at this time. Pharmaceutical excipients are substances that have no therapeutic value in terms of providing healing to the patient who takes the final pharmaceutical product. But such substances are critical to the administration of those substances. For example, take a tablet of a painkiller. The active ingredient is the substance that relieves the pain (e.g., paracetamol, ibuprofen) but this has to be held in a binder, commonly lactose. Other ingredients can be added to help the tablet disintegrate in the intestinal tract thereby releasing the painkiller, which can be absorbed by the patient. Thus, the properties of excipients mirror those of many cosmetic ingredients and indeed many of these substances are in common use by both industries, particularly those with surface active properties. Thus, several members of EFfCI were also engaged in supplying the pharmaceutical industry and it was these companies that suggested a nascent excipient GMP guide be used as the basis of GMP for cosmetic ingredients. Such an approach was attractive from two viewpoints:

1. the GMP had been defined with the chemical and biotechnological syntheses in mind;
2. many companies supplied both pharmaceutical and cosmetic customers, so having a similar GMP would be easier and more effective to implement.

The EFfCI guide was prepared by an international team of cosmetic ingredient suppliers during 2004 and 2005 based on a new definition of Excipient GMP for pharmaceuticals, the IPEC–PQG (International Pharmaceutical Excipients Council–Pharmaceutical Quality Group) Excipient GMP Guide.
The IPEC and the UK PQG both had a long history of defining excipient GMPs. Their collaboration at this time established a set of GMPs for excipients that matched the manufacturing technologies used to prepare those materials and which gave an appropriate degree of assurance over product quality for pharmaceutical applications. These organizations gave EFfCI permission to use a draft of their Guide and to revise and adapt it to suit the particular needs of the cosmetic ingredient manufacturing sector.

The IPEC–PQG Excipient GMP guide was itself a fusion of two earlier documents that these two organizations had developed independently. Through their collaboration a more definitive standards was obtained and one that is increasingly finding worldwide approval. Their guide was aligned with the clause number and titles in ISO 9001:2000. The rationale here was that ISO 9001:2000 had found widespread acceptance in the chemical and biotechnology industries and that it was an excellent foundation on which to build the specific controls required for GMP. In short, organizations would find it simple to implement the GMP requirements on top of their ISO 9001:2000 quality management system.

It was because of these key elements of the IPEC–PQG GMP Guide that the EFfCI team was able to keep the majority of the text in their guide, word-identical. This allows manufactures who supply both industries to maximize leverage in the application of what to all intents is one set of management controls, and to be selective where necessary with those needed for pharmaceutical applications, which require a more thorough implementation. This means that the EFfCI GMP can be applied in an effective manner in one manufacturing facility without distorting the cost base.

### 5.5 Key Features of the EFfCI GMP Guide

Many organizations that manufacture chemicals are already registered to ISO 9001:2000. This familiarity with the requirements of that standard meant that it was an obvious choice for the structure of the IPEC–PQG GMP Guide, and EFfCI saw no reason to alter that arrangement. After all many cosmetic ingredient suppliers also supply excipients to the pharmaceutical industry because the functionality offered by these products can often be put to identical uses (e.g., emulsifiers, binders). A double advantage for such organizations was that if they were already compliant with the GMP in the IPEC–PQG GMP Guide then they would be compliant with the GMP in the EFfCI GMP Guide for cosmetic ingredients.
By aligning the clauses in the guide with the major headings in ISO 9001:2000 organizations will be able to see at a glance where their management systems need to be enhanced and this allows for a simpler uptake in organizations than trying to map the new GMP requirements onto an existing quality management system.

The vast majority of the recommendations in the EFfCI GMP Guide do not place any additional requirements on an organization that is already compliant to ISO 9001:2000. The emphasis throughout though is on the key principles of GMP.

Within Section 4, *Quality Management System*, the guide emphasizes the need for written procedures to cover quality critical activities. In this respect, the need for a written document is additional to ISO 9001:2000, which somewhat famously only requires six written documents. Such a quality management system was felt to be outside the core principles of GMP where defined procedures are needed to ensure consistent manufacture of products. There was, however, one major addition to ISO 9001:2000 in this section, the inclusion of an additional Clause, 4.3 *Change Control*. It was felt by both IPEC–PQG and EFfCI that the issue of change control was not clearly emphasized within ISO 9001:2000 and that users would benefit from some further guidance on the subject. For example, one key area that requires effective change control is managing the impact of altering the origin of raw materials (e.g., animal, mineral, vegetable, or "synthetic"), particularly with respect to the effect on the cosmetic customer’s label claims. A basic ISO 9001:2000 quality management system might not have enough sensitivity on this topic, and substituting one supplier of a raw material with another that happens to meet the chemical specification may not highlight the change in origin.

