

Addressing specific regulatory excipient requirements in the marketing authorization

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Outline

- **Challenges of excipient vs. API registration**
- **Classification of excipients**
- **Excipient guidance**
- **Registration challenges of well-known vs. new excipients**
- **The basis for successful registration: Excipient master files**
- **Safety assessment of excipients**
- **Hot topics**
- **Industry concerns**
- **Case study: Registration of a novel excipient**
- **Summary & conclusion**

Glossary

CMC	-	Chemistry, Manufacturing and Controls
EMA/ EMEA	-	European Medicines (Evaluation) Agency
API	-	Active Pharmaceutical Ingredient
FDA	-	Food and Drug Administration
CDER	-	Center for Drug Evaluation and Research
IIG/ IID	-	Inactive Ingredient Guide/ -Database
DMF/ EMF	-	Drug Master File/ Excipient Master File
Ph. Eur./ EP	-	European Pharmacopoeia
USP	-	United States Pharmacopoeia
CEP/ CoS	-	Certification of Suitability of the European Pharmacopoeia
ICH	-	International Conference on Harmonization
CTD	-	Common Technical Document
(A)NDA	-	Abbreviated New Drug Application

How are Excipients "approved"?

- Cross-references to pharma/ food/ cosmetic compendia
- Reference in an ANDA/ NDA/ BLA for a particular function in a drug product
- Part of positive list of colors and flavors in EU food legislation (E-numbers)
- FDA can announce substances to be “GRAS” (*generally recognized as safe*) or approve a “FAP” (*Food additive petition*)

Evaluation of „*precedence of use*“:

- FDA IID publishes use of excipient in a licensed medicine, route of administration, potency
- In Japan, MHLW publishes JPED: use, route of administration, patient exposure
- In Canada, Health Canada publishes acceptable non-medicinal agents
- **In the EU, there is no equivalent („ask the regulatory agencies“)**



“*Per se – approval*” for excipients impossible without a corresponding formulated drug product!

API vs. Excipient Requirements in a Marketing Authorisation

Requirement	APIs	Compendial Excipients	New Excipients	Novel Excipients
Efficacy	+*	-	-	-
Safety	+*	-	+ / -	+
Quality	+	+	+	+
CMC (Master File)	+	-	+ / -	+
FRCs	- / +	+ / -	+ / -	+ / -
cGMP (ICH Q7)	+	- (IPEC, ISO)	- (IPEC, ISO)	- (IPEC, ISO)

*For generic applications (ANDAs) reference to originator product

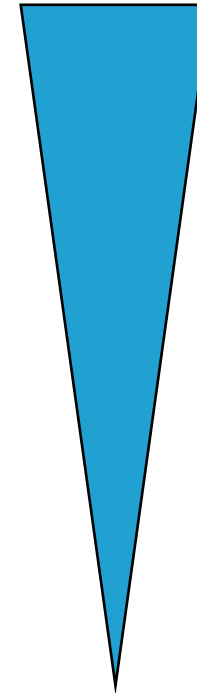
Excipients in Drug Products: Many Differences to APIs

- Excipients are pharmacologically inactive materials from different origins (biological or biotech products, minerals, chemical synthesis-based, etc.)
- Excipient composition: Excipients often contain concomitant (production related) components or processing aids
- Amount of excipient in the dosage form can be higher than API
- Suppliers of excipients do not necessarily know the final use of their product (-> difficulty to help users select appropriate grades)
- Excipient manufacturers usually supply their material to different users (pharma, food, cosmetic, etc.)

