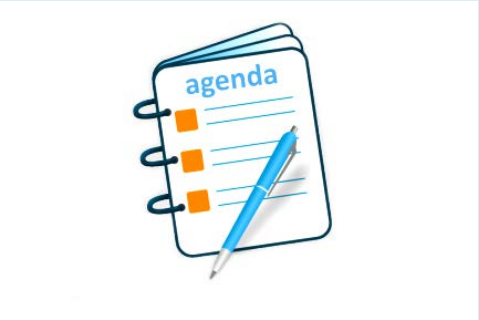
Izazovi u razvoju i primeni monografija gotovih lekova Evropske farmakopeje

Dr. sci. med. spec. Marija Malešević

Sadržaj



Istorijat

- Istorijat Ph. Eur.
- Istorijat monografija gotovih lekova

Struktura monografije gotovih lekova

Izazovi u razvoju monografija

- Različiti profili nečistoća
- Kriterijum za ponovljivost
- Test oslobađanja aktivne supstance

Izazovi u primeni monografija

- Mišljenje regulatornih tela
- Mišljenje kontrolnih laboratorija
- Mišljenje industrije

Zaključak

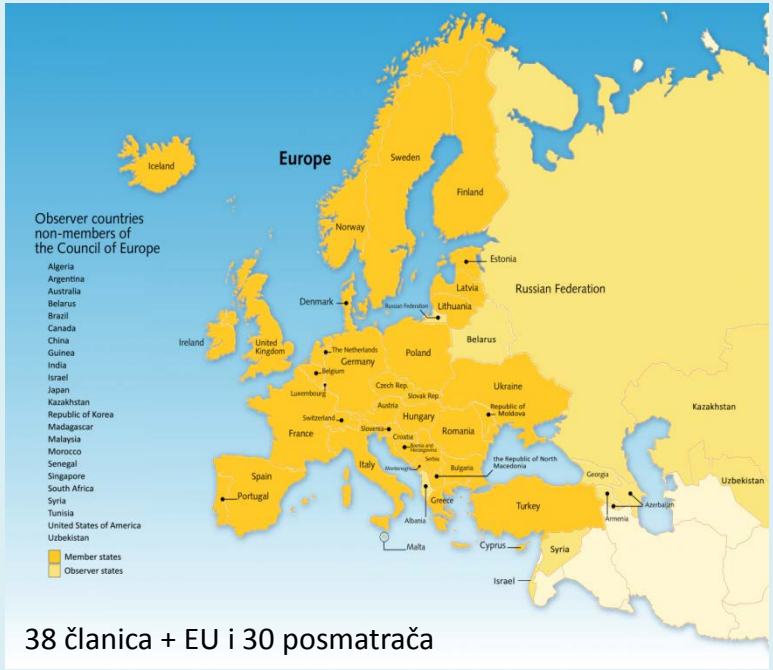
ISTORIJAT

Istorijat Ph. Eur.

- Ustanovljena 1964.

(Konvencija o izradi Evropske farmakopeje)

  - Monografije API i ekscipijenasa
  - Biološki lekovi
  - Homeopatski lekovi
  - Biljni lekovi
  - Radiofarmaceutski lekovi
  - **NIJE obuhvatala monografije gotovih hemijskih lekova**



38 članica + EU i 30 posmatrača

Istorijat monografija gotovih lekova (1)

2012.

- Komisija Ph. Eur. je odobrila pilot projekat razvoja monografija gotovih lekova sa hemijskim API
  - API pod patentnom zaštitom (*single-source*/P4 procedura)
  - API za koje postoje generički proizvođači (*multi-source*/P1 procedura)

2014.

- Prošireno područje primene Ph. Eur. i na gotove lekove (akcenat stavljen na API pod patentnom zaštitom)

2015.

- Odobrena i publikovana prva monografija gotovih lekova u Ph Eur. 8.7 (Sitagliptin tablete)

2016.

- prva monografija gotovih lekova u Ph Eur. stupila na snagu 1. aprila 2016

Istorijat monografija gotovih lekova (2)

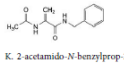
2019.

