外用药物制剂体外透皮试验技术要求概况

详细介绍 ：

3.1 皮肤

3.2 IVPT方法开发

3.3 样品分析方法的选择

3.4 数据统计分析

??????????????????

???[1]?? ?[1]?? ?[1]????[2*]????[1]

?1. ??????????????????2. ????????????????

????????????? **????**?2023?11?23?

????????? **????**????????

????*in vitro* permeatic test?IVPT???

????????????????????????IVPT???????

??/?????[1, 2] ??Q3????????????????????????????pH???????/?????????????????????????????????????[1, 3, 4]?

????????????Q1?????Q2??????????Q3????????????????????[3, 5, 6] ????????IVPT?????????????????????????????????IVPT??[3, 7]

???????IVRT?IVPT????A?B?C???????????[8]?

???IVPT??pH??????????????????????? ???2022?4?????????????????????????????USP?2022?5????“PF 48 Semisolid drug products-performance tests”[9]???2022?10?????????????FDA????????“*In vitro* permeation test studies for topical d submitted in ANDAs”[2]?????FDA?????????EMA??????????PMDA??

1 ???????

?????????????????????????????2018??2020??2022?????????????????CDE??????????????????????????????????[10]??????????????? [11]?????????????????????????[12]???IVPT????????

USP?FDA?EMA?PMDA??1997??????????????????????????1???

Table 1 Related Policies and Technical Regulations for Topical Products in Different Countries or Regions?1 ??????????????????????

Table 1 Related Policies and Technical Regulations for Topical Products in Different Countries or Regions?1 ??????????????????????

??	????	????	????
USP	General Chapters 3: Topical and transdermal drug products-product quality tests[4]	2023	?????????????????
	PF48(3): General Chapters 1724: Semisolid drug products-performance tests[9]	2022	???IVRT ?IVPT????????????????????IVPT????????
FDA	SUPAC-SS: Nonsterile semisolid dosage forms; scale-up and postapproval changes: chemistry, manufacturing, and controls; *in vitro* release testing and *in vivo* bioequivalence documentation[13]	1997	??????????????????????????IVRT??????????????????
	Draft guidance on acyclovir[14]	2016	??IVRT?IVPT?????????????????USP<1724>[9] ???????FDA?????????IVPT?USP<1724>?FDA IVPT
	In vitro permeation test studies for topical drug products submitted in ANDAs[2]	2022	???????????????????????IVPT??????????????????
	Physicochemical and structural (Q3) characterization of topical drug products submitted in ANDAs[3]	2022	???????????????????Q3????IVPT??????????????
??	Guideline on quality of transdermal patches[15]	2014	?IVRT?IVPT?????????????????????????????????????
	Draft guideline on quality and equivalence of topical products[7]	2018	
??	Guideline on biological equivalence for formulation changes of topical products (semisolid products and patches)[8]	2010	???????????????????????????????????IVRT?IVPT???

Guideline on biological equivalen for formulatic changes of topical products (semisolic products and patches): questions and answers [16]	2010

2 ????

IVPT??????????????????VDC??????FDC??USP???3???VDC??????1-3?FDC??????4??VDC???????FDC??????????????????????[9]?

??USP<1724>?????????????????????????????????±5%??0.01 mL????????????????????7 mL????????VDC????????????????????????30 min????????????????????????????????????32 ??VDC???????400?600 rpm????????????????????????????????????6?12????????

