

《局部起效化学仿制药体外释放（IVRT）与体外透皮研究技术指导原则（征求意见稿）》

详细介绍：

????

5 ??????????????????????

6 ???????(????????????)?

7 ??????(In Vitro Release Test?????IVRT)

8 ??????(In Vitro Permeation Test?????IVPT)

9 ?????????????????????????

10 ?????????????????????????

11 ?????????????????????????

12 ?????????????????????????

13 ?????????????????????????

14 ?????????????????(????????????

15 ?????????????????)?IVRT ?IVPT ?????

16 ?????????????????????

17 ?????????????????????????

18 ?????????????????????????

19 ?????????????????????????

20 ???IVRT/IVPT ?????????????

21 ??????????????????IVRT ?IVPT ???

22 ??????????????????????1~6? ???

23 ??????(1)?????(2)?????(3)?????24 (4)?????????(5)????????(6)???

25 ?????????

26 ?????????????????????

27 ?????????????????????

28 ?????????????????????

29 ?????????????????

30 ????????(IVRT)₃₁ (?) IVRT ?????

32 ??????????????????????IVRT ???

33 ?????????????????????????(??

34 ??????) ?????????????????

35 ??????????????????????IVRT ?????

36 ??????????????????????37 (?) IVRT ???

38 ?????????????????????

39 ?????????????????????

40 ?????????????????????

41 ?????????????42 1.??
43 ??????IVRT ??????????????
44 ??????????????????????????
45 ?????????????????????46 2.?
47 ?IVRT????????????????(??
48 ???????????/? ?????????/? ???) ?
49 ???(? 0.45?m ?) ??????????????1?
50 IVRT?????????????????????
51 ??????????????????????????
52 ???IVRT????????????????????
53 ??????????????????????????
54 ??
55 3.????
56 ??????????????????????????
57?????????IVRT ?????????pH ???
58 ??
59 ?IVRT?????????????????????
60 ??????????????????????????
61????pH5 ~ 7 ???-?????????
62 ??????????????????????????
63 IVRT????????????????????????
64 ??????????????????????????
65? (??) ?????? (r2?0.97)? ??????????
66 ?????IVRT ??????????????????
67 ?????
68 4.????
69 ??????????IVRT?????????????
70 ???/? ??????????(Steady-StateRelease
71 Kinetics)?1? ??????????????????????
72 ??????5 ??????????????????????
73 ?????(Steady-StateReleaseRates)?????????
74 ???4 ??????????????????????????
75 ?????????????????????(??76 30 ??????) ??????????????????????
77 ?????????????????????????78 ±15 ??±2% (????????)?2?
79 ??????????????????????????
80 ?????????????????(±5%)?????
81 ?????????????????????IVRT??
82????????????????????83 (Pseudo-Infinite Dosing)?3? ??????????????
84 ??????????
85 ??????????????????????????

86?????? (?????? 600 rpm)₁?₈₇ (?) IVRT ?????₂?
88 ??IVRT????????????????
89 ?????????????????????
90 ?????????????IVRT ??????
91??????
92 ??????IVRT ?????????
93????????????????₉₄ 1.????
95 ?????????????????
96????????????????
97 ?????????????????(??₉₈ 32C±0.5C) ????? ?????????
99 ???????±10%₁₀₀ 2.??
101 IVRT????????????
102????(?? 32C±0.5C????6 ??)????
103 ?????????????
104 ?????????
105????????
106????????????100%
107 ± 5%?
108 3.????
109 ?????????
110 ?????????
111 ?????????
112 ?????? (?? ?????????)
113 ?????????????₁₁₄ 4.???
115 ?????????
116 ?????????21C ₁₁₇ ±2C????50%RH±20%RH??
118 5.????
119 ?????????
120 ?????????(????????)?
121 ?????????(r₂ ??0.97)????
122 ?????????IVRT ?????
123 ?????????₁₂₄ 6.????
125 ?????????(??) ?????
126 ?????????
127 ??????%(CV)?????(%CV)
128 ??????15%?????/?/?/?/
129 ?????????
130 ??????
131 7.??? (Dose Depletion)
132 ?????????