- publikovana prva monografija gotovih lekova za API za koje postoje generički proizvođači – *multi-source products* (Rosuvastatin tablete

9 usvojenih monografija do sada:

Product	Monograph number	Ph. Eur. supplement
Sitagliptin tablets	2927	8.7
Raltegravir tablets	2938	9.5
Raltegravir chewable tablets	2939	9.5
Lacosamide tablets	2989	9.8
Lacosamide oral solution	2990	9.7
Lacosamide infusion	2991	9.7
Deferiprone tablets	2986	9.8
Deferiprone oral solution	2990	9.7
Rosuvastatin tablets	3008	10.1

STRUKTURA MONOGRAFIJE GOTOVIH LEKOVA



K. 2-acetamido-*N*-benzylprop-2-enamide.

07/2019:2989

LACOSAMIDE TABLETS

Lacosamidi compressi

DEFINITION

Tablets containing *Lacosamide (2992)*.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210–400 nm.

Results: the UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances. Liquid chromatography (2.2.29).

Solvent mixture: acetonitrile R, water R (13:87 V/V).

Test solution. To 10 tablets add a suitable volume of the solvent mixture to obtain a concentration of lacosamide of 2-4 mg/mL. Shake vigorously for 30 min, sonicate for 10 min and allow to stand for 30 min. Dilute a suitable volume of the supernatant with the solvent mixture to obtain a concentration of lacosamide of 1.0 mg/mL.

Reference solution (a). Dissolve 20.0 mg of *lacosamide CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c). Dissolve 2 mg of *lacosamide impurity D CRS* and 3 mg of *lacosamide impurity F CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 10 mL with the solvent mixture.

Column:

- *size: l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase: end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (5 µm);
- *temperature:* 35 °C.

Mobile phase: methanesulfonic acid R, acetonitrile R1, water for chromatography R (0.75:130:870 *V/V/V*).

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 5 µL of the test solution and reference solutions (b) and (c).

Run time: 2.5 times the retention time of lacosamide.

Identification of impurities: use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and F.

Relative retention with reference to lacosamide (retention time = about 6 min): impurity D = about 0.4; impurity F = about 0.5.

System suitability: reference solution (c):

- *resolution:* minimum 1.5 between the peaks due to impurities D and F.

Calculation of percentage contents:

- for each impurity, use the concentration of lacosamide in reference solution (b).

Limits:

- *unspecified impurities:* for each impurity, maximum 0.2 per cent;
- *total:* maximum 1.0 per cent;
- *reporting threshold:* 0.1 per cent.

Dissolution (2.9.3, Apparatus 2).

The tablets comply with the test and the acceptance criterion described below, unless otherwise justified and authorised.

Dissolution medium: 10.3 g/L solution of *hydrochloric acid R*. Use 900 mL of the medium.

Rotation speed: 50 r/min.

Time: 30 min.

Analysis. Liquid chromatography (2.2.29).

Test solutions. Samples withdrawn from the dissolution vessel and filtered.

Reference solution. Using sonication, dissolve a suitable quantity of *lacosamide CRS* in a suitable volume of the dissolution medium to obtain a concentration of lacosamide corresponding to the theoretical concentration of lacosamide in the test solution, based on the labelled content of the tablets.

Column:

- *size: l* = 0.05 m, Ø = 4.6 mm;
- *stationary phase: end-capped octadecylsilyl silica gel for chromatography R* (3 µm);
- *temperature:* 35 °C.

Mobile phase: trifluoroacetic acid R, acetonitrile R1, water for chromatography R (1:300:700 *V/V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 2 µL.

Run time: 2.5 min.

System suitability: reference solution:

- *repeatability:* maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the amount of dissolved lacosamide ($C_{13}H_{18}N_2O_3$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *lacosamide CRS*.

Acceptance criterion:

- *Q* = 80 per cent after 30 min.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection: test solution and reference solution (a).

