ADHERENCE OF cGMPS FOR ATYPICAL ACTIVES FOR USE AS ACTIVE PHARMACEUTICAL INGREDIENTS: SURVEY OF INDUSTRY

by

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(Under the Direction of David Mullis)

ABSTRACT

Atypical Actives play a significant role in the manufacturing of over-the-counter (OTC) and prescription ($R_{x)}$ drugs. The FDA expects manufacturers of Atypical Actives to follow the ICH Q7 Guidance Document for current Good Manufacturing Practices (cGMPs); however it has been widely reported that not all Atypical Actives are manufactured in accordance with this Guidance.[11,16,17,25,34,59] What do Industry Professionals think the level of cGMPs should be to manufacture Atypical Actives? To answer this question, surveys were distributed to manufacturers and industry professionals to determine if higher or lower cGMP standards were required to manufacture "Atypical Actives". The data set revealed that respondents employed by a member company of IPEC, believe that the cGMP standards for "Atypical Actives" should not be as strict as for "typical" Active Pharmaceutical Ingredients.

INDEX WORDS: Good Manufacturing Practices, Food and Drug Administration, Atypical Actives, Active Pharmaceutical Ingredients, Consumer Healthcare Products Association, CHPA International Pharmaceutical Excipients Council, IPEC

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DEDICATION

I dedicate this thesis to my wife Heather, who is my life and never-ending source of love, patience, and support. She has sacrificed so much for me to achieve my goal of higher education. This is also dedicated to my daughter, Ruby, and to my Mom and Dad, who made me believe that anything is possible if you are willing to put in the work and the time.

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CHAPTER 1

INTRODUCTION

Active Pharmaceutical Ingredients, or APIs, are any substances or mixtures of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product.[1] Active ingredients are intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. In other words, it is the chemicals in the drugs that make the medicine work. The FDA requires that APIs are manufactured in accordance with current Good Manufacturing Practices (cGMPs). Current Good Manufacturing Practices are systems that assure the proper design, monitoring, and control of the facilities and processes utilized during manufacturing, so that each batch of medicine will meet quality standards to be safe and effective.[2] This is not solely meeting a specification, e.g. assay. The "c" refers to "current", which represents the constant evolving technologies and controls used by manufacturers to comply with regulations. CGMPs establish a strong quality management system, and if properly maintained, help prevent contamination, mix-ups, deviations, nonconforming materials, and errors. For API Good Manufacturing Practices, the FDA expects manufacturers to comply with the provisions described in the guidance document "ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients."[2] Guidance documents are documents prepared by an official organization, or regulatory agency, describing the interpretation of a policy or "current thinking" on a regulatory

issue.[3] The International Conference on Harmonization (ICH) is a global organization that brings together the drug regulatory authorities and pharmaceutical industries of Europe, Japan, and the United States.[4] ICH Guidances, such as ICH Q7, are developed through a scientific consensus among Europe, Japan, and the US with the overall goal of protecting human health from an international perspective. Although technically a guidance document and not legally binding, the FDA's expectation to comply with ICH Q7 is clear and is stated as such in the FDA's *API Process Inspection Manual* (utilized by inspectors), which states "ICH Q7 represents the FDA's current thinking on cGMPs for APIs. Thus, API facilities that follow this guidance will be considered compliant with the cGMP requirements".[5] FDA ensures compliance to current Good Manufacturing Practices through on-site inspections.[5] On-site inspections include the facilities that manufacture APIs as well as the finished drug products. If a manufacturer is not following cGMPs, the APIs or drug product(s) it produces are considered "adulterated" under the law.[6] Adulteration means that the drug/API was not manufactured under conditions complying with current Good Manufacturing Practices. Identifying noncompliance and "adulteration" typically occurs through the issuance of a Form 483 at the end of an inspection. A Form 483 is issued to a firm's management at the end of an inspection when conditions may constitute violations of the Food, Drug, and Cosmetic Act.[7]

1.1 Usage of Atypical Actives

There are two types of drugs in the US market: prescription (R_x) and over-the-counter (OTC).[8] Prescription drugs are prescribed by a doctor, are intended for use by one individual, and are regulated by the FDA through the New Drug Application (NDA) process. NDAs contain all animal, human, and chemical data showing how the drug is manufactured and how the drug

acts within the human body. OTC drugs do not require a doctor's prescription, may be purchased in the public market, and are regulated through OTC drug monographs. OTC drug monographs can be described as "recipe books", containing the requirements to market an OTC drug. Drug monographs contain: acceptable ingredients for use in a formulation, allowable dosage levels, formulations, and labeling requirements. Drugs that conform to a monograph may be marketed without further FDA clearance; however OTC drugs in which a monograph has not been established must go through the NDA approval process. The make-up of prescription and OTC drugs are mixtures of materials known as active and inactive ingredients. Inactive ingredients are referred to as excipients, while active ingredients are referred to as Active Pharmaceutical Ingredients, or APIs. The API is the drug itself, intended to provide a pharmacological, or other direct effect, in the diagnosis, cure, mitigation, treatment, or prevention of disease.[8] Ingredients that meet this definition may be used as an API in a drug product. Excipients are the inactive ingredients in a drug, typically used as fillers, diluents, solvents, emulsifiers, preservatives, coloring agents, etc.[9] After these ingredients are mixed through various processing steps, the end result is known as a dosage form. Examples of dosage forms include: pills, lotions, aerosols, and liquids. The way a dosage form enters the body is referred to as the Route of Administration.[10] There are approximately one hundred Routes of Administration for drugs to enter the body, e.g. topical (through the outer surface of the body), transdermal (through the dermal layer of the skin), and oral (administered through the mouth).

There are clear guidelines for the FDA's expectations of current Good Manufacturing Practices of Active Pharmaceutical Ingredients (API) for human use, which is demonstrated through the ICH Q7 Guidance Document. However, there is not a specific guidance the FDA has adopted for the cGMPs of excipient manufacturing. The FDA's expectations are if the excipient

will be used in the manufacturing of a drug product, appropriate cGMPs should be applied.[9] Currently, there is a group of over 100 ingredients being utilized in drug products as APIs but are typically used as: excipients, food additives, cosmetic ingredients, or for other industrial purposes.[11] These ingredients are commonly referred to as "Atypical Actives". "Atypical Actives" are typically found in OTC monograph drugs, but may also be found in prescription drug formulations which have a long history of safe usage and precede historical pharmaceutical regulations.[12] Drug manufacturers may claim these types of ingredients for use as APIs if they have been approved by the FDA. Figures 1 and 2 demonstrate how an ingredient may be used as an inactive ingredient in one formulation, and then as an active ingredient in a different drug formulation[13,14]:

Figure 1: (Inactive: Isopropyl alcohol)

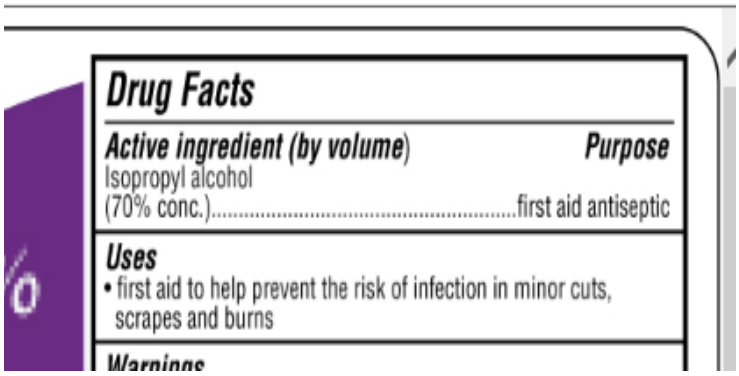

Figure 2: (Active: Isopropyl alcohol)

Claiming an ingredient as an API is legal, as long as the ingredient has been approved by the FDA for use as an API.[8] Since these ingredients have historically been utilized for other purposes than an APIs, e.g. excipients, then API cGMP compliance may not be followed. Table 1 contains a list of ingredients that have been identified for use as "Atypical Actives". Most of the "Atypical Actives" are included in the FDA's OTC Active Ingredients Chart, while others were identified throughout the literature:[15,16,17]

Table 1: Atypical Actives

Drug Category	List of Atypical Active Ingredients
Ingestibles: weight control // antidiarrheal // cough-cold expectorant // antacid // laxative // poison treatment // stimulant // antiflatulent // diuretic	Alginic acid, Potassium citrate, Sodium chloride // Aluminum oxide (Alumina), Bismuth subsalicylate // Ammonium chloride, Pine tar // Calcium carbonate, Calcium phosphate, Magnesium carbonate, Potassium bicarbonate, Magnesium hydroxide // Polycarbophil, Polyethylene glycol, Cellulose, Mineral oil, Sorbitol, Glycerine // Ipecac syrup, Charcoal // Caffeine // Simethicone // Urea
***Ophthalmics*:** demulcent // emollient	Hypromellose // Paraffin
Oral: anesthetic // relief of oral discomfort	Phenol // Potassium chlorate
External Analgesics: acne // antifungal // astringent/disinfectant // topical antitussive // skin protectant	Benzoyl peroxide, Resorcinol, Salicylic acid // Boric acid, Povidone // Calamine, Eucalyptus oil, Honey, Isopropyl alcohol, Starch, Witch hazel // Camphor, Menthol // Dimethicone, Kaolin, Lanolin, Petrolatum, Zinc oxide, Oatmeal
Intravenous: promotion of dieresis	Mannitol**

*material is listed in the FDA Drug Monograph API List as a digestive aid; however in this piece of literature[6] the therapeutic use is "intravenous" and is being manufactured as an Atypical Active. In addition, confirmation of the material's use for "intravenous use for promotion of dieresis" was found at the NIH's DailyMed website.[18]

Most of the "Atypical Actives" in Table 1 are listed in drug monographs and used in OTC drugs, and are therefore Generally Recognized as Safe and Effective (GRASE) by the FDA.[19] Figures 1 (Simethicone)[20], 2 (Salicylic acid)[21], and 3 (Bismuth Subsalicylate)[22] represent examples of OTC drugs containing Atypical Actives:

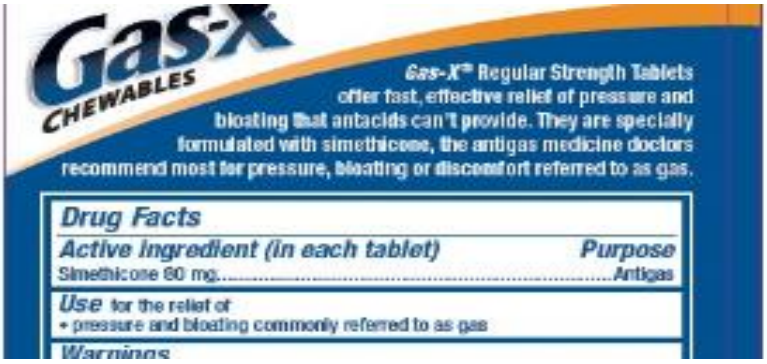

Figure 3: Simethicone Example

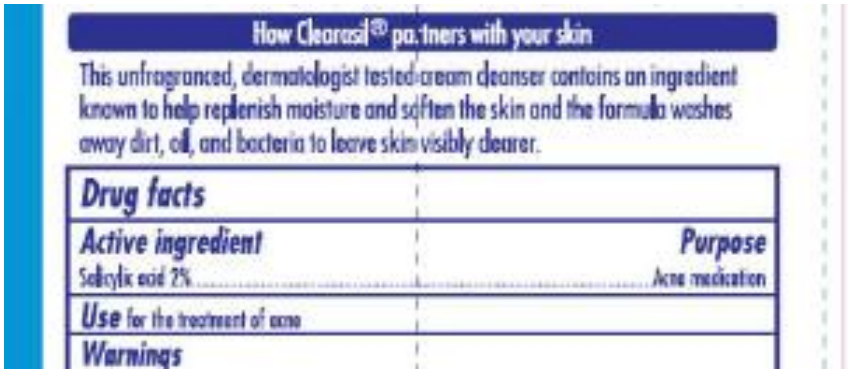

Figure 4: Salicylic acid Example

Figure 5: Bismuth subsalicylate Example

Most "Atypical Actives" present low public risk. These ingredients are safe for excipient use, typically utilized for less serious conditions, have well known chemical properties, and contain low toxicities.[23] Although the risk to public health may be considered low in comparison

to “typical” APIs, the level of cGMPs that all API manufacturers are expected to meet by the FDA are in the ICH Q7 Guidance.

The primary focus of this research was to identify, gather, and examine the manufacturing industry’s views and opinions regarding the cGMP requirements for “Atypical Actives”. Through literature review and the researcher’s professional working experiences with APIs and “Atypical Actives”, a foundation and basis for the research was formed and the topic was selected. It was identified there was a gap that existed between the cGMPs for “typical” actives and “Atypical Actives”. In addition, a lack of transparency for the cGMP expectations existed among three primary groups: the FDA, ingredient or “Atypical Active” manufacturers, and finished drug manufacturers. The reality is the FDA has not given specific formal guidance to the industry regarding the cGMP requirements except that “Atypical Active” manufacturers should follow the ICH Q7 Guidance or equivalent. There have been several attempts by proficient members in the manufacturing industry to query the FDA’s current thinking, through seminar presentations and journal articles. There needed to be a set of data or a research study that involved a larger population of the individuals that are commonly affected by these materials. Most journal articles or presentations about the subject were authored by only one or two individuals. Therefore, this research was chosen to pursue a larger and more robust set of opinions from a larger sample. The intent was to survey the manufacturing industry, exclusive from the FDA, to gather their opinions on the topic. If the proposed sample size was met, i.e. N=86, then the results drawn would represent the opinions of the entire industry who work with “Atypical Actives”. However, only 44 completed and qualified surveys were returned. In order to diversify the population, the researcher sought to survey people who were employed by companies that would represent both “Atypical Active” manufacturers and finished drug

manufacturers who potentially use these ingredients in their drug products. This reason is why member companies of IPEC, CHPA, and other "Atypical Active" manufacturers were sought out.

Questions for the survey were developed from the literature review in conjunction with the researcher's experience. Therefore, preconceived notions were established by the researcher, and hypotheses of the outcomes from the survey. Although hypotheses were developed for this research, the outcomes had the potential to vary greatly. First, most of the articles and presentations given by industry professionals were individuals associated with the "Atypical Active" manufacturers that are an affiliation with IPEC. In these presentations and journal articles, scenarios and justifications were given that lower cGMP standards would be adequate to manufacture "Atypical Actives", for example using the IPEC/PQG cGMP Guidance for excipients, The reasons given were that most "Atypical Actives" have been in production for a long time and are typically safe for use. Therefore, the researcher hypothesized that a majority of those respondents affiliated with IPEC would lean towards lower cGMP standards for "Atypical Actives" vs. the higher standards defined in ICH Q7. Finished drug manufacturers are end users of "Atypical Actives", and may never see the actual operations involved in manufacturing the materials. Therefore finished drug manufacturers may be "disconnected" from the actual cGMPs employed at the "Atypical Active" manufacturing sites. In addition, finished drug manufacturers are procuring these materials and are therefore customers of the "Atypical Active" manufacturers. Customers may expect the highest quality of material, and so it was hypothesized that respondents affiliated with CHPA, that is the finished drug manufacturers, would lean towards higher cGMP standards for "Atypical Actives" to be in accordance with ICH Q7.

