



VYSOKÁ ŠKOLA  
CHEMICKO-TECHNOLOGICKÁ  
V PRAZE

# ODHALOVÁNÍ PADĚLKŮ LÉČIVÝCH PŘÍPRAVKŮ KOMBINACÍ SPEKTROSKOPICKÝCH A SEPARAČNÍCH TECHNIK

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Martin Kuchař

4.10.2021, Vitatox

# Substandard, falsified (SF) medical products

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WHO definition (2017):

- **Substandards:** "out of specification", authorized medical products that fail to meet either their quality standards or specifications, or both
- **Unregistered/unlicensed medical products:** not undergone evaluation and/or approval by the National or Regional Regulatory Authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation
- **Falsified medical products:** deliberately/fraudulently misrepresent their identity, composition or source.

# Falšování léčiv

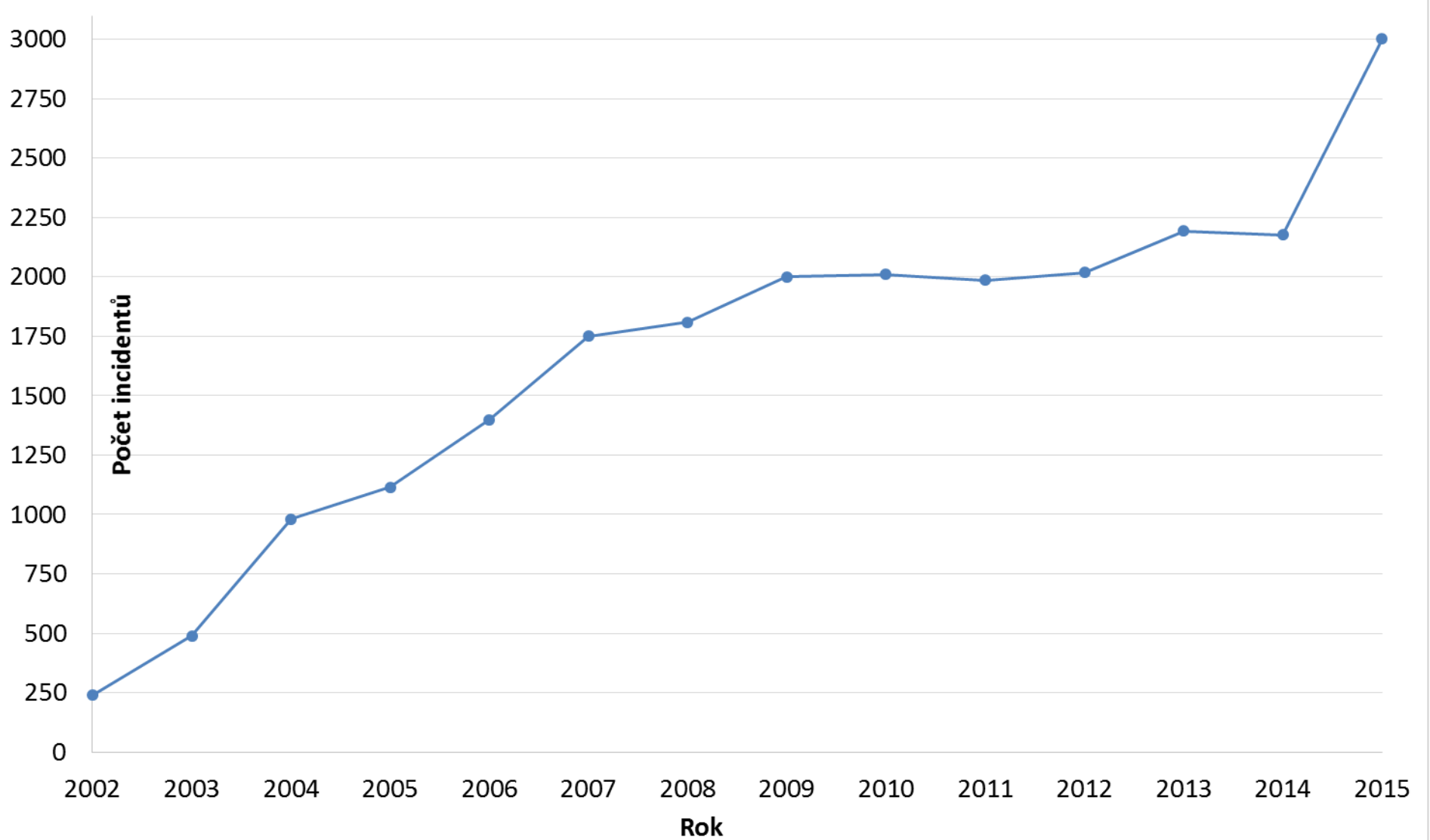
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- Vzdávající fenomén (dostupnost vybavení)
- Jiné API, kontaminaci, prodloužené datum expirace
- Až 20% všech produktů na trhu jsou falzifikáty (objem trhu 50 mld. USD)

- Rozvojový svět: antimalarika, antibiotika
- Rozvinuté země: „life-style“ léčiva, především erektilní dysfunkce, benzodiazepiny a anabolické androgenní steroidy (AAS)



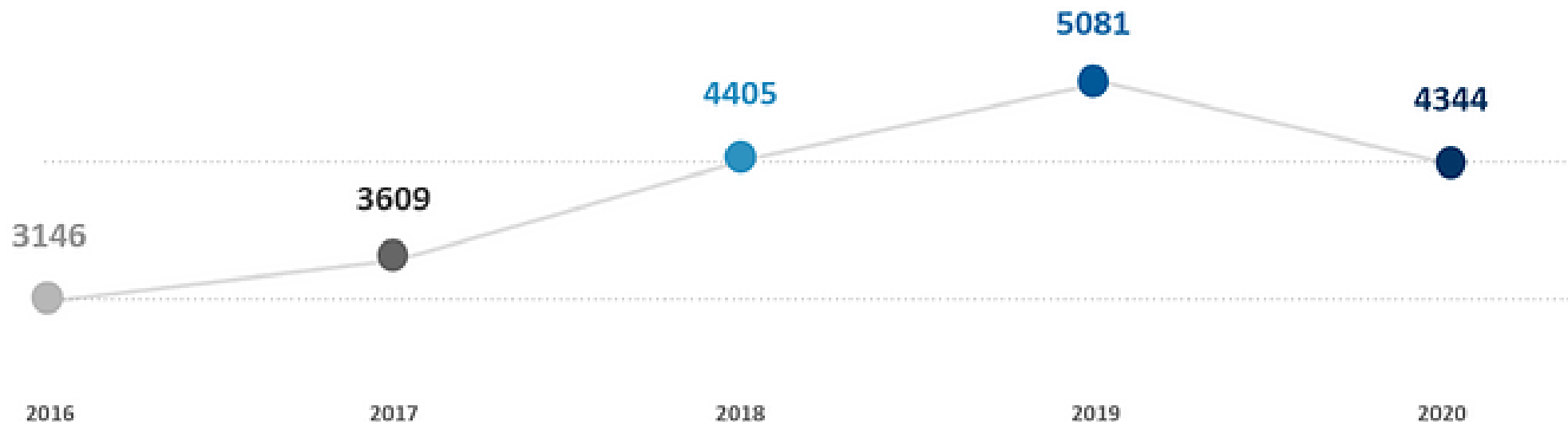
# Incidenty falšování léčiv v letech 2002-2015



