The regulation of pharmaceutical excipients.

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ABSTRACT

Pharmaceutical excipients are vital components of drug formulations and are generally considered pharmacologically inert. Control of excipient manufacturing and distribution is now considered a key priority by regulatory authorities and pharmaceutical manufacturers, because adulteration of pharmaceutical excipients has resulted in adverse effects in patients. Furthermore, with the emergence of novel excipients and delivery systems, better quality and supply control of pharmaceutical excipients becomes increasingly important in the context of *in vivo* performance. Recognizing the critical role that excipients play in pharmaceutical dosage forms necessitates that excipient suppliers meet the quality requirements of the pharmaceutical industry and the pharmaceutical industry as a whole must work to assume integrity of the supply chain.

KEY WORDS: Pharmaceutical excipients, quality, IPEC, Rx–360, EXCiPACT™, IPEA, NSF-363, functionality, novelty

INTRODUCTION

In addition to the active pharmaceutical ingredient (API), the finished medicinal product generally contains inactive ingredients, known as excipients, e.g., co-solvents, preservatives, colorants, surfactants or sweeteners (1, 2). According to the US Food and Drug Administration (FDA) "an inactive ingredient is any component of a drug product other than the active ingredient" (3). This definition of a pharmaceutical excipient is now considered an essential component of the drug formulation. Excipients are considered essential for several purposes including facilitating product manufacturing, aiding in identification, modulating stability, preservation and delivery, as well as, increasing product acceptability (4, 5). Excipients can be derived from natural sources or synthesized either chemically or by other means, such as fermentation. They range from simple, usually highly characterized, organic, or inorganic molecules to highly complex materials that are difficult to fully

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characterize (6, 7). However, the majority of excipients are not specifically manufactured for use in pharmaceutical products, rather they have other uses in the chemical and food industries. Complex supply chains and increased dependence on outsourced manufacturing create the potential for counterfeit or substandard excipients to enter the supply chain causing potential problems in manufacturability, alteration of bioavailability and shelf life with consequent adverse effects in patients. Therefore, careful testing of excipients and auditing of their supply chains is necessary to ensure their safety in the final medicinal product. Although the pharmaceutical industry has been strictly regulated for years, excipients have been generally less so.

The importance of excipient quality is gaining recognition in the pharmaceutical industry and regulatory agencies across the globe. Many governments are developing legislation and regulations that will impact the way excipients are sourced and controlled. This review discusses the quality, functionality and novelty related aspects of pharmaceutical excipients together with the regulatory efforts by the pharmaceutical industry and various regulatory agencies across the globe.

QUALITY ASPECTS

The quality of excipients is critical to assure the safety and efficacy of medicines (8). The volumes for excipients used in pharmaceutical products make up only a small percentage of the total volume of bulk chemicals manufactured. In this context, not all excipient manufacturers and distributors are aware of, or recognize the specific quality requirements for excipients (9). Pharmaceutical manufacturers are required to ensure that excipients are suitable for use in their products not only by specification, sampling and testing, for which there are detailed regulatory requirements, but also that they are manufactured to an appropriate standard of Good Manufacturing Practices (GMP). The supply chain for a pharmaceutical excipient starts at the source of the raw or starting material of the excipient and continues through until used by the finished product manufacturer. All parties involved in the supply chain should be aware that an excipient must be of pharmaceutical grade and manufactured, repackaged, and handled in accordance with such rules and regulations.

There are many challenges associated with excipient quality management, managing extended supply chains and developing certification schemes for the manufacture and supply of excipients (10). Not satisfactorily meeting these challenges creates the potential for counterfeit or substandard excipients to enter the supply chain. Several incidents where pharmaceutical excipients have caused harm to patients have led to stricter regulations to ensure that the required characteristics for pharmaceutical excipients are monitored and met (11-13). A recent drug contamination incident reported in March 2012 involved the discovery of 77 million medicinal gelatin capsules made from industrial grade gelatin that contained chromium, a carcinogenic heavy metal (14). China's State Food and Drug Administration (SFDA) has published a list of 28 high-risk excipients that require a manufacturing license before they can be used in pharmaceutical products. The US FDA Center for Drug Evaluation and Research (CDER), limited the use of certain phthalates as excipients in CDER-regulated products due to potential human health risks associated with exposure to dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) (15).

The lack of stringent regulation of excipients worldwide, and an inadequate scrutiny of the supply chains can, and has resulted in, the deliberate adulteration of excipients which in turn could potentially cause, and has caused, life threatening harm to patients. Therefore, auditing and monitoring of excipient manufacturing and supply chains is essential in order to demonstrate a commitment to the production of high quality excipients.