The researcher's background is in the over-the-counter drug (OTC) and cosmetic markets. Similar concepts that are used in OTC manufacturing may be applied to this study. OTC drug manufacturers gain knowledge of the FDA's current thinking on cGMP topics through Guidance Documents. The concept of Guidance Documents may be applied to this research study as well. The implementation of a Guidance Document would give makers and users of "Atypical Actives" a pathway to develop and adhere to cGMPs. Since all parties may be impacted by the issuance of a Guidance Document, it was hypothesized for this study that a majority of all respondents would be in favor of the FDA issuing a Guidance Document for the cGMPs of "Atypical Actives".

In the OTC drug industry, there must be a way for both the API manufacturer to know the cGMP expectations of the finished drug manufacturer. In reverse, finished drug manufacturers must expect a certain level of cGMPs from the API manufacturer. In the researcher's experience, a common way these two groups agree to "terms" on the cGMPs of the API is through a Quality Agreement. A Quality Agreement is a legally binding contract between an API manufacturer and the finished drug manufacturer that outlines specific quality standards that are to be met by the API manufacturer. This same contract may be used to connect the cGMP expectations between "Atypical Active" manufacturers and the finished drug manufacturers. It is hypothesized that the majority of respondents will agree that a Quality Agreement should be in place between the two manufacturers. While the hypotheses for requiring both Guidance Documents and Quality Agreements would have been ideal for both "Atypical Active" and drug manufacturers, the results could have varied significantly. An alternative to the Guidance Document is that one or more of the groups do not feel that a Guidance Document is required from the FDA and that lower cGMPs, such as IPEC GMPs, are adequate to manufacture "Atypical Actives".

CHAPTER 2

LITERATURE REVIEW

2.1 Regulatory Actions involving Atypical Actives

The FDA requires that all drugs are manufactured to be in conformance with cGMPs.[24] They do not differentiate between APIs and finished pharmaceuticals in Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act when describing adulteration. Therefore, inadequate cGMPs (or adulteration) for Atypical Actives have lead to Regulatory actions. According to a 2011 article in *Pharmaceutical Technology*, entitled "Atypical Actives Gain Attention"[25], there are cases in which the FDA has inspected "Atypical Active" manufacturers, issued a Form 483, and have banned the importation of products after inspections of the manufacturing facilities.[6] A Form 483 is issued to a company at the end of an FDA inspection in which conditions have been observed by inspector that may be in violation of the FD&C Act.[26] These observations indicate that the "Atypical Active" (or drug, device, food, or cosmetic) is considered adulterated, may lead to adulteration, is misbranded, and/or may be harmful to public health. In 2005, the FDA inspected a manufacturer that made calcium carbonate as an excipient, but the finished dosage form drug manufacturer used it as an active ingredient.[7] The calcium carbonate manufacturer received a Form 483 from this inspection due to a lack of compliance with appropriate cGMPs because the finished drug manufacturer was using the calcium carbonate as an API.

One question to be asked is: what causes the lack of cGMP compliance for these material manufacturers? An answer may be found in two reviews of 483s previously issued to

manufacturers of Atypical Actives; and how these deficiencies relate to the respective sections of ICH Q7 and IPEC's cGMP Guide. In 2009, after an FDA inspection, a Form 483 was issued to Dow Corning for the ingredient Simethicone, for not maintaining an adequate stability program.[27] Simethicone is used as an antiflatulent in OTC drug products.[28] One identified deficiency was a review was not being performed for signs of deterioration for samples in their 2nd year after manufacture on stability samples. ICH Q7 states that an on-going testing program should be in place to monitor stability characteristics of APIs.[29] However, this ingredient is identified in Table 1, and is typically used as an excipient. In contrast, the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients states that excipients with a history of being in the market place, historical data may be used to substantiate stability. The Form 483 does not mention how long Dow Corning has been manufacturing Simethicone, but even if Dow Corning has a long history of manufacturing this material, ICH Q7 states that an adequate stability program should be maintained by the API manufacturer.

The purpose and importance of establishing stability information for an API is to confirm that the material maintains the same levels of identity, strength, quality, and purity throughout lifecycle of the ingredient. Stability data is evidence to support retest or expiration dating, as well as confirming proper storage conditions over this timeframe. If the stability program is not adequate, the researcher asserts that the API manufacturer cannot justify and defend the shelf life of the material.

In addition to problematic stability programs, other compliance issues have been found at "Atypical Active" manufacturers,. A second issue was identified during a 2014 FDA inspection of J.M. Huber, manufacturer of the "Atypical Active", Calcium Carbonate USP. J.M. Huber was cited a Form 483 for not properly following the testing protocol found in the current

USP monograph .[30] USP monographs are specifications that contain tests, procedures, and acceptance criteria that may be used to confirm the strength, quality, and purity of a medicinal ingredient. Insufficient testing is an indicator of weak cGMP compliance. The FDA recognizes USP monographs as the standards for testing drug substances (APIs) in the US, as well as excipients and "Atypical Actives", and has been recognized as such by the FD&C Act since it was enacted in 1938.[31]

In a more publicized case of API contamination and lack of proper cGMPs for a drug, in 2007 over 149 people died from tainted heparin, due to a contaminant introduced into the manufacturing process that was undetected in routine quality testing.[32] Subsequent FDA inspections found multiple cGMP deficiencies, including unclean heparin production tanks, poor control of raw materials from vendors, and a lack of an effective process to remove impurities from batches of processed heparin. Although heparin is not listed as an Atypical Active in Table 1, it underscores the importance of proper cGMP implementation and maintenance. Proper cGMPs are not always demonstrated by way of a Certificate of Analysis. Certificates of Analysis (CofA) are documents issued by a manufacturer's Quality Assurance group that confirms a regulated product meets its product's specification. The heparin testing CofA stated that all testing met the specification.

Proper cGMPs are imperative in "typical" API and "Atypical Active" manufacturing, especially considering the risks to the finished dosage form manufacturer. 21 CFR 211, the cGMP regulation for Finished Pharmaceuticals, states in section 211.84(d) that at a minimum of one identity test must be performed on all incoming lots of raw materials, and a report of analysis may be accepted from the vendor in lieu of performing all specification tests.[33] If the "Atypical Active" manufacturer does not conform to appropriate cGMPs, but all testing passes

specification, this may present a significant risk to the finished drug manufacturer in that they are not receiving the same strength, quality, and purity for the entire batch of "Atypical Active". Testing is typically performed on small samples of a manufacturing batch, e.g. beginning, middle, end (or one composite sample of all three); therefore adequate cGMPs provide process controls to ensure reproducibility is maintained from batch to batch for the "typical" API or "Atypical Active". One way to explain the importance of cGMPs with APIs, "Atypical Actives", or finished drug manufacturing, is to present a parallel comparison with eating at a restaurant. A consumer may eat at a restaurant many times and be completely satisfied with the food every time; however if the Health Department performs a routine inspection of this restaurant and finds health related issues, e.g. rodents, improper storage of food, then the consumer is unlikely to continue eating at the restaurant. This comparison can be made with cGMPs, and the importance of not just accepting purported strength, quality, and purity based off of identification and the other CofA results.

2.2 Concerns from Industry

Due to the incidents of regulatory citations against "Atypical Active" manufacturers, such as banning of importation of "Atypical Actives" for lack of proper cGMPs, issuances of 483s for inadequate stability programs and improper testing against a USP monograph, professionals in the manufacturing industry have presented concerns through public forums and published journal articles. These concerns are presented in the following paragraphs.

In 2014, David R. Shoneker, past chair of IPEC-Americas (International Pharmaceutical Excipients Council) and current Director of Global Regulatory Affairs at Colorcon, gave a presentation on Atypical Actives during an FDA Public Hearing, titled "Atypical Actives,

Importance to OTC Drugs & the Need for a Clear Regulatory Pathway for Use".[8] The FDA Public Hearing was held to obtain input on the Over-the-Counter (OTC) Drug Review. In his presentation, Mr. Shoneker highlighted the potential consequences if FDA requires Atypical Active manufacturers to meet the current ICH Q7 cGMPs, which include: supplier upgrades to facilities and systems to meet ICH Q7 cGMPs would be an unfeasible investment due to limited profit margins, and reformulating the finished dosage form using a new supplier's material could lead to shortages for common OTC drugs. Mr. Shoneker concluded that FDA should issue a Guidance document for the expected level of cGMPs for Atypical Actives, since FDA inspectors have inspected excipient manufacturing plants expecting compliance with ICH Q7 cGMPs.

Another proponent of an FDA Guidance for "Atypical Actives" cGMPs is Janeen Skutnik-Wilkinson, NSF Health Sciences Pharma Biotech Vice President and former Chair of IPEC-Americas. In a 2011 FDA/PDA (Parenteral Drug Association) Workshop[5], she stated "There is no guidance, no regulation specifically for "Atypical Actives" perhaps a guide from FDA would be useful. The lack of clear understanding on expectations of FDA could be a barrier going forward."

Another presentation was given in October 2015 by IPEC, entitled "Atypical Actives; What are Atypical Actives and How Should They Should be Regulated: cGMP and Regulatory Filing Implications". This presentation demonstrated that Atypical Actives may be more scrutinized by the FDA due to the creation of the Food and Drug Administration Safety and Innovation Act of 2012(FDASIA).[34,35] As part of FDASIA, each API manufacturing facility associated with a generic drug submission (ANDA) must register with the FDA, and an annual fee must be paid for each registered API site. The concern is that Atypical Actives may be included in an ANDA, and that registration may increase inspections and require adherence to

ICH Q7 GMPs. This would increase the cGMP compliance costs, along with the fee for registration. These added costs may significantly increase the price of the API to the drug manufacturer, which would minimize or eliminate potential profits to be earned. This presentation identified that the majority of materials Atypical Active manufacturers sell do not go to drug manufacturers; they sell mostly to other industries. In fact, these added costs associated with GDUFA may amount to more than the actual revenue from the sales of the Atypical Active, which could cause the manufacturers of these ingredients to state that the material is for "excipient use only". An example of changing allowed usage may be shown by the DOW Corporation. In October 2014, DOW released a statement that their materials, Methocel™ Hypromellose and Methylcellulose products are not manufactured to ICH Q7 cGMPs. Therefore, DOW does not support the use of these products as API, only as excipients. Hypromellose and Methylcellulose are listed in Table 1 as Atypical Actives. If more Atypical Active manufacturers follow the direction DOW has taken with the Methocel™ products, this could lead to a market shortage of OTC drugs along with a price spike for Atypical Actives. The impact could trickle down and negatively affect the consumer by pulling easy to access products off the shelves and raising the prices on remaining products.

In order to properly evaluate the cGMPs of "Atypical Actives", a risk assessment may be created. For example, if it is determined that an ingredient is being used as an "Atypical Active" in a drug formulation, bridging the gap of the current cGMPs associated with the "Atypical Active" with the ICH Q7 cGMPs should be conducted. It is the drug manufacturer's responsibility to correspond with the ingredient manufacturer to identify and mitigate these gaps. Mitigation is beneficial to the ingredient manufacturer, the drug manufacturer, and the consumer. The concept of risk assessment for Atypical Active cGMPs was acknowledged by the European

Medicines Agency (EMA) in 2008 for the usage of "Atypical Actives", stating that compliance with cGMPs for their API manufacturers is a legal obligation of the manufacturing-authorization holder. The EMA recognized that for a small number of these actives, the primary use of the active is not typically for use in a medicinal product and the producer may not be aiming to meet the specific requirements of the pharmaceutical customer or the country's Regulatory body. This is considered an acceptable practice only if the manufacturing-authorization holder first tries to qualify other sources. If other ingredient sources have been vetted and cannot meet ICH Q7 cGMPs, then the manufacturing-authorization holder should perform a risk-based assessment of the cGMP gaps, and determine if the risk is acceptable to the manufacture of the finished product and minimal risk to the consumer/patient.[36]

A risk mitigation plan may include: 1) maximizing the information in Quality Agreements between ingredient and finished dosage form manufacturers to define specific cGMP requirements, 2) determining whether initial and/or retrospective process validation should be required on three consecutive manufactured batches (Note: it may be more practical to utilize ongoing process capability studies if the material has a history of a stable process (5+ years for example), 3) determine if a stability program is needed (the idea of stability reverts back to reviewing to see if there is a history of material stability), and/or 4) determine if tighter specifications are needed if the material is to be utilized as an API (Note: Corn Starch, Honey, and Colloidal Oatmeals' NF and USP Monographs do not contain Assay tests, which are the tests for Active Ingredient label claims[37,38,39]). Although risk mitigation may bridge this cGMP gap, a point can be made that if there is a history of safe use of the Atypical Active, enhancing the cGMP controls would not be required as long as the material meets specifications. In other

words, it may be inferred that a finished drug manufacturer, in essence, is "purchasing a specification", instead of purchasing an API manufactured under ICH Q7 cGMPs.

2.3 Guidance Documents

Although there are Guidance Documents addressing cGMPs for API manufacturing (ICH Q7), as well as excipient manufacturing (IPEC), there has not been an FDA Guidance Document developed specifically for "Atypical Actives". Guidance Documents are developed to represent the FDA's current thinking on a particular subject. The guidelines are not legally binding, and alternative approaches may be used if the approach is sound and satisfies the requirements of the existing statute or regulation. However, a 2005 study reveals that the FDA believes Guidance Documents are looked upon by the manufacturing drug industry as mostly final, and therefore Guidance Documents are viewed no differently than the regulations themselves.[40] The study also found that the FDA perceives that the industry desires consistency with regulatory expectations, and Guidance Documents allow this consistency along with a level playing field among competitors.

Although Guidance Documents serve as vehicles for communicating FDA's current thinking on cGMP topics, the literature review showed that the pragmatic risk based approach presented by the EMA may be a sound approach to determine cGMPs for "Atypical Actives". In their presentation, the EMA stated that a risk assessment should be performed if an "Atypical Active" manufacturer does not meet the appropriate cGMPs. For example, criterion that may be used in a risk assessment is: if a manufacturing process is dedicated and only uses specific equipment, should there be a Cleaning Validation requirement? According to ICH Q7, cleaning procedures should be validated, and validation should reflect actual equipment usage patterns.

Also, ICH Q7 states that cleaning procedures should be monitored after validation has concluded to ensure the cleaning procedures maintain their effectiveness during routine production of batches. Therefore, the topic of Cleaning Validation for "Atypical Actives" was asked to participants in this research study and was used in part to answer the research question "What are the opinions of industry professionals for cGMP compliance for Atypical Actives?" From the researcher's point of view, if process equipment is dedicated to manufacture one "Atypical Active", and there is data to verify the equipment is free of residual solvents and product carryover from batch to batch, then Cleaning Validation should not be required. In addition, unless the Cleaning Validation was completed at some point during the design phase, an historically well run process should not require Cleaning Validation, for example 5+ years of data, as long as the material is processed through the same equipment without major equipment changes. However, confirming through testing that each batch is free of residual solvents and other carryover may be a timely and costly practice. If Cleaning Validation is performed at the beginning of the development phase of a new process and is determined to be adequate, then batch-to-batch testing confirmation would not be required. For major equipment changes, these should be approved through a Change Control program.[41] A robust Change Control program will evaluate significant changes to the process, and management should determine whether Process and/or Cleaning Validation should be conducted again, as well as determine when to contact the customer as to the critical changes made.