Counterfeit situation. <https://www.psi-inc.org/incident-trends>

# Incidenty falšování léčiv v letech 2002-2015

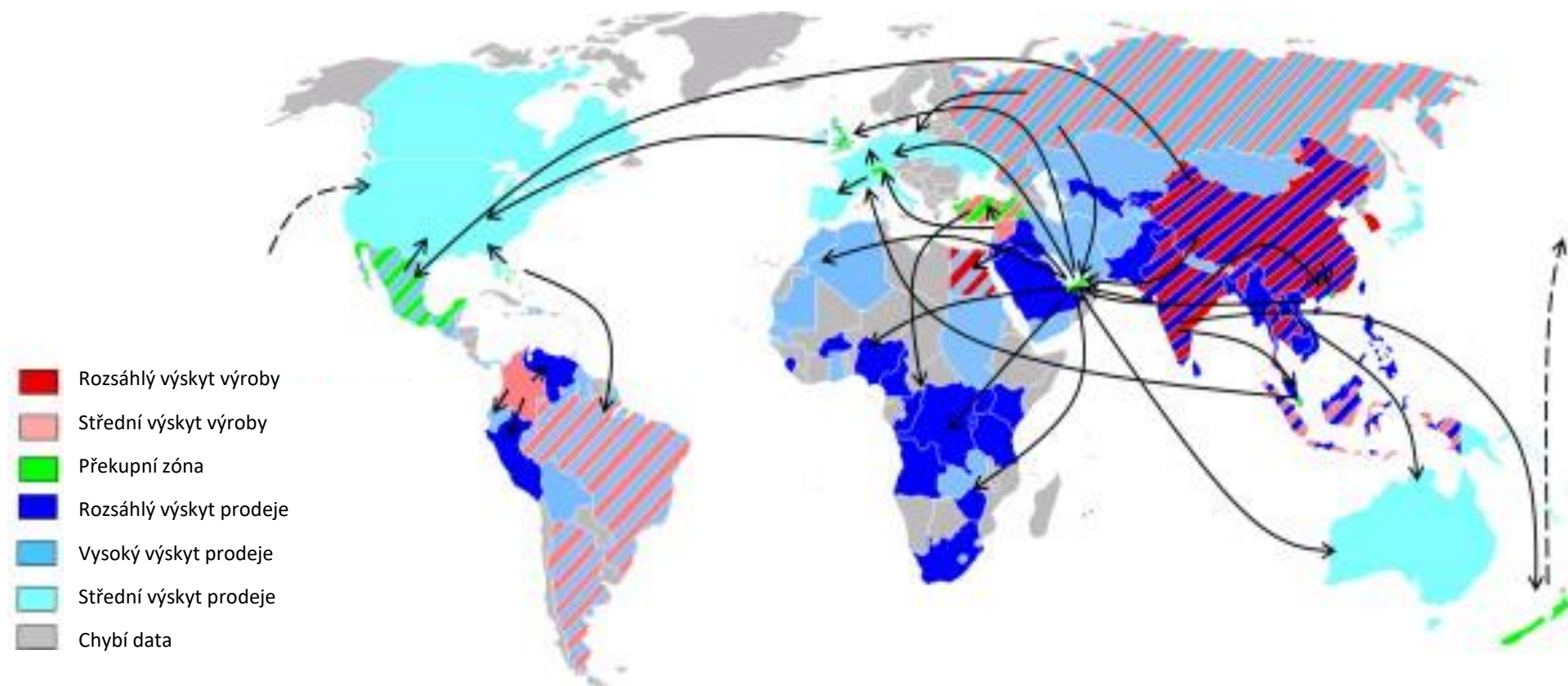
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Counterfeit situation. <https://www.psi-inc.org/incident-trends>

# Globální síť výroby a distribuce falsifikátů léčiv

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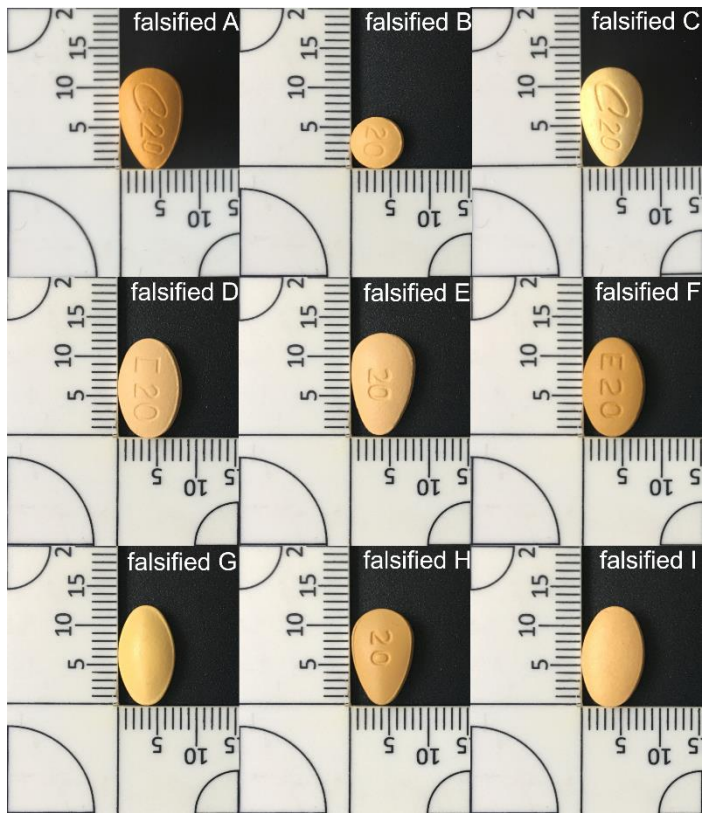
Dégardin, K.; Roggo, Y.; Margot, P., Understanding and fighting the medicine counterfeit market. *Journal of Pharmaceutical and Biomedical Analysis* **2014**,87, 167-175.



# Falsified, original, generic Cialis – přední strana

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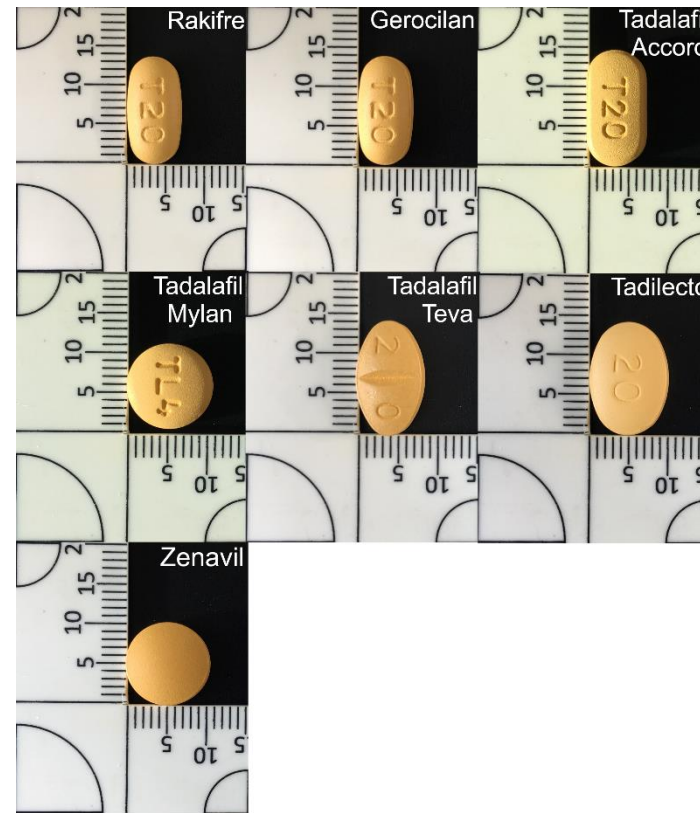
falsified Cialis