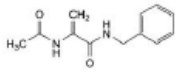
System suitability: reference solution (a):

- *repeatability:* maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the percentage content of lacosamide ($C_{13}H_{18}N_2O_3$) taking into account the assigned content of *lacosamide CRS*.

Opšta pravila

- Obuhvata različite formulacije i jačine istog doziranog oblika sa istom API, kad god je to moguće
- Specifikacija u roku upotrebe leka (*shelf-life spec.*)
- Koristi se u svrhu kontrole kvaliteta leka
- Obavezujuća za sve lekove registrovane u Evropi, ukoliko nije drugačije odobreno
- Retrospektivna primena i na već odobrene lekove
- Proizvođač u svojoj dokumentaciji o leku mora pokazati usklađenost sa monografijom Ph. Eur.



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TESTS

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R, water R* (13:87 *V/V*).

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Mobile phase: *methanesulfonic acid R, acetonitrile R1, water for chromatography R* (0.75:130:870 *V/V/V*).

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Run time: 2.5 times the retention time of lacosamide.

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Relative retention with reference to lacosamide (retention time = about 6 min): impurity D = about 0.4; impurity F = about 0.5.

System suitability: reference solution (c):

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Calculation of percentage contents:

- for each impurity, use the concentration of lacosamide in reference solution (b).

Limits:

- *unspecified impurities*: for each impurity, maximum 0.2 per cent;
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Dissolution (*2.9.3*, Apparatus 2).

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Dissolution medium: 10.3 g/L solution of *hydrochloric acid R*. Use 900 mL of the medium.

Rotation speed: 50 r/min.

Time: 30 min.

Analysis. Liquid chromatography (*2.2.29*).

Test solutions. Samples withdrawn from the dissolution vessel and filtered.

Reference solution. Using sonication, dissolve a suitable quantity of *lacosamide CRS* in a suitable volume of the dissolution medium to obtain a concentration of lacosamide corresponding to the theoretical concentration of lacosamide in the test solution, based on the labelled content of the tablets.

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- *temperature*: 35 °C.

Mobile phase: *trifluoroacetic acid R, acetonitrile R1, water for chromatography R* (1:300:700 *V/V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 2 µL.

Run time: 2.5 min.

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Acceptance criterion:

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ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection: test solution and reference solution (a).

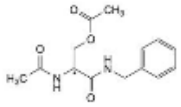
System suitability: reference solution (a):

- *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

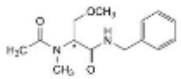
Calculate the percentage content of lacosamide ($C_{13}H_{18}N_2O_3$) taking into account the assigned content of *lacosamide CRS*.

IMPURITIES

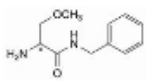
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph): *B, C, D, E, F, I, K*.



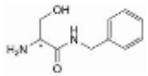
B. (2*E*)-2-acetamido-3-(benzylamino)-3-oxopropyl acetate,



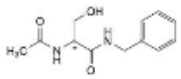
C. (2*E*)-*N*-benzyl-3-methoxy-2-(*N*-methylacetamido)-propanamide,



D. (2*E*)-2-amino-*N*-benzyl-3-methoxypropanamide,

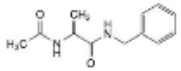


E. (2*E*)-2-amino-*N*-benzyl-3-hydroxypropanamide,



F. (2*E*)-2-acetamido-*N*-benzyl-3-hydroxypropanamide,

I. phenylmethanamine,

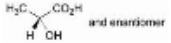


K. 2-acetamido-*N*-benzylprop-2-enamide.

01/2017:0458

LACTIC ACID

Acidum lacticum



$C_3H_6O_3$ M_r 90.1

DEFINITION

Mixture of 2-hydroxypropanoic acid, its condensation products, such as lactoyl-lactic acid and polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It is usually the racemate ((*RS*)-lactic acid).

Content: 88.0 per cent *m/m* to 92.0 per cent *m/m* of $C_3H_6O_3$.

CHARACTERS

Appearance: colourless or slightly yellow, syrupy liquid.

Solubility: miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in 10 mL of *water R*. The solution is strongly acidic (*2.2.4*).