CHAPTER 3

METHODOLOGY

This chapter describes the methods used for the research. A review of the literature pointed out there are specific regulations for the required cGMPs of both prescription and over-the-counter drugs (21 CFR 210 and 211), an FDA recognized Guidance for the cGMPs of Active Pharmaceutical Ingredients (ICH Q7), as well as a recognized Guidance for inactive ingredients, or excipients (IPEC/PQG GMP Guide). However, a Guidance Document is noticeably absent for ingredients known as “Atypical Actives”. This is problematic to the drug manufacturing industry, as it creates a potential for misinterpretation of the FDA’s expectations for the cGMPs of “Atypical Actives”. The primary focus of this research study was to ascertain the perceptions and opinions of various industry professionals regarding the cGMPs for “Atypical Actives". The following are presented in this chapter:

- Research Questions and Survey Instrument
- Target Population
- Sample Size
- Research Design
- Survey Instrument
- Data Analysis

3.1 **Research Questions**

The primary goal of this research study was to ascertain different perceptions by Industry professionals for the applications of cGMPs of Atypical Actives. The research questions for the study were as follows:

1. What are the opinions of Industry professionals for cGMP compliance of "Atypical Actives"?
2. What differences in opinions exist among industry professionals involving different risks associated with "Atypical Actives"?
3. What are the opinions of Industry professionals regarding an FDA Guidance Document for "Atypical Actives" cGMPs?
4. Are there differences of opinions among Industry professionals based on demographics, type of employment, size of their company, and other related factors?

In order to answer the Research Questions, a qualitative and quantitative study was developed using an online survey technique. Surveys are popular ways to conduct market research, and web-based data has been shown to be more accurate, reliable, and efficient than other survey techniques, e.g. telephone surveys.[42] The first research question was answered through a section of questions in the survey that asked about "higher vs. lower" cGMP standard requirements for "Atypical Actives". Results and discussions regarding the survey questions are found in Chapters Four and Five. Other independent questions in the survey were also designed to answer the first research question. The second research question was answered through a set of questions asking the respondents if "higher vs. lower" cGMP standards were required based on risk, i.e. the routes of administration of the "Atypical Active", and if the "Atypical Active" was used in prescription and/or over-the-counter drugs. The third research question was answered by asking the participants if they believed the FDA should publish a Guidance Document for the cGMP requirements for "Atypical Actives". The fourth research question was answered based on the different groups identified in the survey through demographical information.

3.2 Potential Outcomes and Benefits

The results obtained from this study may provide a robust and diverse set of opinions from members of both IPEC and CHPA, along with other experienced professionals, regarding the requirements of Atypical Active cGMPs.

3.3 Target Population

Since the purpose of this study was to ascertain industry professional perceptions regarding excipients used as APIs, the researcher surveyed a population of professionals in the fields of ingredient manufacturing, excipient manufacturing, and drug manufacturing. The survey participants were identified using the International Pharmaceutical Excipients Council (IPEC)[43] Members and the Consumer Healthcare Products Association (CHPA)[44] Member Companies. In addition to these resources, manufacturers of ingredients that would be considered Atypical Actives were contacted to participate in the survey. These companies were not members of IPEC or CHPA. As part of contacting other manufacturing companies not affiliated with CHPA or IPEC; another association, the Society of Chemical Manufacturers and Affiliates (SOCMA), was contacted to request dispersement of the survey to its member companies as well.[45] SOCMA is the self-proclaimed voice of the specialty chemical industry. Their member companies include specialty chemicals and ingredients used in commercial and consumer products. SOCMA's member list contains ingredient manufacturers that produce materials identified in Table 1 of this study.

Diversifying the survey population was intended to minimize bias because it gives all potential respondents an even chance to participate in the survey. However, due to a low response rate, N=44, the survey population was not as diversified as intended and may have

introduced some level of selection bias. This is further discussed in the Limitations section of the report. Initial contacts were made through each company's website and the companies listed on the member pages of IPEC, CHPA, and SOCMA. Once contact was established, an email containing a link to the survey was delivered via email. Participants were given two weeks to complete the survey after distribution. One follow-up reminder email was sent after seven calendar day if no response was received.

3.4 Sample Size

Assuming a study population of 800 industry experts, the researcher needed to survey N=86 professionals in order to report a 95% Confidence Interval with a 10% Margin of Error. Typical response rates through online/emailed surveys are around 25%; therefore a minimum of 344 surveys needed to be distributed.[46] The researcher attempted to survey 86 participants and sent email communications to them; however only 44 completed and qualified surveys were received in which the inclusion criteria were met. One respondent met the inclusion criteria, but only answered questions 1-13. The portion of the survey completed by this respondent was still used in the final tally of data. Through interim analysis of the reported data, it was calculated that 44 respondents provided a sufficient sample size to appropriately report statistically significant results. This is discussed further in the Results and Discussion sections.

3.5 Research Design

The researcher identified a target population and provided the sample with a validated questionnaire to seek perceptions relating to cGMPs for Atypical Active ingredients. In developing the questionnaire, ICH Q7 was chosen as the primary reference document. There are

many sections in the ICH Q7 guidance document. For economical purposes, the aspects of this study focused on the areas identified through the Literature Review that may differentiate the cGMPs of "Atypical Active" manufacturers from "typical" API manufacturers.

To answer the research questions, a survey instrument was developed and distributed to professionals experienced in the drug industry (see "Target Population"). Table 1 has been separated into each Drug Monograph Category (e.g. Ingestibles, External Analgesics), in order to create some of the survey questions to evaluate material risk in relation to cGMPs. In an effort to maximize survey responses and serve as a proactive measure to initiate contacts, a "pre-notification" letter was emailed to potential participants.

3.6 Instrument Development and Validation

The study was a cross sectional exploratory study design of industry professionals. Industry experts were provided a survey to gather opinions about Atypical Active cGMPs. Data from the survey were used to answer the research questions. The length of the survey was delimited to 26 questions to facilitate responder participation and allow completion within a reasonable amount of time, preferably 10-20 minutes.

The survey was developed by the researcher based on review of previous presentations and literature articles given by professionals in the excipient and API manufacturing industries. Although ICH Q7 contains 20 total chapters, the survey focused on the areas identified as potential gaps between cGMPS of "typical" APIs and "Atypical Actives". These gaps were found throughout the literature review, which compared cGMP differences between "typical" API manufacturing and "Atypical Active" manufacturing. For example, full cGMPs for "typical" APIs are applied early in the manufacturing process, whereas "Atypical Active" cGMPs are

applied later in the process. This creates the potential for process and cleaning validation gaps, since the whole production process has not been evaluated.[24] A reason for this potential gap is that most "Atypical Actives" have been manufactured in large vessels in long production trains for an historically long time, and therefore manufacturers may not think strict cGMPs are required throughout the entire process. Another gap found in the literature review was a lack of communication between the finished drug manufacturer and "Atypical Active" manufacturer about the use of the ingredient. Articles reviewed stated that the IPEC GMP Guidance (lower GMP standard) was acceptable for "Atypical Actives"; however, these articles were written typically by one or two authors, and not a comprehensive set of opinions among a diverse population. In order to maintain a reasonable length to the survey and collect data based on the potential gaps, the survey did not focus on the chapters/subchapters of ICH Q7 that are gaps between cGMPs of "typical" APIs and "Atypical Actives", e.g. Personnel Qualifications, Materials Management, etc. Omission of these areas does not lessen their individual and collective importance to an overall robust cGMP system.

As presented in section 3.4 "Sample Size", a total of 344 emails were needed to be dispersed. However, after 344 emails were sent out, an adequate number of qualified surveys had not been completed. Therefore, an additional 24 emails were sent out to receive enough completed responses (44) to achieve statistically significant data. In total, there were 368 emailed surveys which were configured on the web-based validated survey platform, Survey Monkey.[47] The first set of questions were asked to determine the validity and inclusion criteria of the participant. The second set of questions was designed to gather demographical information. The remaining questions were centered around gathering the participants' opinions on the cGMP requirements necessary to manufacture safe and effective Atypical Actives. There were 26 total

questions on the survey, a variety of single answer Likert-style, "yes/no", and "choose one". The Likert-style questions were on a five point scale, i.e. Strongly Disagree, Moderately Disagree, Neither Agree nor Disagree, Moderately Agree, and Strongly Agree. In addition to the three sections of questions, the end of the survey contained a section for suggestions and free form comments about Atypical Active cGMPs. There was no monetary incentive given to participants to take the survey.

In order to test the appropriateness of the survey, in terms of: level of difficulty, clarity and construction of requirements and questions, and assumption of time limit completion; a focus group was recruited with three individuals who met the inclusion criteria. The three individuals agreed to the Inform Consent clause and had ≥ one year of experience working with Active Pharmaceutical Ingredients (API), drug excipients, and/or finished drugs. The purpose of the focus group was to help revise the structure of the survey, with the intent of minimizing any potential bias in the construct, comprehension, and validity of the questions. Another way to minimize bias was to remove any selection bias, i.e. by selecting a target population of CHPA members, IPEC members, and other professionals in the drug/ingredient manufacturing industry.[48] These three groups have direct contact with Atypical Actives and have the experience and competency to comment on the subject. Three people for the focus group were considered an adequate number to validate the survey, so that a smaller number of participants would provide a greater depth of discussion on the construct and comprehension of the survey. In addition to the three focus group members, the researcher's thesis committee of three members also reviewed and commented on the structure of the questions in the survey.

The focus group study was conducted between May 3, 2016 and May 4, 2016. The members of the focus group were encouraged to recommend any needed changes to the flow and

understanding of the survey, as well as suggest any additional questions that may yield further supporting information. Also included in the discussion was the recommended demographical questions, which would give information about the respondents and were believed to be possible predictors of engagement. There were minor suggestions received from the focus group, and all three of the survey links operated properly. Therefore, review and execution of the survey by the focus group allowed the researcher to validate the survey instrument. All three surveys completed by the focus group were removed after the closure of the study, and were not included in the final tallying of data.

3.7 Data Analysis

For the data generated from the participation survey, descriptive statistics were reported for each of the questions found in the study questionnaire, as well as demographical characteristics of the respondents. Data were entered into a validated statistical program, IBM SPSS Software, which calculated counts and percentages for categorical variables and means, and standard deviations for continuous variables.[49] Tables, Figures, and Charts were displayed to study the relationships among each of the research questions, demographics, and other variables in the study. A One-way analysis of variance (ANOVA) table was used to compare the equality or differences of the three or more means (independent groups). ANOVA is based on comparing the variation between data sets to variation within each particular sample.[50] The ANOVA test is a parametric statistical test based on the following assumptions: the samples come from populations that are normally distributed, the observations are independent, and the groups have constant or homogeneous variance.

The inclusion/exclusion criteria for this study were:

Table 2: Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Are currently employed by one of the companies listed in either the IPEC or the CHPA Member Listings Directory, or employed by a manufacturer of an ingredient listed in Table 1 that is not a member of IPEC (and/or) Have current or previous experience of ≥1yr. working in the R_x/OTC drug industry, experience working with Active Pharmaceutical Ingredients, and/or working with R_x/OTC drug excipients	Are not currently employed by one of the companies listed in either the IPEC or the CHPA Member Listings Directory, or employed by a manufacturer of an ingredient listed in Table 1 that is not a member of IPEC (or) Does not have current or previous experience of ≥1yr. working in the R_x/OTC drug industry, experience working with Active Pharmaceutical Ingredients, and/or working with R_x/OTC drug excipients
Must be 18 yrs. of age or older	Are not 18 yrs. of age or older
Must be able to read and respond in English	Unable to read and respond in English

3.8 Institutional Review Board Process

Prior to subject recruitment, and since the study involves human subjects, the survey design was submitted to the University of Georgia's Institutional Review Board (IRB) for review and approval. IRB approval is a required element to ensure the protection of human subjects both by the university and under the US federal law set forth in Title 45 Code of Federal Regulations (CFR) Part 46.[51] A draft of the survey, which included the Informed Consent page, was submitted to the UGA IRB board. The survey demonstrated the language and structure of the questions to be asked as well as how the researcher was protecting the anonymity of the subjects throughout the research process. In addition, the researcher explained how all data would be protected along with potential risks and benefits proposed by the research. The UGA IRB application, survey design, and associated materials were approved on February 2, 2016, with an expiration date of February 1, 2021. The study was given the protocol ID: STUDY00003082.

3.9 Removal of Questions Prior to Survey Distribution

From the results of the focus group study, it was determined that the answers to two questions could be inferred by the researcher, based on the design of the survey and the population recruited for the research study. Therefore, two questions were removed from the final survey. The two questions removed from the survey based on assumptions made about all of the respondents were: 1) all participants were 18 years of age or older, and 2) respondents could read and respond in English. The age requirement was listed on the Informed Consent page. In addition, any person having $\geq$ one year of working with APIs, excipients, and/or drugs, must be 18 years of age or older. It was also inferred that the respondents could read and respond in English. This criterion was inferred because the Informed Consent page and survey were in English. These two questions were removed before any surveys were sent out.

CHAPTER 4

RESULTS

Chapter One provided background information on the concept of current Good Manufacturing Practices (cGMPs) and how the FDA expects Active Pharmaceutical Ingredients to be made. It also introduced the concept of "Atypical Actives." Chapter Two reviewed the literature on "Atypical Actives" and the manufacturing industry's concerns regarding how these ingredients are being made and regulated by the FDA. The second chapter also described the use of formal Guidance Documents that the FDA publishes. The Guidance Documents are used by pharmaceutical manufacturers to understand the FDA's current thinking on specific topics of manufacturing. Chapter Three described the purpose of the study, the research questions, and the procedures used to survey industry professionals about their opinions regarding the manufacture of "Atypical Actives." Chapter Four discussed the results from the survey that answer the research questions introduced in Chapter Three.

4.1 Survey Response Rates

In order to gather the opinions of professionals regarding the cGMP requirements needed to manufacture "Atypical Actives," a survey was submitted to different organizations, individuals, and manufacturers. The organizations included the Consumer Healthcare Products Association (CHPA) and the International Pharmaceutical Excipients Council (IPEC). The researcher also emailed surveys to colleagues and current or previous coworkers who also met

the inclusion criteria. This form of sampling was stratified sampling.[52] Stratified sampling is a form of random sampling in which the population is divided into two or more sub-groups, or strata, according to one or more common attributes. The strata in this study consisted of the following groups: respondents who worked for a member company of IPEC, worked for a member company of CHPA, did not work for members of either organization, or were unsure if they worked for either organization. The common attributes among the four strata were that they all possessed working knowledge of APIs, "Atypical Actives", drug excipients, and/or finished drugs. The number of qualified responses was disproportionate in that an unequal number of responses were received for each stratum. An ideal study with stratified random sampling is considered to be superior to random sampling because the process reduces potential sampling error and purports a greater level of representation. However, due to the unequal number of responses as well as the low response rate, sampling bias may have been introduced into the survey. Due to the potential sampling bias, the results of the study may only be applied to those who responded and may not apply to anyone other than to those who responded.

In addition to these emails, the researcher reached out to other companies identified through the internet as manufacturers of "Atypical Actives." The results of the groups surveyed are discussed in the following paragraphs.

There were three routes utilized to contact potential participants. The first was to contact members of the CHPA and IPEC. Each organization's website displayed a primary contact person's email. Both CHPA and IPEC were contacted via email requesting an email list of their members. Organizational policies prohibited IPEC and CHPA from giving out their member email lists, however, both organizations agreed to forward the researcher's email containing the survey link to their members. In total, there are 94 members of IPEC, and 77 members of CHPA.

The second route was to contact the researcher's current and past coworkers and colleagues, each of whom was sent the same email and survey link that was sent to CHPA and IPEC. The third route to potential participants was through an internet search of companies who manufacture the ingredients found in Table 1. Many of the companies' websites did not have direct contacts to their personnel, but most contained a "Contact Us" tab. Most of these companies' "Contact Us" tabs directed the researcher to a "general inquiry" or "sample request" email box. The same email and survey link was sent to these general mailboxes. However, if a company's website gave specific email addresses of personnel, e.g. Quality Assurance, Regulatory Affairs, and/or Technical Services, then a separate email containing the survey was sent to these personnel.