original



generic Cialis

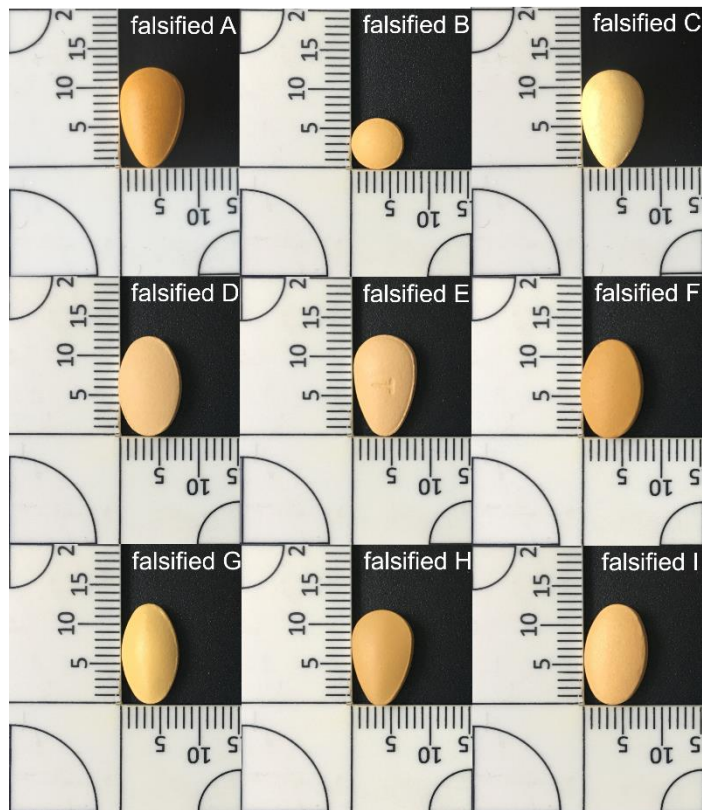




# Falsified, original, generic Cialis – zadní strana

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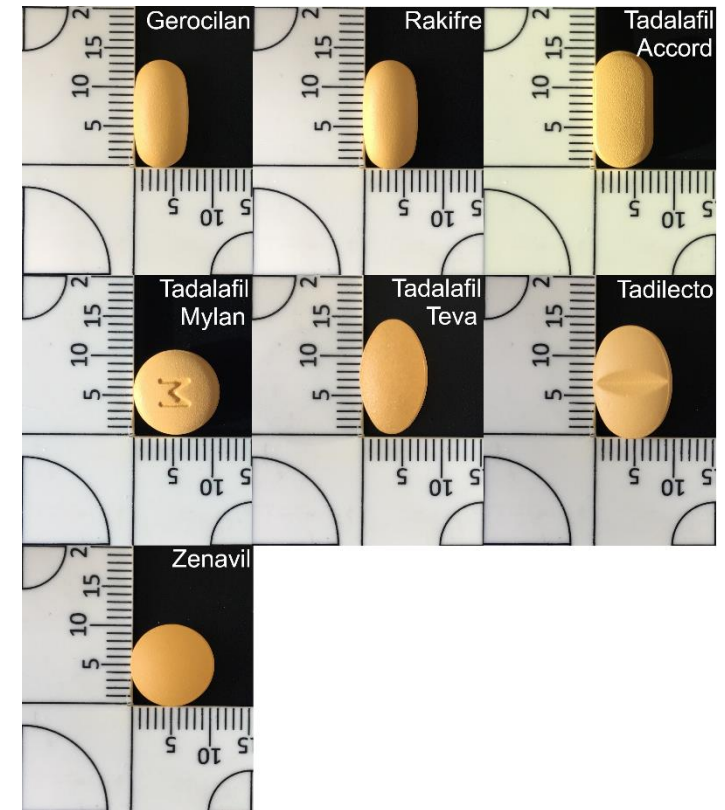
falsified Cialis



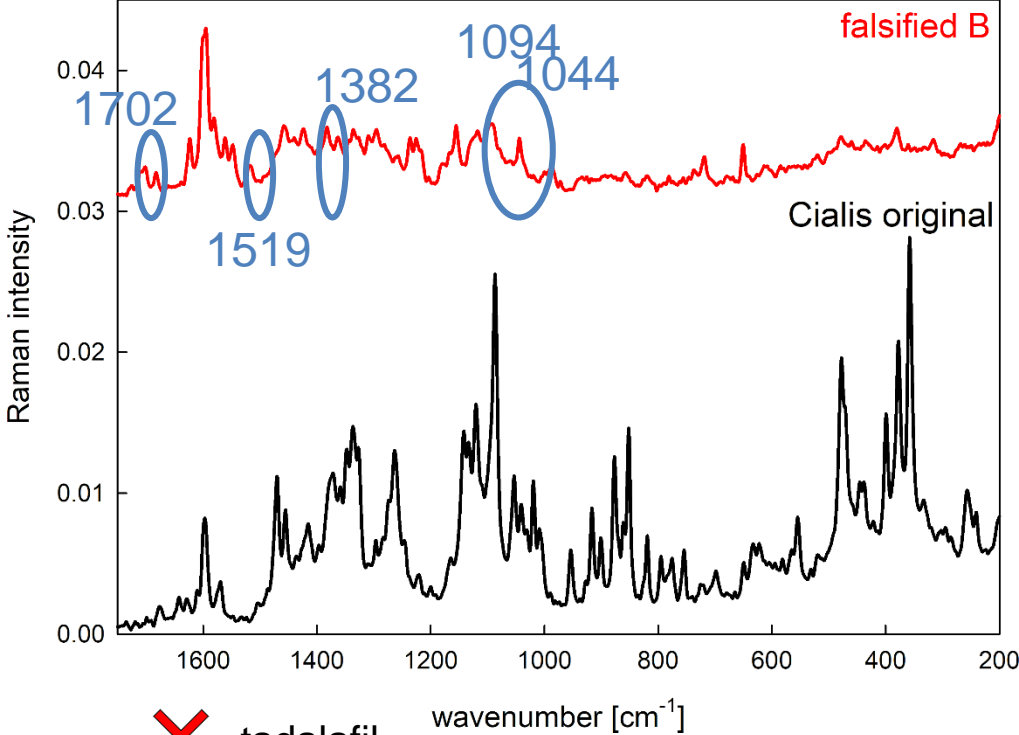
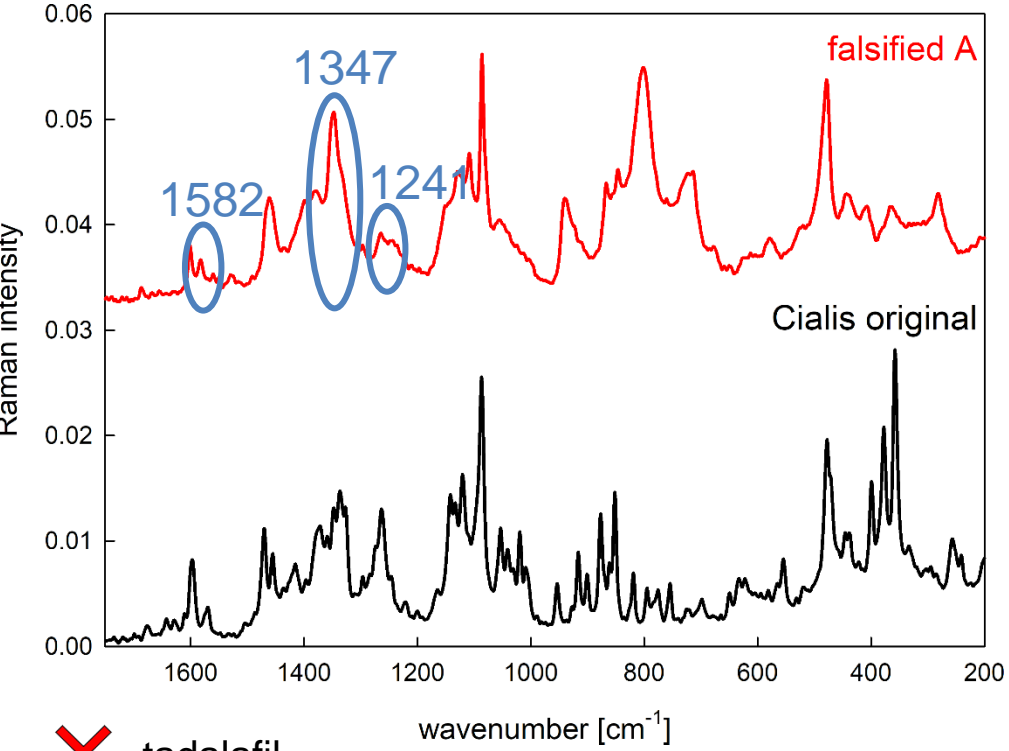
original







generic Cialis



# Ramanova spektroskopie



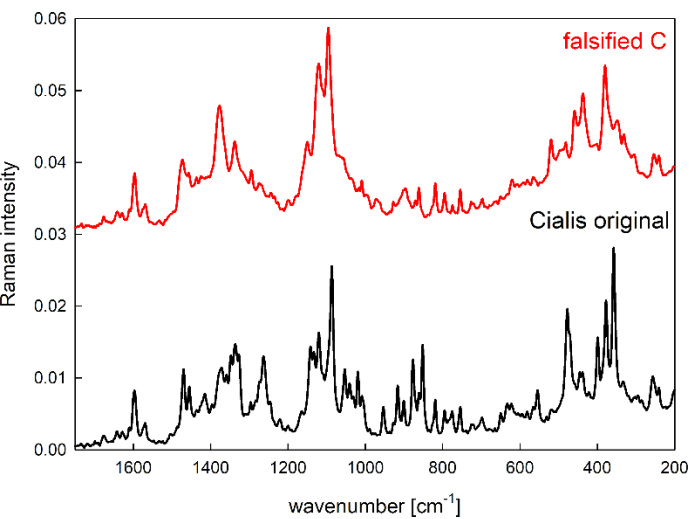
-  **tadalafil**
-  **sildenafil – base and citrate**