This has been recognized by the regulatory agencies, as well as, the excipient and pharmaceutical industries resulting in the establishment of regional International Pharmaceutical Excipients Councils (IPECs) beginning in 1991 (16). The objective of the councils is to formulate regulations that can provide a basis for improving excipient quality and patient safety. Regional IPECs and their affiliate organizations around the world have also established the IPEC Federation, to allow the excipient industry to speak with one voice and promote the best use of excipients in medicines resulting in the improvement of patient treatment and safety. The IPEC Federation represents the four existing regional IPECs i.e., IPEC-Americas, IPEC Europe, IPEC Japan and IPEC China. In addition, the IPEC Federation has been collaborating with a group of companies in India to assist them in developing an IPEC organization in the Indian Subcontinent. IPEC-India is expected to become registered as a formal trade association during 2013. IPEC has published many guidelines, programs and proposals on various aspects of excipient control. These IPEC initiatives are designed to address specific needs related to excipient quality control (Table 1).

Table 1 IPEC Guidelines and Initiatives

IPEC Guidelines and Initiatives
IPEC Certificate of Analysis Guide - 2013
IPEC Excipient Stability Program Guide - 2010
IPEC Excipient Composition Guide - 2009
IPEC Quality Agreement Guide & Template - 2009
IPEC Excipient Composition Guide - 2009
Quality Agreement Guide - 2009
The IPEC GDP Audit Guideline – 2008, 2011
Qualification of Excipients for Pharmaceutical Use - 2008
The IPEC-PQG GMP Audit Guideline - 2008
Excipient Pedigree White Paper- 2008
The IPEC GDP Guideline - 2006
The IPEC-PQG GMP Guideline - 2006
IPEC Excipient Information Package (EIP) – 2005, 2009, 2013
IPEC-Americas Excipient Master File Guide - 2004
IPEC Significant Change Guide – 2000, 2009

Excipient GMP

In 1995, the first voluntary standards for good manufacturing practice for pharmaceutical excipients was published jointly by IPEC-Americas, IPEC Europe, and their member companies. The World Health Organization (WHO) adapted it for use by its national member states. Following the release of an updated IPEC guidance in 2001, the United States Pharmacopoeia (USP) used it as the basis for General Chapter <1078> in the USP 35-NF 30 (17).

Later, beginning in 2003, IPEC-Americas and IPEC Europe entered into an agreement with the Pharmaceutical Quality Group (PQG), to produce an appropriate new and updated Guide for the manufacture of excipients for pharmaceutical use. This Guide was published jointly by the three regional IPECs in January 2006 (18). It incorporated the IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, 2001 with the PQG's PS 9100:2002 Pharmaceutical Excipients. This Guide provides the excipient manufacturers and their customers an assurance that excipients manufactured in accordance to it would meet the principles of internationally accepted good manufacturing practice.

Pharmaceutical Excipient GDP

In order to provide a guide for companies involved in the pharmaceutical excipient supply chain, a joint document by IPEC-Americas and IPEC Europe, entitled the "Good Distribution Practice Guide for Pharmaceutical Excipients", was published in 2006 (19). This guide provides a source of additional explanatory notes to the WHO technical report entitled "Good Trade and Distribution Practices for Pharmaceutical Starting Materials" (20). Also available through IPEC are both a Significant Change Guide and a Certificate of Analysis Guide (COA) for Bulk Pharmaceutical Excipients. The Significant Change Guide was developed to help excipient manufacturers

evaluate the significance of manufacturing changes on excipient quality and to assess the risk that those changes would have on drug products containing that excipient. It also recommends which particular changes might require communication to the excipient customer and regulatory authorities. An updated Guide, published in 2009, further addressed concerns about bovine spongiform encephalopathy (BSE), genetically modified organisms and allergens. The updated Guide also contains a new section to assist manufacturers in developing an impurity profile(s) (21). A Significant Change Guide is also available in the USP 32-NF 27 as General Chapter <1195> Significant Change Guide for Bulk Pharmaceutical Excipients based on the IPEC Guide (22).