In total, 368 surveys were emailed between May 10, 2016 and June 20, 2016. The emails included information about the survey as well as a link to the secure survey website which was hosted by http://www.surveymonkey.com. Once participants selected the link they were able to agree to the Informed Consent and complete the instrument online. A request was made in the email asking the respondent to complete the questionnaire within two weeks of receipt, per the IRB approval. Results were sent to the researcher through the Survey Monkey tool in aggregate and anonymous form and were downloaded into the IBM SPSS software program for analysis. Of the 368 requests sent out, 85 responses were returned. This yielded an initial response rate of 23.1%. The first survey was received on May 9, 2016, and the last response returned on June 28, 2016. There were 55 participants who completed the survey (14.9%). However, the inclusion criteria stated that the participant must agree to the Informed Consent clause, and have at least one year of experience working in one or more of the following: the prescription drug (R_x) or over-the-counter (OTC) drug industry, working with Active Pharmaceutical Ingredients (API), and/or working with drug excipients. These requirements excluded ten of the participants

who completed the survey. Of these ten, two did not agree to the Informed Consent, and eight did not meet the experience requisite. Therefore, the completion rate of the "qualified" surveys was 45 out of 368, or 12.2%. The low response and completion rate can likely be attributed to the researcher's attempts to contact companies through the "Contact Us" general email boxes. A majority of these companies' websites did not contain individual employees' email addresses. Another possible reason for the low completion rate is that attempts were made to contact companies residing in countries where the primary language is not English, e.g. India and China. Approximately 40% of all pharmaceuticals are made in Asia, so gathering opinions from manufacturers in these types of countries were considered to be important to the overall study results.[53]

From the request made through the primary contact at CHPA, there were 14 qualified surveys returned, which represented 31.1% of the total response pool. From the request made to IPEC, there were 13 qualified surveys returned, which represented 28.9% of the total response pool. Eight respondents said, "I am not employed by a member company of IPEC, CHPA, or an ingredient manufacturer/ supplier found in Table 1," which represented 17.8% of the total response pool. Finally, there were ten respondents who said, "I am not sure if I am employed by IPEC, CHPA, or an ingredient manufacturer/supplier found in Table 1." The qualified surveys from this group represented 22.2% of the total response pool. Therefore, there were 44 completed and qualified surveys which met the inclusion criteria and used in the data analysis. There was one qualified respondent who stopped the survey after question 13. However, the answers generated for this incomplete survey were incorporated into the final results and conclusions. Specific respondent characteristics from the qualified surveys are presented in the following sections.

4.2 Survey Respondent Characteristics

Of the 45 qualified respondents, 38 had current job titles that reflected a principal focus in Regulatory Affairs or Quality Assurance. The high proportion of participants in these positions is important because these two groups are typically responsible for ensuring that manufacturers' materials and products are safe and effective, and that the public's health is advanced and protected.[54] Regulatory Affairs protects consumers by ensuring compliance with FDA regulations and minimizing the risks associated with those affected products. In addition, RA personnel are also committed to the highest quality of their products to effectively meet consumers' needs. The respondents with Quality Assurance (QA) as a principal job focus are also highly valued. The FDA expects drug manufacturers to have a Quality Assurance Unit that is responsible for monitoring and managing the quality of the facilities, equipment, personnel, methods, practices, testing, records, and controls in order to be in compliance with FDA regulations.[55] The QA group is intentionally separated from the Manufacturing and Operations Departments; essentially QA will not have any conflicts of interest with the personnel engaged in the actual manufacture of the materials or products. Highlighting the importance of the feedback from the respondents working in RA or QA is not intended to minimize the importance of the opinions of the other qualified surveys received. The remaining respondents represented a mix of current occupations which included: General Manager, Physician, Product Development Specialist, Consultant to IPEC Americas as Excipient GMP Subject Matter Expert (SME), Registered Nurse, Product Development Scientist, and Retired. All seven of these professionals also have at least year of experience working with APIs, excipients or drug products, and their results will be tabulated the same as those in RA and QA. Figure 6 presents the diversity of the respondents' occupations:

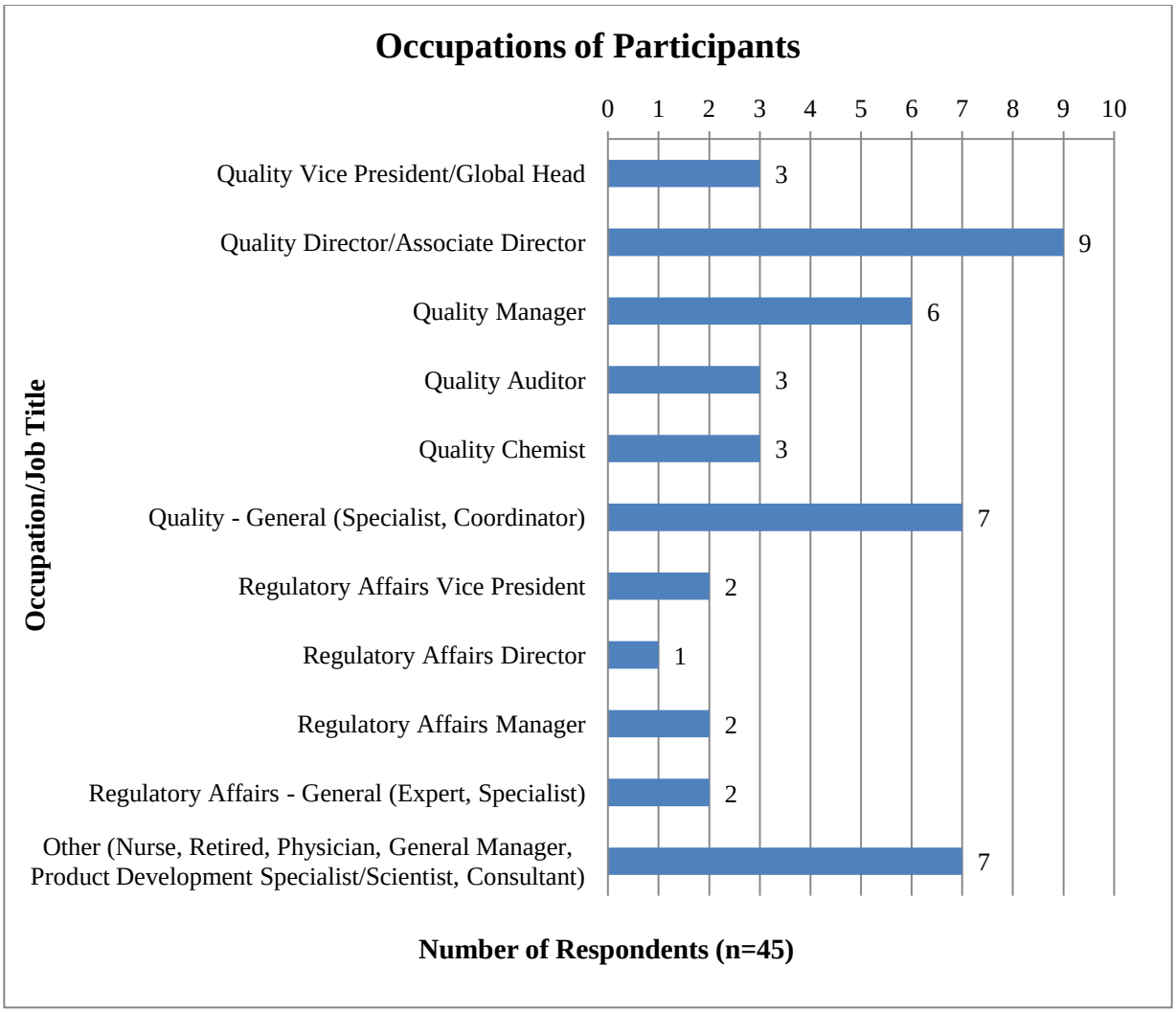

Figure 6: Occupation of Participants

The participants were asked about the number of employees at the companies where they worked; the majority (60%) worked at companies with more than 500 employees (see Figure 7).

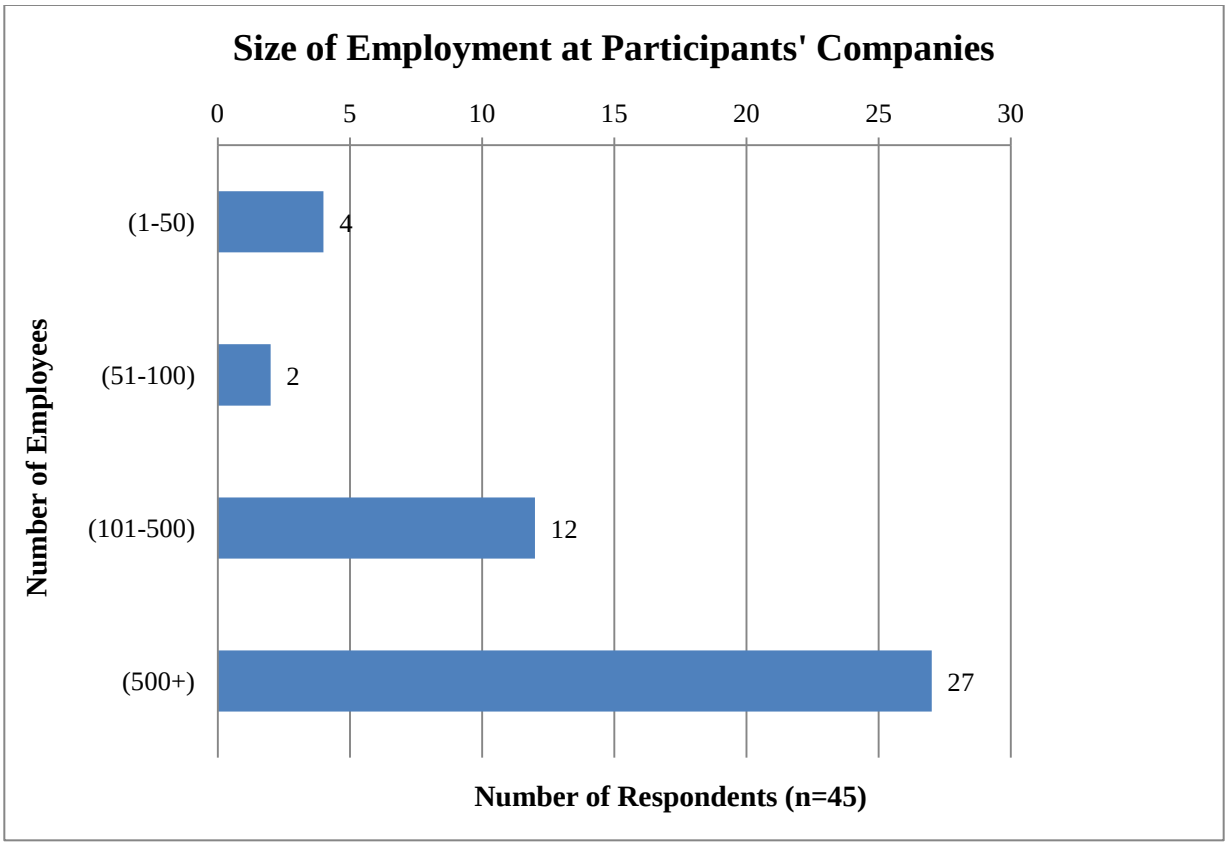

Figure 7: Size of Employment at Participants' Companies

Participants were asked about their experience in the industry working with APIs, Excipients, or drug products (Figure 8). The largest group, 71%, has been working in these industries for at least ten years.

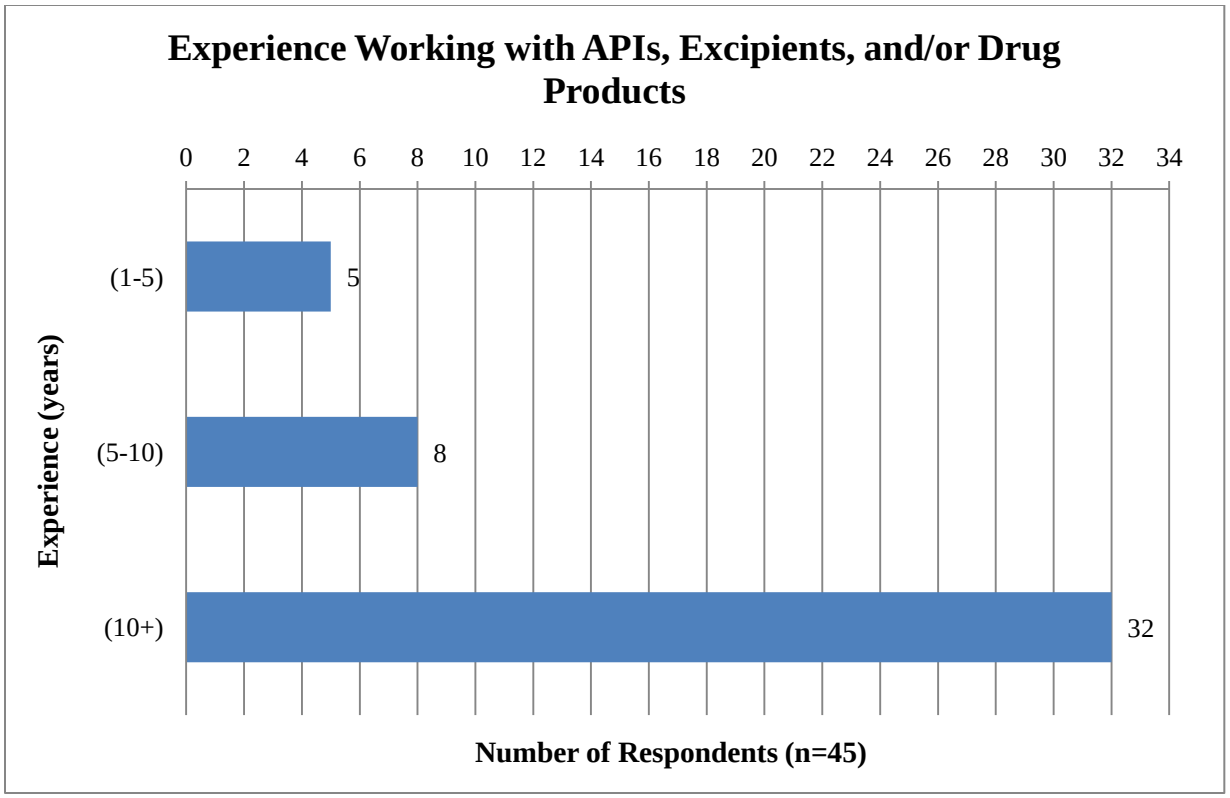

Figure 8: Experience Working with APIs, Excipients, and/or Drug Products

Eighty-nine percent (89%) of the respondents were located in the United States; this includes one in each of the following states: Alabama, California, Arizona, Connecticut, Kentucky, Delaware, Georgia, Illinois, Massachusetts, Michigan, Missouri, North Carolina, Ohio, Pennsylvania, and Virginia. There were two respondents from both Texas and South Carolina, three from both New Jersey and New York, and fifteen from Tennessee. There was also one respondent from each of the following countries: Canada, the United Kingdom, Japan, and Germany. Finally, one participant listed his location as "Retired."