-  **tadalafil**
-  **vardenafil**

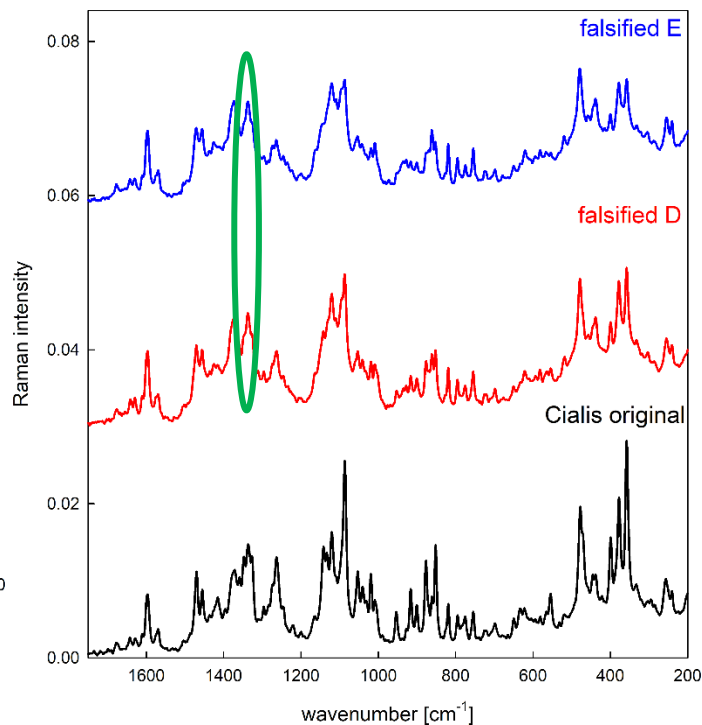
• verified *via* IR spectroscopy

# Ramanova spektroskopie

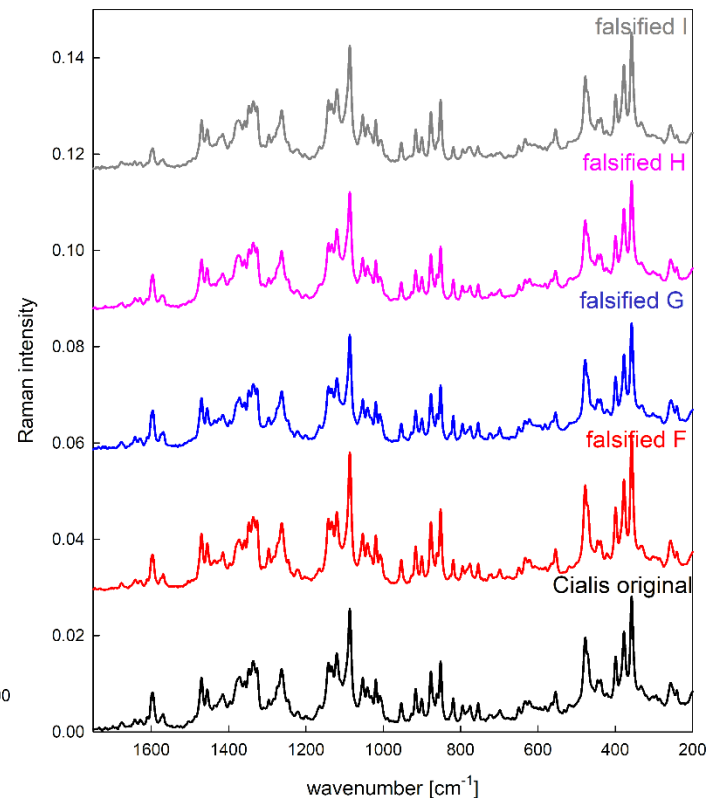
- tadalafil potvrzen v těchto tabletách



MCC  
stearate Mg



škrob  
CaCO<sub>3</sub>

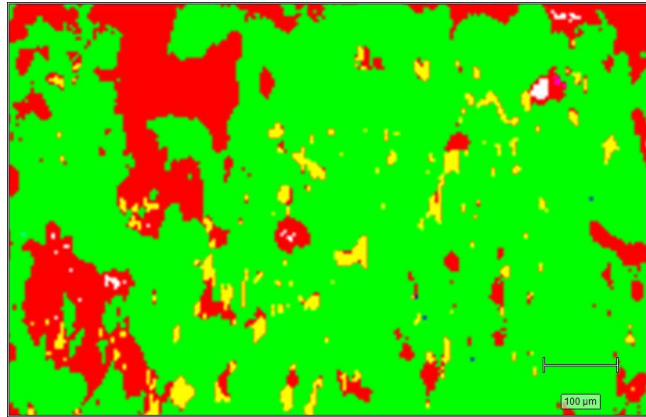


- verified *via* IR spectroscopy

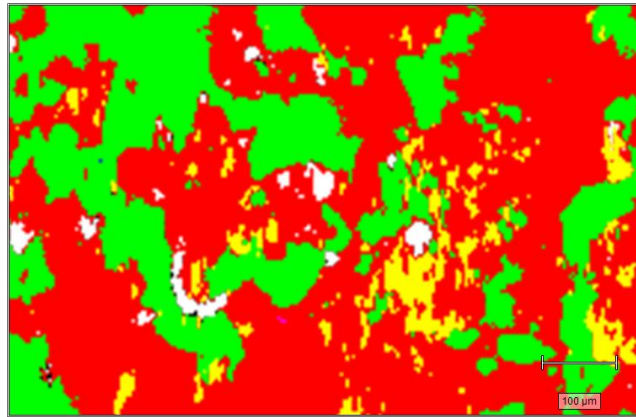
# Mapování s využitím Ramanovy spektroskopie

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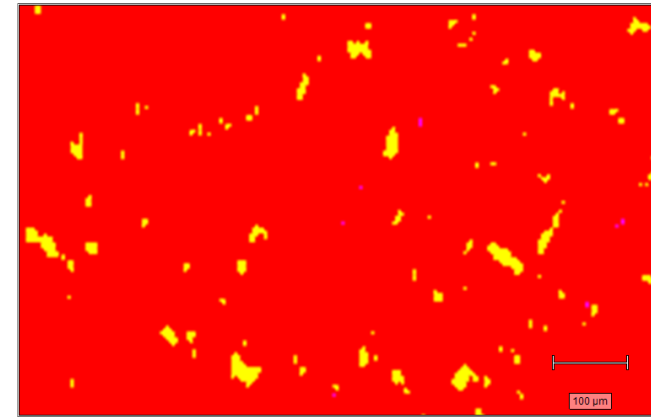
Cialis