Classification of Excipients and Regulatory Challenges




- **NCEs**
- **Chemical modification of an existing excipient**
- Physical modification of an existing excipient (family of different grades)
- Food additive or GRAS substance used for the first time in a drug product
- New route of administration or higher dosage of existing excipients
- **Mixtures of existing excipients**
- **Separate compendial excipients...**

Innovative excipient (use):
Demanding assessment



Common excipient (use):
Simple assessment

Innovative Excipients (use): A Challenge to Regulation

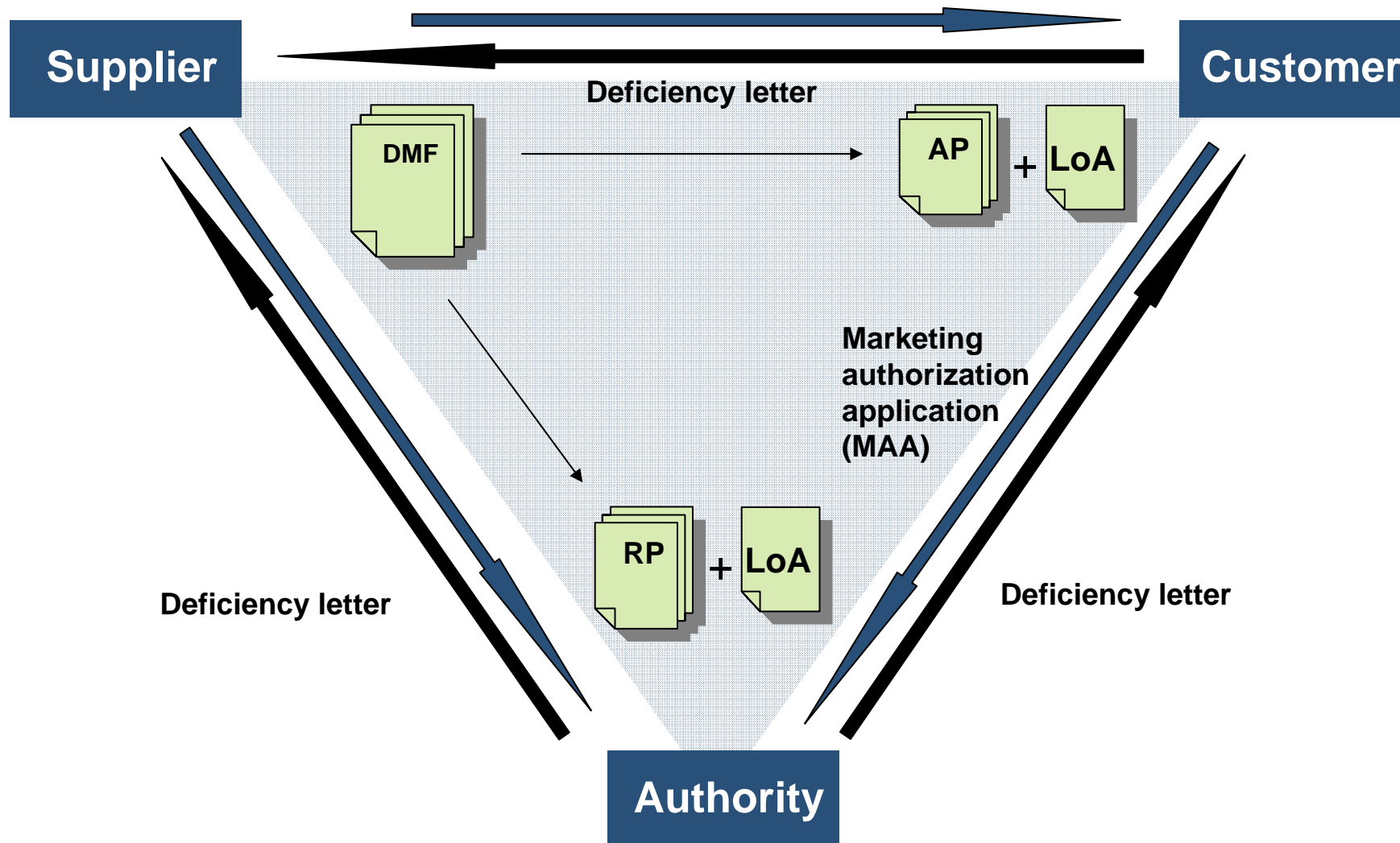
- **Need for new & novel excipients is triggered by various trends:**
 - New lipophilic, high molecular weight entities  **Solubilizers**
 - Low permeability  **Absorption enhancers**
 - Innovative protein drugs  **New stabilizing systems**
 - Micro-/ nano-scaled carrier systems
 - Trend to orally disintegrating tablets (ODTs)
 - Trend from animal to synthetic materials (BSE/TSE, ...)
 - Extension of products patent lifecycle
 - Optimization of production