The survey asked the respondents to identify themselves as working for a member company of either CHPA or IPEC. CHPA is the Consumer Healthcare Products Association, representing the manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements.[44] IPEC is the International Pharmaceutical Excipients Council, and is an industry

association involved in developing, implementing, and promoting the use of appropriate standards for pharmaceutical excipients.[43] Figure 9 presents their distribution.

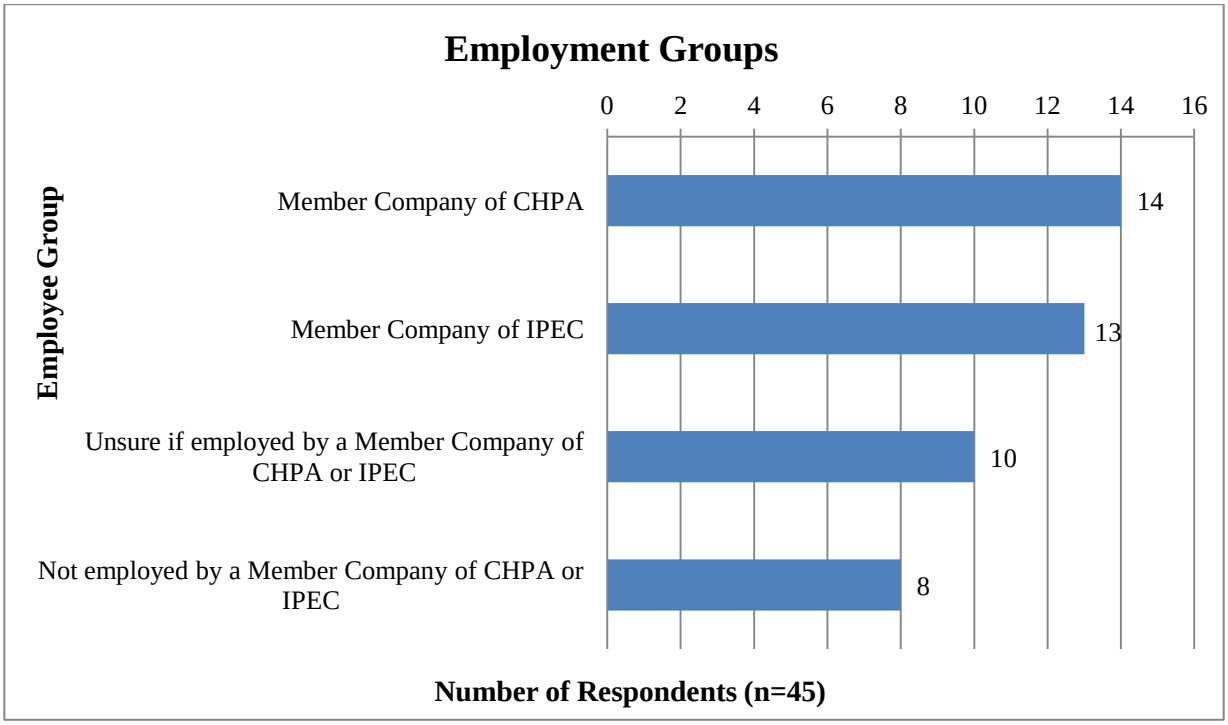

Figure 9: Employment Groups

4.3 Survey Results

The main part of the questionnaire consisted of 20 items, most of which addressed, in one way or another, how tightly the cGMP standards for "Atypical Actives" should be followed. (Several items that did not address this issue directly, and whose scores did not correlate with those of the remaining items, will be discussed separately.)

All of the items were scored on five point Likert scales, from "Strongly Disagree-1 pt." to "Strongly Agree-5 pt." Most of the items were written in such a way that "Strongly Agree" indicates a preference for stricter guidelines and manufacturing standards for "Atypical Actives." However, five of the items were phrased in such a way that "Strongly Agree" meant that lower

standards were acceptable for "Atypical Actives." Therefore, the scores for these questions were "reverse coded", so that a higher score indicated greater agreement with strict adherence to cGMP standards. The phrasing of the questions was developed by the researcher through a review of the literature, and the survey was validated by the focus group. There are no specific reasons for the structure or phrasing of those questions that required reverse coding for the scoring. However, the three focus group members were in agreement that all of the questions were phrased and worded appropriately and clearly for the reader. These are the items that were reverse coded:

(14) "I believe that an Atypical Active manufacturer that has demonstrated a history of stable manufacturing for five or more years should no longer be required to maintain a Process Validation program for the Atypical Active."

(15) "Cleaning Validation should not be required for Atypical Actives manufactured on "dedicated" equipment."

(16) "Cleaning Validation should not be required for Atypical Actives manufactured on "non-dedicated" equipment."

(17) "The FDA should accept a lower level of Good Manufacturing Practices (GMPs) for Atypical Actives than that set by the ICH Q7 if there is a history of five or more years of stable manufacturing data."

(25) "The IPEC/PQG GMP Guide for Pharmaceutical Excipients is an acceptable GMP standard for Atypical Actives."

Questions #14 and #17 ask the reader if cGMP standards should be relaxed if there is a history of five or more years of stable manufacturing data on file. A stable manufacturing process is achieved through consistent results and product yield over a timeframe, for example

five years.[56] A Quality or Process Engineer performs process capability and process output studies to determine the performance or stability of the process.

Although all of the items address the issue of high standards, they can be divided into two broad clusters that appear to be potentially distinct; therefore, the items were grouped into two sub-scales. The first sub-scale, called "Guidance8," addresses the issue of how tightly cGMPs should be followed for "Atypical Actives" when compared to the ICH Q7 Guidance. It consists of the following eight items:

Guidance8

(7) The ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Ingestibles."

(8) The ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Ophthalmics."

(9) ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Oral."

(10) ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "External Analgesics."

(11) ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Intravenous."

(23) The ICH Q7 GMPs should be followed for Atypical Actives used in prescription drugs.

(24) The ICH Q7 GMPs should be followed for Atypical Actives used in over-the-counter (OTC) drugs.

(25) The IPEC/PQG GMP Guide for Pharmaceutical Excipients is an acceptable GMP standard for Atypical Actives.

The second sub-scale, called Manufacturing7, addresses the issue of the level of controls needed to manufacture "Atypical Actives." It consists of the following seven items:

Manufacturing7

(13) I believe that a new Atypical Active process should require successful completion of three consecutive manufacturing batches for the process to be validated.

(14) I believe that an Atypical Active manufacturer that has demonstrated a history of stable manufacturing for five or more years should no longer be required to maintain a Process Validation program for the Atypical Active.

(15) Cleaning Validation should not be required for Atypical Actives manufactured on "dedicated" equipment.

(16) Cleaning Validation should not be required for Atypical Actives manufactured on "non-dedicated" equipment.

(17) The FDA should accept a lower level of Good Manufacturing Practices (GMPs) for Atypical Actives than that set by the ICH Q7 if there is a history of five or more years of stable manufacturing data.

(21) An on-going stability testing program should be in place for Atypical Actives.

(22) I believe that impurity profiles should be required for Atypical Actives.

A third scale was also developed to capture a comprehensive set of data, which combined the 15 total from each of the sub-scales, Guidance8 and Manufacturing7. This third scale was entitled "Whole_Scale". All of the scales were created by adding the scores for each item and dividing by the number of items in each scale. By constructing the scales in this manner, it was possible to compare scores on all three scales; even though one contains seven items, another

contains eight items, and the Whole_Scale contains fifteen items. This way of constructing scales also makes it possible to analyze the scores of respondents who do not answer every question.

Each of the scales was tested for inter-question reliability, as measured by Cronbach's alpha. The closer alpha is to 1.00, the greater the internal consistency of the questions being measured.[57] For survey research, the conventional standard for acceptable reliability is alpha ≥ 0.70.[58] Both sub-scales, and the Whole_Scale, meet this standard.

Table 3: Inter-item Reliability

Scale	Cronbach's alpha
Guidance8 = [Q7,8,9,10,11,23,24,25]	0.926
Manufacturing7 = [Q13,14,15,16,17,21,22]	0.704
Whole_Scale = [Q7,8,9,10,11,13,14,15,16,17,21,22,23,24,25]	0.904

Table 4 presents the descriptive statistics for each of the scales. Note: one respondent stopped after answering questions 7-11 in the Guidance8 scale.

Table 4: Scale Descriptive Statistics

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Guidance8	45	1.00	5.00	3.5694	.99842
Manufacturing7	44	1.71	4.57	3.5000	.78094
Whole_Scale	45	1.60	4.73	3.5215	.84103
Valid N (listwise)	44				

As noted above, respondents were divided into four groups:

1) Member of CHPA (N=14)
2) Member of IPEC (N=13)
3) Not employed by either group (N=8)
4) Unsure if they are employed by either group (N=10).

As seen in Figure 10 and Table 5, the mean values for all three scales are lower for Group 2 (IPEC) than for Groups 1, 3, and 4. For the sub-scale Guidance8, Group 2 has a mean value of 2.75, while the other three groups have mean values that are above 3.5. For the sub-scale Manufacturing7, Group 2 has a mean value of 3.0, while the other three groups have mean values above 3.5. For the Whole Scale, Group 2 has a mean value of 2.8, while the other groups have mean values greater than 3.5. In short, on both sub-scales and on the Whole Scale, members of IPEC (Group 2) advocate a more relaxed adherence to guidelines and manufacturing standards than do members of the other groups. The IPEC members may feel that due to a history of stable manufacturing, that "Atypical Actives" are just as safe and effective with the lower cGMP standards.

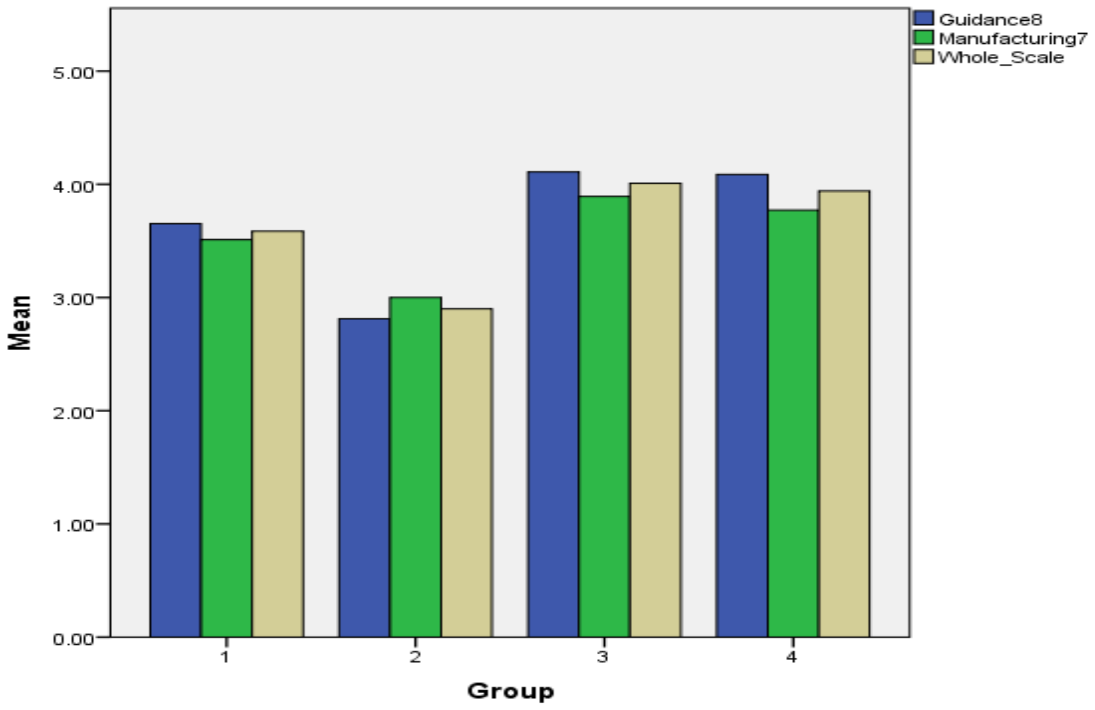

Figure 10: Bar Graph of Individual Groups

Table 5: Descriptive Statistics for Individual Groups

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Guidance8	1	14	3.6518	.75348	.20138	3.2167	4.0868	2.38	4.75
	2	13	2.7500	1.07771	.29890	2.0987	3.4013	1.00	4.50
	3	8	4.1094	.76309	.26979	3.4714	4.7473	2.75	5.00
	4	10	4.0875	.71698	.22673	3.5746	4.6004	2.38	4.75
	Total	45	3.5694	.99842	.14884	3.2695	3.8694	1.00	5.00
Manufacturing7	1	14	3.5102	.69696	.18627	3.1078	3.9126	2.57	4.57
	2	12	3.0000	.90556	.26141	2.4246	3.5754	1.71	4.43
	3	8	3.8929	.63315	.22385	3.3635	4.4222	2.71	4.57
	4	10	3.7714	.58786	.18590	3.3509	4.1920	2.86	4.57
	Total	44	3.5000	.78094	.11773	3.2626	3.7374	1.71	4.57
Whole_Scale	1	14	3.5857	.64007	.17107	3.2161	3.9553	2.80	4.67
	2	13	2.8308	.93754	.26003	2.2642	3.3973	1.60	4.47
	3	8	4.0083	.68493	.24216	3.4357	4.5809	3.00	4.73
	4	10	3.9400	.47811	.15119	3.5980	4.2820	3.07	4.53
	Total	45	3.5215	.84103	.12537	3.2688	3.7742	1.60	4.73

To test whether the differences among these group means were statistically significant, a one-way analysis of variance was conducted. The analysis indicated that differences in group means for the Manufacturing sub-scale was statistically significant at $p < .05$, and that the differences in group means for the Guidance sub-scale, and the Whole Scale, were significant at $p = .001$. This means that it is unlikely that these differences in group means could have occurred by chance alone, and that therefore, similar differences to those found in this sample would also be found in the larger population from which this sample was drawn.[50]

Table 6: ANOVA for Scales

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Guidance8	Between Groups	13.840	3	4.613	6.301	.001
	Within Groups	30.021	41	.732		
	Total	43.861	44			
Manufacturing7	Between Groups	4.973	3	1.658	3.120	.037
	Within Groups	21.252	40	.531		
	Total	26.224	43			
Whole_Scale	Between Groups	9.908	3	3.303	6.382	.001
	Within Groups	21.215	41	.517		
	Total	31.123	44			

The next set of results concerns five questions on the survey were independent of the grouped scales, that is, questions 12, 18-20, and 26. These questions addressed various aspects of the relationship between the finished drug manufacturers and "Atypical Active" manufacturers. The differences in group means are interesting; however, given the fact that these are individual items rather than scales, the differences in group means are not statistically significant.

Participants were asked if they believe a Quality Agreement should be in place between an "Atypical Active" manufacturer and a finished drug manufacturer. Quality Agreements are not currently required by the FDA; however a Quality Agreement may serve as a legally binding contract which outlines the specific cGMP standard to which the "Atypical Active" should be manufactured. The mean score for all respondents was 4.40, which indicates a high degree of agreement that Quality Agreements should be in place. Members of IPEC had the lowest score, with a mean of 4.17. Table 7 gives the descriptive statistics for all four groups.

Table 7: Quality Agreements between Drug and Atypical Active Manufacturer

Group	N	Mean
1 (CHPA)	14	4.29
2 (IPEC)	12	4.17
3 (Not employed by member company of CHPA or IPEC)	8	4.63
4 (Unsure if employed by member company of CHPA or IPEC)	10	4.50
TOTAL	44	4.40

Participants were asked if they believe the FDA should publish a freestanding Guidance Document for the cGMPs of "Atypical Actives." Guidance Documents are the vehicle the FDA uses to convey their current thinking on specific regulatory subjects, including Good Manufacturing Practices. The mean of the forty-four respondents was 4.18, which again indicates a high level of agreement that a Guidance Document would be useful. Members of CHPA had the lowest mean score at 3.71. Table 8 gives the descriptive statistics for all groups.

