FORMALIZOVANA PROCENA RIZIKA ZA UPOTREBU POMOĆNIH SUPSTANCI ZA PROIZVODNJU NESTERILNIH LEKOVA

SA ASPEKTA PROIZVODJACA LEKOVA

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Beograd, Februar 2022

POMOĆNE SUPSTANCE

- Do 90% gotovog farmaceutskog proizvoda može biti ekscipijent
- Ekscipijenti obično nemaju farmaceutski efekat

Ekscipijent:
bilo koji sastojak osim API-ja i pakovanja!

- **ALI:** može uticati na API funkciju / galenske proizvode! (primer: bioraspolozlivost)

pr. može uvesti kontaminacije

➡ smrti od kontaminacije dietilen glikolom u glicerolu (2006.)

Regulativa

SMERNICE ZA FORMALIZOVANU PROCENU RIZIKA ZA ODREĐIVANJE ODGOVARAJUĆE DOBRE PROIZVOĐAČKE PRAKSE ZA POMOĆNE SUPSTANCE KOJE SE UPOTREBLJAVAJU U PROIZVODNJI LEKOVA ZA HUMANU UPOTREBU (2015/C 95/02)

Ove smernice su donete na osnovu odredbe petog stava člana 47. Direktive 2001/83/EC

Nosilac dozvole za proizvodnju lekova dužan je da, utvrđivanjem odgovarajuće deobe proizvođačke prakse, obezbedi da pomoćne supstance (ekscipijensi) budu odgovarajuće za upotrebu u proizvodnji lekova.

Odgovarajuća dobra proizvođačka praksa za pomoćne supstance za proizvodnju lekova za humanu upotrebu utvrđuje se na osnovu formalizovane procene rizika u skladu sa ovim smernicama

POMOĆNE SUPSTANCE - vrste i funkcije

- **Vezivna sredstva – Drže sastojke zajedno**

(Laktoza, manitol • Skrob, celuloza • Želatin • PVP, PEG)

- **Vezivno sredstvo za raspadanje**

(Cellulose, microcrystalline)

- **Boi, aromi, zasladjivaci**

- **Sredstvo protiv slepljivanja ili sredstvo za klizanje**

(Talc, Sillica)

- **Sredstvo za povećanje viskoziteta**

(Carbomer)

- **Konzervansi**

(Parabeni, Limunska kiselina, Vitamin A)

FORMALIZOVANU PROCENU RIZIKA - POMOĆNE SUPSTANCE

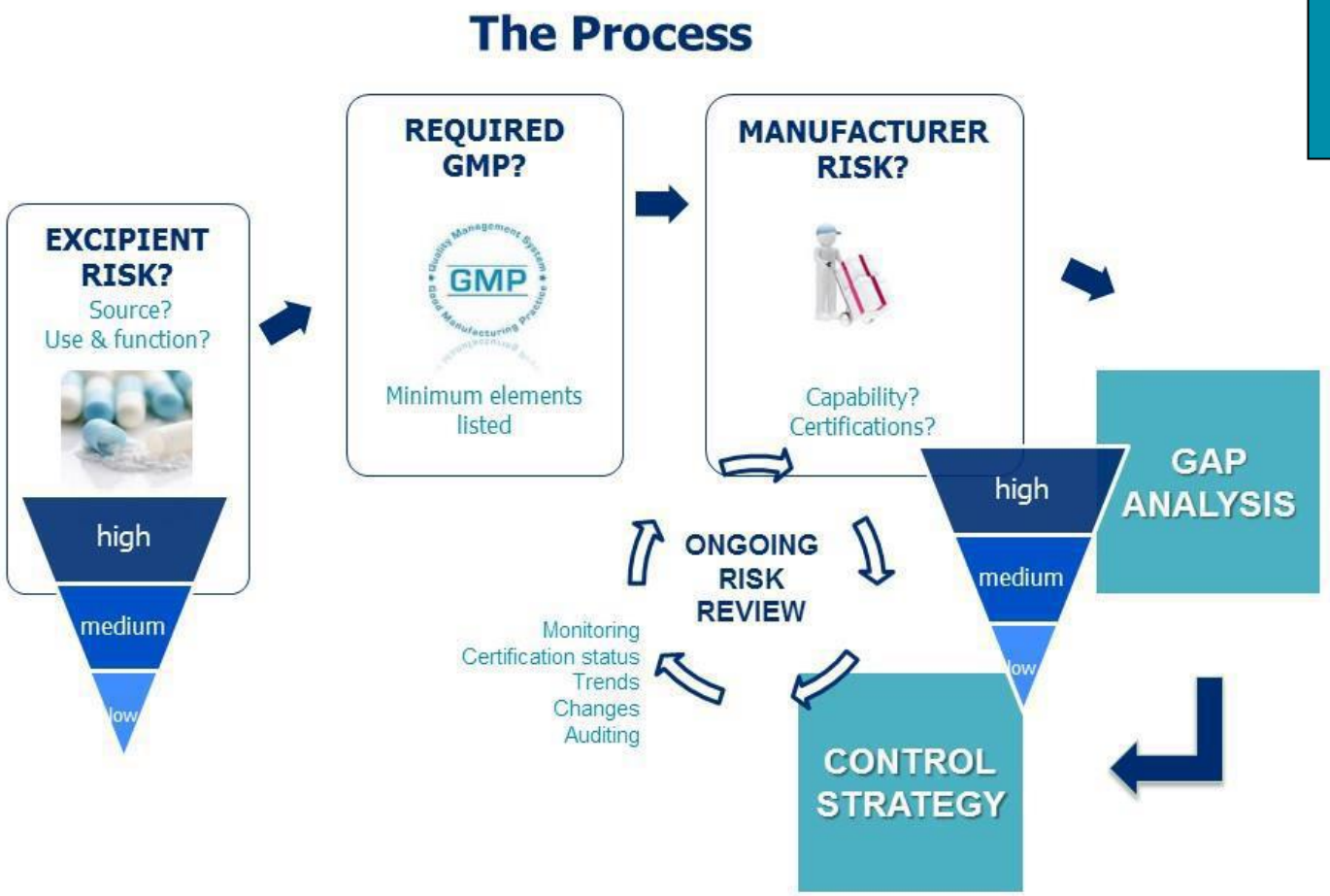
Smernica *ICH Q9*, sadrži načela i primere alata za Upravljanje rizikom kvaliteta koji se mogu primeniti na pomoćne supstance