B. Relative density (*2.2.5*): 1.20 to 1.21.

C. It gives the reaction of lactates (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in 42 mL of *1 M sodium hydroxide* and dilute to 50 mL with *distilled water R*.

Appearance. The substance to be examined is not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Ether-insoluble substances. Dissolve 1.0 g in 25 mL of *ether R*. The solution is not more opalescent than the solvent used for the test.

Sugars and other reducing substances. To 1 mL of solution S add 1 mL of *1 M hydrochloric acid*, heat to boiling, allow to cool and add 1.5 mL of *1 M sodium hydroxide* and 2 mL of *cupri-tartaric solution R*. Heat to boiling. No red or greenish precipitate is formed.

Methanol (*2.4.24*): maximum 50 ppm, if intended for use in the manufacture of parenteral preparations.

Citric, oxalic and phosphoric acids. To 5 mL of solution S add *dilute ammonia R1* until slightly alkaline (*2.2.4*). Add 1 mL of *calcium chloride solution R*. Heat on a water-bath for 5 min. Both before and after heating, any opalescence in the solution is not more intense than that in a mixture of 1 mL of *water R* and 5 mL of solution S.

Sulfates (*2.4.13*): maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*): maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*): less than 5 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. Before use, neutralise the test solution to pH 7.0-7.5 with *strong sodium hydroxide solution R* and shake vigorously.

ASSAY

Place 1.000 g in a ground-glass-stoppered flask and add 10 mL of *water R* and 20.0 mL of *1 M sodium hydroxide*. Close the flask and allow to stand for 30 min. Using 0.5 mL of *phenolphthalein solution R* as indicator, titrate with *1 M hydrochloric acid* until the pink colour is discharged.

1 mL of *1 M sodium hydroxide* is equivalent to 90.1 mg of $C_3H_6O_3$.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Naslov i definicija

Naslov

- INN + farmaceutski oblik (bez naziva soli i stepena hidratacije)
- Bez oznake jačine (obuhvata sve odobrene jačine i formulacije, kad god je to moguće)

SITAGLIPTIN TABLETS

Sitagliptini compressi

DEFINITION

Tablets containing *Sitagliptin phosphate monohydrate (2778).* *They comply with the monograph Tablets (0478) and the following additional requirements.*

Content: 95.0 per cent to 105.0 per cent of the content of sitagliptin ($C_{16}H_{15}F_6N_5O$) stated on the label.

Definicija

- Referenca na monografiju API
- Precizan farmaceutski oblik (unakrsna referenca na opštu monografiju za farmaceutske oblike)
- Informacija o obliku soli i stepenu hidratacije
- Informacija o sterilnosti za sterilne proizvode
- Informacija o sadržaju aktivnog principa koja se navodi na pakovnom materijalu

Identifikacija

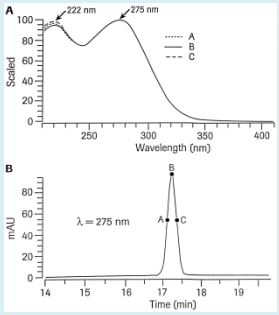
Kombinacija dve metode za nedvosmislenu identifikaciju:

Spektroskopska:

- IR
- UV/VIS

Hromatografska:

- LC
- GC



Najčešća kombinacija:

- UV-spektar
- Rt sa hromatograma

Korišćenje PDA (DAD) detektora

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results: the UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

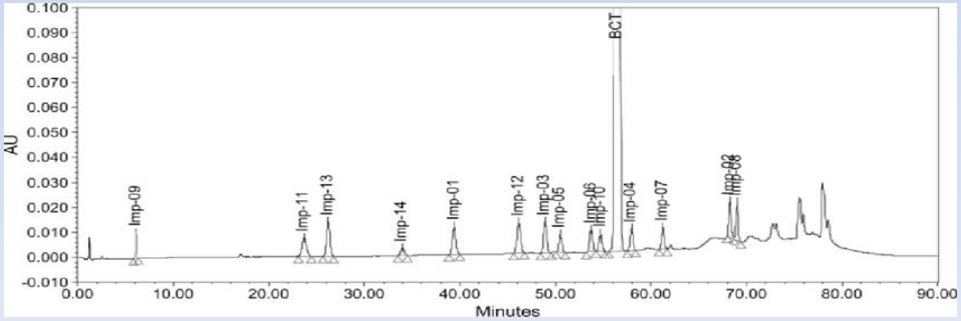
B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