Table 8: Guidance Document for "Atypical Active" cGMPs

Group	N	Mean
1 (CHPA)	14	3.71
2 (IPEC)	12	4.17
3 (Not employed by member company of CHPA or IPEC)	8	4.50
4 (Unsure if employed by member company of CHPA or IPEC)	10	4.60
TOTAL	44	4.18

Participants were asked if they believe that when an "Atypical Active" passes all of the requirements in a testing specification, then the level of cGMPs are not important. Testing specifications are the mechanism typically used to release an ingredient or drug product to a customer or to market. The overall mean score on this question was 1.66, which means that most participants disagreed that testing results could replace cGMPs. It should be noted that this question is phrased in the opposite direction from the others: a high score indicates agreement that looser standards would be acceptable, a low score indicates a preference for tighter standards. Members of CHPA had the highest score at 2.07. Table 9 gives the descriptive statistics for all groups.

Table 9: Testing Specifications take place of cGMPs

Group	N	Mean
1 (CHPA)	14	2.07
2 (IPEC)	12	1.50
3 (Not employed by member company of CHPA or IPEC)	8	1.50
4 (Unsure if employed by member company of CHPA or IPEC)	10	1.40
TOTAL	44	1.66

Participants were asked that if manufacturers of "Atypical Actives" are required to maintain the ICH Q7 cGMP standard and it raises their cost of manufacturing, should there be a price increase to sell the "Atypical Active." As cGMP controls are increased in a manufacturing environment, the costs associated would increase. The mean score of all respondents was 3.86, with IPEC having the highest score of the groups at 4.67. That is, members of IPEC were more likely than others to agree that increased manufacturing costs should be passed along to the finished drug manufacturers. Table 10 gives the descriptive statistics:

Table 10: Increased Cost of Manufacturing for cGMPs

Group	N	Mean
1 (CHPA)	14	3.64
2 (IPEC)	12	4.67
3 (Not employed by member company of CHPA or IPEC)	8	3.25
4 (Unsure if employed by member company of CHPA or IPEC)	10	3.70
TOTAL	44	3.86

Participants were asked that if they believe if it is the responsibility of the finished drug manufacturer – not the manufacturer of the "Atypical Active" – to ensure the "Atypical Active" manufacturer is complying with cGMPs. The "Atypical Active" manufacturer may not be aware of how the ingredient is being used in the drug product if not directed by the drug manufacturer, that is, as an active or an excipient. The mean score of all respondents was 2.52, with IPEC having the highest score at 3.33. That is, IPEC members were the most likely to agree that responsibility for compliance with standards should rest with manufacturers of the finished drugs rather than manufacturers of the ingredients. Table 11 gives the descriptive statistics:

Table 11: Responsibility of Drug Manufacturer for cGMPs of "Atypical Active"

Group	N	Mean
1 (CHPA)	14	2.43
2 (IPEC)	12	3.33
3 (Not employed by member company of CHPA or IPEC)	8	1.88
4 (Unsure if employed by member company of CHPA or IPEC)	10	2.20
TOTAL	44	2.52

The last section of the survey offered respondents an opportunity to comment on the issues and offer suggestions. All but one of the commentators had at least ten years' experience in the industry. To provide some context for their remarks, Table 12 describes the groups to which the commentators belong (1=CHPA, 2=IPEC, 3=Not employed by CHPA or IPEC, and 4=Unsure if employed by CHPA or IPEC member).

Table 12: General Comments about cGMPs for "Atypical Actives"

Group	General Comments
4	"I think it is important to consider the intended use of the atypical active. For instance, if menthol is a flavoring ingredient, it should not require validation like an API would. However, if it is intended to be the active ingredient, it should require validation of the manufacturing process."
1	"Atypical active ingredients carry different levels of risk based on the application. In theory, strong quality systems should be designed to ensure consistent quality standards are defined and meet. Removal or lowering of standards or requirement lends itself to downstream risks to the manufacturer who assumes the majority of the risk currently."
1	"Each material must be studied individually for its manufacturing process, likely impurities, application as a drug ingredient etc. and have a commensurate USP monograph."
1	"Some regulation of basic GMPs is required but not to the level of ICH Q7. Atypical Actives in my experience have a long history of safe usage. Some atypical actives are commodities on the world market and stiff requirements would cause the manufacturers to discontinue sales to the pharma industry."
2	"The EXCiPACT and ANSI NSF/IPEC/363 GMP standards incorporate risk assessment and mitigation requirements that make them perfectly acceptable and sufficient for Atypical Actives. ICH Q7 is inappropriate for Atypical Actives. Excipients like Ethanol, Potassium Citrate, sorbitol, etc. are made in large plants for economy of scale with the primary market being food. FSMA and 21CFR117 already ensure the products are safe for direct use by the patient in regards to Biological, Physical and Chemical Hazards but lack the controls for quality to ensure functionality. The IPEC GMPs and related certification GMP standards (EXCiPACT and ANSI) provide the quality aspect in addition to the risk mitigation controls in food. IPEC GMPs are sufficient for Atypical Actives."
3	"Atypical Actives should be held to a higher standard than plain APIs."
2	"IPEC GMP provides a minimum basis for excipient GMP. Atypical actives require this as a minimum but elements of ICH Q7 have to be performed in addition. For Question 26: in case the drug product manufacturer uses the atypical API in consent with the API manufacturer the API manufacturer will be held responsible for complying with GMPs for APIs. That is why a guidance on authority's expectation on GMPs for atypical actives is required. Otherwise, manufacturers of atypical API might consider stopping supply to drug product manufacturers that uses the products as atypical APIs. A risk

Group	General Comments
	based concept of appropriate GMPs to be defined by the DP manufacturer on basis of IPEC / Excipact / ANSI GMPs with additional Q7 elements might be a solution."
4	"I believe the customer expects a high level of safety when consuming or applying a drug product therefore it is the responsibility of the manufacturers to ensure the customers' expectations are met no matter cost or time. To me, it is the pure form of definition of purpose for a quality department."
1	"For #26, both the API and FG manufacturers should be responsible for GMPs."
2	"The legal position is clear: there is no such thing in law as an Atypical Active (I reply therefore in accordance with my understanding of US law). But these materials do exist, industry is not compliant and the FDA is not enforcing the law so there is a problem. So I respond to those questions that propose solutions (noting the Agency cannot accept them without a legal mandate)."
3	"I have not kept up with the literature."
3	"All medications should be monitored and tested for purity. Medications are already so over-priced, that an increase cost of testing should not increase the price."
1	"I think it should be regulated to a degree...many excipients manufacturers choose not to follow any guides such as IPEC/PQG which forces companies to create a Quality Agreement forcing some type of guidance for the supplier."
2	"Makers of Atypical Active should formally agree to application including route of administration. User of Atypical Active should assess that appropriate GMPs are in place and require notification of significant changes."
2	"As stated, many atypical actives are used in dozens of ingestible applications with a long history of safe use. The regulations impacting these items should be relaxed."

4.4 Limitations

There were several limitations involved in a study of this type which were identified after the study had commenced. The first is identifying and contacting specific individuals to take part

in the study. The researcher reached out to several organizations that were identified to be ideal candidates for the study in order to obtain specific email listings for their members. The organizations contacted requesting email lists were: CHPA, IPEC, and SOCMA. This was determined to be a challenge because none of the organizations' policies allowed them to give out email addresses to the public. However, CHPA and IPEC were very helpful in stating that they would distribute the survey internally to each of their members. SOCMA responded that they did not have an email list of their members and encouraged the researcher to contact their members through each company's website.

There were other limitations identified in this study. The study proposal stated that 86 respondents would be required to complete the study; however due to a low response rate of 12.2%, there were only 44 qualified and completed surveys. This is a limitation in the study and therefore the data set may not be representative of the entire sample population, only those who participated in the research.

Only people contacted through email participated; therefore if it was against their company's policy to fill out surveys, then these companies were eliminated from possible participation. Emails were only sent to individuals and company websites that were part of IPEC, CHPA, and/or were identified as manufacturers of ingredients listed in Table 1. This also eliminated potential participants who do not have email addresses or have access to email.

4.5 Disadvantages

The study was conducted in an online setting which introduced the following potentials for bias:

- The survey was not structured to limit a participant from taking it more than once; therefore the honesty of the respondent was critical to the outcome of the study.
- The participants may have been overwhelmed by the study and did not take the time to fully read and digest each question, possibly why one respondent stopped the survey after the 11th question.

There is also a chance that the respondents were not familiar with the concepts of Atypical Actives, which led to a possible disadvantage in taking the study. However, knowing the concepts of Atypical Actives was not a prerequisite for the survey. Since there was no interaction between the researcher and the respondent, other than the email requests for the survey, there were no other communication links to ask for clarification if needed, which was also a disadvantage or limitation in this research.

4.6 Disclosure

The researcher declares no post-study conflicts of interest or financial interests included in this study, including any grants, employment, gifts, or stocks. All funding associated with the survey software, Survey Monkey, and the researcher's statistician was privately funded by the researcher.

4.7 Response Rate and Interim Analysis

During the course of the study, the response rate was less than expected or anticipated based on previous survey studies of this type and the proposed sample size of N=86. With a sample size of N=45 for qualified respondents, the researcher made a decision to perform interim analysis on the current data set at that time. The interim analysis indicated a statistically

significant difference in the group means for the developed scales at $p = 0.001$. Therefore, it was determined by the researcher and the thesis committee that the data set was sufficient to close the study. However, the researcher post hoc recognized other ways to improve the respondent pool and expand the sample size. The professional online networking website, LinkedIn contains groups affiliated with IPEC and CHPA.[59] In addition, LinkedIn contains a "message" button in which an individual may be reached directly. This could potentially solve the hurdle the researcher faced while attempting to reach respondents through the company websites.

CHAPTER FIVE

DISCUSSION AND CONCLUSION

The intent of this chapter is to summarize and discuss the findings of the study, draw conclusions from the results, and give recommendations for future policies and research directives. The first section presents information on the reliability and validity of the survey instrument, as well as an interpretation of the scoring system. The next section summarized the key findings, and evaluated the respondents' opinions of higher standards versus lower standards for "Atypical Actives". This section will also discuss the respondents' opinions for those questions unrelated to "higher vs. lower" standards. The third section detailed the limitations, disadvantages, disclosures, and future research implications identified by the researcher. The last section drew conclusions to close out the report.

The primary purpose of the study was to assess professionals' opinions experienced in the excipient, Active Pharmaceutical Ingredients (API), and drug industries, regarding the cGMP requirements to manufacture "Atypical Actives". While "Atypical Actives" are generally viewed as relatively safe and effective with low public risk, these materials are categorized as Active Pharmaceutical Ingredients (API) when claimed as active drug substances in over-the-counter (OTC) and prescription (R_x) drugs. If an ingredient is claimed as an active drug substance, the FDA expects materials to be manufactured to a level of cGMPs in the ICH Q7 Guidance or an equivalent standard. To the knowledge of the researcher, this is the first study of its kind investigating the viewpoints of the manufacturing industry about "Atypical Actives". Therefore

this was an opportunity look at the topic through a review of literature analysis and an online survey.

5.1 Instrument Validity and Reliability

The questions in the survey used to measure the study objectives and research questions had satisfactory face validity which was evaluated by the focus group. The combination of the satisfactory face validity and acceptable Cronbach's alpha values calculated from the questions in the survey scales, supports the reliability of the survey instrument; however due to the small sample size, the data set may not be representative of the entire sample population and only represents the opinions of those who participated in the research.

The questions in the survey were scored based on the answers given by the respondents. There were five options to choose from for questions 7-26: "Strongly Disagree", "Moderately Disagree", "Neither Agree nor Disagree", "Moderately Agree", or "Strongly Agree". Each of the selections was coded on a scale of 1 to 5, i.e. "Strongly Disagree" to "Strongly Agree". If the respondent chose "Neither Agree or Disagree", the question was scored as a '3'. To interpret the scoring metrics, scores for individual responses and group means above '3' meant that the individual or group was in favor of higher cGMP standards for "Atypical Actives". If the score for a question or group mean was below '3', the individual or group was in favor of lower cGMP standards for "Atypical Actives". The answers for questions 12, 18, 19, 20, and 26 did not apply to this logic and will be discussed separately.

5.2 Higher vs. Lower Standards

In order to thoroughly examine the opinions of industry professionals, the researcher divided the results of the survey into three scales that were sub-topics of similar themes which address previous areas of concern about "Atypical Actives" identified in the Literature Review. Therefore, the three scales were created for 15 of the 20 total questions with a general theme of "higher vs. lower" standards. The first scale was entitled "Guidance8" and contained eight questions. The questions in this first scale addressed the following sub-topics: the required standards based on risks involved with categories or routes of administration of the "Atypical Active" (i.e. ingestible, ophthalmic, oral, external analgesic, intravenous), secondly the level of standards based on the type of finished drug the "Atypical Active" is used (i.e. prescription (R_x) vs. over-the-counter (OTC)), and thirdly would the IPEC/PQG cGMP Guidance (less stringent cGMP standard) be adequate to adhere to manufacture "Atypical Actives". As a whole for all respondents, the first scale generated a mean score of 3.57, thus indicating that the manufacturing industry "Moderately Agrees" that ICH Q7 should be used for "Atypical Actives". However, a disparity was identified when the individual groups were examined (i.e. employed by a member company of CHPA-Group 1, employed by a member company of IPEC-Group 2, Not employed by a member company of CHPA or IPEC-Group 3, or Unsure if employed by a member company of CHPA or IPEC-Group 4). The respondents from Group 2 garnered a mean score of 2.75 for this scale, signifying a consensus that the respondents who represent the Excipients and "Atypical Active" manufacturers lean towards "Moderately Disagrees" with the questions in the first scale. In particular, for the question asking about the IPEC cGMP Guidance being used in place of ICH Q7, the mean score was 4.42 for Group 2, which leans heavily towards "Moderately to Strongly Agree". The other three groups answered

that ICH Q7 (higher standards) should be applied for these sub-topics, with scores of: Group 1 – 3.65, Group 3 – 4.11, and Group 4 – 4.09.

The second scale was entitled "Manufacturing7"and consisted of seven questions. For this second scale, respondents were asked questions about the levels of manufacturing requirements needed for "Atypical Actives". The content of the questions were modeled after the sections of the ICH Q7 relating to the following sub-topics, and if they should be required for "Atypical Actives": Process Validation, lower or higher standards if there is a history of stable manufacturing, Cleaning Validation, a Stability program, and Impurity Profiles. As a whole for all respondents, a mean score of 3.50 was generated, thus indicating that the industry "Moderately Agrees" or leans more towards higher standards for these sub-topics. However, conversely, Group 2, yielded a mean score of 3.00, representing a neutral stance overall, that is "Neither Agrees or Disagrees". The other three groups yielded similar scores as the first scale: Group 1 – 3.51, Group 3 – 3.89, and Group 4 – 3.77. In order to draw conclusions from this set of data, the researcher looked at the results of the individual questions in this scale to identify if there were any differences among the groups. There were two questions that yielded results differentiating Group 2 from the other groups. For question 13, the respondents were asked if Process Validation should be required on three consecutive manufacturing batches. The results were similar for all groups in that the higher standard was preferred, i.e. Group 1 – 3.93, Group 2 – 3.93, Group 3 – 4.50, and Group 4 – 4.19. However, in contrast, question 14 asked if Process Validation should be required if the "Atypical Active" has a history of five or more years of stable manufacturing data. The results to this question were meaningfully different, i.e. Group 1 – 3.79, *Group 2 – 2.67*, Group 3 – 3.25, and Group 4 – 3.63. A similar concept was asked in question 17, that if higher standards should be required (ICH Q7) if there is a history of five or

more years of stable manufacturing data for "Atypical Actives". The results were again very different, i.e. Group 1 – 3.36, *Group 2 – 1.58*, Group 3 – 3.00, and Group 4 - 3.10. The main take away from this second scale is Group 2 believes the standards may be relaxed when there is historical data showing a trend of stable manufacturing, for example five or more years of data. In contrast, the other groups "Moderately Agree" that the ICH Q7 higher standard should be applied despite what historical manufacturing data is on file.