Načela Upravljanja rizikom kvaliteta treba primenjivati za procenu rizika kvaliteta, bezbednosti i funkcije svih pomoćnih supstanci, kao i za klasifikaciju pomoćne supstance, npr. kao niskorizične, srednjerizične ili visokorizične

REGULATIVA

1. Za svaku upotrebljenu pomoćnu supstancu svakog proizvođača, proizvođač lekova treba da utvrdi rizike u pogledu kvaliteta, bezbednosti i delovanja svake pomoćne supstance od njenog porekla - bilo životinjskog, mineralnog, biljnog, sintetskog itd. - do njenog ugrađivanja u gotov farmaceutski oblik
2. Nakon utvrđivanja i dokumentovanja profila rizika pomoćne supstance, proizvođač lekova treba da utvrdi i dokumentuje elemente iz važeće smernice dobre proizvođačke prakse, za koje smatra da su potrebni za kontrolu i održavanje kvaliteta pomoćne supstance
3. Nakon utvrđivanja odgovarajuće dobre proizvođačke prakse potrebno je izvršiti analizu aktivnosti i sposobnosti proizvođača pomoćne supstance radi utvrđivanja razlika u odnosu na propisanu dobru proizvođačku praksu.
4. Nakon utvrđivanja odgovarajuće dobre proizvođačke prakse za pomoćnu supstancu i profila rizika proizvođača pomoćne supstance, treba da se sprovodi stalna analiza rizika

Na osnovu rezultata analize rizika, potrebno je preispitivanje i izmena utvrđene strategije kontrole.



Supplier Risk Category	Material & Usage Risk Level			
	Low	Medium	High	
High	Medium	High	High	
Medium	Low	Medium	High	
Low	Low	Low	Medium	

Najjednostavniji pristup objedinjujući sve informacije u dve vrednosti

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Rizik:
5=high risk;
3=medium risk;
1=low risk

Pomocna supstanca – TALC

Potrebno je definirati:

Naziv pomocne supstance: TALC

Dobavljac: Kompanija A

Proizvodjac: Kompanija B

1- Priroda pomocne supstance

Excipient poreklo	TSE/BSE Risk	mogućnost virusne kontaminacije	mogućnost mikrobiološke ili kontaminacije endotoksinima/ pirogenima	moguće prisustvo nečistoća poreklom iz sirovina, npr. aflatoksini ili pesticidi,	nečistoća koje nastaju tokom procesa i prenose se u proizvod, npr. ostaci rastvarača i katalizatori;	moguće prisustvo drugih nečistoća prenesenih iz drugih procesa, u nedostatku namenske opreme i/ili pogona	kontrolu ambijentalnih i uslova skladištenja/transporta, uključujući i upravljanje hladnim lancem	složenost lanca snabdevanja	stabilnost pomoćne supstance	dokaze o integritetu pakovanja
1	1	1	1	1	5	5	1	5	1	1

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Rizik:
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Pomocna supstanca – TALC