ISO 9001:2000 is quite explicit and well laid out in regard to Section 5, *Management Responsibility*, and EFfCI merely repeated much of that standard but with the obvious emphasis on GMP, particularly within the clauses on internal communication. The ISO 9001 clauses on training and competency were compatible with the key GMP principle on this topic and so did not need further amplification.

However, the same could not be said of Section 6, *Resource Management*. This is one of the areas where another additional section was added, 6.2.3 *Personnel Hygiene*, as this aspect of GMP is of particular concern when products are exposed to the manufacturing environment and thus to
operational personnel. There is always a risk of product contamination through this vector. Whereas ISO 9001:2000 is very explicit in Sections 6.3, *Infrastructure*, and 6.4, *Work Environment*, there is a need to provide a lot of guidance in these areas to ensure that the facilities themselves and the operational environment do not pose a threat to product purity. As a result, several sub clauses to both sections have been added covering subjects such as equipment maintenance, utilities, and water quality. The latter is a key ingredient, either intentionally or otherwise and the control of the water quality is very important especially with regard to microbial issues. Most if not all cosmetic manufacturers consider microbial contamination of the cosmetic as their number one threat to product quality and end-user safety.

Within *Work Environment*, the emphasis is on maintaining product purity through appropriate cleaning routines not only of the manufacturing equipment but also of the facilities themselves ("housekeeping"). The section also introduces the concept of a pest control program. Whereas cosmetic ingredient suppliers will often have such arrangements in place they can be divorced from quality assurance—reports may be issued to site management but the potential impact on product quality is not considered. The EFfCI GMP Guide makes a number of recommendations in this area to ensure that the proper consideration is made of pest control reports in relation to the impact on product quality.

Of course, GMP is all about product purity and so Section 7, *Product Realization*, has a number of key additions to ISO 9001:2000. Key here is the need for good manufacturing records that allow traceability of activities to individuals and to the materials consumed in the production process. That said, there are few additional points until Section 7.4, *Purchasing*. Here there is a clear need to verify the quality of the purchased material before use (Section 7.4.3) preferably by performing at least an identity test on goods receipt. Very recent incidents with the contamination of glycerin with ethylene glycol have clearly illustrated the risks that organizations can be exposed to if they have not implemented good GMP controls in this area.

*Production and Service Provision* is a major section in the EFfCI GMP Guide and as expected provides a lot of detail over the GMP manufacturing process. Key areas emphasized in the guide link back to the key GMP principles of explicit instructions, cleanliness, control over ingredients including those such as solvents that can be reused and records of equipment use. The key aspects of packaging and labeling of the cosmetic ingredient are
also covered although additional comments on these topics follow in the sections on *Identification and Traceability* (Section 7.5.3) and *Product Preservation* (Section 7.5.5). In this, the need for the package to protect the cosmetic ingredient without interacting with it is made explicit, not only whilst the cosmetic ingredient is on the manufacturing facility but also in the distribution chain.

The section concludes with 7.6 *Control of Measuring and Monitoring Devices*, but the guide merely requotes ISO 9001:2000, which is quite detailed on this subject, as are the early clauses of Section 8, *Measurement Analysis and Improvement*.

But Section 8.2.4, *Monitoring and Measurement*, contains a wealth of guidance on the GMP principles in this area, covering laboratory testing and release procedures. With regard to the latter the concept of an Out-of-Specification (OOS) procedure is introduced. This is a key GMP concept and has been reduced to the scientific minimum in the EFfCI GMP Guide. One requirement is to evaluate the reasons for an OOS result and to only discount that result if just cause has been found. Otherwise, the temptation would be to accept and use the result that gives the most favorable outcome. Following the GMP principle of traceability, the guide recommends that samples of each batch (or lot) be retained by the cosmetic ingredient supplier so that the quality of the material can be investigated post manufacture and delivery. The guide also recommends that certificates of analysis be provided with each batch (lot) delivered to customers as this is a key GMP record for both parties.

The guide also makes suggestions on how organizations can approach the definition and justification of retest or expiry intervals for their cosmetic ingredients. These are the intervals for which the certificate of analysis remains valid (retest) and for which the cosmetic ingredient is still suitable for purpose (expiry interval). The commonly used term “shelf life” has been avoided because it can be used interchangeably to mean either interval. It should be noted that a retest interval can be extended by retesting the batch in question and if still conforming to specification a revised certificate of analysis can be issued. Of course, the same is not true of the expiry interval as after this time the cosmetic ingredient might have deteriorated in quality such that it cannot be used, and no manner of testing will put that right!