The goal of the IPEC Certificate of Analysis Guide (COA) is to standardize the content and suggest a format for COAs for excipients. It also defines the roles and responsibilities for the excipient manufacturer and distributor. COAs are legal documents signed by manufacturers or by distributors and used by excipient users to ensure that an excipient product meets the defined specifications. These documents provide evidence of the identity of a given product, and accompany each batch or delivery of an excipient (23). The original Guide was first published in 2000, however, changes in the global pharmaceutical industry and regulatory area have necessitated its revision and the latest version was released in 2013 (24). A COA guide is also published in the USP 32-NF 27 as General Chapter <1080> Bulk Pharmaceutical Excipients-Certificate of Analysis (25).

Additionally, IPEC has developed an Excipient Information Package (EIP) to integrate information related to excipient qualification and sourcing into a standard package. This package minimizes the need for the volume of questionnaires and surveys required to obtain information from multiple customers. The IPEC Excipient Information Package (EIP) is set up in a similar manner to a Material Safety Data Sheet (MSDS) with designated sections to include specified data on specific topics. The 2005 version has now been superseded by the 2013 Excipient Information Package (EIP), and can be used by excipient suppliers to provide a standardized set of documents to exchange data between suppliers and their customers. The EIP package includes a site quality overview, a product regulatory datasheet and a site and supply chain security overview (26).

Pharmaceutical excipients supplier qualification

Implementation of supplier assessment and audit programs serve to provide assurance of the integrity of the supply chain, and authenticate the 'pedigree' of the excipient. Excipient suppliers, distributors and the pharmaceutical industry are fully committed to control the quality excipients throughout the supply chain, and ensure this by self-regulation and through accredited auditing bodies. However, not every pharmaceutical excipient user audits every excipient supplier, either due to time/monetary constrains or because they adopt a deliberate risk based approach. It is sometimes impractical for the pharmaceutical excipient companies, both logistically and economically, to host a plethora of audits from all direct and indirect pharmaceutical customers. Regulators worldwide recognize this challenge and now allow pharmaceutical companies to rely on third-party audits and certification that can reduce the audit burden for all concerned. Currently, the main comprehensive programs available to pharmaceutical manufacturers for the purpose of auditing excipient suppliers and ensuring drug efficacy and patient safety are Rx–360, EXCiPACT™ and IPEA. NSF International is also in the process of drafting the ANSI NSF-363 standard, as a basis for a quality management system for the manufacture of pharmaceutical excipients. An overview of these programs is show in Table 2.

Table 2 Major audit and certification programs for excipients supplier qualification

	IPEA Certification	EXCiPACT™ Certification	Rx-360 Audit	NSF 363 (not yet a standard)
GMP Standard	IPEC-PQG	ISO 9001 + GMP Annex based on IPEC-PQG	Rx-360 Audit Guide (based on ISO 9001:2008)	ANSI GMP standard for excipients
Auditor Training/ Qualification	IPEA/Yes	IPEA/Yes	Sub-contractor/No	IPEA/Yes
Accreditation	ANSI	None	None	ANSI
Certification	Yes – to IPEC standards	Yes – to IPEC standards	No	Yes – to IPEA standards

Rx–360

The Rx-360 is a non-profit international industry organization established in 2009 (27). The goal of this organization is to develop and implement enhanced global quality systems and processes that will help ensure product quality and authenticity throughout the supply chains. . Members of the Rx-360 Consortium include pharmaceutical companies, contract manufacturers, excipient suppliers, auditors and associations such as the IPECs and the Pharmaceutical Quality Group (PQG) working together to achieve these objectives (28). Rx-360 has adopted or issued a number of standards, check-lists and guidelines to help manage supplier qualification programs. Rx-360 actively engages with global regulatory agencies such as the European Medicines Agency (EMA), the US FDA, the WHO, the European Directorate for the Quality of Medicines & Healthcare (EDQM), and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) (29).

The two primary programs of the consortium are to set up a system for carrying out shared audits of suppliers and to conduct joint audits. In the shared audits program, Rx-360 member suppliers make completed audit reports of their companies available to each other via a secure database. This, of course, requires permission from the supplier and may involve removing some commercially sensitive information. In third party joint audits, the member companies jointly audit a supplier via third party auditors commissioned by Rx-360. EXCiPACT™ has recently agreed that Rx-360 can use the EXCiPACT™ GMP standard for pharmaceutical excipients for their shared auditing program (30, 31).