More and more innovative medicines contain innovative excipients with improved/ new functionality particularly in times of less innovative APIs

Stakeholders have to realize the need for better regulation

Triangular Relationship between User, Supplier and Authority:



Common Registration Scenario: Compendial approach



Excipients described in Ph. Eur. or in the pharmacopoeia of an EU Member State

*“Reference to the current edition of the pharmacopoeia. Rationale for grade selection. In-house tests proven to be equivalent. It may be necessary to add tests/acceptance criteria to the pharmacopoeial specification, depending on the intended use/**FRCs**.”*

Excipients described in a third country pharmacopoeia

“Compliance with the monograph of a third country pharmacopoeia (e.g. USP-NF and JP). Justified specifications in accordance with the general monograph of Ph.Eur. Substances for Pharmaceutical use.”

Excipients not described in any pharmacopoeia *(but well-known)*

Specification for the excipient based on the following types of tests:

- *Physical characteristics*
- *Identification tests*
- *Purity tests, including limits for total and individual impurities, which should be named*
- *Assay or limit tests if necessary and corresponding validation parameters*
- *[..] e.g. tests on parameters influencing the performance of the dosage form*

Types of Excipients

- *Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product 01/2008:*
<http://www.emea.europa.eu/pdfs/human/qwp/39695106enfin.pdf>
- Excipients presented as a **mixture of compounds**: Details of the composition (qualitative and quantitative) required.
- Novel excipients **and** excipients presented as a **mixture of compounds**: Bibliographical data on the chemistry **and on the toxicology** and the field in which it is already used.
- Annex 1: **Mixed excipients**: ready-for-use preparations. Quantitative and qualitative composition, specification as a whole and of each component required.
 - This nebulous guidance offers much space for interpretation
 - IPEC differentiates between „*mixed*“ and „**co-processed excipients**“ (combined excipients with physically modified properties; not achievable by simple mixing and without chemical change)

Novel Excipients: Definition in EU

- A novel excipient is an excipient which is being used for the first time in a drug product, or by a new route of administration. It may be a new chemical entity or a well established one which has not yet been used for human administration and/or for a particular human administration pathway in the EU and/or outside the EU.

<http://www.emea.europa.eu/pdfs/human/qwp/39695106enfin.pdf>

- The data should be presented according to the Common Technical Document (CTD) Module 3 sections P.1, P.2, P.4, P.5, P.8 and A.3.

Novel Excipients: Required Data

- ...Full **details of manufacture, characterization, and controls**, with cross-references to supporting **safety** (non-clinical and/or clinical) data, should be provided.

The information should provide the **same level of detail** as that provided for a **drug substance**, and according to the drug substance format.

This detailed information should be provided in CTD section A.3 unless the information is provided in an appropriately referenced Excipient MF (not applicable for EU!).

Safety Assessment: Precedence of Use



- If there is **no precedence of use** in a drug product, then the material is to be considered a new excipient and a toxicological assessment should be made to demonstrate the safety of the material in the intended pharmaceutical application at the specified use level.
- The *USP-NF Excipient Biological Safety Evaluation Guidelines* <1074> provides guidance on conducting a safety assessment of a novel excipient. In the U.S., the FDA has also issued **guidance on non-clinical studies for new excipients**.