falsified G



falsified C



tadalafil – yellow

monohydrate lactose – green

HPC – blue

sodium croscarmellose – white

MCC – red

stearate Mg – magenta

SDS - cyan

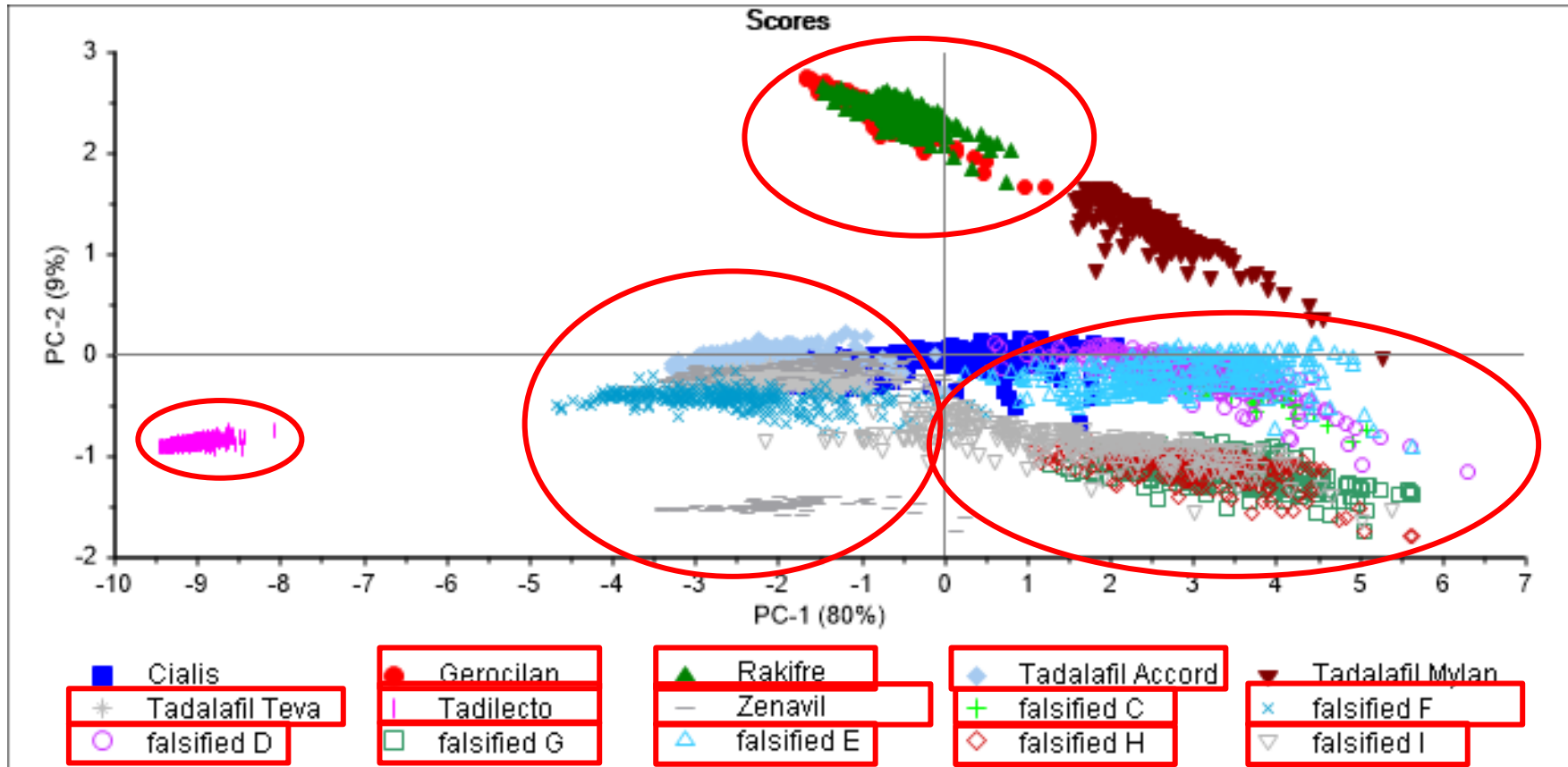
tadalafil – yellow

MCC – red

stearate Mg – magenta

# PCA

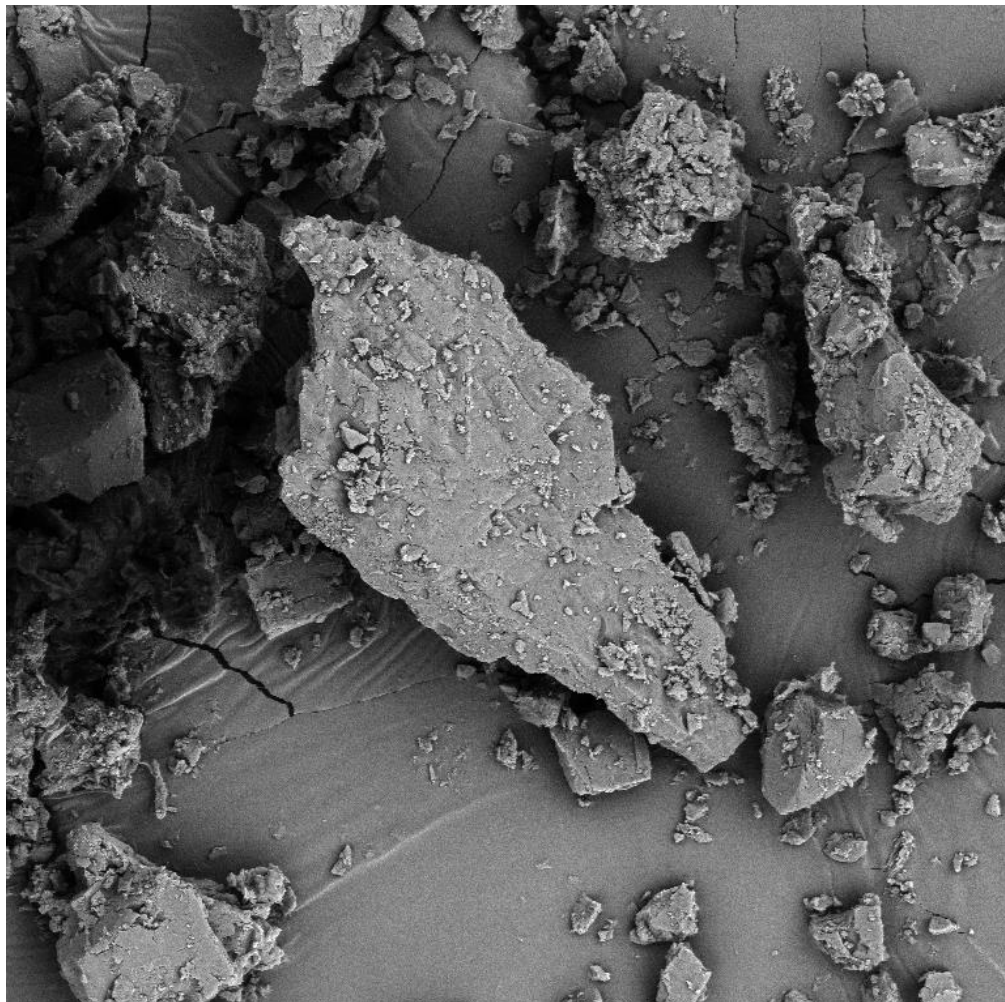
## Principal Component Analysis





# SEM

## Mokr  granulace: lakt za s API – tadafafil



SEM HV: 10.00 kV  
View field: 216.7  $\mu\text{m}$   
SEM MAG: 1.00 kx

WD: 7.794 mm