1- Priroda pomocne supstance

Excipient poreklo	TSE/BSE Risk	mogućnost virusne kontaminacije	mogućnost mikrobiološke ili kontaminacije endotoksinima/ pirogenima	moguće prisustvo nečistoća poreklom iz sirovina, npr. aflatoksini ili pesticidi,	nečistoća koje nastaju tokom procesa i prenose se u proizvod, npr. ostaci rastvarača i katalizatori;	moguće prisustvo drugih nečistoća prenesenih iz drugih procesa, u nedostatku namenske opreme i/ili pogona	kontrolu ambijentalnih i uslova skladištenja/transporta, uključujući i upravljanje hladnim lancem	složenost lanca snabdevanja	stabilnost pomoćne supstance	dokaze o integritetu pakovanja
3	1	1	1	1	5	5	3	5	1	1

- **poreklo:** životinjskog (5) mineralnog, biljnog (3) sintetskog (1)
- **TSE:** nemamo informaciju (5) životinjskog (3) mineralnog, biljnog, sintetskog (1)
- **virusne kontaminacije**: informacija od dokumentacije proizvodjaca (znamo da nisu bioloski produkti rizik =1)
- **mikrobiološke ili kontaminacije endotoksinima/pirogenima**: informacija od dokumentacije proizvodjaca (sintetsko/mineralno poreklo rizik = 1)
- **moguće prisustvo nečistoća poreklom iz sirovina, npr. aflatoksini ili pesticide:** informacija od dokumentacije proizvodjaca (sintetsko/mineralno poreklo rizik = 1)
- **nečistoća koje nastaju tokom procesa i prenose se u proizvod:** informacija od dokumentacije proizvodjaca (nemamo informaciju (5)
- **moguće prisustvo drugih nečistoća prenesenih iz drugih procesa, u nedostatku namenske opreme i/ili pogona:** namenska oprema/pogon (1), namenska oprema (3), nenamenska oprema/pogon (5)

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

Excipient poreklo	TSE/BSE Risk	mogućnost virusne kontaminacije	mogućnost mikrobiološke ili kontaminacije endotoksinima/ pirogenima	moguće prisustvo nečistoća poreklom iz sirovina, npr. aflatoksini ili pesticidi,	nečistoća koje nastaju tokom procesa i prenose se u proizvod, npr. ostaci rastvarača i katalizatori;	moguće prisustvo drugih nečistoća prenesenih iz drugih procesa, u nedostatku namenske opreme i/ili pogona	kontrolu ambijentalnih i uslova skladištenja/transporta, uključujući i upravljanje hladnim lancem	složenost lanca snabdevanja	stabilnost pomoćne supstance	dokaze o integritetu pakovanja
3	1	1	1	1	5	5	3	5	1	1

Rizik:

5=high risk;

3=medium

1=low risk

- **kontrolu ambijentalnih i uslova skladištenja/transporta, uključujući i upravljanje hladnim lancem**

Proizvodni uslovi / čuvanje / transport bez potrebne kontrole = 1
Proizvodni uslovi / čuvanje / transport do 30°C = 3
Proizvodni uslovi / čuvanje / transport od 2-8°C ili 8-15°C = 5

- **složenost lanca snabdevanja**

Snabdevanja direktno od proizvođača = 1
Snabdevanja preko jedan trgovac = 3
Snabdevanja preko vise od jednog trgovca = 5

- **dokaze o integritetu pakovanja**

Temper seal, originalna etiketa proizvođača; pakovanje je čvrsto = 1
Originalna etiketa proizvođača; pakovanje je čvrsto = 3
Originalna etiketa proizvođača; pakovanje se lako može kompromitovati = 5

- **stabilnost pomoćne supstance**

Ekscipijent je stabilan, proizvođač je dostavio izjavu / studiju stabilnosti = 1
Ekscipijent je stabilan (* iskustveno), proizvođač nije dostavio izjavu / studiju stabilnosti = 3
Ekscipijent nije stabilan ili proizvođač nije pružio adekvatan dokaz = 5

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

Dokumentacija proizvodjaca

Specifikacija, SDS lista, izjave, Technical Data Sheet, Regulatory Data sheet, upitnik…

General product information

Product origin:	Mineral
Geographic origin:	Europe
CAS #:	14807-96-6
EINECS#:	238-877-9
Customs Code:	2526 20 00

BSE (Bovine Spongiform Encephalopathy) / TSE (Transmissible Spongiform Encephalopathy)

EMEA/410/01 guidelines on BSE/TSE are not relevant as these talc grades are mineral products; they are not derived from animal or human origin products and have not come in contact with such products during the manufacturing process. They should not, therefore, transmit Bovine Spongiform Encephalopathy or Transmissible Spongiform Encephalopathy.

Allergens

Talc is a naturally occurring mineral.
None of the allergens listed in the regulations below are contained or added during any stage of the production process of these talc grades.
For more information on the allergens refer to :
- Annex III, reference 67 to 92 of the European Regulation (CE) n°1223/2009;
- Annex II of European Regulation (UE) N°1169/2011 on the provision of food information to consumers.