US-Guidance for Industry:

Non-clinical studies for the safety evaluation of pharmaceutical excipients



A: Safety pharmacology according to ICH S7A: Standards for all new excipients

B: Excipients for “short-term use”: 14 or less days/therapy

1. Acute tox., 2. ADME (ICH S3A, S3B), 3. Genotox. (ICH S2B), 4. 1-Month-repeat dose-tox, 5. Reprotox (ICH S5A und S5B) incl. teratogenicity tests at non-rodents

C: Excipients for “intermediate use”: 2 weeks – 3 months/therapy

1. A und B, plus 3 month repeat dose-tox.; if applicable: studies with parenteral application

D: Excipients for “long-term use”: > 3 months/therapy

1. A, B, C, 2. 6 months-repeat-dose tox. at rodents with max. dose, 3. chronic tox. at a mammal (no rodent) with the appropriate application. If tox. and pharmacological findings in subchronical studies were not positive, 6 month data sufficient (otherwise 9-12 months), 4. carcinogenicity study or justification of abandonment

E: Excipients for pulmonal, parenteral oder topical drug products

- A, B, C, D, with adequate administration, allergisation study, parenteral: hemolysis, kreatinin kinase, protein binding; topical: if applicable: ocular irritation

Drug Master File Procedure USA



- Two relevant types of DMFs:
 - Type IV DMF: Excipient, colourant, flavour, essence or material DMF;
 - Type V DMF: FDA accepted references not included in Types I-IV, e.g., toxicological data.
- Published list of registered DMFs: <http://www.fda.gov/cder/dmf/>
- No differentiation between *open* and *closed part* of DMF
- DMF can be submitted to the FDA independent from ANDA/NDA/BLA
- Assessment of DMF once specific application with reference to DMF is filed
- Changes are to be reported, annual updates are mandatory
- CTD format not mandatory

JP Master File Guideline: enforced as of April 1st, 2005



- DMF plus Japanese QOS
- J DMF consists of open and closed part, like EU DMFs
- (e)CTD format accepted
- Categories of JMFs:
 - I - API /intermediates used for drugs*
 - II - new excipients (!)
 - III - medical devices
 - IV - others (packaging etc.)

* Veterinary drugs may be filed at Ministry of Agriculture Forestry and Fisheries

Hot Topic #1: European Excipient Master Files



- In contrast to Japan, Canada and the US, in Europe, for materials where a Certificate of Suitability is not available, confidential information needed to support the drug product filing by a pharmaceutical manufacturer must be supplied directly to the drug manufacturer e.g. by using confidentiality agreements.
- Communication with the regulatory bodies on the topic which is one of the key topics for IPEC Europe
- IPEC Europe Initiative on Excipient Master Files has been implemented to meet the need, create awareness with the EU stakeholders and authorities (mission statement).

Hot Topic #2: Genotoxic Impurities

- The current regulatory guidance is unclear regarding the scope: APIs and drug products are mentioned, however excipients are not explicitly mentioned.
- IPECs position is that excipients should not be treated in the same manner as APIs as prescribed by the CHMP note for guidance from January 2007(CHMP/QWP/251344/2006):
<http://www.emea.europa.eu/pdfs/human/swp/519902en.pdf>



Genotoxic impact of an excipient can only be evaluated in consideration of its specific use in the formulation

Hot Topic #3: Metal catalysts/ Metal reagents residues



- New EMEA-Guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/QWP/4446/2000)
- In force since 1st September 2008
- Objective: maximum acceptable concentration limits of metal residues arising from the use of metal catalysts or metal reagents in the synthesis of drug substances **and** excipients
- Residues from other sources (manufacturing equipment and piping, bulk packaging, the environment, cleaning solvents etc) considered sufficiently limited by GMP/GDP

Metal catalysts or metal reagents residues

- **The manufacturers of pharmaceutical substances must provide a clear statement on the identity and quantity of all metal residues present in their compounds to the drug product manufacturers**
- **Metal residues are evaluated for their potential risk and placed into three classes:**
 - Class **1** Metals: Metals of **significant** safety concern
 - Class **2** metals: Metals of **low** safety concern
 - Class **3** metals: Metals of **minimal** safety concern
- **Exposure limits are set taking into account the route of administration**