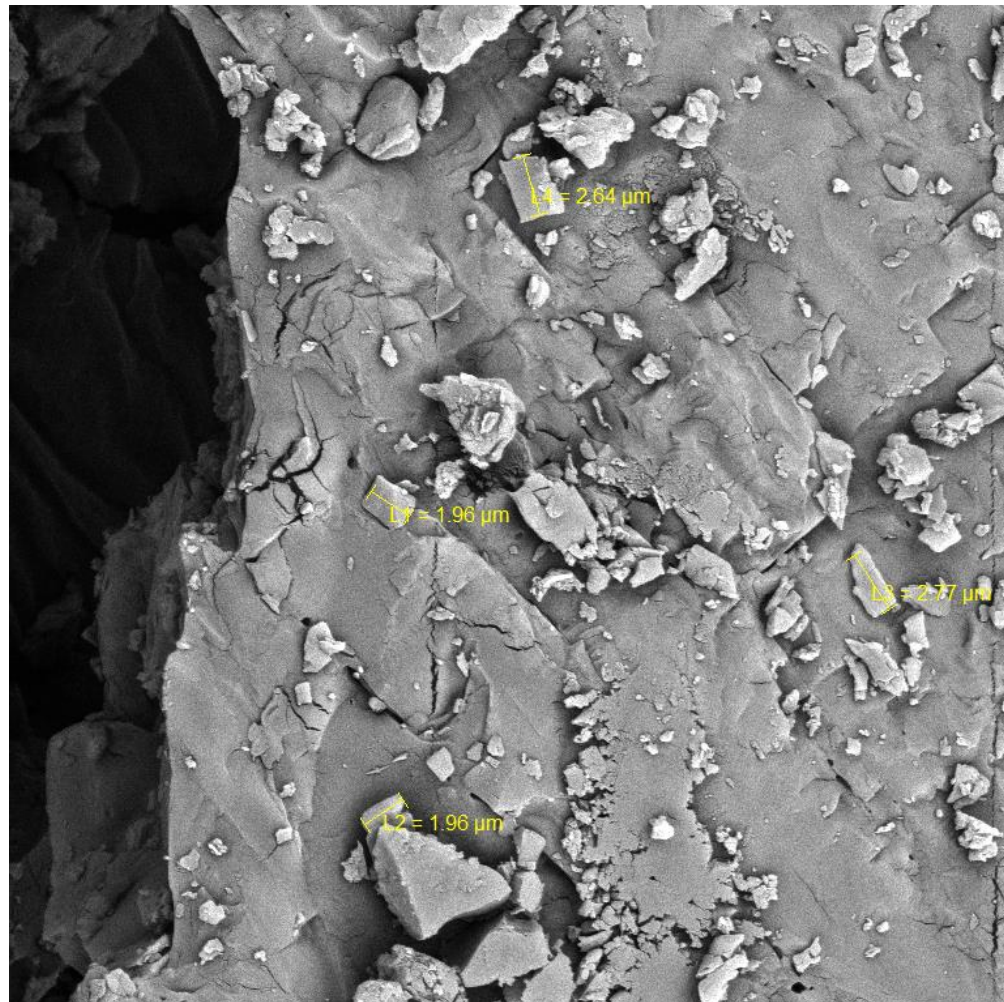
Det: BSE

Date(m/d/y): 03/04/21

50  $\mu\text{m}$

MIRAX TESCAN

Zentiva



SEM HV: 10.00 kV  
View field: 43.34  $\mu\text{m}$   
SEM MAG: 5.00 kx

WD: 7.794 mm

Det: BSE

Date(m/d/y): 03/04/21

10  $\mu\text{m}$

MIRAX TESCAN

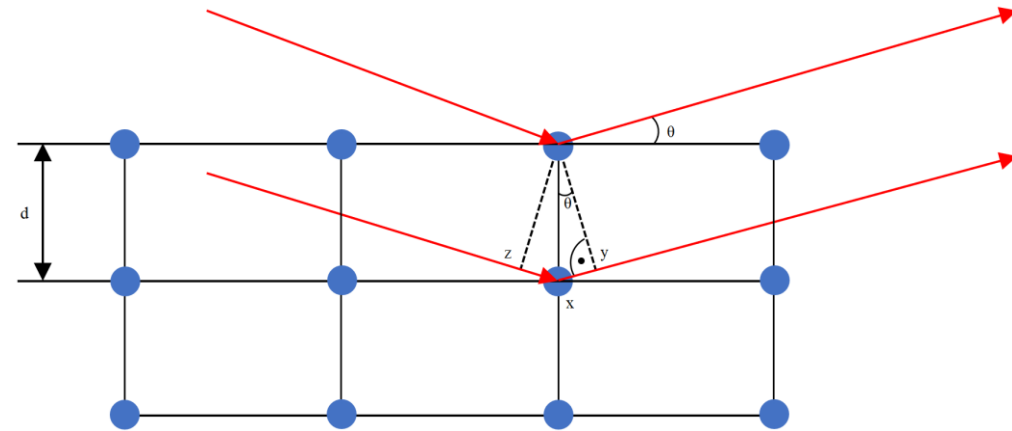
Zentiva

# XRPD - Difrakce rentgenového záření

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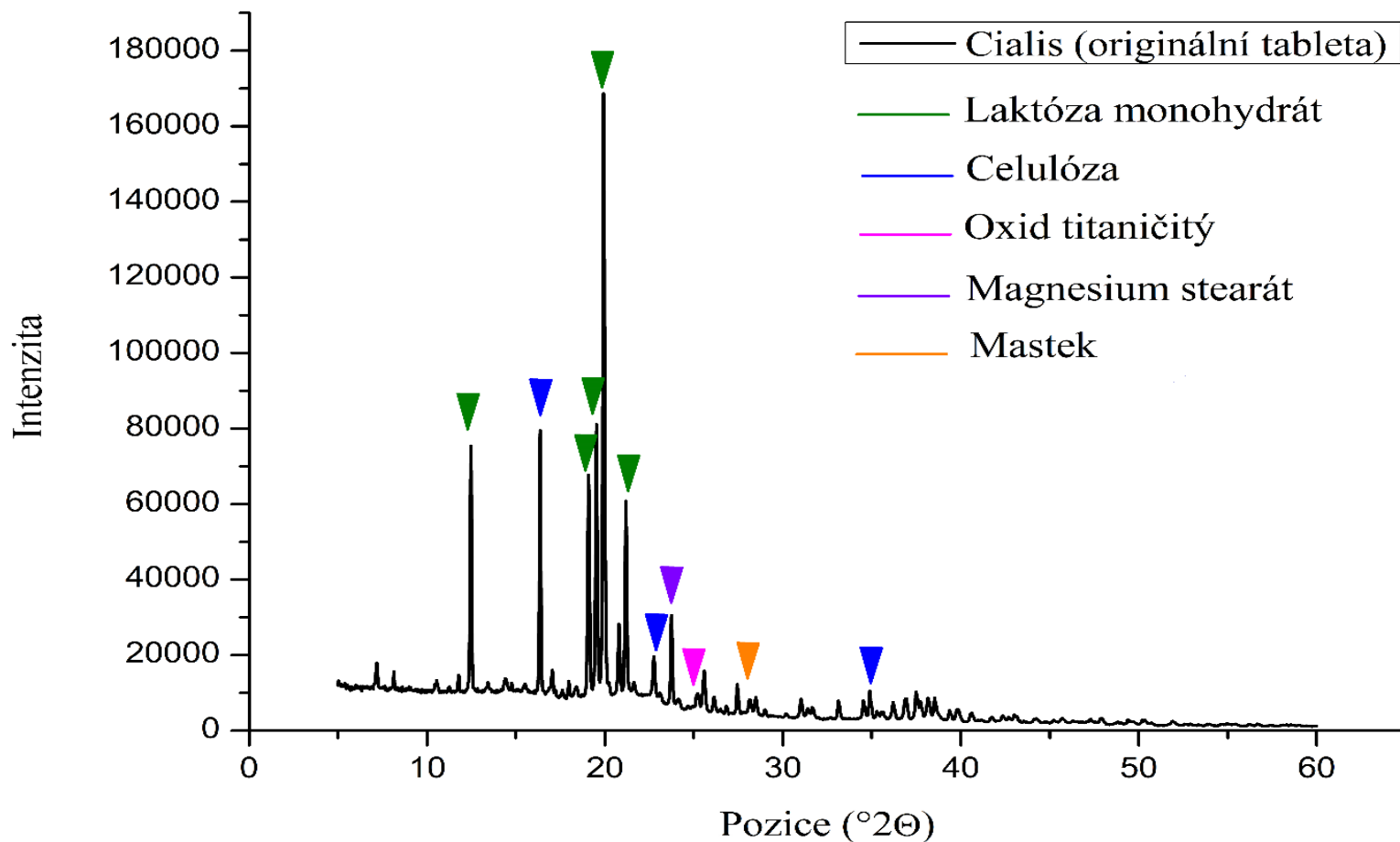
*Braggova rovnice*  
 $2d \sin \theta = n \lambda$