Ispitivanje nečistoća

- Prate se <u>samo degradacioni proizvodi</u>
- <u>Sintetske nečistoće se ne kontrolišu</u> (kontrolisane su u API), osim u slučaju kad su ujedno i degradacioni proizvodi, i ne uzimaju se u obračun za ukupne nečistoće
  - Primer:

reporting threshold : 0.1 per cent; disregard the peaks due to impurities A and B.

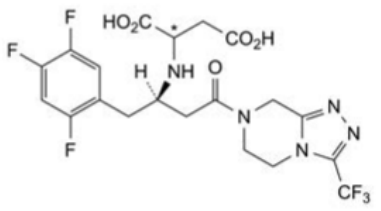


Lista nečistoća

- Na listi se navode <u>sve nečistoće koje se mogu detektovati navedenom metodom</u>
- Nečistoće koje su iste kao načistoće u API zadržavaju iste oznake (npr. Impurity A, B, C ...)
- Nečistoće koje se pojavljuju samo u gotovom proizvodu nose prefiks FP (npr. Impurity FP-A, FP-B, FP-C ...)

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph): *FP-A, FP-B, FP-C, FP-D, FP-E.*



FP-A. 2-[[(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-yl]amino]butanedioic acid,

Određivanje sadržaja

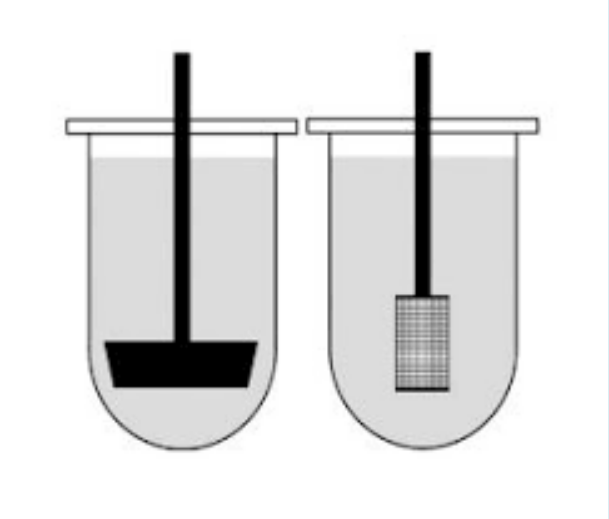
- *Stability-indicating* metoda (najčešće HPLC)
- Zahtev najčešće 95-105%
- Uopšteni zahtevi za ponovljivost (*repetability*) još nisu definisani, već se određuju od slučaja do slučaja
  - najčešće RSD ≤ 1,5% (n=6)
  - ne važi 2.2.46. zahtev, koji se odnosi na monografije API

Table 2.2.46.-1. – *Repeatability requirements*

	Number of individual injections			
	3	4	5	6
B **(per cent)**	**Maximum permitted relative standard deviation**			
2.0	0.41	0.59	0.73	0.85
2.5	0.52	0.74	0.92	1.06
3.0	0.62	0.89	1.10	1.27

Oslobađanje aktivne supstance

- Metoda i zahtevi – obavezujući
- Fleksibilnost: *unless otherwise justified and authorised*
  - General notices: The expresion *„unless otherwise justified and authorised“* means that the requirements have to be met, unless the competent authority authorised a modification or an exemption where justified in particular cases.
- UV ili HPLC metoda - kvantifikacija preko CRS ili specifične apsorbancije
- Raspadljivost umesto oslobađanja za čvrste oralne oblike sa brzorastvarajućom API i trenutnim oslobađanjem - ICH Q6B (npr. *sitagliptin tablets*)



Dissolution (*2.9.3*, Apparatus 2).