Residual solvents

No chemical additives, including solvents, are used or added during any stage of the production process. Therefore, these grades are compliant with ICH Q3C (R7) of European Medicine Agency (Guidelines for residual solvents – 15 October 2018) and US Pharmacopoeia general chapter <467>.

Shelf life

These talc grades are chemically stable, inert and non-reactive. They can, therefore, be stored for an indefinite period in a cool, clean and dry covered area with no significant detrimental effects. These talc grades do not have an expiry date and do not have a shelf life when stored in original containers and as instructed. However a 60 month shelf life is recommended (unless otherwise stated in the Certificate of Analysis).

2.2 – Undesirable substances

Imerys Talc Europe produces its uncoated talc products from natural ores that have simply been processed.
No treatment by irradiation or ionisation is done during the manufacturing process; and no radioactive product has intentionally been added.

None of the following product categories are used in the manufacturing process of our uncoated talc products:
- Any product of vegetal origin, in particular latex, gluten or aflatoxins, genetically modified organism (GMO) or genetically modified derived ingredient;
- Any pesticides, mycoplasme or molds, vegetal hormones or growth promoters;
- Any product of animal/human origin and therefore cannot transmit Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathy (BSE/TSE);
- Endocrine disruptors;
- Preservatives or antioxidants.

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

Rizik:

5=high risk;

3=medium risk;

1=low risk

2- Uloga u formulaciji

farmaceutski oblik	udeo pomoćne supstance u sastavu leka	funkciju pomoćne supstance u formulaciji	poznati ili mogući uticaj na kritična svojstva kvaliteta leka	Acceptable Daily Intake- ADI	ADI Risk	poznate defekte na globalnom nivou	složenost sastava pomoćne supstance
1	(20%) 1	Sredstvo protiv slepljivanja ili sredstvo za klizanje	1	ADI not specified	1	1	1

- **farmaceutski oblik**

Oralni cvrsti formi = 1

Oralni tečni formi, Polucvrsti formi = 3

Sterilni formi = 5

- **udeo pomoćne supstance u sastavu leka**

0-25% = 1

25 – 50% = 3

>50% = 5

- funkciju pomoćne supstance u formulaciji

Sredstvo protiv slepljivanja, sredstvo za klizanje, Vezivno sredstvo, Lubrikans = 1

Zaslađivač, boja, emulgator, emolijens, zgusnjivac, kapsula, Antipeneće sredstvo = 3

Stabilizator, aroma, antioksidans, antimikrobna sredstva, Rastvarač = 5

- **ADI rizik***

Pomoćne supstance koje se ne resorbuju, ADI nije specificiran, ADI nije limitiran, ADI nije dodeljen; nad 1000 mg/den; nad 1000 mg/kg/bw = 1

100-1000 mg/ден; 100-1000 mg/kg/bw = 3

Nema podatke; 0-100 mg/ден; 0-100 mg/kg/bw = 5

*

ADI: According to manufacturer's Regulatory documentation

ADI: According to JECFA (Joint FAO/WHO Expert Committee on Food Additives)

ADI: According to the Annex of the European guideline CPMP/463/00 "Excipients in the label and package leaflet of the medicinal products for human use

ADI: According to manufacturer's specification/recommendation

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

2- Uloga u formulaciji

farmaceutski oblik	udeo pomoćne supstance u sastavu leka	funkciju pomoćne supstance u formulaciji	poznati ili mogući uticaj na kritična svojstva kvaliteta leka	Acceptable Daily Intake- ADI	ADI Risk	poznate defekte na globalnom nivou	složenost sastava pomoćne supstance
1	(20%) 1	Sredstvo protiv slepljivanja ili sredstvo za klizanje	1	ADI not specified	1	1	1

- poznate defekte na globalnom nivou

Dobra istorija kvaliteta širom sveta (ni jednom u tri godine)= 1

Retki problemi sa kvalitetom (jednom u tri godine) = 3

Istorija lošeg kvaliteta na globalnom nivou (više od jednom u tri godine); poznat slučaj falsifikata = 5

- **složenost sastava pomoćne supstance**

Jedna komponenta = 1

Dve ili tri komponenti = 3

Vise od tri = 5

Rizik:

5=high risk;

3=medium risk;

1=low risk

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

3- Održiv kvalitet

Poznate defekte na lokalnom nivou	Provera (Audit)
1	3

- poznate defekte na lokalnom nivou
Nisu registrovani nedostaci u kvalitetu = 1
Najmanje jedan nedostatak kvaliteta je registrovan = 3
Registrovano je nekoliko nedostataka kvaliteta = 5

- **Provera (Audit)**
Uradjena u poslednjih 5 godina = 1
Uradjena, zadnja provera vise od 5 godina = 3
Nije uradjena, negativan ishod = 5

Rizik:
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3=medium risk;
1=low risk

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

Rizik:

5=high risk;

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Excipient poreklo	TSE/BSE Risk	mogućnost virusne kontaminacije	mogućnost mikrobiološke ili kontaminacije endotoksinima/ pirogenima	moguće prisustvo nečistoća poreklom iz sirovina, npr. aflatoksini ili pesticidi,	nečistoća koje nastaju tokom procesa i prenose se u proizvod, npr. ostaci rastvarača i katalizatori;	moguće prisustvo drugih nečistoća prenesenih iz drugih procesa, u nedostatku namenske opreme i/ili pogona	kontrolu ambijentalnih i uslova skladištenja/transporta, uključujući i upravljanje hladnim lancem	složenost lanca snabdevanja	stabilnost pomoćne supstance	dokaze o integritetu pakovanja
3	**1**	**1**	**1**	**1**	**5**	**5**	**1**	**5**	**1**	**1**

farmaceutski oblik	udeo pomoćne supstance u sastavu leka	funkciju pomoćne supstance u formulaciji	poznati ili mogući uticaj na kritična svojstva kvaliteta leka	Acceptable Daily Intake- ADI	ADI Risk	poznate defekte na globalnom nivou	složenost sastava pomoćne supstance
1	**(20%) 1**	Sredstvo protiv slepljivanja ili sredstvo za klizanje	**1**	ADI not specified	**1**	**1**	**1**

Poznate defekte na lokalnom nivou	Provera (Audit)
1	**3**

Risk assessment		
Total risk	Total possible risk	Risk score
35	**95**	**36.8**

Rizik (%) = zbir svih rizika / ukupan mogući maksimalni rizik x 100

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – TALC

Rizik:
5=high risk;
3=medium
1=low risk

Risk assessment			Gap analysis and defining appropriate actions		
Total risk	Total possible risk	Risk score	Appropriate GMP level	Actual GMP Level	Action needed
35	95	36.8	ISO 9001 + Part of EudraLex Volume 4	EXCiPACT+ ISO 9001	Annual review of documentation

Risk Score	Level	Appropriate GMP level
< 25%	Low Risk	ISO 9001
26-50%	Medium Risk	ISO 9001 + Part of EudraLex Volume 4
51-75%	High Risk	EXCiPACT certificate
>75%	Critical Risk	EU GMP, Vol. 4, Part II

- Ako proizvođač poseduje ekvivalentan ili viši nivo GMP od onog koji proizilazi iz analize rizika, tada se za tog proizvođača preporučuje samo praćenje kvaliteta proizvoda i ažuriranje potrebne dokumentacije koja dokazuje odgovarajući GMP status. Za takve proizvođače se preporučuje uvođenje reduciranog testiranja vlezne kontrole

- Ako proizvođač ima niži nivo GMP od onog definisanog analizom rizika, tada za tog proizvođača treba identifikovati i dokumentovati elemente EudraLex part 4 zahteva za koje se smatra da su neophodni da bi se obezbedila adekvatna kontrola kvaliteta ekscipijensa. U takvim slučajevima preporučuje se intenzivnija komunikacija u odnosu na deo koji treba da bude obuhvaćen određenom izjavom ili dokumentacijom, a ako nije dostupan, preporučuje se provera proizvodnih objekata, skladišta ili lanca snabdevanja materijalom .

- Na kraju, ako je rizik drastično veći i ne može se smanjiti i prihvatiti, preporučuje se suspendovanje dobavljača/proizvođača i pronalaženje novog.

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – Laktoza

Rizik:
5=high risk;
3=medium
1=low risk

Sifra	Excipient	Dobavljac	Proizvodjac	Adresa
123456	LACTOSE MONOHYDRATE	Company 1	Company 2	XXXXX

Excipient poreklo	TSE/BSE Risk	mogućnost virusne kontaminacije	mogućnost mikrobiološke ili kontaminacije endotoksinima/pirogenima	moguće prisustvo nečistoća poreklom iz sirovina, npr. aflatoksini ili pesticidi,	nečistoća koje nastaju tokom procesa i prenose se u proizvod, npr. ostaci rastvarača i katalizatori;	moguće prisustvo drugih nečistoća prenesenih iz drugih procesa, u nedostatku namenske opreme i/ili pogona	kontrolu ambijentalnih i uslova skladištenja/transporta, uključujući i upravljanje hladnim lancem	složenost lanca snabdevanja	stabilnost pomoćne supstance	dokaze o integritetu pakovanja
5	**1**	**1**	**1**	**1**	**1**	**5**	**3**	**3**	**1**	**1**

farmaceutski oblik	udeo pomoćne supstance u sastavu leka	funkciju pomoćne supstance u formulaciji	poznati ili mogući uticaj na kritična svojstva kvaliteta leka	Acceptable Daily Intake- ADI	ADI Risk	poznate defekte na globalnom nivou	složenost sastava pomoćne supstance	**Poznate defekte na lokalnom nivou**	**Provera (Audit)**
1	**(60%) 5**	Tablet/ Capsule filler and binder	**1**	1g	**3**	**1**	**1**	**1**	**5**