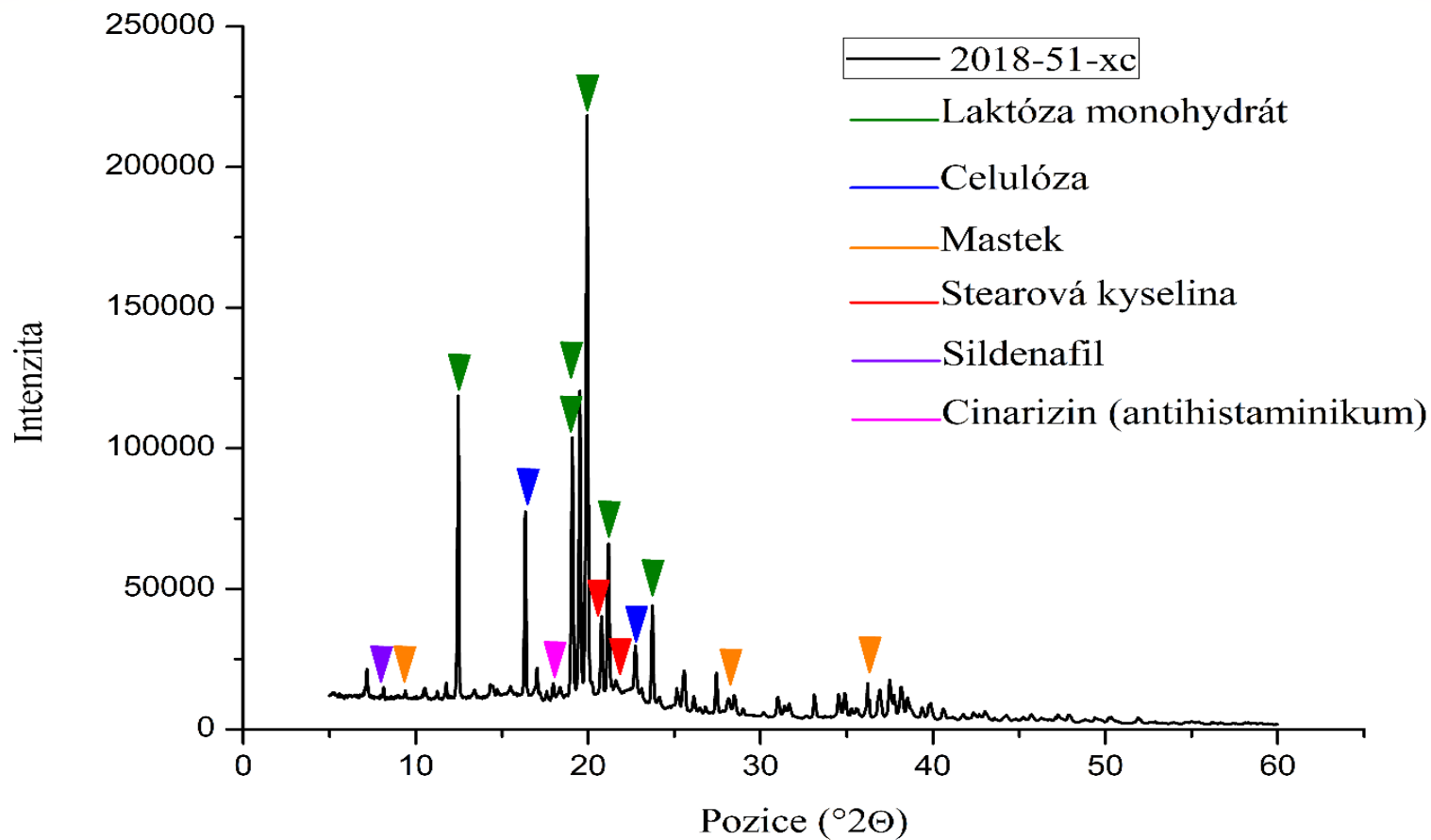


# XRPD – originální tableta cialis

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# XRPD – padělek cialis



# Případová studie benzodiazepiny - 1

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- Vzorek č. 1 – zadrž Policie ČR



- Žádost o znalecký posudek
- Spolupráce se společností TEVA

# Případová studie benzodiazepiny - 1

- Vzorek č. 2 – nákup na internetu

## Browse by category

Digital Goods 49698  
Drugs 64290  
Drugs Paraphernalia 341  
Services 4383  
Other 3405

## Onion mirrors

exhjtuty6ml5u54.onion  
verified

jd6yhuwcivehvdt4.onion  
t3e6ly3uoi4zwc2.onion  
7ep7ackrunzdcw3l.onion  
vilpaqbrmvizecjo.onion  
igyifrhvxq33sy5.onion  
6qlcfcg6zq2kyacl.onion  
x3x2dwb7jasax6tq.onion  
bkjcpa2klkmmowwq.onion  
xytjctfendzeby22.onion  
nhib6cwhfsoyigv.onion  
k3pd243s57ttnpa.onion

## View order

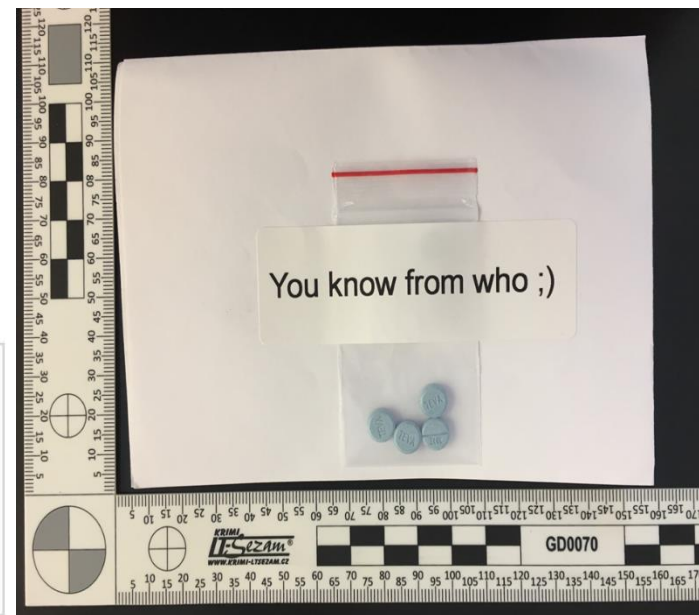
<b>Product</b>	500x TEVA Diazepam Tablets <input type="checkbox"/> FREE NDC
<b>Order date</b>	10/05/2018
<b>Package sent</b>	11/05/2018
<b>Ships from</b>	UK
<b>Marked received</b>	Yes
<b>Escrow</b>	Yes
<b>Payment</b>	Bitcoin (BTC)
<b>Quantity</b>	1
<b>Unit Price</b>	฿0.01199 (£83.1896)
<b>Shipping option</b>	European Union (EU) (฿0.001434)
<b>Total Price</b>	฿0.01343 (£93.1396)
<b>Order id</b>	3891137
<b>Order status</b>	Completed
<b>Vendor</b>	<input type="checkbox"/> (3950) (4.83 )
<b>Disputed</b>	No
<b>Buyer rating</b>	★★★★★



## Product description

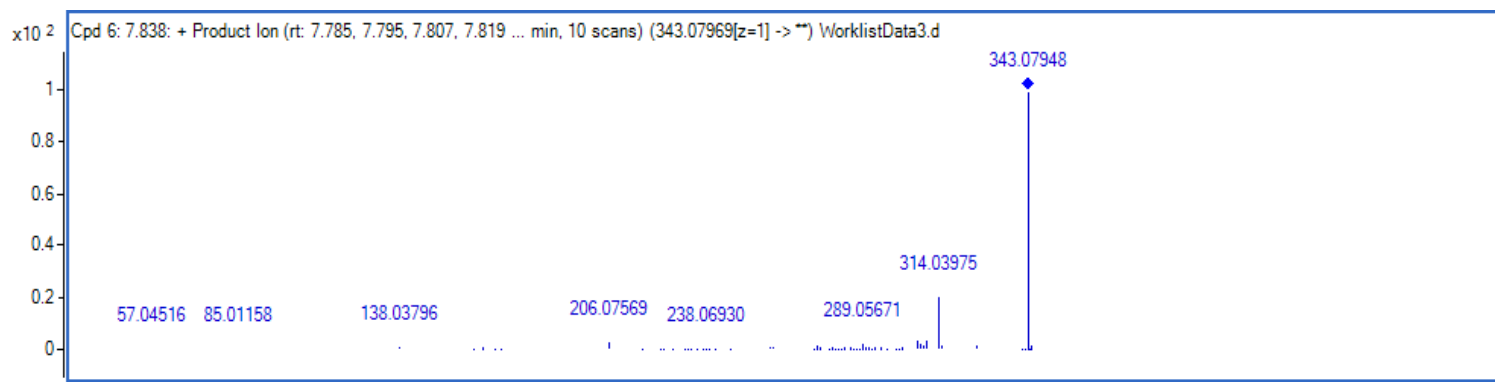
\*\*\*We are the same DiazepamDirectUK from AlphaBay, the moderators have confirmed this and you check that on our profile under Vendor Verification. Please note we do not have a Reddit account and someone is on there posting as us so ignore whatever he's saying.\*\*\*

- This listing is for 10 x 500x TEVA Diazepam tablets that come in beautiful sealed jars. There is limited stock on this product so buy fast!
- We always ship the same day the order is received providing the order is placed before 3pm UK time.
- Sent Via 1st Class Royal Mail Signed For. Shipping is free for UK buyers however the postage cost for EU orders is £9.95.
- Sent discreetly with great stealth.
- Please note we only ship to the UK and EU.

