



1 23 February 2017
2 EMA/CHMP/267194/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept paper on revision of the guideline on the**
5 **requirements for clinical documentation for orally inhaled**
6 **products (OIP) including the requirements for**
7 **demonstration of therapeutic equivalence between two**
8 **inhaled products for use in the treatment of asthma and**
9 **chronic obstructive pulmonary disease (COPD) in adults**
10 **and for the treatment of asthma in children and**
11 **adolescents.**
12

Agreed by Respiratory Drafting Group	October 2016
Adopted by CHMP for release for consultation	23 February 2017
Start of public consultation	22 March 2017
End of consultation (deadline for comments)	30 June 2017

13
14 The proposed guideline will replace ' guideline on the requirements for clinical documentation for orally
15 inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence
16 between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary
17 disease (COPD) in adults and for use in the treatment of asthma in children and adolescents' (Doc. Ref.
18 CPMP/EWP/4151/00 Rev. 1).

19
20 Comments should be provided using this [template](#). The completed comments form should be sent to
RespiratoryDG@ema.europa.eu

21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

Keywords	therapeutic equivalence, asthma, COPD, orally inhaled
----------	---



22 1. Introduction

23 This concept paper concerns a revision of the guideline directed to the requirements for demonstration
24 of therapeutic equivalence between two inhaled products. The guideline focuses on hybrid applications
25 but may be applicable also for other applications that are based on demonstration of therapeutic
26 equivalence compared to a reference product, such as line extensions and variations. The guideline
27 was originally published in September 2000 and was revised between September 2007 and January
28 2009 (henceforth referred to as Revision 1).

29 2. Problem statement

30 Since the last revision, several MAAs with the aim to demonstrate therapeutic equivalence compared to
31 a reference product concerning orally inhaled products have been submitted for regulatory review to
32 the National Competent Authorities. The proposed revision is aimed at updating the guideline to reflect
33 knowledge gained from regulatory experience.

34 Demonstration of therapeutic equivalence of two orally inhaled products moves in a stepwise fashion
35 from *in vitro* studies (step 1), to pharmacokinetic studies (step 2), to pharmacodynamic and clinical
36 safety/ efficacy studies (step 3). This should be clearly described in the revised guideline. *In vitro*
37 aspects relevant for the establishment of therapeutic equivalence are described in this guideline but
38 reference is also given to the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products
39 (EMA/CHMP/QWP/49313/2005).

40 Establishing therapeutic equivalence based on *in vitro* data only has proved to be difficult. Also,
41 showing therapeutic equivalence based on PD/clinical data is challenging because of difficulties in
42 ensuring assay sensitivity. Pharmacokinetic studies seem to be simpler, shorter and more
43 discriminative in order to demonstrate similar efficacy and safety without the need for additional
44 clinical data. These aspects should be reflected in the revised guideline.

45 In addition, during the review of applications based on the requirements given in Revision 1, a number
46 of issues were discussed with regard to choice of batches, strengths and study population in
47 pharmacokinetic studies. The principles that were established need to be included in the revised
48 version.

49 Since Revision 1 was published, there have also been advances in inhaler technology of pressurised
50 metered dose inhalers (MDI) and dry powder inhalers (DPI) resulting in better drug delivery
51 characteristics. Also, nebuliser technology has advanced with the development of smaller and more
52 portable devices. Demonstration of equivalence between a consistently performing new device (which
53 is desirable) and a more variable but established device is challenging. This may have an impact on the
54 development needs, which need to be considered.

55 Few products have been approved in children based on the current requirements to demonstrate
56 therapeutic equivalence in the paediatric population. For most of these products, the demonstration of
57 therapeutic equivalence was based on *in vitro* data only. This indicates that the clinical data
58 requirements in paediatrics as detailed in the guideline might be difficult to comply with. Thus,
59 requirements for different paediatric age groups should be reviewed and, if appropriate, revised.

60 3. Discussion (on the problem statement)

61 The following items have been identified and would need to be addressed in the revised guideline:

62 General comments:

- 63 • Despite the emphasis in the document on hybrid/abbreviated developments, the name of the
64 guideline as well as some sections refer to full developments. The name of the guideline should be
65 adapted accordingly.