The EXCiPACT™ certification process

A consortium of industry associations, namely the European Fine Chemicals Group (EFCG), the International Pharmaceuticals Excipients Council (IPEC) Europe, IPEC Americas, the European Association of Chemicals Distributors (FECC), and the Pharmaceutical Quality Group (PQG) launched the EXCiPACT™ certification scheme in February, 2012. The EXCiPACT™ program provides an independent certification of manufacturers and suppliers of pharmaceutical excipients as a means of ensuring patient safety, by ensuring supplier quality, while minimizing the overall supply chain costs. EXCiPACT™ aims to ensure that cGMP and cGDP requirements are applied to pharmaceutical excipients through a recognized auditing and certification process, thereby increasing safety and reliability, as well as, transparency of the pharmaceutical supply chain. EXCiPACT™ standards are annexes to ISO standards 9001, 19011, and 17021 and organizations must be ISO certified before EXCiPACT™ can apply. The EXCiPACT™ certification scheme has four core standards covering critical aspects, i) a set of GMP requirements based on the IPEC-PQG GMP Guide for Pharmaceutical Excipients and incorporated as an annex to ISO 9001:2008, ii) a set of GDP (Good Distribution Practices) based on the IPEC GDP Guide and the IPEC-PQG GMP Guide

for Pharmaceutical Excipients, incorporated as an annex to ISO 9001:2008, iii) a set of requirements for auditor competency incorporated as an annex to ISO 19011:2002, guidelines for quality and/or environmental management systems auditing, and iv) a set of requirements for certifying bodies incorporated as an annex to ISO/IEC 17021:2006, conformity assessment requirements for bodies providing audit and certification of management systems (32).

By including the GMP and GDP annexes to ISO 9001:2008, excipient suppliers which are certified to these standards would be able to use them as the basis for implementing the GMP and GDP compliant quality systems within their organizations and to be audited by certifying bodies who would assess them to ISO 9001 and GMP/GDP simultaneously. Further, auditor competency is assured by requiring that they register with EXCiPACT™. However, competent auditors are not the only unique element in EXCiPACT™. To assure impartiality and independence, the EXCiPACT™ Registered Auditors contract to an EXCIPACT™ Registered Certifying Body (33). Thus excipient suppliers who have selected an EXCiPACT™ registered certifying body and have had a successful audit are awarded an EXCiPACT™ Certificate. These EXCiPACT™ Certified excipient suppliers are then anticipated to be able to provide not only the certificate but also the audit reports to their pharmaceutical customers to demonstrate effective implementation of GMP/GDP in their organization. In this manner holders of EXCiPACT™ Audit Reports are able to verify that both the auditors, as well as, the certifying body were registered with EXCiPACT™. This dual process minimizes the risks and maximizes the benefits to all concerned. Rx-360 and EXCiPACT™ have entered into collaboration and now implemented an agreement so that all Rx-360 audits assessing excipient suppliers use the EXCiPACT™ standards (34).

International Pharmaceutical Excipients Auditing Inc.

Recognizing the importance of supplier qualification and auditing to improve supply chain security, IPEC-Americas established the International Pharmaceutical Excipients Auditing, Inc. (IPEA) in 2001 to perform qualified third party audits of excipient manufacturers. These audit reports can be shared with user companies throughout the industry. The formation of IPEA and its recent ANSI accreditation is a major step forward in providing the industry with an alternative for obtaining GMP audit information from their suppliers. Potentially IPEA could become an EXCiPACT™ Registered Certifying Body as it already has the necessary infrastructure in place being accredited by the American National Standards Institute (ANSI) to ISO/IEC Guide 65 (which is equivalent to ISO/IEC 17021). The competence and independence of their qualified auditors and certification board members are key features of the IPEA program and meet the core requirements for EXCiPACT™ registered certifying bodies. However, IPEA does not yet offer ISO 9001 certification but would consider joining their certification program with a provider of ISO 9001 certification under the EXCiPACT™ banner. At this time IPEA is not an EXCiPACT™ registered certifying body (35).

NSF / ANSI 363

NSF is an independent, not-for-profit, non-governmental organization and an accredited standards developer for the American National Standard Institute (ANSI). ANSI is a private, nonprofit organization that administers and coordinates the US voluntary standardization and conformity assessment systems. The NSF joint committee organized to prepare the excipient GMP standard, designated as NSF 363. NSF 363 is working on developing the joint IPEC-PQG GMP Guide for Pharmaceutical Excipients into an American National Standard suitable for recognition by FDA. The most significant new requirement in

NSF 363, not found in the joint IPEC-PQG guide, involves the use of risk management to ensure consistent quality of excipients. The provisions for risk assessment in NSF 363 are new in that they are to be formally conducted and documented (36). However, as with the EXCiPACT™ GMP and GDP Standards, it is an audited standard. Regulators will expect that acceptable and credible assessment to this standard will require Certifying Bodies to demonstrate that they meet the standards equivalent to those adopted by EXCiPACT™ and IPEA, especially auditor competency and the independence of the Certification Board. Although NSF/ANSI 363 and the EXCiPACT™ Standard share the same lineage in the IPEC-PQG GMP Guide there are differences that need to be ironed out before they can be used interchangeably.