Risk assessment			**Gap analysis and defining appropriate actions**		
Total risk	**Total possible risk**	**Risk score**	**Appropriate GMP level**	**Actual GMP Level**	**Action needed**
41	**95**	**43.2**	**ISO 9001 + Part of EudraLex Volume 4**	**EXCiPACT**	**Annual review of documentation**

Rizik (%) = zbir svih rizika / ukupan mogući maksimalni rizik x 100

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – Laktoza

Dokumentacija proizvodjaca – Excipient Information Package

Section 2 – Manufacturing, Packaging, Release Site, and Supplier Information

Site of production, packaging, product release, warehousing	**Molkerei MEGGLE Wasserburg GmbH & Co. KG** **Megglestr. 6-12** **83512 Wasserburg** **Germany** Further on referred to as **MEGGLE**. **MEGGLE** is a global supplier and one of the largest and best-known consumer dairy-product manufacturers in Europe as well as one of the leading producers of pharmaceutical excipients worldwide. **MEGGLE** is a subsidiary of Meggle AG. Organizational charts are available on request.
Other production sites	For milled **Product** Production site: Davisco Food International, Inc., Le Sueur, MN, USA
Other warehousing sites	Other qualified warehousing sites are authorised.
Site of Analytical testing / Contract labs	**MEGGLE** In addition, qualified contract labs are authorised. Responsibility for the outsourced analyses remains with MEGGLE.
Exclusive Distribution Channels	No
GMP or GDP compliance statement / EXCiPACT™	GMP according to the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients and USP General Information Chapter <1078> is implemented. GDP principles, based on the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients, are implemented. **MEGGLE** is GMP and GDP certified according to EXCiPACT™ standard for the manufacturing, testing, storage and distribution of lactose and co-processed excipients used as pharmaceutical excipient or claimed for pharmaceutical use.
Multi-purpose site	The site is a multipurpose site authorized by the German Official Veterinary Authorities according to EC Hygiene Regulation (EC) No. 853/2004 for dairy operation.
Multi-purpose / dedicated equipment	Sieved and milled **Product** is manufactured and packed on dedicated equipment. Cleaning validation is installed. Agglomerated **Product** is manufactured and packed on equipment on which excipients based on the **Product** are produced also. Cleaning validation is installed. Spray-dried **Product** is produced on equipment where mainly excipients based on the **Product** are produced. Cleaning validation is installed.

Section 3 – Physical-chemical Information

CAS Number	64044-51-5
EINECS Number	200 559 2
Chemical information	Chemical Name: O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate Molecular formula: $C_{12}H_{22}O_{11}\cdot H_2O$ Molecular weight: 360.3
Origin Information	Animal origin. The **Product** is produced from whey which is gained from milk (bovine).
Synonyms	Milk sugar; INCI name: Lactose
Brief description of manufacture	The **Product** is produced in accordance with the general procedures published in the journal "Die Pharmazeutische Industrie" Vol. 56, (1994) No. 9, p.835:

1. Whey	Raw material: Whey with a pH value between 3.5 and 6.5 and a dry matter (DM) content of approx. 6 %.
2. Concentration	The raw material is concentrated in a vacuum evaporator until the dry matter content reaches approx. 60 %. During the process the temperature exceeds 60 °C (140 °F) for some minutes.
3. Crystallization	The concentrate is cooled down. Lactose crystallises.
4. Separation	The lactose crystals are separated with the help of decanters/screen centrifuges.
5. Washing	The lactose crystals are washed several times with drinking water. → Starting Material: Edible grade lactose
6. Refining **1st GMP relevant step**	A 60 % solution is obtained from washed crystals by adding hot water (drinking water). Activated coal/inorganic filter auxiliaries are added. Refining takes place at more than 97 °C (206 °F) and during a period of more than 30 minutes.
7. Filtration	Refining is followed by filtration at approx. 95 °C (203 °F).
8. Crystallization	The pure lactose solution is cooled down. Lactose crystallises.
9. Separation	The lactose crystals are separated with the help of decanters/screen centrifuges.
10. Drying	Drying of lactose crystals with the crystals reaching a temperature of more than 70 °C (158 °F).
11. Finishing	In physical process the desired granulation or modification is brought about; subsequently, the product is packaged.