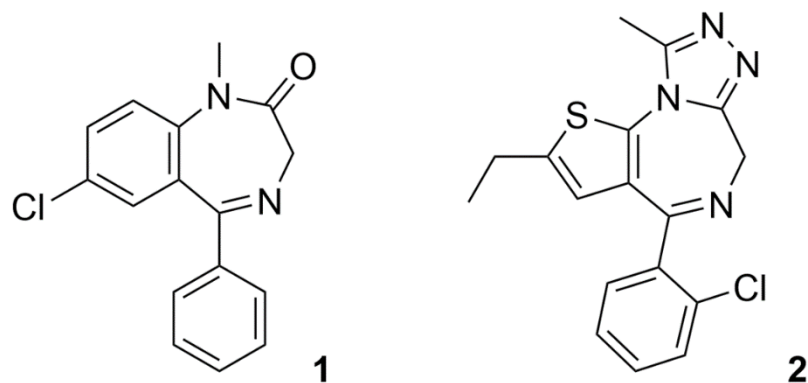


# Případová studie benzodiazepiny - 1

- Vzorek – analýza obou vzorků LCMS (QTOF Agilent 6550)



ESI ionization,  
positive mode,  
collision energy 20V

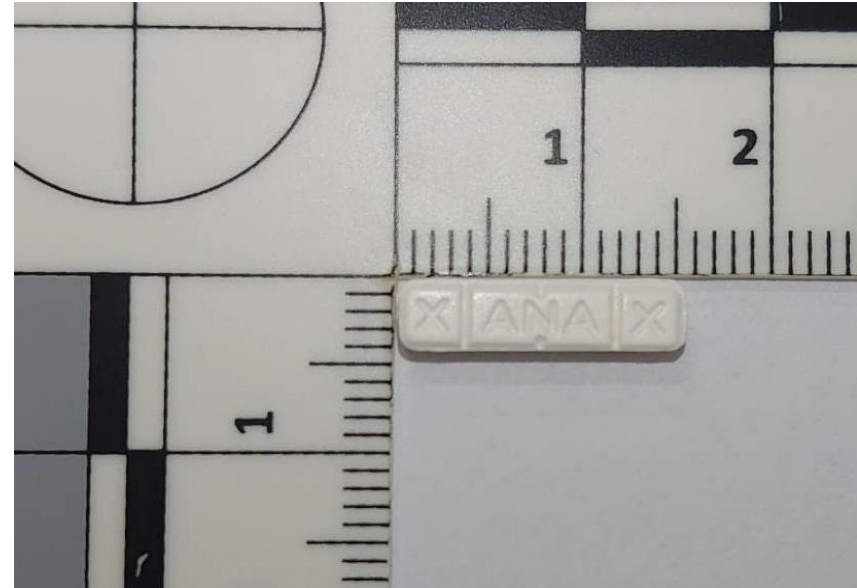


diazepam (**1**, C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O), etizolam (**2**, C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>S)

# Případová studie benzodiazepiny - 2

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- Vzorek č. 1 – zadrž Celní správa



- Žádost o znalecký posudek
  - První posudek KÚ – pravděpodobně clonazolam, bez určení obsahu
  - Žádost o kvantifikaci – určení rozsahu tr. činu

# Případová studie benzodiazepiny - 2

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## Zadání

- confirmovat přítomnost klonazolamu
- kvantifikace klonazolamu

## Problém

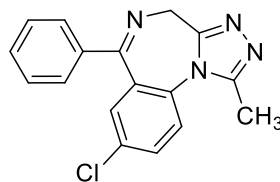
- relativně drahý standard s dlouhou dodací lhůtou

## Řešení

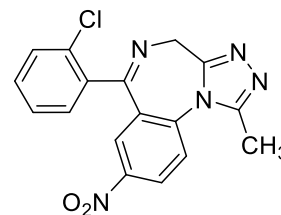
Preparativní izolace aktivní látky, charakterizace a využití jako analytický standard

## Vásledek

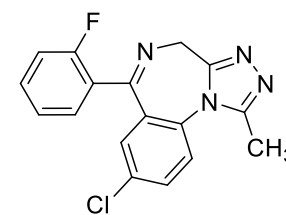
Ve vzorku byla nalezena průměrná koncentrace **421,1 µg** klonazolamu v jednom gramu zajištěných tablet.



Alprazolam



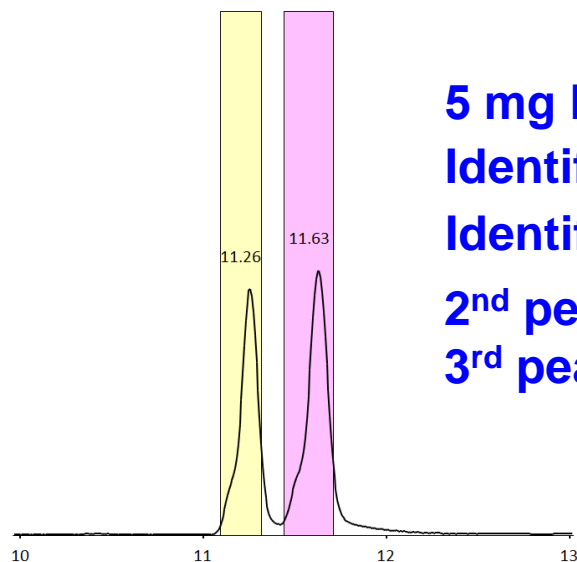
Clonazolam



Flualprazolam



# Případová studie benzodiazepiny - 2

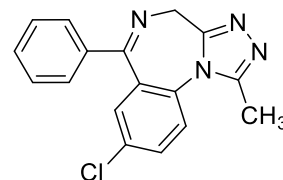


5 mg každé látky  
Identifikace HR-MS

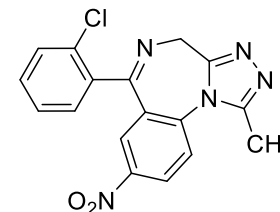
Identifikace NMR

2<sup>nd</sup> peak: Clonazolam

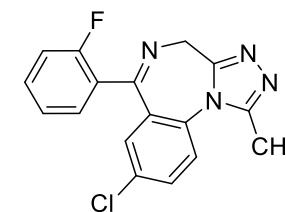
3<sup>rd</sup> peak: Flualprazolam



Alprazolam



Clonazolam

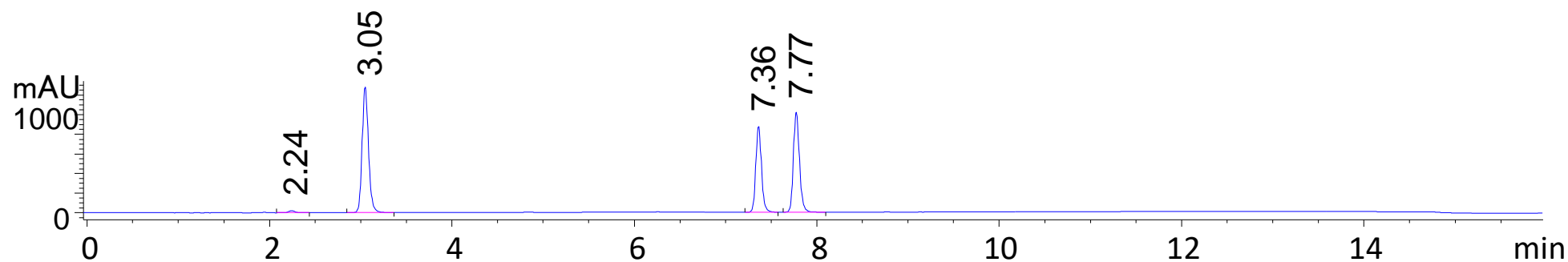


Flualprazolam

Mobile phase

A: H<sub>2</sub>O / 0.1% HCOOH + 2 mM HCOONH<sub>4</sub>

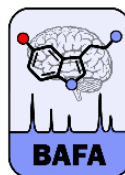
B: CH<sub>3</sub>CN / 0.1% HCOOH



Astra C18-HE 150×4,6 mm ID, 5 μm, flow rate of 1 mL/min, laboratory temperature, detection wavelength: 254 nm



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CHEMICKO-TECHNOLOGICKÁ  
V PRAZE**



**Laboratoř  
Forezní Analýzy  
Biologicky  
Aktivních Látek**

**ZENTIVA**

**teva**

## Poděkování

Laboratoř forezní analýzy biologicky aktivních látek

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RNDr. Lucie Janečková, Ph.D. – stanovení benzodiazepinů

Ing. Bronislav Jurásek, Ph.D. – darknet

Ústav analytické chemie a Zentiva

Ing. Dita Spálovská – Ramanovo mapování

Ministry of the Interior of the Czech Republic (VJ01010043) and Specific  
University Research No A2\_FCHI\_2021\_024