Metal catalysts or metal reagents residues

Classification	Oral Exposure		Parenteral Exposure		Inhalation exposure *
	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)	PDE (ng/day)
Class 1A: Pt, Pd	100	10	10	1	Pt: 70 *
Class 1B: Ir, Rh, Ru, Os	100**	10**	10**	1**	
Class 1C: Mo, Ni, Cr, V Metals of significant safety concern	250	25	25	2.5	Ni: 100 Cr (VI): 10
Class 2: Cu, Mn Metals with low safety concern	2500	250	250	25	
Class 3: Fe, Zn Metals with minimal safety concern	13000	1300	1300	130	

Doc. Ref. EMEA/CHMP/SWP/4446/2000

Metal catalysts or metal reagents residues

- **Not used:** not used at all, or used during SM production and „not likely to be present“ (residues consistently removed, i.e., residues found below 30% of limits given in the guideline)
- **Used:** introduced in the process after the SM, or metal residues are likely to be present
 - „likely to be present“: If used in the last stage or if used in earlier stages and not consistently removed, i.e., residues found above 30% of limits given in the guideline
 - „not likely to be present“: Residues consistently removed, i.e., residues found below 30% of limits given in the guideline

Industry Concerns (I)

- **Setting of reasonable specifications**

Metals not likely to be present should not be listed in the manufacturers CoA/ Specification" (as applicable for Residual Solvents)

- **Protection of IP**

IP-relevant heavy metal or other purity information can not always be provided to customers; therefore authorities are requested by industry to provide a workable regulatory system for confidential but relevant excipient information (provided by CEPs only for compendial substances; ongoing IPEC EMF project)

Hot topic #4: Residual solvents

- FDA has recently issued papers and deficiency letters requesting that applicants declare all residual solvents used in the drug substance manufacturing process.
- This requirement goes beyond ICH Q3C and USP <467> which only require that solvents „likely to be present“ be declared and upon which our current residual solvent statements are based.
- USP <467> additionally lists ethylene oxide.



vs.



vs.



Industry Concerns (II)

No mix-up of Regulatory and GMP requirements

(since regulatory dossiers are restricted to impurities associated with the manufacture therein which excludes e.g. discussion on hypothetical cross-contamination)

Examples:

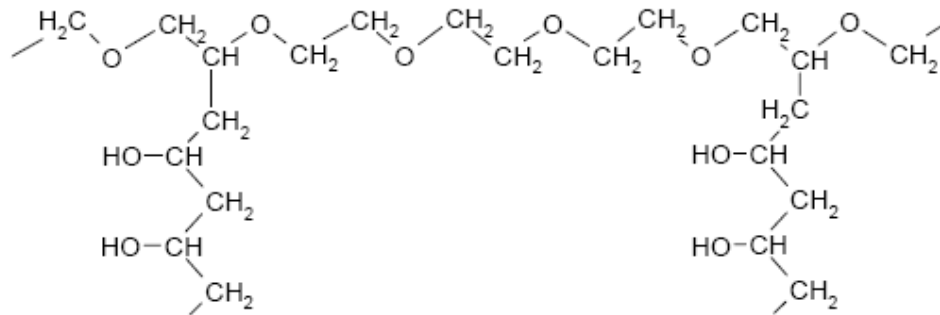
1: Draft USP chapter requires to screen for metals

2: FDA OGD requirement: Submission of supplier qualification regarding residual solvent information

3: FDA deficiency letter to US DMF: Cleaning-validation information of an excipient had to be submitted to the Agency

Case study: Registration of a novel excipient (Kollicoat[®] IR)

- **Market need: Coatings with improved performance**
 - **New generation of fast sprayable instant-release coatings (Kollicoat[®] IR, polyvinyl alcohol-polyethylene glycol *grafted* copolymer)**
 - **Advantages: low viscosity of polymer solution, flexibility of the coating (no plasticizer required), rapid dissolution rate, spraying of high solids content possible due to low viscosity (saves production costs and cleaning procedures)**
 - **Kollicoat[®] IR is the backbone for many further BASF developments**
 - **Chemical structure:**