133 ??IVRT ??????????????????
134 ?????????????????????(??
135 ??????????????????????)?
136 ?????????????????1g????????137 5%????????????50mg????????6
138 ???IVRT ?????????????????10mg?
139 ???50mg ???????10mg????????20%?
140 ?????????????(Average Percentage Dose
141 Depletion)?
142 ?????????????????30%??
143????30%?????????????????
144 ??????????????????????
145?????????????
146 8.???— ????????? (Discrimination-147 Selectivity, SensitivityandSpecificity)
148 ?????????????????IVRT ???
149 ?????????????2,????????
150 IVRT ?????????IVRT ?????????
151 ??????????????????????
152 ??????????????????????
153 ??????????????????????
154 ??????
155IVRT ?????????IVRT ?????????156 ?????????????????????157
????????????????????158 ?????????????????????159 ?????????????????
160????????IVRT ??????
161 IVRT ?????????IVRT ?????????162 ?????????????????????163????????????
IVRT ??????(164 ?) ?????????????????????165 ?r2 ?????IVRT ?????IVRT?????
????????????????IVRT????167 ? (??) ?????? r2 ??0.95????????168 ??169 9.??
????????IVRT????????171????????(??- 1°C ?+1°C ???32°C±0.5°C)?172
????????(????????+10%?-10%)? ??173 ??????(? ???/?pH ??????)????174 ???(??
????????)? 175 ???IVRT ?????????IVRT?????“176 ??????”????????
?????
177 IVRT????????????178 (?) ??????
179 ?????????????????????
180 ?????????????3?
181 ?????????????????
182 ?????????????(6 ~ 8 ?)
183 ???2,????ICH M10 ?????????
184 ??????
185 (?) IVRT ?????1?
186 ?????????????????IVRT?
187 ?????????

188 ?IVRT????????????????
189 ?????????????????????
190 ??????IVRT ?????????
191 ???????6 ?????????IVRT
192 ?????????????????????
193 ????(ABABAB?BABABA)?????194 (?) ??????????1?
195 ??????????????????(t1?
196 t2 ?)?????(??? μg/cm2 ???)?????
197 ?????????????????????t ?
198 ?????????????????
199 ?????????????????
200 Mann-WhitneyU????????
201 ???????(?) ??? 90%????
202 ??????????????????203 (R)????????(T)???? R?
204 ?????????????????
205 ????????????? (T)????????
206 ? (T) -?? (R) ?????????T/R ?????
207 ?????????TS ?????????RS ?
208 ?????????T/R ?????
209 ?1. ??????(TS)?????(RS)?

	RS1	RS2	RS3	RS4	RS5	RS6
TS1	TS1/RS1	TS1/RS2	TS1/RS3	TS1/RS4	TS1/RS5	TS1/RS6
TS2	TS2/RS1	TS2/RS2	TS2/RS3	TS2/RS4	TS2/RS5	TS2/RS6
TS3	TS3/RS1	TS3/RS2	TS3/RS3	TS3/RS4	TS3/RS5	TS3/RS6
TS4	TS4/RS1	TS4/RS2	TS4/RS3	TS4/RS4	TS4/RS5	TS4/RS6
TS5	TS5/RS1	TS5/RS2	TS5/RS3	TS5/RS4	TS5/RS5	TS5/RS6
TS6	TS6/RS1	TS6/RS2	TS6/RS3	TS6/RS4	TS6/RS5	TS6/RS6

210????T/R ???????36 ?T/R ?????
211????????8 ???29 ?????????
212 ??(??? 100)????? 90%????????
213?????90%~111%????????
214 ???????????????4 ?(2 ??
215 ??2 ??????6 ???) ??? ?????
216?12 ???????????18 ?T/R ?????
217 ?????????324 ?T/R ?????
218 ???????110 ???215 ?????(????
219 ???????90%????????)?? 90%~111%
220 ?????????
221 ????????(IVPT)222 (?) IVPT ?????
223 IVPT????????????