66 In vitro equivalence studies (Step 1)

- 67 • The Guideline referred to in this concept paper and the Guideline on Pharmaceutical Quality of
68 Inhalation and Nasal Products (EMA/CHMP/QWP/49313/2005) are written to complement each
69 other and should always be read in conjunction. The criteria for pharmaceutical equivalence should
70 thus be in line with corresponding requirements in the pharmaceutical guideline.
- 71 • The use of only comparative *in vitro* data (Step 1) may be considered acceptable if the product
72 satisfies all of the criteria (compared with the reference product) as laid down in the guideline.
73 However, specific requirements on representative batches, dose proportionality, flow dependency
74 and stage grouping are not well described in the current guideline. In addition, these aspects are
75 important to support the PK studies. Thus, specific information on these aspects could be included
76 in the revised guideline as appropriate.
- 77 • *In vitro* data to support extrapolation of therapeutic equivalence from asthma to COPD or vice-
78 versa and to justify the use of healthy volunteers in PK studies, instead of patients, need to be
79 specified.
- 80 • Specific requirements on data with spacers need to be addressed.
- 81 • Specific aspects related to new inhaler technologies should be discussed and included in the
82 guideline.

83 Pharmacokinetic studies (Step 2)

- 84 • The adequacy of using PK data to demonstrate similar efficacy and safety without the need for
85 additional clinical data should be addressed.
- 86 • Given the limitations with imaging studies to conclude on therapeutic equivalence, the current
87 recommendation should be reviewed.
- 88 • The current version states that pharmacokinetics should be studied in the intended patient
89 population. This statement needs to be revised and specific information should be given regarding
90 when healthy volunteers may be used for demonstrating therapeutic equivalence.
- 91 • Requirements for PK data on spacers and nebulisers should be reviewed.
- 92 • Variability in particle-size distribution between batches of the reference product or within a single
93 batch of a reference product through their storage period can be significant. The acceptability of
94 pre-specifying a correction factor when demonstrating bioequivalence and the data to support such
95 a proposal e.g. *in vitro in vivo* correlation (IVIVC) need to be addressed.

96 Pharmacodynamic / clinical studies (Step 3)

- 97 • The recommendations regarding study design, study population, endpoints, timing of measurement
98 and acceptance criteria to demonstrate therapeutic equivalence should be standardised to the
99 extent possible.

- 100 • Specific recommendations for fixed-dose combinations depending on the combination (e.g.
101 LABA/LAMA combinations) should be given in the revised guideline.
- 102 • Recommendations are needed as to whether pharmacodynamic data obtained in healthy volunteers
103 can be used to show therapeutic equivalence.
- 104 • Requirements for user studies on different inhaler devices and the required test panels (e.g.
105 handling studies) should be addressed in more detail.

106 Data requirements in children and adolescents

- 107 • Data requirements for the paediatric population need to be discussed and re-considered in the
108 revised guideline.

109 **4. Recommendation**

110 The Respiratory drafting group recommends revising the current guideline on orally inhaled products
111 taking into account the issues identified above.

112 **5. Proposed timetable**

113 Released for consultation in March 2017, deadline for comments 30 June 2017, proposed date for
114 release of draft guideline during 2018, deadline for comments 6 months later.

115 **6. Resource requirements for preparation**

116 The update of the guideline will involve representatives of Member States from the Respiratory drafting
117 group and it should be discussed in approximately three of their meetings.

118 **7. Impact assessment (anticipated)**

119 The document is intended to provide guidance on how to establish therapeutic equivalence for orally
120 inhaled products used in asthma and COPD. In addition, it will be useful to reach a common approach
121 for the assessment of these products and scientific advice given by European regulatory authorities.

122 **8. Interested parties**

123 The pharmaceutical industry, European learned societies and scientific organisations (e.g. the
124 European Respiratory Society). Consultation with other working parties or committees (e.g. QWP,
125 PKWP and PDCO) will be initiated as appropriate.

126 **9. References to literature, guidelines, etc.**

127 Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMA/CHMP/QWP/49313/2005)

128 Clinical pharmacology and pharmacokinetics: question and answers (PKWP), question 3.3 and 3.4.

129 QWP Question & Answers on inhalation products.