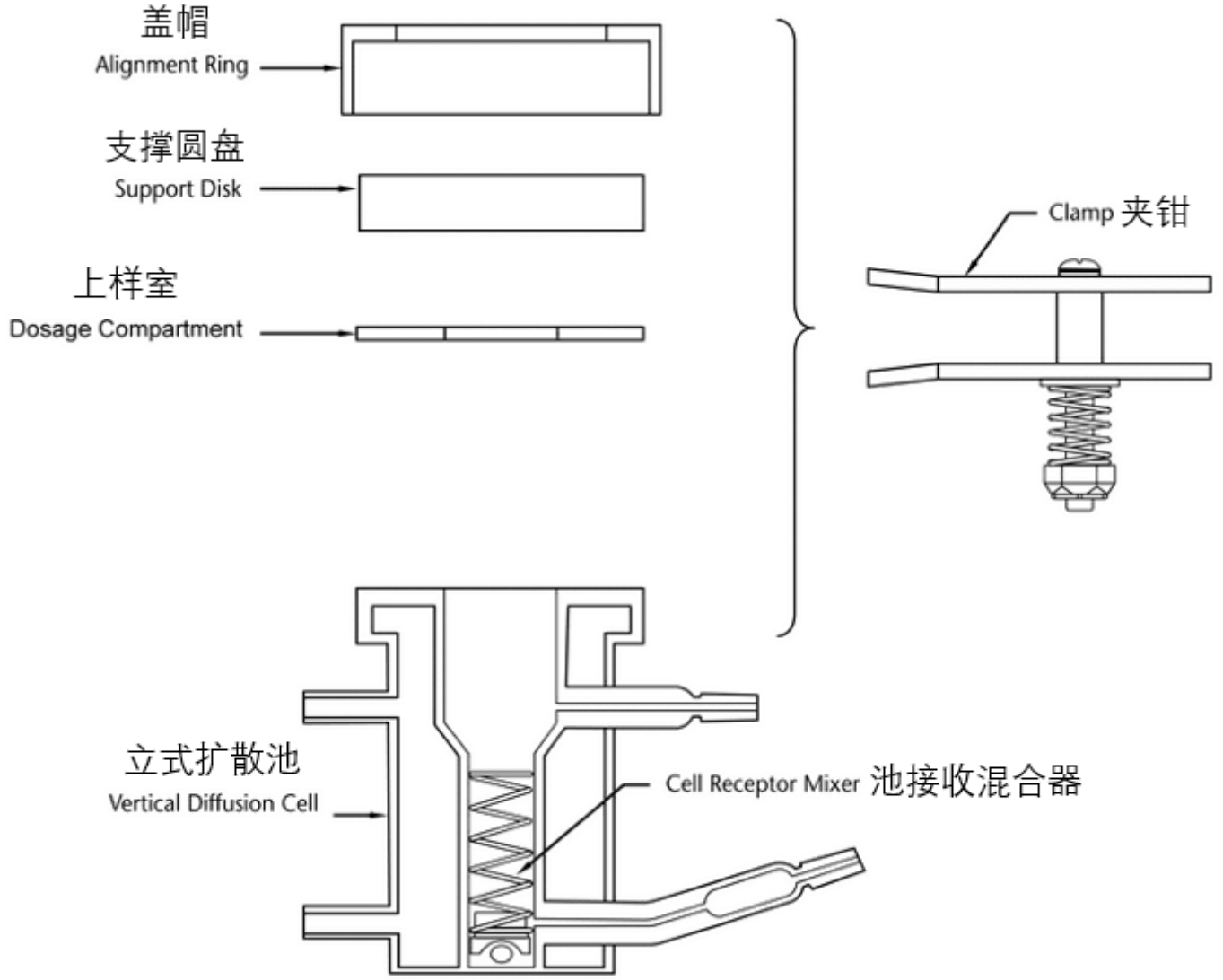

Fig.1 Example of Possible Design for VDC — Model A?1 VDC???A??????????