Section 8.3, *Control of Nonconforming product*, includes the concepts of reprocessing (performing a previously executed manufacturing operation
again) and reworking (performing a new manufacturing operation) in relation to recovery of nonconforming product. The key GMP principles of traceability through preparation of suitable records in regard to what happened and who approved the activity are emphasized in the guide.

The remaining sections mirror the corresponding clauses in ISO 9001:2000.

5.6 Key Differences to IPEC–PQG GMP Guide for Pharmaceutical Excipients

Reference has been made to the fact that the EFfCI GMP Guide is based on the IPEC–PQG GMP Guide. This guide has been developed to define a suitable GMP for the manufacture of substances that are used as the inactive components in pharmaceutical products. Whereas many such products will also find application as cosmetic ingredients, the standards required to assure end-user safety are much higher in the pharmaceutical industry. After all, pharmaceuticals are used to help people whose health is already compromised. Thus, the GMP in the IPEC–PQG GMP Guide provides a higher degree of assurance about product purity by a more thorough application of the key GMP principles.

These are focused on the need to generate a more comprehensive set of knowledge about consistency of the method of manufacture, the impurities, and stability of the product. Such investments require recovery of their associated costs, and in general the GMP required for excipients requires that the GMP be more comprehensively documented and that scientific evidence of product purity and stability be gathered under stricter conditions. The EFfCI GMP Guide, therefore, removed some of these associated costs but maintained the requirement to adopt the key GMP principles.

These differences crudely equate to “do GMP” in the EFfCI GMP Guide whereas for pharmaceutical excipients the requirement is to “do and document GMP.”

These key differences between the EFfCI GMP Guide and the IPEC–PQG GMP Guide are:

- Change Control (4.3): There remains a need to have a system for managing change and for consideration to be made to notify customers when changes are implemented but does
not require that the changes be approved by the quality unit (a term used to describe either or both the Quality Control and/or the Quality Assurance departments), nor for there to be suitable records made of the change process as well as the changes themselves nor a consideration of the impact on any regulatory filings. This theme of the quality unit having specified responsibilities associated with being custodians of product quality is a recurring theme for excipients GMP, which is not mirrored in the EFfCI GMP Guide.

- **Consistency of the Manufacturing Process:** There is less emphasis on performing studies and documenting this. Such retrospective analysis of processes can yield useful information, but when each batch is subjected to 100% testing the law of diminishing returns applies, which is why it was not included in the EFfCI GMP Guide.

- **Environmental and Production Hygiene Controls:** It is rare in the cosmetic ingredient industry for a “clean room” to be required. Even though microbial and particulate controls are necessary for cosmetic ingredients it is usual to be able to meet the necessary standards with an effectively implemented housekeeping and hygiene program.

- **Incoming Materials:** There is no stipulation that physical audits be performed on suppliers, rather that they be approved in a suitable manner.

- **Equipment Cleaning:** This should be performed, but there is no need to gather evidence of the effectiveness of the cleaning process. Typically for excipients this would require a comprehensive study of surface residues and quantification or residues in rinse solvents, which can involve a major scientific effort.

- **Batch Release:** There is no need to evaluate the deviations from the standard conditions for each batch manufactured.

- **Stability studies:** There is no requirement to perform these on the product.

Of course, cosmetic ingredient manufacturers and suppliers can choose to adopt a more comprehensive set of GMP recommendations, such as those elaborated in the IPEC–PQG GMP Guide. But the focus in developing the EFfCI GMP Guide was to recognize that resources cannot be allocated to such duties when there is no commercial benefit to be gained. It was preferred to ensure that these resources be directed at actually performing the key GMP principles.
5.7 Conclusions

The EFfCI GMP Guide was developed as a result of the threat that the GMP for final cosmetic manufacture was going to be applied to cosmetic ingredients. Potentially this could have resulted in inappropriate controls and unreasonable costs being imposed on the cosmetic ingredient suppliers. Therefore, the emphasis in the guide was for cosmetic suppliers to concentrate on implementing the key GMP principles during the manufacture and supply of these ingredients. With a sector specific definition of GMP now in place, cosmetic companies and their customers can be assured that the ingredients have a high degree of purity resulting in safer cosmetics. Of course, the successful implementation of the EFfCI GMP Guide will not prevent cosmetic manufacturers from placing other requirements on their suppliers, such as the audits hinted at in ISO 22716:2007. But at least once they arrive they should witness a facility that is making product that is safe and fit for purpose.

Note

1EFfCI is a European trade association that was established in 2000 to represent the manufacturers of chemical and natural ingredients for the cosmetic industry. It advocates the collective interests of more than 100 cosmetic ingredient companies.