The tablets comply with the test and the acceptance criterion described below, unless otherwise justified and authorised.

Dissolution medium: 10.3 g/L solution of *hydrochloric acid R*. Use 900 mL of the medium.

Rotation speed: 50 r/min.

Time: 30 min.

Analysis. Liquid chromatography (*2.2.29*).

Calculate the amount of dissolved lacosamide ($C_{13}H_{18}N_2O_3$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *lacosamide CRS*.

Acceptance criterion:

– Q = 80 per cent after 30 min.

IZAZOVI U RAZVOJU MONOGRAFIJA

- Različiti profili nečistoća
- Kriterijum za ponovljivost
- Test oslobađanja aktivne supstance

Različiti profili nečistoća

- **PROBLEM:**

Profil degradacionih proizvoda može da se razlikuje od formulacije do formulacije (npr. interakcija API sa ekscipijensima)

Da li raditi reviziju metode kad se utvrde nove nečistoće?

Šta ako nije moguće razviti jednu metodu za sve degradacione proizvode od svih proizvođača?

Više od jedne metode za kontrolu nečistoća?

- **REŠENJE:**

Degradacione proizvode koji su različiti od onih u Ph. Eur. monografiji proizvođač mora da prati i kontroliše u svom proizvodu – isti pristup kao i kod monografija API

- Validirana interna metoda

Revizija metode, uključivanje novih degradacionih proizvoda.

Kriterijum za ponovljivost HPLC metode za određivanje sadržaja API

- **API** (zahtev za sadržaj 98-102%):

RSD za 6 injiciranja: 0,85%

- prema Technical guide

- **Gotov lek** (zahtev za sadržaj 95-105%):

RSD za 6 injiciranja: ????

Mogućnosti:

0,85%

2,12%

1,5% - konsenzus Ph. Eur. radne grupe

	Number of individual injections				
	3	4	5	6	10
B (%)	Maximum permitted relative standard deviation				
1.0	0.21	0.30	0.37	0.42	0.60
1.5	0.31	0.44	0.55	0.64	0.90
2.0	0.41	0.59	0.73	0.85	1.20
2.5	0.52	0.74	0.92	1.06	1.51
3.0	0.62	0.89	1.10	1.27	1.81
3.5	0.72	1.04	1.22	1.48	2.11
4.0	0.83	1.19	1.46	1.70	2.41
4.5	0.93	1.33	1.65	1.91	2.71
5.0	1.04	1.48	1.83	2.12	3.01

Test oslobađanja aktivne supstance

- Mora biti dovoljno diskriminatoran da obezbedi:
  - Konzistentnost od serije do serije
  - Konzistentnost sa serijama na kojima je dokazana zadovoljavajuća efikasnost i bezbednost (*bio-batches*)
  - Prepozna serije kod kojih nešto nije u redu
- Zavisi od sastava leka (*product-specific*)

Nedoumice:

- Da li jedan Ph. Eur. test oslobađanja API može da bude primenljiv na različite formulacije od različitih proizvođača?
- Da li uvrstiti više različitih metoda i limita za ispitivanje oslobađanja API u istoj monografiji?

Npr. Diltiazem kapsule USP – 20 *dissolution* metoda

Test oslobađanja aktivne supstance – trenutni pristup

- Ph. Eur. test oslobađanja je obavezujući (*unless otherwise justified and authorised)*
- Služi samo u svrhu kontrole kvaliteta (dokaz da se dovoljna količina aktivne supstance rastvori u razumnom vremenu)
- Nije namenjen da dokaže bioekvivalenciju niti da uporedi disolucione profile u slučaju *biowaver-a*.
- Proizvođač ovo mora da demonstrira za svoj proizvod i da ga uporedi sa referentnim proizvodom

Potencijalni problem:

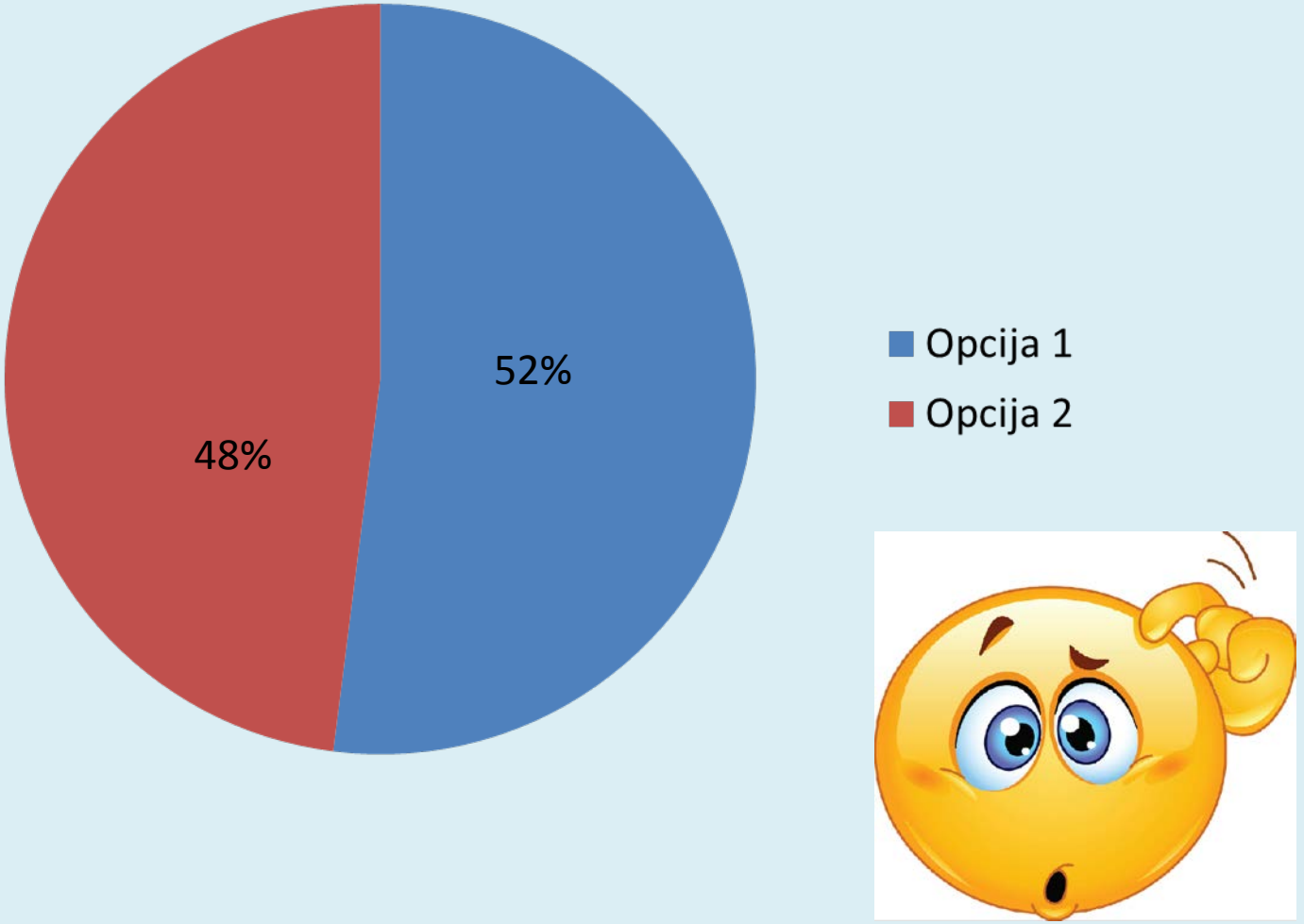
Dodatno vreme za proizvođača da utvrdi (ili NE) usklađenost sa Ph. Eur. – gubitak vremena (DA ili NE?)

DA LI JE OVO DOBAR PRISTUP?