224 ??????????????????????
225 ?????????????IVPT ???????
226 ?????????????????????
227 IVPT?????????????????
228 ??????????
229 IVPT????(FluxProfiles)????????230 (Pharmacokinetic Profiles)???? IVPT
?????
231????????????????(Cmax)???- ???
232 ???? (AUC)???IVPT?????????
233 ?????????????????????“??
234 ????? (Cutaneous Pharmacokinetics)”?????“?
235 ??????????????????” 4?
236?????????????????
237 ??????????????????
238 ?IVPT ????
239 (?) IVPT ????
240 1.IVPT ??
241 ?????IVPT ??????????
242 ??????????????????
243 ?????????
244 2.IVPT ????1,3,4?
245 ?????????/?????????
246 ??????????????????
247 ?????????(?? ??????????
248 ??????) ??????(? ?????????
249 ??)?
250 ??????????????????
251 ??????????????????
252?????????????????
253 ??????????????????
254 ?????????????32±0.5??
255 ??????????????
256 ?????????IVPT?????????
257 ?(Non-Dermatomed)??? ?????????/???
258 ???
259 3.IVPT ??????
260 ??????????????????
261 ??????????????????
262 ??????????????
263 ?IVPT ??????????

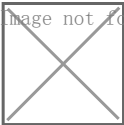
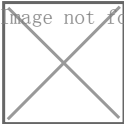
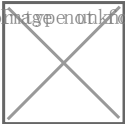
264 ?????????????????????????/??
265 ?????????????????????????
266 ???₄?
267 ?????????????????????????
268 ?????????????????????????
269 ?????????????????????????
270 ?????????₂₇₁ 4.IVPT ???₄?
272 ????????pH ?????????????
273 ?????????????????????
274 ?????????????????????????
275 ?????????????????????????
276 ?????IVPT ?????????????????
277 ?????????????????????????
278 ?????????(???????)????????
279 ?????????(?? ??????????)?
280 ?????????????????????[???0. 1%₂₈₁ (w/v)? 0.2% (w/v)]????20 ??(?? Oleth-20
282 Volpo-20, ?Brij-20?CAS?9004-98-2) ?????????
283 ????????????????? (??????
284 ??????????)????????????
285 ????
286 ?????????????(?? ? 0. 1%?
287 ??????0.01%?????)????????
288 ?????????/????????????
289 ?????????????????₂₉₀ 5.IVPT ???₄?
291 ?????????IVPT ?????????????
292 ?????????????????????????
293 ?????????????(??) ?????
294 ?????????????????????????
295 ?????????????????????????8
296 ???????
297 ?????????????????????????
298 ?????????(??) ?????????
299 ?????????????????????????
300 ?????????????????????????
301 ?????????????????????????
302 ?????????????????????????
303 ?????????????????IVPT ?????
304 ????????????????? ????₃₀₅ ????????????????????????? 306
????????????????????₃₀₇ ?(±5%)???????????? 2~15mg/cm₂ ??₃₀₈ ?₁?
309 ?????????????????₃₁₀ ?????(???? 600 rpm)?

311 ?????????????????(? 4~6 ?)312 ??IVPT ?????????????????4 ??313 (?)
312 ?????4314IVPT ?????????????????315????????????IVPT ?????316 ??????
313 1.????318 ????????????????319 ????????????????320????????
314 ????????????????(??321 32C±0.5C)????? ????????????322 ????????±10%?323
315 ????324 ????????????????325 ????????????????
316 ????????
317 3.????
318 ????????????
319 ????????????
320 ????????????
321 ????? (?? ??????????????)
322 ?????????????????)?333 4.????
323 ????????????
324 ????????????????21C 336 ±2C????50%RH±20%RH??
325 5.????? (Permeation Profile and Range)
326 ????????
327 ??? (CumulativePermeation Profile)???????? 340 (??????) ?????????
328 ???
329 6.????
330 ????????
331 ????????????????
332 ????????????(%CV)???????? ??
333 ?????
334 ????????????????
335 ????????????350 7.????
336 ????????
337 ??IVPT????????
338 ????????????(??
339 ?????????????)?
340 ????????????10mg????
341 ??5%????????500?g????
342 ?48 ???IVPT????????35810?g????500?g ?????10?g????359 2%
343 ????????(????
344 ??)?
345 8.???—????
346 ????????IVPT ?????
347 ?????????4? ?????
348 ????IVPT????IVPT?????“?
349 ????????????”????