FUNCTIONAL ASPECTS

Pharmaceutical excipients contribute unique functionalities to formulations which in turn determine their clinical performance. A greater understanding of the functional benefits of excipients has led manufacturers to turn to excipients as a means to improve pharmaceutical formulations. An excipient may have several intended uses depending on the formulation, manufacturing process, and dosage form, and consequently, there are many applications for a particular excipient. Thus, requirements for a particular excipient and formulation may not be suitable for the same excipient in another formulation. The quantitative performance properties or critical material attributes (CMAs) (e.g. particle size, particle size distribution, or specific surface area) of an excipient must be identified and controlled, to ensure that the drug product critical quality attributes (CQAs) are achieved and maintained throughout the drug product's shelf life (37).Thus, selecting performance tests requires an understanding of excipient's role and the CMAs relevant to a particular dosage form.

Pharmaceutical excipients are manufactured and supplied in compliance with standards established by the US Pharmacopeial Convention (USP) and published in its Compendia, US Pharmacopeia and National Formulary (USP-NF) (38). USP-NF excipient monographs establish a minimum set of specifications (tests, analytical procedures, and acceptance criteria) for identity, quality, and purity with very few requirements for CMAs that relate specifically to excipient functionality or performance. Excipients manufactured to comply with compendial standards may therefore not have all the CMAs identified using compendia monograph test methods and specifications (39, 40). The labeling section of the monographs provides the excipient user with specific information, e.g., to distinguish between different grades, provide information on permitted additives and so on. Some of the tests, however, may also relate to excipient performance.

The USP also participates in the Pharmacopeial Discussion Group (PDG) with the objective to harmonize pharmacopeial standards in the US, Europe and Japan. Excipient manufacturers supply their products across the world and harmonization reduces their burden of having to perform analytical procedures in different ways, using different acceptance criteria, in order to satisfy pharmacopeial requirements that vary across regions. Several of these General Chapters have reached an advanced sign-off stage in the PDG process (41).

In this direction, the joint advisory panel on General Chapter <1059> Excipient Performance, under the excipient general chapter and excipient Expert Committees, developed the informational General Chapter <1059> Excipient Performance, official in USP 33-NF 28, 2nd Supplement, February 2011. The introduction of the USP Excipient Performance Chapter <1059> provides an overview of key functional categories and related dosage forms of excipients identified in the USP-NF. The General Chapter describes which properties

might be important for a particular excipient in a particular application, standard test methods to assess excipient performance, and test procedures that may not be presented in USP-NF monographs (42). Further, the General Chapter <1059> avoids possible confusion with mandatory tests and labeling requirements specific to a USP-NF excipient monograph. Chapter <1059> does not impose limits or specifications, as the required excipient properties will vary and depend upon the drug product, manufacturing process, quantity, and the excipient's intended function (43). Thus, General Chapter <1059> may help formulators identify and monitor excipient properties that they determine are important to excipient function and performance using test methods that are not typically included in compendial monographs. Furthermore, General Chapter <1059> provides a way for applying QbD principles to excipient quality control by correlating excipient properties and drug product performance (44, 45).

NOVEL EXCIPIENTS

Novel excipients are required to improve the performance, solubility and/or membrane permeability of new drug moieties, as well as, to aid modern manufacturing processes (46). A novel excipient may include a new chemical entity, a new innovation that has not been used in any drug approved by regulatory authorities or a combination of excipients containing new chemical entity/entities (not in approved drugs) and excipients that are already in approved drugs in a mixed or co-processed state. FDA and ICH define an excipient "novel" if it is used for the first time in a medicinal product. Most drugs are formulated with commonly used and allowed excipients that are already included in FDA's Inactive Ingredients Database (IID) as well as those listed in the compendia. There are at present no formal regulatory procedures for the approval of stand-alone excipients (47). Currently, new or novel pharmaceutical excipients can only be approved as a part of a marketing application.