Test oslobađanja aktivne supstance – EDQM upitnik

- Januar 2019. - Upitnik za sve zainteresovane strane: industrija, laboratorije, regulatorna tela, farmakopeje...
- Da li menjati trenutni pristup?
- Dve ponuđene opcije:
  - Opcija 1: trenutni obavezujući pristup + dodatno pojašnjenje za fleksibilnost (*If, for a given medicinal product, this method and the acceptance criterion prove not to be sufficiently discriminatory to assure batch-to-batch consistency, a different method and/or acceptance criterion must be provided in the marketing authorisation application and is subject to approval by the competent authority.”)*
  - Opcija 2: monografija za gotove lekove neće sadržavati ni metodu ni limite za oslobađanje API. Sprovođenje ovog testa ostaje obavezujuće za proizvođača prema opštim monografijama za dozirane oblike, a svaki proizvođač mora imati svoju metodu i limite. Primer metode i limita se može dati u EDQM Knowledge databazi.

Test oslobađanja aktivne supstance – EDQM upitnik rezultati



IZAZOVI U PRIMENI MONOGRAFIJA GOTOVIH LEKOVA

- Mišljenje regulatornih tela
- Mišljenje kontrolnih laboratorija
- Mišljenje industrije

Mišljenje regulatornih tela

Prednosti:

- Harmonizovani standard za celu Evropu – standardizovan kvalitet lekova
- Lakša procena, ukoliko lek odgovara monografiji Ph. Eur.

Potencijalni problemi:

- **Uticaj na postojeće proizvode – retrospektivna primena**
  - Varijacija – usklađivanje sa Ph. Eur. iako je interna metoda odgovarajuća?
  - Dokazivanje ekvivalentnosti između dve metode-interne i farmakopejske (uporedna validacija)
  - Dodatni posao za proizvođača i regulatorno telo
  - Šta ako se utvrdi da proizvod ne odgovara farmakopejskim zahtevima? Povlačenje, iako je on ranije registrovan?
- **Uticaj na nove proizvode:**
  - Svi lekovi moraju da zadovolje jedan standard – potencijalna potreba za širenjem granica (smanjenje kvaliteta)/Da li će procenjivač imati mogućnost da traži suženje granica?
  - Ako proizvod zadovoljava farmakopejski zahtev za *dissolution*, da li proizvođač mora da potvrdi diskriminatornost?
  - Ako proizvod NE zadovoljava farmakopejski zahtev šta raditi? Odbiti proizvod? Revizija monografije? Kad?

Mišljenje kontrolnih laboratorija

Prednost:

Standardizovan metod i zahtevi u farmakopeji olakšavaju laboratorijama kontrolu kvaliteta i vode ka standardizovanom kvalitetu lekova na tržištu.

Mišljenje industrije

Inovator

- Standardizovan kvalitet lekova na tržištu
- Isti zahtevi za sve zemlje Evrope, uz minimalne promene inicijalnih uslova inovatora
- Dodatni resursi i troškovi (dodatni posao oko izrade i implementacije monografije, varijacije...)

Generik

- Standardizovan kvalitet lekova na tržištu
- Isti zahtevi za sve zemlje Evrope
- Dobra početna tačka za razvoj i poređenje generičkih lekova

ZAKLJUČAK

Zaključak

Sve zainteresovane strane smatraju postojanje monografija za gotove lekove u Ph. Eur. pozitivnim korakom.

Najčešće navođene poteškoće i nedoumice su:

- Test oslobađanja aktivne supstance: metoda i zahtevi (obavezujući ili ne?)
- Uticaj na postojeće proizvode (retrospektivna primena) – Šta ako se utvrdi neusklađenost sa Ph. Eur.?
- Da li usklađenost sa monografijom oslobađa proizvođača obaveze sprovođenja studije bioekvivalencije, poređenja disolucionih profila itd.?
- Da li se uskraćuje procenjivaču mogućnost dodatnih zahteva?

ŠTA VI MISLITE?

HVALA NA PAŽNJI!

Agencija za lekove i medicinska sredstva Srbije

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