366 ?????????IVPT ??????????????
367 ??????“?????????”?????????
368 ?????????????IVPT?????????????
369 ?????????????IVPT ?????????????
370 ??????????????????????????????
371 ?????????????????????(???)???
372 ????(Potency) ??????(?) ???????
373 ???/?IVPT ?????/??????????????
374 ???IVPT ???IVPT ?????????????
375 ??????????????????????????????
376?????(????????????????????)?
377 IVPT????????????????????(?? ??
378 ???IVPT??)?? ??? IVPT ?????????
379?????????????????????????????
380 ???₄????????????IVPT ?????????
381????IVPT ?????????????????(??₃₈₂ 4 ~ 6 ?????)???????????? 4 ???
383????₃₈₄ 9.???
385 ?????????(?? ??????) ????
386 ??????????????????????????????
387 ??????????????????????????????
388 ??????????????????????????????
389????IVPT ?????????????IVPT ?????₃₉₀ (?) ?????????
391 ??????????????????????????????
392 ??????????????????????????
393 ??????????????????????????????
394 ?????????????????????????₃₉₅ (6 ~ 8 ?) ????????? ICH M10 ?????
396 ??????????????????
397 (?) ?????? (????) ??????₁?
398 ??????????????????????????????
399 ????
400????????????????????₄₀₁ (????????????????????) ??????
402 ?????????
403 (?) IVPT ??????₄?
404 ?????????????????????IVPT ?
405 ?????????????????????₄₀₆ 1.????
407 ??????????????????????????
408 ?????????₄₀₉ 2.???
410 ??IVPT????????????????????
411?????????????????????????????
412 ?????????????

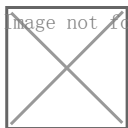
413 3.??
414 ?IVPT ?????????????????????415 (????) ?????????????????????
416????????????????????????????
417????
418a. ABABAB...
419 b. BABABA...
420 ????
421 ?IVPT ?????????????????????
422 ?????????????????????????
423 ?????????????????????????
424 ?????????????????????????
425 ?????????????IVPT ?????????????
426 ??IVPT ?????????????????????
427 ?????????????????????????
428????????????????????????
429 ?????????430 4.IVPT ??
431IVPT????????????????????
432 ?????????????????????????
433 ??(J)???????????? ?????????????
434 ?????????????
435 ??(?????) ???? Y-????????
436 X-??????Y-??“J”??????/?/?/? (??ng/
437cm²/h)????????????????????
438????????????????????????
439 ?????????????????????(?????/?/?
440 ?ng/ cm²)???? Y-????????X-??
441 ?????????????????????
442 ?(?? 2.0 ng/mL)????????????(??443 6.0 mL)????????????(??444 1 c
)????????????????????
445 ????2 ?????????J ?????????
446 J = [(2.0 ng/mL) × (6.0 mL)]/ (1 cm²) / (2 h) = 447 6 ng/cm²/h
448 ?????????????????????
449 ?????????????????????
450????????2 ?????????????????451 0 ?2 ?????????(?? 1 ??)?
452 ?????????????????????(AMT)?
453 AMT ?????????(????????)?
454 ?????????????
455????????????(Jmax????
456?????)? AMT????????
457????????Cmax ?AUC ?????????