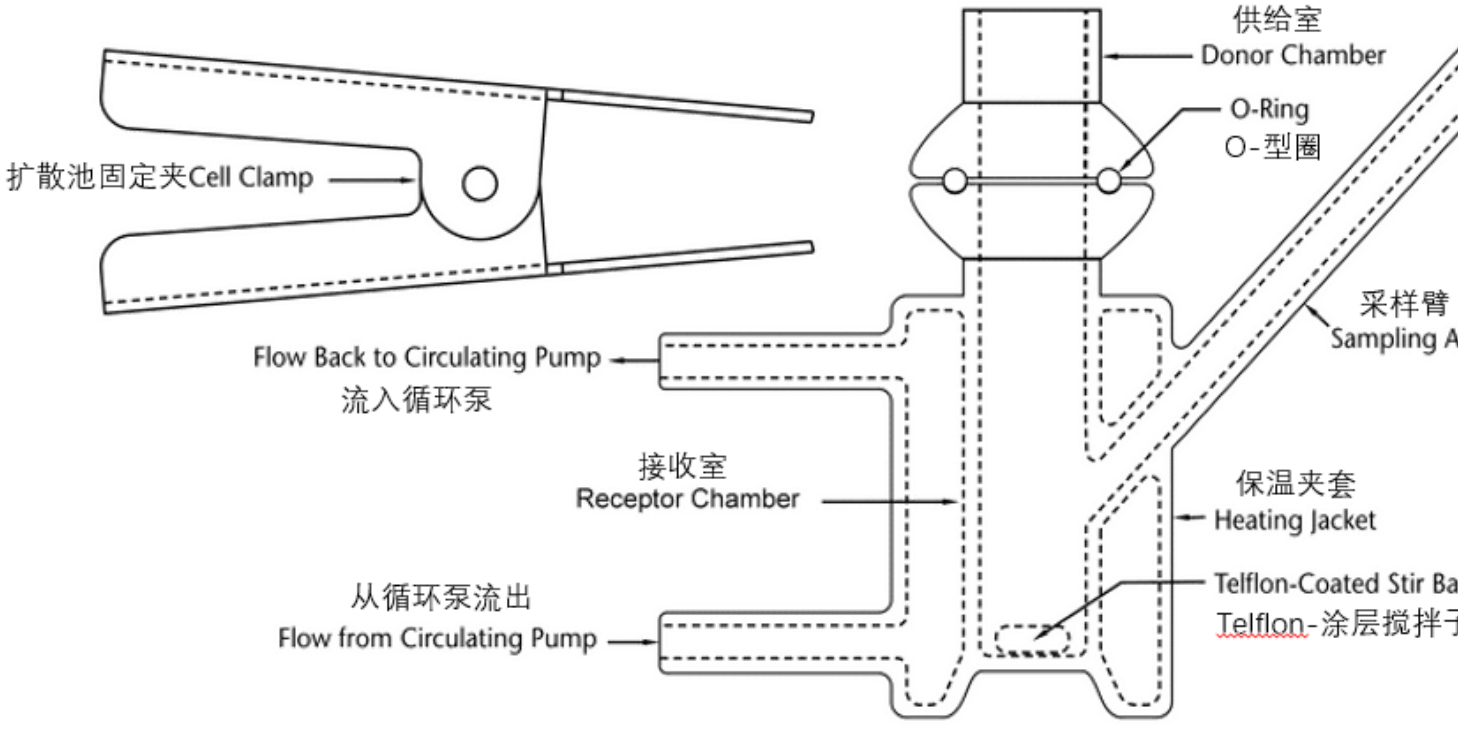

Fig.2 Example of Possible Design for VDC — Model B?2 VDC???B??????????