The third scale combined scales 1 and 2 (Guidance8 and Manufacturing7) and was labeled as "Whole_Scale". The Whole_Scale provided a broad perspective of the overall viewpoints in regards to "higher vs. lower" standards for "Atypical Actives". The mean scores from the Whole_Scale correlate with the results found in scales 1 and 2: Group 1 – 3.59, Group 2 - 2.83, Group 3 – 4.01, and Group 4 – 3.94. In addition, the results in all three scales were proven to be statistically significant at the $p < 0.05$ level ($p = 0.001$ for scale 1, $p = 0.04$ for scale 2, $p = 0.001$ for scale 3).

This section will discuss the possible reasons there were significant differences in opinions, especially for Group 2, whose respondents represent the excipient and "Atypical Active" manufacturers. There may be several explanations of why Group 2 believes lower standards are acceptable to manufacture "Atypical Actives". First, those in Group 2 who are employed by IPEC member companies may work more closely with "Atypical Actives" in their day-to-day responsibilities as opposed to the other respondents. Therefore, they may be more "exposed" to the current environment of "Atypical Active" manufacturing. After all, the chemicals that are being used as "Atypical Actives" are typically used as excipients and for other industrial purposes, such as usage in petrochemicals, foods, and plastics.[25] The materials are produced in large bulk vessels, and were initially created for use as inactive ingredients in drugs, not active

ingredients. Since the majority of these ingredients are sold for other purposes, the manufacturers have little incentive to comply with ICH Q7; it would require drastic upgrades to their facilities. Secondly, IPEC represents the excipient manufacturers, whereas CHPA represents the OTC finished drug manufacturers; so the scope and expectations from a business perspective may be different for each group. The CHPA respondents are typically involved with the end use of the "Atypical Active" along with many other components of the drug, such as the inactive ingredients, packaging materials (e.g. containers, closures), and artwork and design of the package. They may feel that the most important part of that finished product is the active ingredient itself, since active ingredient is the foundation for the major claims they are making for selling the product, that is that it may be used in the diagnosis, cure, mitigation, treatment, or prevention of a disease or to affect the structure and function of the body.[5] Therefore, finished drug makers would expect their active ingredients meet the highest standards of cGMPs. As for the other respondents who did not identify with either working for a member company of IPEC or CHPA, offered the same opinions as Group 1 – CHPA members, in that higher standards should be required to manufacture "Atypical Actives". This is an indication that these respondents view active ingredients in drugs should be manufactured according to the ICH Q7 Guidance, regardless of whether they are for an OTC or R_x.

The opinions of the researcher for cGMP adherence vary in comparison to the results found for this set of data for each of the groups. For the questions regarding risk and manufacturing, i.e. questions found in Scales Guidance8 and Manufacturing7, there should be a risk based approach conducted for these "Atypical Actives" to determine the adequate cGMPs. "Atypical Actives" carry different levels of risk and therefore the intended use needs to be examined. For example, "Atypical Actives" for use as an external analgesic, e.g. Salicylic acid

used in a cream, the IPEC/PQG cGMP Guidance may be acceptable with elements of ICH Q7 applied. For example, if a manufacturer of Salicylic acid (topical powder) shows stable manufacturing data over a timeframe, such as five years, then a Process Validation Program would not be necessary. There is historical data to verify the material has been manufactured successfully. However, ICH Q7 states that an ongoing stability program needs to ensure the API maintains its strength, quality, and purity over time. In this case, a stability program would need to be implemented and maintained for Salicylic acid to ensure it retains the properties it purports. On the other hand, an "Atypical Active" such as Mannitol (intravenous), would need to require full ICH Q7 cGMPs due to the risk it carries. A robust Process Validation Program would be required to manufacture these higher risk materials. Quality, safety, and efficacy should be built into a product through Process Validation, and so quality cannot be competently assessed by in-process or finished product testing alone. Process Validation ensures that each step of the manufacturing process is controlled so that the entire batch of material meets it specifications. For example, part of a failing batch of Mannitol, which would be used as an injection, would cause a lot more harm to a patient as opposed to part of a failing batch of topical cream containing Salicylic acid.

5.3 Quality Agreements

Other results gathered from this study are that most respondents agree that a Quality Agreement should be in place between an "Atypical Active" manufacturer and finished drug manufacturer (total mean 4.40 = "Moderately Agree"). Interestingly, only one of the 44 responses to this question was "Moderately Disagree" and only five responses were "Neither Agree or Disagree". This means that 86.7% of the respondents are in favor of needing a Quality

Agreement between the "Atypical Active" and finished drug manufacturers. Quality Agreements are legally binding documents that are mutually agreed upon and signed between the two parties.[60] Implementing a Quality Agreement is a pragmatic approach to close any cGMP gaps that may be identified when the "Atypical Active" is being evaluated for use. It creates a mutual understanding of the quality and regulatory requirements needed for material supply to the drug manufacturer. A Quality Agreement may reduce or eliminate unseen cost issues that may arise unexpectedly from miscommunication or ad hoc more demanding cGMP requirements.

A Quality Agreement between an "Atypical Active" manufacturer and finished drug manufacturer is important to have in place to define the quality of the material. All roles and responsibilities for both parties should be defined within the Quality Agreement. The cGMP elements to include in the Quality Agreement may be approached from a risk based perspective, but must be agreed upon by all signing entities. First, the "Atypical Active" manufacturer needs to state if the equipment used to manufacture the ingredient is dedicated to the system or if other materials are manufactured on the same equipment. If the equipment is dedicated, there is less possibility of contamination, or carryover, from previous manufacturing batches of other materials. This contamination typically occurs in non-dedicated equipment. If the equipment is non-dedicated, then the Quality Agreement needs to define the cleaning procedures that will remove any previous raw materials and any solvents that are used in the process. The FDA expects all drug manufacturers to have written procedures in place on how cleaning processes will be validated.[61] In addition, the Quality Agreement needs to define how the stability of the material will be verified and maintained. For example, if an "Atypical Active" manufacturer has historical data showing the material is stable for two years and is still in specification, then this

may be evidence to not require an ongoing stability program. Ongoing stability programs are defined in section 11.5 of the ICH Q7 Guidance as "A documented, on-going testing program should be designed to monitor the stability characteristics of APIs". Lastly, regardless of whether the "Atypical Active" is manufactured in small scale vessels or in large continuously processing vessels, or is considered high or low risk, all impurities should be removed through the cleaning process. Impurities in a manufacturing process are classified as organic impurities, inorganic impurities, and residual solvents. The basic tenet for removing impurities in APIs is that all impurities must be controlled throughout the development and routine manufacture to ensure the safety and quality of the API is maintained throughout its use in a drug product.[62] Therefore, control of impurities should be listed in the Quality Agreement.

However, some finished drug manufacturers may not find value in Quality Agreements with "Atypical Active" manufacturers, if they feel that the controls in place are adequate to ensure the safety, quality, and efficacy of the material. For example, finished drug manufacturers may perform onsite audits of their "Atypical Active" manufacturers, getting a first-hand view of the cGMPs being performed. In addition, finished drug manufacturers may increase the testing requirements on incoming "Atypical Actives". 21 CFR 211 states that a finished drug manufacturer may accept a raw material based on the Certificate of Analysis, as long as one identification test is performed with each incoming receipt of the raw material.[63] In lieu of only performing an identification test, the drug manufacturer may perform assay and impurities' testing.

5.4 FDA Guidance Documents

A challenge API and drug manufacturers face is interpreting the FDA regulations. To mediate this challenge, the FDA releases Guidance Documents.[64] Guidance Documents represent the FDA's current thinking on a topic. While these documents are not legally binding, they serve as a tool manufacturers may use to increase compliance in their operations. The results from the survey show that the respondents are in favor of FDA creating a Guidance Document to address their current thinking of how to apply cGMPs for manufacturing "Atypical Actives" (mean score for all respondents 4.18 = "Moderately Agree"). The drug industry has been calling for the FDA to draft a Guidance on the topic since 2011.[11] However, delays in releasing FDA Guidances are not uncommon. For example, it took the FDA three years to finalize a Guidance Document on the topic of Biosimilarity after the draft was released in 2012.[65] If the FDA would at least release a draft Guidance for "Atypical Actives", it would provide the clarification needed for manufacturers to develop strategies to meet the expectations of the Guidance.

To approach the FDA and propose a draft Guidance regarding cGMP compliance for "Atypical Actives", the following question should be answered: why is there a need for a Guidance when the FDA's current thinking is ICH Q7 for any ingredient used as an API? One answer may contain the following rationale: "typical" APIs are manufactured in small scale batches that were designed to be used as an APIs and therefore in alignment with ICH Q7; whereas "Atypical Actives" are typically manufactured in large continuous production vessels. This makes it very challenging for the "Atypical Active" manufacturer to comply with all facets of the ICH Q7. In addition, the costs applied to maintaining ICH Q7 are rarely justified from a business perspective due to limited profit margins and the main usage in other non-pharmaceutical applications. The fallout may be a financial impact to customers if the "Atypical

Active" manufacturers are required to upgrade their facilities to meet ICH Q7. A Draft Guidance from the FDA would solve a lot of transparency issues seen from the manufacturing industry.

5.5 Testing Specifications

In the FDA Guidance on the Quality Systems Approach for Pharmaceutical cGMP Regulations, a statement reads "Quality should be built into the product, and testing alone cannot be relied upon to ensure product quality".[66] The respondents were asked if meeting the results of a testing specification could replace cGMPs. The results were uniform, with a consensus opinion that testing could not take the place of cGMPs for "Atypical Actives" (mean score of 1.66 = "Moderately to Strongly Disagree"). In fact, only two respondents answered the question as "Moderately Agree" that testing could replace cGMPs (4.5%). This likely outcome is that it is widely practiced that testing is not performed on 100% of a batch of manufactured material or product, only a small portion of the batch is tested, e.g. beginning, middle, end. Therefore, proper cGMPs act as controls to ensure that the beginning, all the way to the end, of a manufacturing batch is both safe and effective. CGMPs do not describe how work is to be performed, they define that the required outcome of the work being performed is accurate. CGMPs also serve to identify and correct the instances in which the material or product does not conform to the requirements to deem it safe and effective, and allows for corrections to be made to the process before the material/product is released to customers or consumers.

5.6 Increased Costs

There are other risks involved with raising the standards for manufacturing "Atypical Actives". The data demonstrated that all groups agree that the cost of a material should go up if

an Atypical Active manufacturer is required to follow ICH Q7 (mean score for all respondents – 3.86 = "Moderately Agree"). Higher standards mean suppliers will have to upgrade their facilities in order to adhere to ICH Q7, causing the price of the material to rise and potentially force some "Atypical Active" manufacturers (who typically sell the material as excipients) to stop selling the material to OTC and Rx drug makers. This would diminish the supply and potentially cause a shortage of the current material, and may cause a shortage of the finished drugs in the market. The FDA should adopt the EMEA's stance, who in 2008, stated that an alternative source should be sought after if the current manufacturer cannot fully comply with the API cGMP standards.[66] The EMEA states that if no options are available, then a risk based approach should be taken and adequately documented. Perhaps the FDA should take the same stance as the EMEA. However, problems may arise with this "pragmatic" approach, as the EMEA termed it. If other viable sources are available, for instance a manufacturer who does comply with ICH Q7 but charges too much for the material, but the drug manufacturer uses material from an "Atypical Active" manufacturer who does not manufacture to ICH Q7, then the FDA may still hold the drug manufacturer accountable since a viable option was available.

5.7 Responsibility of cGMP Adherence

For the last set of results from this survey, the respondents were asked if they believed if it was the responsibility of the finished drug manufacturer, not the responsibility of the "Atypical Active" manufacturer, to ensure that the proper cGMPs were in place to manufacture the "Atypical Active". Interestingly, as a whole the mean score was 2.52, or "Moderately Disagree". However, when examining the results of the individual groups, Group 2 (IPEC) yielded a mean score of 3.33, signifying an opinion that they "Moderately Agree" it is the drug manufacturer's

responsibility. The other three groups yielded scores in the other direction, i.e. Group 1 – 2.43, Group 3 – 1.88, and Group 4 – 2.20. Therefore, 71.1% of the respondents feel that it is the responsibility of the "Atypical Active" manufacturer to meet cGMP requirements for the usage of the material. It can be interpreted from these results if the material is for use in the finished drug product as an API, then the "Atypical Active" manufacturer holds the responsibility that the ICH Q7 cGMPs are being met.

The researcher agrees more closely with the IPEC group for the responsibility of cGMP adherence (mean for IPEC: 3.33 = "Neither Agree or Disagree"). The researcher believes it is the responsibility of both the "Atypical Active" manufacturer and the finished drug manufacturers to adhere to the proper cGMPs. In April, 2015, the Taiwanese FDA announced a recall order of 23 products that were removed from pharmacies because drug makers of the "Atypical Actives" Magnesium carbonate and Calcium carbonate could not demonstrate that the materials used as APIs in medicines were of appropriate quality.[67] These materials met a food grade and not a pharmaceutical grade. This is an example demonstrating the importance of cGMP compliance by both manufacturers.

In this research, industry professionals were distributed surveys, which were collected and analyzed by the cumulative scores from a series of attitudinal questions. The results of the surveys generated several key findings about the opinions of industry professionals regarding the cGMP standards for "Atypical Actives". First, the results show that the respondents employed by a member company of IPEC, who represent excipient and "Atypical Active" manufacturers, have statistically significant differences in opinion regarding the cGMP standards needed to manufacture "Atypical Actives". This group strongly indicated that lower cGMP standards are acceptable than the cGMPs in the ICH Q7 Guidance for Manufacturing APIs. Secondly, the FDA

should publish a Guidance Document to address their current thinking of the cGMPs expected for "Atypical Actives". Drafting a Guidance Document was confirmed by all groups of respondents in the study (mean score for all respondents, 4.18 = "Moderately Agree"). The Guidance Document would need to specifically outline the FDA's current thinking on the level of cGMPs needed to manufacture and use "Atypical Actives" in drug formulations. Thirdly, a majority of the respondents, 55.6%, either "Strongly Disagree" or "Moderately Disagree" that it is the responsibility of the finished drug manufacturer to ensure proper cGMPs are being conducted for the manufacture of "Atypical Actives"; whereas 24.4% "Moderately Agree" or "Strongly Agree" that it is the finished drug manufacturer's responsibility. Therefore, the majority of the respondents agree that it should be the "Atypical Active" manufacturer's obligation to ensure proper cGMPs. Finally, an ideal way to prevent or minimize misconceptions about the required cGMPs would be to sign a Quality Agreement between the "Atypical Active" manufacturer and the finished drug manufacturer. A Quality Agreement would contain details about the cGMP standards that are needed to be met in order to supply the material. All groups were in agreement that a Quality Agreement should be in place between the "Atypical Active" and finished drug manufacturer (mean score for all respondents 4.40 = "Moderately Agree"). A Quality Agreement detailing the cleaning processes, stability data, and impurity testing requirements would bridge any transparency cGMP gaps. This not only harmonizes both sides, but it also serves as a legal document which may be referenced in cases where significant problems arise which may question the Good Manufacturing Practices of the "Atypical Active", for example FDA 483 citations, Warning Letters, or drug recalls.