458????????(????????) ?????
 459 ?????????
 460 ?????IVPT???????(CI)?
 461 a. ??????????(Jmax)
 462 b. ????????????? (AMT)
 463 ?????IVPT????????????
 464????(????????) ?????????
 465 ??4 ??????
 466 ?IVPT ?????????????????
 467 ?????????????????????
 468 ?????????????????/?????
 469????????????????????
 470 ???/?????????????????471 (?) ??????????4?
 472 1.??SABE (Scaled Average BE) ??????
 473 ???IVPT ?????????????
 474 ?????????
 475 a. (uT? uR) ? e²w(2) R?95%?????
 476 ??0 (????????????????)?
 477b. T?R????????????478[1/m,m]????m=1.2500?
 479 2.??ABE (Regular Average BE) ??????
 480????IVPT ??????uT ? uR ?90%??
 481 ??[0.8000, 1.2500]????????
 482 ?????????
 483 ??????
 484 1. ????(USP)???<1724> Semisolid Drug Products
 485 — Performance Tests.
 486 2. FDA?InVitroReleaseTestStudiesforTopicalDrug
 487 ProductsSubmittedinANDAs. October 2022
 488 3. EMA?Draftguidelineonqualityandequivalenceof
 489 topicalproducts. October 2018
 490 4. FDA: InVitroPermeationTestStudiesforTopicalDrug
 491 ProductsSubmittedinANDAs. October 2022
 492 5. ??????(????????)???
 493 ?????????????????(2010 ?11
 494 ?)
 495 6. ?????????????
 496???????? (??)?(2021 ?3 ?)

497 ???IVPT?????4?
 498 ??????????(T)????(R)?
 499 ??????????n ?????T ??
 500 ?_{jth}(j = 1, ... , n) ??? r_{jT}?????
 501 ??R ??_{jth} (j = 1, ... , n) ??? r_{jR} ?????
 502 ?????(j)????(i)?????
 503 ?????
 504 T_{ij}= ?????_{jth}????_{ith}????
 505 IVPT ?? (Jmax ?AMT) ????? (i = 1, 2, ..., r_{jT}, j=506 1, 2, ... , n)
 507 R_{ij}= ???(????)? _{jth}????_{ith}?
 508 ?????IVPT ?? (Jmax ?AMT) ????? (i = 1,509 2, ..., r_{jR}, j= 1, 2, ... , n)
 510 r_{jT}= ?????_{jth}???????? (j=511 1, 2, ... , n)
 512 r_{jR}= ???(????)? _{jth}?????
 513 ??? (j= 1, 2, ... , n)
 514 r? = r₁(R)+ r₂(R)+ ... + r_{nR}= R?????
 515 n= ???
 516 ?????????T ??R??n????
 517 ??????????????????
 518 ??????????????
 519 ?????????T= T₁(T)= T₂(T)= ?520 = T_{nT} = T₁(R)= T₂(R)= ? = T_{nR}?
 521 ?????????(?????????)
 522 ?????????) ?????(?? ??????
 523 ?????????) ??????????
 524 ??????????????????
 525 ??????????????????
 526 ??????????????????
 527 ??????????
 528 ???BE ??????????
 529 ?????????(T?R)?
 530 ???????3 ??????
 531 ??1
 532 ??IVPT?(Jmax ?AMT)?????
 533 ??S_{wR}?????
 534 S_{wR}= () 1/2
 535 ???  .j=  ?i (r)  1 R_{ij}?????j????T_{jR}
 536 ??????
 537 ??S_{wR}?0.294????2, 3.1 ?4.1?????

538 ???????(SABE)????? IVPT ????BE

539 ??SwR ?0.294?????2, 3.2 ?4.2?????T



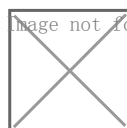
540 ??(TOST)?????????(ABE)????? IVPT

541 ????BE

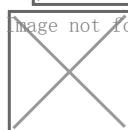
542 ??2

543 ??T ?R ?????????????(I?)?????(se₅₄₄(I?)) ?????? (df?)?