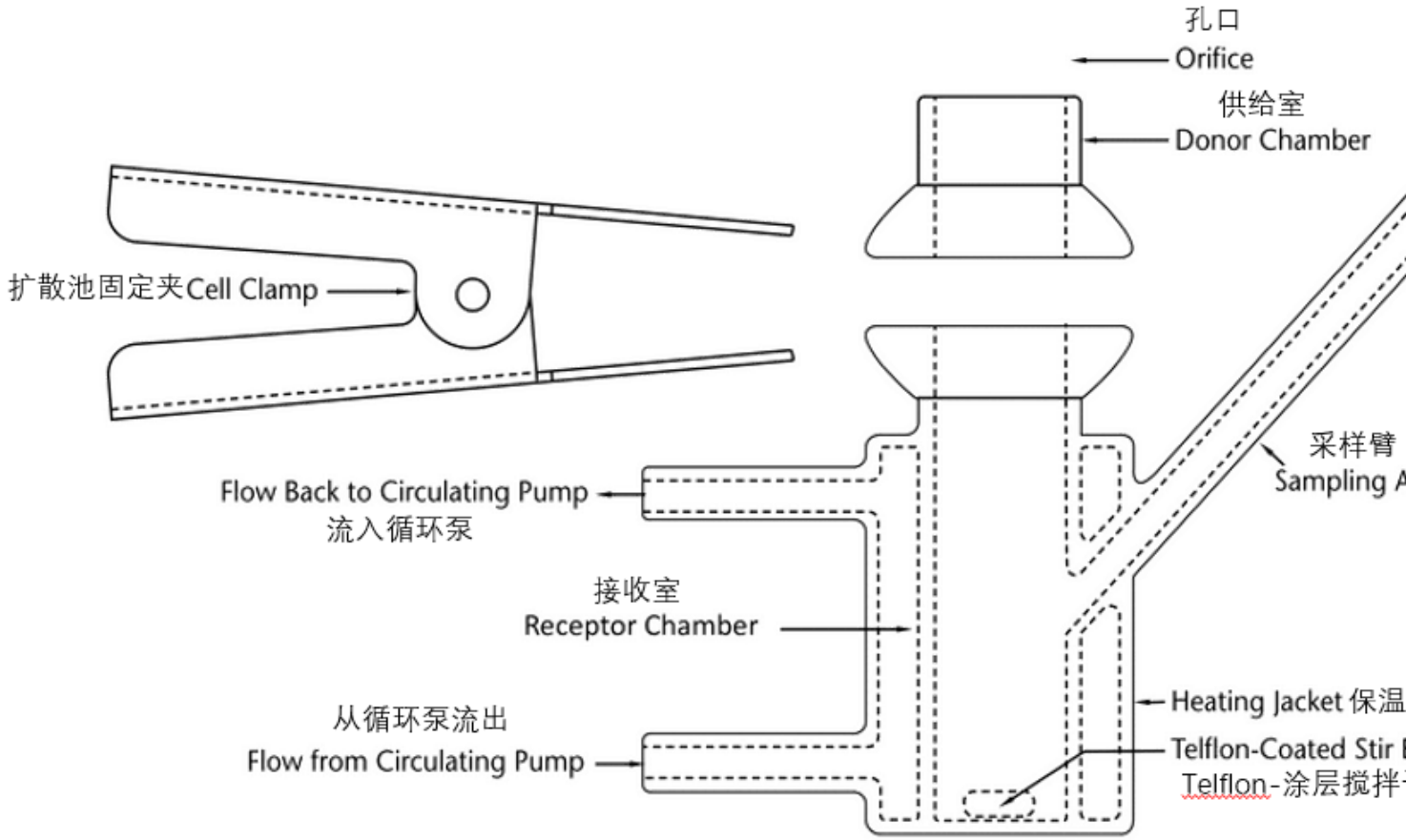

Fig.3 Example of Possible Design for VDC — Model C?3 VDC???C??????????