Detailed description of manufacture	Starting material Starting material for the **Product** is edible grade lactose. Edible grade lactose is produced by **MEGGLE** from raw material bovine whey. List of approved suppliers for raw material whey is installed. Suppliers of raw material whey have been qualified, are evaluated continuously and audited according to audit plan. Raw material whey is bought according to specification and tested and approved by **MEGGLE**. Testing is performed according to defined sample code (frequency, sampling, parameters, methods, limits).
	Water For production of sieved and milled **Product** water intended for human consumption according to Directive 98/83/EC is used which is obtained from own wells. For production of agglomerated and spray-dried **Product** demineralised water made from water intended for human consumption according to Directive 98/83/EC is used. The water is treated with UV and filtered. No chemical treatment. For production of demineralised water the water is treated with ion-exchanger, with reverse-osmosis, with UV and is filtered. Drinking water comes from own wells. Internal and external analytical control of the water according to Directive 98/83/EC and defined MEGGLE sample code is installed. Internal and external analytical control of demineralised water according to defined MEGGLE sample code is installed. Production The **Product** is produced in accordance with the above mentioned flow chart. The first GMP relevant step is the refining of starting material edible grade lactose. Continuous production. Closed equipment. Sieves and permanent magnet (approx. 9000 Gauss) are installed. Packaging, Labelling Packaging directly in line after production. Filtered air and over pressure in the packaging area. Monitoring of temperature and humidity in packaging area. Only new packaging. Packaging is not reused. Labelling of bags: Pre-printed bags and printing of lot code during packaging. Packaging has a tamper proof closure. Warehousing, Transport No opening of packaging after production. Electronical control of quarantine/hold/release status in warehouse computer system. FIFO is performed. Monitoring of temperature and humidity in the warehouse. Transport: See Part III of the EIP Quality Control IPC testing according to defined sample code (frequency, sampling, parameters, methods, limits). Testing of finished product according to defined sample code (frequency, sampling, parameters, methods, limits). Retained samples Retained samples are kept for shelf life + 1 year.

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – Laktoza

Dokumentacija proizvodjaca – Excipient Information Package

Section 4 - Regulatory Information

Compendial compliance and other regulatory status	The Product complies with - the monograph "Lactose Monohydrate" of Ph. Eur. This monograph is harmonized with USP-NF and JP. - Codex Standard for sugars No 212-1999. - FCC monograph "Lactose". - Standard of Identity 21CFR 168.122.
Drug Master File (DMF) or EDQM Certificate of Suitability or other Master File Availability	No DMF submitted. No EDQM Certificate of Suitability applied for. No other Master File submitted.
Animal testing	See www.meggle-pharma.com
Aflatoxin	
Allergens	
BSE / TSE	
Conflict minerals	
Genotoxic impurities	
Gluten	
GMO	
GMP, GDP, EXCiPACT™	
GRAS, Inactive ingredient Database	
Ionising radiation	
Latex	
Melamine, cyanuric acid	
Metal catalysts and metal reagent residues	
Nanotechnology	
Nutritional Values	
Packaging material	
Proposition 65	
REACH	
Residual Solvents	
Stability tests	
Viral safety	

Section 5 - Miscellaneous Product Information

Lot/Batch Numbering System	L yyww A aaaa with L <year of production> <week of production> A <article number>
Batch Definition	Continuous production of 1 to 7 days within specification.
Expiration date and Recommended Re-evaluation Interval	Shelf life: See www.meggle-pharma.com Recommended storage conditions: See specification Retesting: **MEGGLE** does not define a retest period because **MEGGLE** does not perform any retesting and there is no stability data after the shelf life available from **MEGGLE**. Under the full responsibility of the customer, the customer may retest and use the products after the defined shelf life. For this **MEGGLE** will not accept any liability
Composition declaration	**100% Lactose Monohydrate Ph. Eur. / USP-NF / JP**
Common uses	Pharmaceutical excipients for oral application
Packaging and labeling information	Packaging material is specified. The Packaging material is new and not reused. The packaging material conforms to all relevant legal requirements for packaging material of Germany and the EC. It is suitable to come into direct contact with the product. The following information is given on the packaging, either printed or labelled. - Trade name of the product / - Identification mark of production site (DE-BY 111-EG) - Description of the product / - Origin - Net weight / - Lot number (Lyyww Azzzz: Explanation see above) - Recommended storage conditions / - "D-Nr xxx.": Production day (001-999) - Expiry Date Y yy W ww (with Y <year> W <week>) / - Sxxxx or "K-Nr.xxxx": Number of package unit - **MEGGLE** address / - Possible:- "F-Nr.": Number of production order Packaging units: See www.meggle-pharma.com Packaging has a tamper proof closure.
MSDS	Material Safety Data Sheet (MSDS) can be provided on request.

PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Pomocna supstanca – Laktoza

Dokumentacija proizvodjaca – Excipient Information Package

Section 2 - Compliance Evidence

ISO registration number and registrar certificates	• All activities of MEGGLE are covered by the certification of ISO 9001 and ISO 14001. • Certificates: See www.meggle-pharma.de • First certification according to ISO 9001 was in 1994. • First certification according to ISO 14000 was in 2001.
GMP Inspections by Competent Authorities (Regulatory Agencies) including outcome	• MEGGLE is liable to the permanent supervision of the Official German Veterinary Authority according to Regulation (EC) No. 853/2004 with identification mark DE-BY 111-EG.
General GMP statements	• GMP according to the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients and USP General Information Chapter <1078> is implemented. • MEGGLE GMP statement: See www.meggle-pharma.com
Other certifications or external audit programs	• Not applicable for Lactose Monohydrate Ph.Eur., USP/NF, JP and co-processed excipients.

SGS

Certificate DE17/819943082

The management system of

MEGGLE GmbH & Co. KG

Megglestr. 6-12
83512 Wasserburg Germany

Has been assessed and certified as meeting the requirements of

EXCiPACT Good Manufacturing Practices and Good Distribution Practices for Pharmaceutical Excipient (2017)

For the following activities

Manufacturing and distribution of lactose-based excipients, co-processed excipients, tabletting agents and blending agents for use as pharmaceutical excipients

This certificate is valid from 01/07/2020 until 30/06/2023 and remains valid subject to satisfactory surveillance audits.
Issue 3. Certified since 27/07/2014.
Re certification audit due before 09/05/2023.
This certificate is not valid without a valid ISO 9001 certificate

Authorised by

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PRIMER PROCENU RIZIKA - POMOĆNE SUPSTANCE

Korisni Linkovi

https://www.ipec-europe.org/guidelines.html

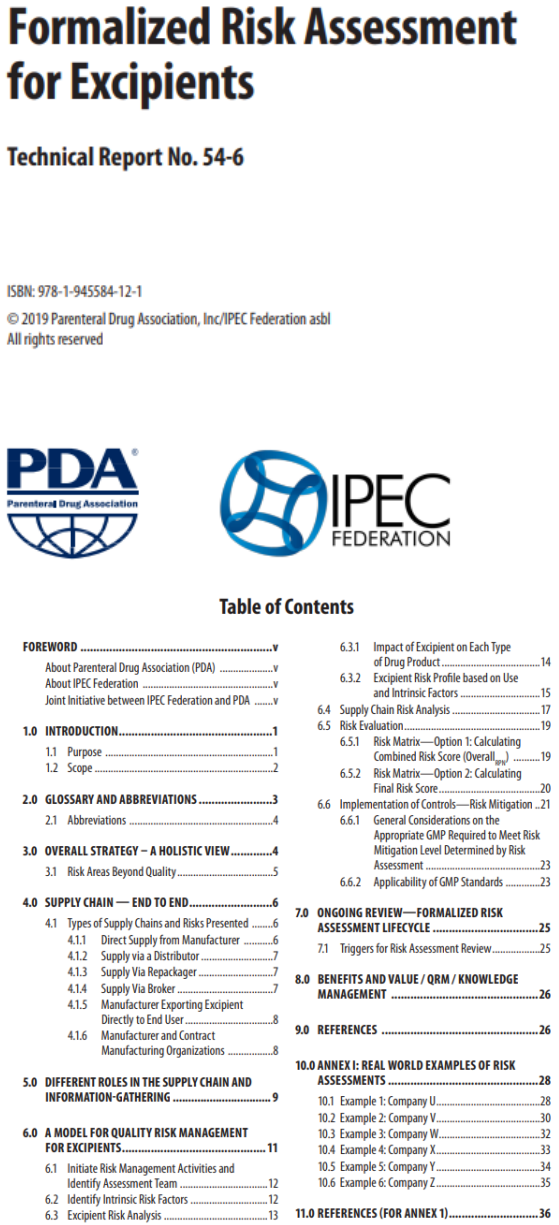
https://www.excipact.org/

EXCiPACT™ je je osnovan od strane nekoliko najuticajnijih farmaceutskih asocijacija, European Fine Chemical Group (EFCG), International Pharmaceutical Excipients Council (IPEC) Europe, IPEC Americas, European Association of Chemical Distributors (FECC), and the Pharmaceutical Quality Group (PQG)

EXCiPACT™ je nezavisna šema koja nadgleda nezavisnu certifikaciju proizvođača i dobavljača ekscipijenasa . Ukoliko proizvođač poseduje ovaj certifikat to znači da je povećana bezbednost za pacijenta kroz povećanje kvaliteta sirovina. Osnovu za EXIPACT GMP i GDP certifikaciju predstavlja ISO 9001:2015.

Technical Report for Formalized Risk Assessment for Excipients
- a model for quality risk assessment for excipients
guidance on key GMP elements required for an excipient considering its source, supply chain and subsequent use
- a collection of actual examples from excipient users in the pharmaceutical industry

https://store.pda.org/TableOfContents/2019TR54-6_TOC.pdf



Formalized Risk Assessment for Excipients

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PDA Parenteral Drug Association

IPEC FEDERATION

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HVALA NA PAŽNJI