CHAPTER 6

RECOMMENDATIONS

Future studies are needed to thoroughly understand the critical risks involved with inadequate cGMPs and the effects that result from them with "Atypical Actives". Further research involving a larger group may provide more data and more leverage to encourage the FDA to formally address the issue of "Atypical Actives" through a Guidance Document. Other research could specifically target the opinions of FDA personnel who work with APIs and finished drug products.

Due to a low response rate (12.2%), there were only 44 qualified and completed surveys in this research. In order to improve the response rate, researchers in future research may utilize online networking websites such as LinkedIn to approach and contact industry professionals. This avenue of contact was not utilized in this research. A larger budget in future research would allow the opportunity to survey a broader and more global pool of respondents. In this research, 89% of the respondents were from the United States.

Future research on this topic that uses a survey instrument may broaden the Likert scale to even numbers. A five point Likert scale was used for this research. While an odd numbered scale allows respondents to select a middle option, or neutral option; an even numbered scale basically forces respondents to take sides, e.g. "Agree" or "Disagree". An even numbered scale may be advantageous to know what direction a respondent is leaning.

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Appendix 1: Survey Questionnaire

Survey Title: Regulations of Good Manufacturing Practices for Atypical Actives

Section of Study: Informed Consent

Dear Colleague:

My name is Josh Aslinger, a graduate student under the direction of professor David Mullis in the Department of BioPharma Regulatory Affairs, at The University of Georgia. I invite you to participate in a research study entitled "Adherence of GMPs for Atypical Actives for Use as Active Pharmaceutical Ingredients: Survey of Industry". The purpose of the study is to gather opinions from professionals working in the pharmaceutical and ingredient manufacturing industry, regarding the regulations of GMPs for "Atypical Actives." Before beginning the survey, Informed Consent must be obtained from you as required by the UGA Graduate School. Please read below:

The inclusion criteria for this survey are as follows: you must be 18 years of age or older, and have at least 1 year of experience working in one or more of the following: 1) the prescription drug and/or over-the-counter drug industry, 2) working with Active Pharmaceutical Ingredients, 3) working with drug excipients, 4) a member company of IPEC, 5) a member company of CHPA, 6) or a manufacturer of a material(s) recognized as an "Atypical Active". Please see the table at the bottom of the page for a list of commonly recognized "Atypical Actives".

Participation will be in the form of a survey, consisting of 27 total questions. The survey should take about ten minutes to complete. The first few questions will ask about your experience in the pharmaceutical industry. The rest of the questions will ask your opinion about the manufacture of Atypical Actives. Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty. Your participation in this research study has no bearings on your employment status or will not affect your employment status. In addition, if you are not comfortable answering all of the questions, please skip those you do not wish to answer. If you decide to stop or withdraw from the study at any time, the information/data collected from or about you up to the point of your withdrawal will be kept as part of the study and may continue to be analyzed.

The identification of all participants will be kept confidential. The software used for the administration of this survey maintains anonymity of the survey responses. Your answers will be combined with many others participating in this study and will be used only for statistical analysis. In total, there will be approximately 344 surveys sent out to potential study participants. The only persons who will have access to the data will be the researcher, Josh Aslinger, and the advisor, Dr. David Mullis. The results of the research study may be published, but your name or any identifying information will not be used. In fact, the published results will be presented in summary form only.

Please note: Internet communications are insecure and there is a limit to the confidentiality that can be guaranteed due to the technology itself. However, once the materials are received by the researcher, standard confidentiality procedures will be employed.

1

The findings from this project may provide information on the industry's current thinking on GMP requirements for Atypical Actives. There are no known risks or discomforts associated with this research.

If you would like to see the final results of the survey, or have any questions about this research project, please feel free to contact me at anytime: Josh Aslinger, Email: jasli01@uga.edu, Telephone: 423-645-9822. Questions or concerns about your rights as a research participant may be directed to The Chairperson, University of Georgia Institutional Review Board, Telephone (706) 542-3199; Email address: irb@uga.edu.

Sincerely,

Josh Aslinger

Master of Science Candidate

Department of BioPharma Regulatory Affairs, the University of Georgia

Table 1

Drug Category	Examples of Atypical Active Ingredients
Ingestibles: weight control // antidiarrheal // cough-cold expectorant // antacid // laxative // poison treatment // stimulant // antiflatulent // diuretic	Alginic acid, Potassium citrate, Sodium chloride // Aluminum oxide (Alumina), Bismuth subsalicylate // Ammonium chloride, Pine tar // Calcium carbonate, Calcium phosphate, Magnesium carbonate, Potassium bicarbonate, Magnesium hydroxide // Polycarbophil, Polyethylene glycol, Cellulose, Mineral oil, Sorbitol, Glycerine // Ipecac syrup, Charcoal // Caffeine // Simethicone // Urea
Ophthalmics: demulcent // emollient	Hypromellose, Paraffin
Oral: anesthetic // relief of oral discomfort	Phenol, Potassium chlorate
External Analgesics: acne // antifungal // astringent/disinfectant // topical antitussive // skin protectant	Benzoyl peroxide, Resorcinol, Salicylic acid // Boric acid, Povidone // Calamine, Eucalyptus oil, Honey, Isopropyl alcohol, Starch, Witch hazel // Camphor, Menthol // Dimethicone, Kaolin, Lanolin, Petrolatum, Zinc oxide
Intravenous: promotion of diuresis	Mannitol

1. Do you agree to the terms listed above? By clicking Yes, you consent that you are willing to answer the questions in this survey.

- ◯ Yes
- ◯ No

2

Survey Title: Regulations of Good Manufacturing Practices for Atypical Actives

Section of Study - Part I: Your experience in the pharmaceutical industry

Background: ***The FDA expects manufacturers of Active Pharmaceutical Ingredients (API) to comply with the ICH Guidance, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7". However, some people believe that ICH Q7 GMPs should not be applied to Atypical Active manufacturers. What are your thoughts? The following table is presented again identifying some common Atypical Actives, in several drug categories:***

Table 1

Drug Category	Examples of Atypical Active Ingredients
Ingestibles: weight control // antidiarrheal // cough-cold expectorant // antacid // laxative // poison treatment // stimulant // antiflatulent // diuretic	Alginic acid, Potassium citrate, Sodium chloride // Aluminum oxide (Alumina), Bismuth subsalicylate // Ammonium chloride, Pine tar // Calcium carbonate, Calcium phosphate, Magnesium carbonate, Potassium bicarbonate, Magnesium hydroxide // Polycarbophil, Polyethylene glycol, Cellulose, Mineral oil, Sorbitol, Glycerine // Ipecac syrup, Charcoal // Caffeine // Simethicone // Urea
Ophthalmics: demulcent // emollient	Hypromellose, Paraffin
Oral: anesthetic // relief of oral discomfort	Phenol, Potassium chlorate
External Analgesics: acne // antifungal // astringent/disinfectant // topical antitussive // skin protectant	Benzoyl peroxide, Resorcinol, Salicylic acid // Boric acid, Povidone // Calamine, Eucalyptus oil, Honey, Isopropyl alcohol, Starch, Witch hazel // Camphor, Menthol // Dimethicone, Kaolin, Lanolin, Petrolatum, Zinc oxide
Intravenous: promotion of diuresis	Mannitol

2. Do you have at least 1 year of work experience in any of the following: 1) the prescription drug and/or over-the-counter drug industry, 2) working with Active Pharmaceutical Ingredients, 3) or working with drug excipients?

- ◯ Yes
- ◯ No

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3. If you answered "Yes" to question 2 above, how long have you worked in one or more of these industries?

- ◯ 1 - 5 years
- ◯ 5 - 10 years
- ◯ 10+ years

4. In what country and state (if applicable) are you currently employed?

Country:

State (if applicable)

5. What is your current job title or role with your company?

Enter your answer here:

6. How many people are employed at your company? (if you are part of a larger company, please include total company's amount)

- ◯ 1 - 50
- ◯ 51 - 100
- ◯ 100 - 500
- ◯ 500+

7. Are you currently employed by any of the following sorts of companies?

- ◯ A member company of IPEC (International Pharmaceutical Excipients Council)
- ◯ A member company of CHPA (Consumer Healthcare Products Association)
- ◯ A manufacturer or a supplier of an ingredient(s) listed in Table 1 above that is ***not*** a member of IPEC
- ◯ I am not employed by any of these sorts of companies.
- ◯ I am not sure if I am employed by any of the sorts of companies.

Survey Title: Regulations of Good Manufacturing Practices for Atypical Actives

Section of Study - Part II: What do you believe about the regulation of Atypical Actives?

This set of questions concerns differences among several categories of drugs.Some people believe that the ICH Q7 GMP Guidance should be required for some categories of Atypical Actives more than others. What do you think?

For easy reference, Table 1 is presented again below. Please refer to it as needed.

Drug Category	Examples of Atypical Active Ingredients
Ingestibles: weight control // antidiarrheal // cough-cold expectorant // antacid // laxative // poison treatment // stimulant // antiflatulent // diuretic	Alginic acid, Potassium citrate, Sodium chloride // Aluminum oxide (Alumina), Bismuth subsalicylate // Ammonium chloride, Pine tar // Calcium carbonate, Calcium phosphate, Magnesium carbonate, Potassium bicarbonate, Magnesium hydroxide // Polycarbophil, Polyethylene glycol, Cellulose, Mineral oil, Sorbitol, Glycerine // Ipecac syrup, Charcoal // Caffeine // Simethicone // Urea
Ophthalmics: demulcent // emollient	Hypromellose, Paraffin
Oral: anesthetic // relief of oral discomfort	Phenol, Potassium chlorate
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Intravenous: promotion of diuresis	Mannitol

8. The ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Ingestibles."

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

9. ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Ophthalmics."

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

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10. ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Oral."

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

11. ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "External Analgesics."

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

12. ICH Q7 GMP Guidance should be followed for Atypical Actives categorized as "Intravenous."

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

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Survey Title: Regulations of Good Manufacturing Practices for Atypical Actives

Section of Study - Part II Continued: What do you believe about the regulation of Atypical Actives?

The next group of questions concern more general issues of how drugs are manufactured.

13. A Quality Agreement is a contract between a manufacturer of an Active Pharmaceutical Ingredient (API) and a drug manufacturer; a Quality Agreement defines the level of Good Manufacturing Practice (GMP) to which the API will be manufactured. Quality Agreements are not currently required for the manufacture of Atypical Actives; however some people believe that Quality Agreements should be required. What do you believe?

I believe that a Quality Agreement should be in place between an Atypical Active manufacturer and a drug manufacturer.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

14. The ICH Q7 GMP Guidance states in order to validate a new process for an API, a minimum of three (3) consecutive successful manufacturing batches should be completed. However, some people believe that this criteria should not apply to Atypical Actives. What do you think?

I believe that a new Atypical Active process should require successful completion of three (3) consecutive manufacturing batches for the process to be validated.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

15. Some people believe that the regulations governing Atypical Active manufacture can be relaxed somewhat if a manufacturer can demonstrate a history of stable manufacturing. What do you think about this?

I believe that an Atypical Active manufacturer that has demonstrated a history of stable manufacturing for five or more years should no longer be required to maintain a Process Validation program for the Atypical Active.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

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16. The ICH Q7 GMP Guidance states that Cleaning Validation should be performed on manufacturing equipment of APIs. However, some people believe that if the equipment used to manufacture an Atypical Active is "dedicated," – that is, this is the only ingredient manufactured on the equipment-- then Cleaning Validation should not be required. What do you believe?

Cleaning Validation should not be required for Atypical Actives manufactured on "dedicated" equipment.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

17. At times, Atypical Actives are not manufactured on "dedicated" equipment; that is, other materials are made on the same equipment. Should Cleaning Validation be required for Atypical Actives manufactured on "non-dedicated" equipment?

Cleaning Validation should not be required for Atypical Actives manufactured on "non-dedicated" equipment.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

18. The ICH Q7 GMP Guidance sets a high standard for the manufacture of APIs, which is accepted by the FDA. This standard may be unnecessarily high for Atypical Actives, especially since most Atypical Actives have a history of safe use. What do you believe?

The FDA should accept a lower level of Good Manufacturing Practices (GMPs) for Atypical Actives than that set by the ICH Q7 if there is a history of five or more years of stable manufacturing data.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

19. The FDA accepts the ICH Q7 GMP Guidance Document for the manufacture of "typical" API's. However, manufacturers of Atypical Actives sometimes do not meet the same standards as "typical" APIs, and there is no comparable Guidance Document for the manufacture of Atypical Actives. What do you think about this?

The FDA should publish a Guidance Document defining the expected Good Manufacturing Practices (GMPs) for Atypical Actives.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

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20. Some people believe that as long as an API passes all of the testing requirements defined in a specification, for example a USP specification, then the level of GMPs do not matter. What do you believe?

If an Atypical Active passes all of the specification testing requirements, then the level of GMPs are not important.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

21. If manufacturers of Atypical Actives are required to meet the standards that the ICH Q7 currently requires for "typical actives," the cost of manufacturing these Atypical Actives may increase. What do you think about this?

If maintaining the ICH Q7 standard raises the cost of manufacturing for an Atypical Active, the manufacturer should increase the price of the Atypical Active.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

22. The ICH Q7 GMP Guide states that an on-going testing program should be in place to monitor the stability of APIs. However, some people believe this is not necessary for Atypical Actives, since most Atypical Actives have a long history of safety and effectiveness in the marketplace. What do you think?

An on-going stability testing program should be in place for Atypical Actives.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

23. The ICH Q7 GMP Guide states that an impurity profile should be in place for APIs (for example: organic impurities, inorganic impurities, residual solvents). However, some people believe that Atypical Actives are sold in large manufacturing batches and therefore should not require impurity profiles.

I believe that impurity profiles should be required for Atypical Actives.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

24. The ICH Q7 GMPs should be followed for Atypical Actives used in prescription drugs.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

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25. The ICH Q7 GMPs should be followed for Atypical Actives used in over-the-counter (OTC) drugs.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

26. The IPEC/PQG GMP Guide for Pharmaceutical Excipients is a less-demanding standard than that of the ICH Q7 for "typical actives." Some people believe it would be a more reasonable standard for the manufacture of "Atypical Actives." What do you think?

The IPEC/PQG GMP Guide for Pharmaceutical Excipients is an acceptable GMP standard for Atypical Actives.

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

27. Some people believe that the responsibility lies with the finished drug manufacturer to ensure proper GMPs are followed for the API, while others may think it is the API manufacturer's responsibility. What do you think?

It is the responsibility of the finished drug manufacturer—not the manufacturer of the API—to ensure the Atypical Active manufacturer is complying with Good Manufacturing Practices (GMPs).

Strongly Disagree	Moderately Disagree	Neither Agree nor Disagree	Moderately Agree	Strongly Agree
○	○	○	○	○

28. Please feel free to provide any suggestions or recommendations regarding the GMPs of Atypical Actives:

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