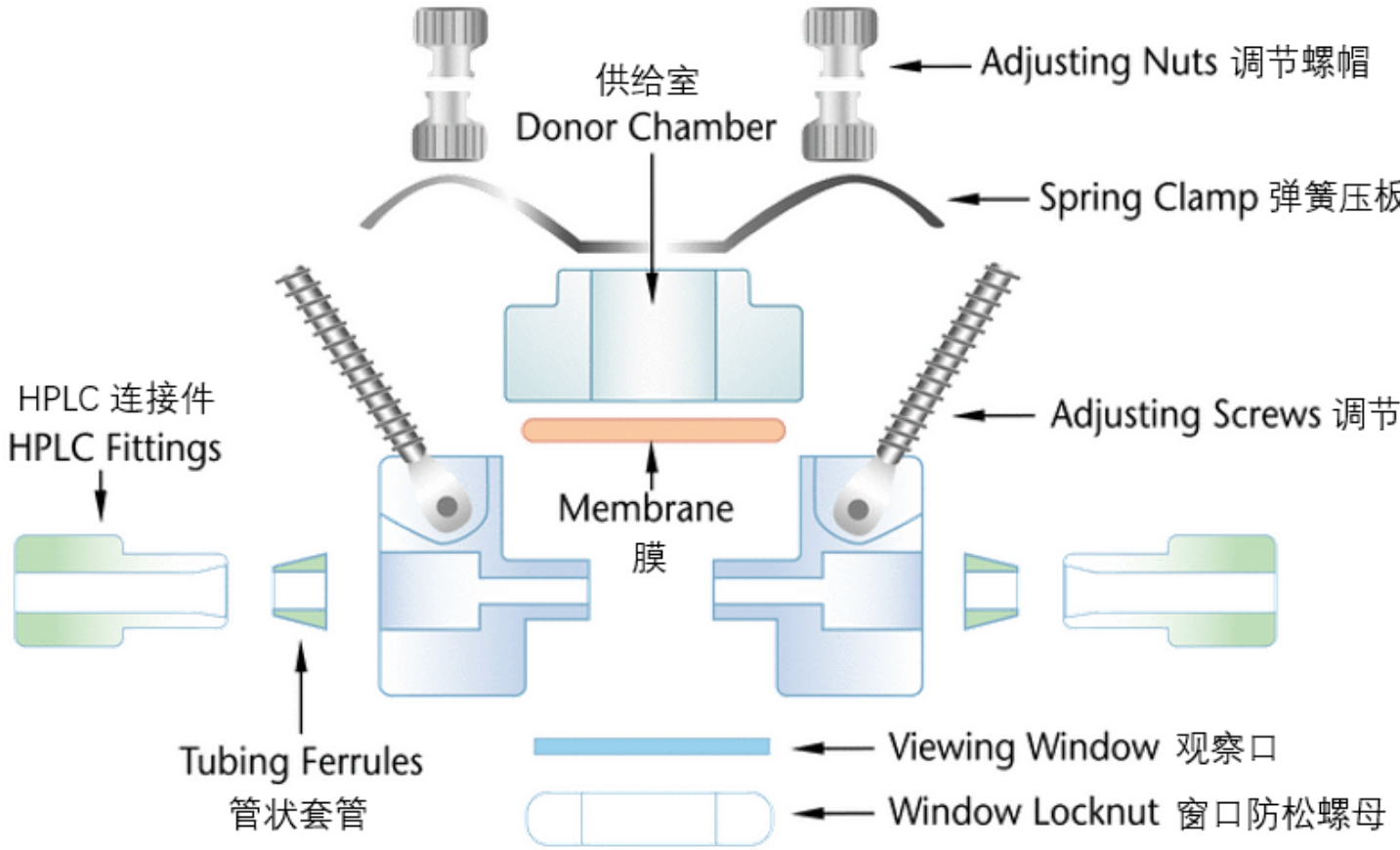

Fig.4 Schematic Diagram Detailing Individual Parts of a Horizontal Flow-through Cell?4 ??????????????????

3 ????

3.1 ??

3.1.1 ?????

EMA在2018年发布的《Draft guideline on quality and equivalence of products》中仅推荐使用离体人类皮肤。PMDA规定可以使用离体大鼠、小鼠或猪的皮肤进行试验[8]**?**

?FDA ???????IVPT???????????????[2, 14]???USP <1724>[9]
??IV
[17, 18]?
???[19, 20]
???[21, 22]????????????????????????IVPT??[23]
???????????????????????IVPT??????????????????????[24]?
???[25]
?????????????????????????IVPT??????????????Yucatan????Landrace??Gottingen????Yorkshire???

3.1.2 ???????

FDA???????????????18?????????????????????/???
[2]??USP????????250?500 μm[9]?
??????1?3??[26]?
????[27]??????????????????-20
???6??????????????????????????????15%?????????????15%?????????TEWL??
MORIN M?[28]
??
?????????????IVPT???

3.1.3 ???????

FDA?EMA??[2, 7]?
USP??[9]?

3.1.4 ????????

???-20 ??-80
??????MORIN M?[28]????????????????????-20 ??-80 ????????????????????????????????????
??
[2]?
???30 min???

3.1.5 ????????

FDA?EMA?PMDA???????????????????[2, 7, 8]?FDA?USP???????????????????????????EMA????????????24
h?????????????????????????????????TEWL??????????/?????TEWL???????[7, 9]?????????TEWL?????????????????????????????????????
FDA???????????????????TEWL????????????????????????????15 g?????15 $g \cdot m^{-2} \cdot h^{-1}$
???TEWL??20 $g \cdot m^{-2} \cdot h^{-1}$
????????????????????????????5 min???????30 min??????????????????????????1.5????????????1.5 eq.?L·cm^{-2} or ~1.5 eq.mg·c
????/??“??”???
[2]?
???

3.1.6 ?????????

FDA???IVPT????????????????????4?6?????????????????????4???????[2]?EMA?????????????????? 12 ???????? 2 ???[7]?PMDA?????
[8]?
????????????????????????????????????10????????????IVPT??????????????????????????????????????FDA?EMA????????????????????

3.2 IVPT????

?????????????????IVPT???????????????????????????????IVPT??

3.2.1 ????????