Registration Requirements of Kollicoat® IR



- Prerequisite for safety studies: No absorption (ADME study) or significant findings of the material after FDA/ICH safety studies performed at BASF toxicology center (ICH „S“ guidelines). Studies have to support safe use in intended dose and route of administration (proof that the investigated and commercial material is identical).
- All three ICH regions (US, EU, Japan) require registrations, i.e. CMC and safety data (safety expert report) for dedicated customers (in the US, the CMC data was included in a type IV DMF, non-clinical data was included in a type V DMF).
- For EU, the main market, no EMF procedure is available, i.e. all data for the new excipient has to be included in the dossier for marketing authorisation of a medicinal product (EMA guideline on excipients).
- After successful registration: Preparation of monographs in the main region(s)

Milestones of a novel excipient registration: Kollicoat® IR



- 2004: CMC and safety data available; DMF submitted to the US FDA, Japanese PMDA and a MAH in Europe
- 2005: Safety studies finalized and safety expert report completed
- 2005: MRP started after successful generic registration in Germany
- 2006: Launches of Kollicoat IR White and Kollicoat Protect, two excipients, derived from Kollicoat IR
- 2006: Assessment report finalised by RMS (BfArM, Germany)
- 2007: After successfully concluded MRP: Application for a monograph
- 2007: Registration of Kollicoat IR by PMDA in Japan via generic application
- 2008: Registration of Kollicoat IR in the US via ANDA
- 2008: Draft Ph.Eur. monograph published in *Pharmeuropa* 20/3 for discussion: Macrogol poly(vinylalcohol) *grafted* copolymer
- 2009: Ph.Eur. and USP draft monograph publication
Based on Ph.Eur. monograph: CEP may be filed
Further Kollicoat IR-based excipients will be launched

Safety issues of Kollicoat[®] IR



- Assessment report: Safety expert report was accepted
- Basis: ADME: no absorption shown by C₁₄-radiolabelled material (high doses up to 1000 mg/kg)
- Oral bioavailability far below 1 % and no accumulation in organs and tissues
- MAH conclusion accepted that the slightly different compositions have no impact on the bioavailability (90 % confidence intervals of the ratios for AUC_{0-last} and C_{max} were within the accepted limits of 0.80 and 1.25).
- No deaths or treatment-related clinical signs were observed in the single- and repeated dose studies, mutagenicity was not observed, no effects in reproduction toxicity studies.
- Taken together, no toxicological concerns about the use of Kollicoat IR as coating agent for oral use.

Summary & Conclusion

- Conflict: Ideal excipient should be “safe by use” and multifunctional
- Current legislation mainly regulates the pharmaceutical manufacturer: QP has to „regulate“ starting materials
- Regulation for excipients relies on pharmacopoeia compliance and quality control; **CMC** details remain intransparent
- No legal obligation for excipient manufacturers to comply with GMP
- No European excipient master file in place
- No common language regarding innovative excipients types (new, novel, pre-mixed, co-processed, etc.)

Status quo: Currently no level playing field: Recent API incidences alert that medicines require safe and appropriately controlled starting materials for both APIs and Excipients

Vision:  Adequate regulation and awareness of excipients gaining in importance in innovative medicines

References & Databases



IPEC Europe

<http://www.ipec-europe.org>

Non-clinical Studies for the Safety Evaluation of Pharmaceutical Excipients

<http://www.fda.gov/cder/Guidance/5544fnl.htm>

Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product

<http://www.emea.europa.eu/pdfs/human/qwp/39695106en.pdf>

France: L`information de référence sur les produits de santé

<http:// Vidal.fr>

US FDA/ CDER: Inactive Ingredient Database

<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>

Thank you for your attention!



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