545 ?????????????????I? ?se (I?) df??



546 $I? = I? = ?_{j(n)=1} I_j ? ? I_j = ?_{i(r)=1} (T_{ij} ? R_{ij})$



547 $S_{I(2)} = ?_{j(n)=1} (I_j ? I?)^2$ (???????)

548 $se(I?) = ?S_{I(2)}/n$

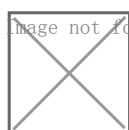
549 $df? = n? 1$

550 ???????????SAS?PROC MIXED(?

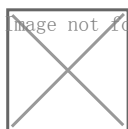
551 PROC GLM)?????I? ?se(I?) df??

552 ??3.1 SABE ?

553 ?SABE ??????????



554 $H_0 : ? e$

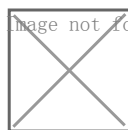
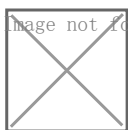


555 $H_a : < e$

556 ???

557 $u_T ? u_R = T ? R$????????

558 $G_{w(2)} R = R$??????????



559 $e = ?_m = 1.2500$ (BE ??) , and $G_{w0} = 0.25$ ₅₆₀ (????)

561 ??????????????????????

562 ??Howe's Approximation (Howe, 1974) (? = 0.05)?
2

563 ?? ($u_T ? u_R$) ? $e G_{w(2)} R ? (1 - ?) * 100\%$????????

564 $X + Y + \text{sign}(V) ? |V|^{1/2}$

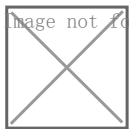
565 ???

566 $X = I?_2 ? se(I?)^2$

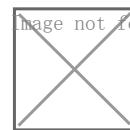
567 $Y = ? e G_{w(2)} R$

568 $X? = (|I?| + t(1?a), df? ? se(I?))$

569 $Y ? = ?e$



570 $\text{sign}(V) = 1 \text{ if } V > 0; 0 \text{ if } V = 0; -1 \text{ if } V < 0$



571 $t(1\alpha, df) \text{ Student's } t(1\alpha, df) \text{ (1-} \alpha \text{)} \text{ } 100 \text{ } X$

n) ??

573 $(1 - \alpha) \text{ } 100 \text{ } \alpha$

574 $3.2 \text{ ABE } \alpha$

575 $\text{ABE } \alpha \text{ } \alpha$

576 $H_0: u_T \text{ } u_R \text{ } \ln(m) \text{ } u_T \text{ } u_R \text{ } \ln(m)$

577 $H_a: \ln(m) < u_T \text{ } u_R < \ln(m)$

578 ??

579 $u_T \text{ } u_R = T \text{ } R \text{ } IVPT \text{ } \alpha$

581 $m = 1.2500 \text{ (BE } \alpha \text{)}$

582 $\ln(m) \text{ } BE \text{ } \alpha$

583 $\alpha \text{ } \alpha \text{ } \alpha$

584 $\alpha \text{ } u_T \text{ } u_R \text{ } (1 - \alpha) \times 100\% \text{ } \alpha$

585 $I \pm t(1\alpha, df) \text{ } se(I)$

586 $t(1\alpha, df) \text{ } t \text{ } (1 - \alpha) \text{ } 100$

587 ????

588 $4.1 \text{ } SABE \text{ (Scaled Average BE)} \text{ } \alpha$

589 ??

590 $IVPT \text{ } \alpha$

591 α

592 a. $(u_T \text{ } u_R) \text{ } e_{Gw(2)R} 95\% \text{ } \alpha$

593 $0 \text{ (} \alpha \text{)}$

594 b. $T \text{ } R \text{ } [1/m, m] \text{ } m = 1.2500$

596 $4.2 \text{ } ABE \text{ (Regular Average BE)} \text{ } \alpha$

597 ??

598 $IVPT \text{ } u_T \text{ } u_R \text{ } 90\% \text{ } \alpha \text{ } [0.8000, 1.2500] \text{ } \alpha$