An excipient would be considered acceptable if it is referenced in, and part of, an approved new drug application (NDA) for a particular route of administration. Acceptable excipients are published in the FDA's inactive ingredient database (IID) along with the approved dosage forms and concentrations (48). This approach has limitations because excipients cannot generally be approved outside a specific route of administration and concentration range listed in the database. Any excipient that is not listed in the FDA's IID or proposed for use in a dosage form or concentration different from those in the database can be considered novel. To add further uncertainty to the process, the format for submitting safety and manufacturing information for a new excipient in an NDA is not clearly defined.

The FDA has attempted to deal with some of the uncertainty related to the safety evaluation of new excipients by publishing a draft guide entitled "Nonclinical Studies for the Development of Pharmaceutical Excipients" in May 2005 (49). These non-critical studies mirror those required for preclinical evaluation of new molecular entities (NMEs). Although the definitions of these studies have helped in the development of new excipients and innovation of new regulatory strategies, they require a significant financial investment from the excipient manufacturers. As a result, the Guide has failed to pave the way for innovation and may actually have further discouraged excipient manufacturers to develop new excipients. This Guide only applies to the evaluation of new excipients as part of an NDA but could be adapted to an independent evaluation process (50).

In summary, the safety evaluation of novel excipients requires comprehensive safety tests which are strikingly similar to those required for a new drug. However, unlike drugs, excipients are considered to be pharmacologically inactive and these tests may represent an 'overkill' approach toward safety evaluation, thereby representing a potential

barrier to the development of new excipients. Regardless of the IID, neither the FDA, nor the ICH standards, distinguish between new chemical entities and modifications of approved excipients, co-processed mixtures of existing excipients, approved excipients proposed for a new route of administration, or excipients approved for use in foods or cosmetics. Some of these excipients may not require the full battery of tests listed in the Guide on excipient safety evaluation.

In an effort to attract and encourage chemical manufacturers and pharmaceutical companies to develop and use new and novel excipients in pharmaceutical applications, the International Pharmaceutical Excipients Council (IPEC) has developed a global Master File guide to meet the industry's need to submit confidential excipient information. The format for the guide will be coordinated and harmonized with the electronic International Committee on Harmonization (ICH) common technical document (CTD) for presenting chemistry, manufacturing, and controls and safety information (51, 52). The goal of the Master File guide is to allow the DMF holder to submit to the regulatory authorities confidential information that supports marketing authorization applications worldwide. IPEC reviewed various guides to prepare the draft excipient Master File guide. The DMF contains manufacturing and controls information and technical data that support the safety and quality of the excipient.

IPEC has further developed an independent excipient review procedure, "IPEC Novel Excipient Safety Evaluation Procedure" which can serve to simplify this issue. This procedure was expected to reduce the cost and uncertainty related to the use of novel excipients in pharmaceutical formulations, thereby encouraging their use in future drug development and providing a much needed boost to drug formulation innovation. These efforts resulted in the evaluation of the first novel excipient, Solutol® HS 15 [Polyoxyl (Macrogol) 15 hydroxystearate] manufactured by BASF, by an independent expert group of IPECs, the Novel Excipient Evaluation Committee (NEEC).The primary function of the NEEC is to compare available data with the studies identified in the "Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" published by the FDA in May 2005, and to evaluate where appropriate bridging approaches could be used to minimize the need for new studies to support the safe use of an excipient (53).

CONCLUSION AND FUTURE PERSPECTIVES

Excipients, being a vital part of medicinal drug products should be regulated to manage risk. Although, excipients are an integral part of a finished pharmaceutical product, the issue of regulation is complex. Unlike APIs, which are developed solely for pharmaceutical use, many excipients are also manufactured for other diverse non-pharmaceutical products, i.e., for use in the food and cosmetics industries. Modern drug delivery systems rely on sophisticated excipients with multiple functions to improve the overall product performance. To encourage pharmaceutical companies to use novel, value-added and approved excipients, a regulatory harmonization with only product specific testing is desirable. This can be helpful for the development of new formulations from old drug molecules. These excipient related issues are required to be addressed globally. The FDA, European Union and ICH have taken initiatives to address these issues and the effort by the IPECs for excipient control is commendable. In the USA EXCiPACT™ became functional on 29th April 2013 and in the near future the IPECs will continue to develop appropriate guides and white papers that encompass the gamut beginning with excipient design and ending with patient use. The IPECs continue to inform industry and regulatory agency representatives through workshops, seminars and webinars. The IPECs are looking forward to expanding their membership numbers to involve more

companies around the world aiming to harmonize the safety of excipients intended for finished medicinal products.

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