USP????IVPT?????????????????????????????????????2?15 mg·cm^{-2}??????????5?10 mg·cm^{-2}????
FDA???1????????????2???????????3??????????????????????4???????????????
[9]?EMA??2?15 mg·cm^{-2}???±5%??[7]?
?????????????????????2 ???[29]
?USP???[9]
?FDA??[2]?
?????????IVPT??2?15 mg·cm^{-2}
???????????????????????????????????????±5%??????IVPT???????????????

3.2.2 ????

IVPT??????????????pH???????????????????????????????????EMA??
?PMDA??80[?1%(w/v)]?????400[?40%(w/v)]??????????[8]?
FDA???????????????????????????????????IVPT??0.1%(w/v)????20???CAS?90
2?????????????????????????????20?????[????0.1%(w/v)?0.2%(w/v)]??????????????????????????6%??????????????????????????????
[2]?
??????????????????????????????????pH 6.8?7.4????????[26]
???????0.15??80[?1%(w/v)]?????400[?40%(w/v)]?????20??[?6%(w/v

3.2.3 ????

FDA?EMA?????????????????????????????(32±1)?[2,7]?PMDA?????(32±0.5)?????????????????????USP?????(37±1)?[9]?

3.2.4 ????????????

??
[2]?
USP?????????12?72 h???????????24 h[9]?EMA?????????24 h????????24 h??????????????????????[7]?PMDA?????????24 h [8]?
???IVPT?????????????????????????24 h??????????????????????????

3.2.5 ???????????

EMA???90%?110%???[7]???
????????????FDA??60 ????????2?3 min???????????????????????[9]?

3.3 ?????????

?IVPT???

3.3.1 ?????????

???EMA???
[7]?

3.3.2 ??????????

???[30]????????45 ???????????50%???????20 min??????????(12.50?20.21)?g·cm^{-2}????[31]?????????????5 min???60
min???????A???????(0.7792±0.1424)?g·cm^{-2}?(1.4895±0.2848)?g·cm^{-2}????[32]?????????????5 min???????????[33]????????????????
min??????????????(13.02±1.05)?g·cm^{-2}?????[34]?????????????12 h????????????(0.2963?1.3656)?g·cm^{-2}?
Cross, S.E[35]???????????-??-???760:233:7?????30 s???????????????????????????Jacques-Jamin C[36]???Soluene-350???6
?????????????????????6-??????????JANKOVSKAJA S[37]???pH?12.0?131 mmol·L^{-1}????????????????????????
???Soluene-
350??g·cm^{-2}
??(500±250)?m???

3.3.3 ???????

USP<1724>???????????????pg?ng???[9]????[38]????????????????????????????????10?60 ng·cm^{-2}·h^{-1}???

??????????????????????-???????????-????FDA???????????6?8?????????????FDA??????????????[2,
??

3.4 ??????

???IVPT?????????????????**Jmax**????ng·cm^{-2}·h^{-1}????????**A$_{total}$**????ng·cm^{-2}
?????FDA?EMA?PMDA??
Jmax?**A$_{total}$**??????????????????**Jmax**???????

3.4.1 FDA

????????????????????????4???????????3???????????????SAS??**Jmax**????S_{WR}?????S_{WR}
?0.294??????????????scaled average bioequivalence???SABE???????????T???TOST??????????average
bioequivalence???ABE????????SABE?????? $(\mu_T-\mu_R)^2-\theta\sigma_{WR}^2$?95%????????0?????????????????????0.8000?1.2500????????????ABE??
?90%?????0.8000?1.2500??????????

3.4.2 EMA

??????????????90%??????80.00%?125.00%??90%??????????????69.84%?143.19%?**Jm**
????????????????????????????????

?????????T????????R??24?????????????????????**Jmax**?????T/R???576?T/R????????T/R?????????????????? $X \pm t \times \frac{S}{\sqrt{n}}$
???*X*???T/R???????????*n*?????*t*?*n*-1?????*t*??90%?????*t*??*n*=6?t=2.015?*n*=12?t=1.796?*n*=18?t=1.740?*n*=24?t=1.714??*s*
???T/R????????????????????????????

3.4.3 PMDA

??????????????????????1??
??????PMDA????????????????????????????F???????????

4 ??

?????CDE?FDA?EMA?PMDA?????IVPT??
IVPT???????????????IVPT???????

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