Fig. 1

Material	Supplier
Lactose monohydrate PhEur	DMV-Frontera Excipients
Mannitol PhEur	S. Black Ltd
Trehalose	Sigma-Aldrich
Sucrose PhEur	Fisher Scientific Ltd
Maltose monohydrate PhEur	S. Black Ltd
Dextran 70kD	Sigma-Aldrich
Povidone K17	IMCD Ltd
Glycine	Fisher Scientific Ltd
Hydrochloric acid SG 1.18	BDH Ltd
2M Sodium hydroxide	Fisher Scientific Ltd
Water for injection	Baxter Healthcare

Fig. 2

Formulation number	Formulation	REM mg/vial	excipient 1 mg/vial	excipient 2 mg/vial
01	REM only	16.32	--	--
02	REM/lactose (1:9)	8.16	73.44	--
03	REM/lactose (1:4.5)	8.16	36.72	--
04	REM/lactose (1:1)	8.16	8.16	--
05	REM/mannitol (1:9)	8.16	73.44	--
06	REM/trehalose (1:9)	8.16	73.44	--
07	REM/sucrose (1:9)	8.16	73.44	--
08	REM/maltose (1:9)	8.16	73.44	--
09	REM/dextran (1:9)	8.16	73.44	--
10	REM/lactose/mannitol (1:4.5:4.5)	8.16	36.72	36.72
11	REM/povidone (1:9)	8.16	73.44	--
12	REM/glycine (1:9)	8.16	73.44	--

Fig. 3

Formulation number	Formulation	excipient 1 mg/vial	excipient 2 mg/vial
02P	lactose	73.44	--
05P	mannitol	73.44	--
06P	trehalose	73.44	--
07P	sucrose	73.44	--
08P	maltose	73.44	--
09P	dextran	73.44	--
10P	lactose/mannitol	36.72	36.72
11P	povidone	73.44	--
12P	glycine	73.44	--

Fig. 4

Formulation number	Formulation	25°C/60%RH	40°C/75%RH
01	REM only	1.06	8.56
02	REM/lactose (1:9)	0.13	0.45
03	REM/lactose (1:4.5)	0.20	0.90
04	REM/lactose (1:1)	0.56	3.54
05	REM/mannitol (1:9)	1.62	8.23
06	REM/trehalose (1:9)	0.14	0.51
07	REM/sucrose (1:9)	0.10	0.22
08	REM/maltose (1:9)	0.14	0.45
09	REM/dextran (1:9)	0.16	0.57
10	REM/lactose/mannitol (1:4.5:4.5)	0.19	0.89
11	REM/povidone (1:9)	0.53	2.99
12	REM/glycine (1:9)	1.30	1.54

Fig. 5A

```
TITL 12161316    Compound CNS7056 Form 1
CELL  0.71073  7.687 29.261 12.376  90.000  97.788  90.000
ZERR    2 0.0001 0.0005 0.0003 0.0000 0.0008 0.0000
LATT  -1
SYMM  -X,Y+0.500,-Z
SFAC C      2.3100  20.8439   1.0200  10.2075   1.5886   0.5687   0.8650 =
            51.6512   0.2156   0.0033   0.0016     1.15   0.7700  12.0110
SFAC H      0.4930  10.5109   0.3229  26.1257   0.1402   3.1424   0.0408 =
            57.7998   0.0030   0.0000   0.0000     0.06   0.3200   1.0079
SFAC O      3.0485  13.2771   2.2868   5.7011   1.5463   0.3239   0.8670 =
            32.9089   0.2508   0.0106   0.0060     3.25   0.7700  15.9994
SFAC BR    17.1789   2.1723   5.2358  16.5796   5.6377   0.2609   3.9851 =
            41.4328   2.9557  -0.2901   2.4595  1000.00   1.1000  79.9040
SFAC N     12.2126   0.0057   3.1322   9.8933   2.0125  28.9975   1.1663 =
             0.5826 -11.5290   0.0061   0.0033     1.96   0.7700  14.0067
SFAC S      6.9053   1.4679   5.2034  22.2151   1.4379   0.2536   1.5863 =
            56.1720   0.8669   0.1246   0.1234    53.20   1.1100  32.0660
UNIT  108. 100.  20.   4.  16.   4.

S80     6   0.23964   0.43139   0.09908  11.00000   0.04634   0.03299 =
        0.04052   0.00002   0.01880  -0.00340
O81         3   0.16028   0.39374   0.15143  11.00000   0.06864   0.04111 =
        0.05255  -0.00210   0.02801   0.00002
O82         3   0.14598   0.47435   0.11207  11.00000   0.08099   0.03603 =
        0.04614   0.00545   0.03373  -0.00236
O83         3   0.42589   0.43401   0.12925  11.00000   0.05754   0.08564 =
        0.05198  -0.01536   0.01792  -0.00644
C84         1   0.20581   0.41866  -0.04324  11.00000   0.05949   0.04444 =
        0.02903   0.00359   0.01728   0.00704
C85         1   0.03624   0.41100  -0.09142  11.00000   0.06649   0.10092 =
        0.05586   0.01088   0.01751   0.00507
C86         1   0.00323   0.39810  -0.20187  11.00000   0.08670   0.14765 =
        0.05902  -0.02096  -0.03160  -0.00004
C87         1   0.14311   0.39209  -0.25693  11.00000   0.07916   0.11651 =
        0.06238  -0.01696   0.00195   0.02481
C88         1   0.30473   0.39806  -0.20987  11.00000   0.09246   0.09710 =
        0.04155   0.00157   0.01795   0.02685
C89         1   0.33456   0.41126  -0.10133  11.00000   0.05999   0.09817 =
        0.07178  -0.01451   0.00886   0.02173
S90         6   0.68868   0.81145   0.51625  11.00000   0.04072   0.02869 =
        0.05437   0.00158   0.00214   0.00223
O91         3   0.79129   0.77464   0.57315  11.00000   0.08025   0.03751 =
        0.04867  -0.00213  -0.00954   0.01626
O92         3   0.52601   0.81933   0.56122  11.00000   0.04778   0.05360 =
        0.06934  -0.00642   0.01702   0.00039
O93         3   0.78935   0.85213   0.50763  11.00000   0.07515   0.04369 =
        0.05025  -0.01354   0.01764  -0.01547
C94         1   0.62446   0.78970   0.38130  11.00000   0.04232   0.04028 =
        0.05049   0.00898   0.00929   0.00525
C95         1   0.74659   0.76959   0.32396  11.00000   0.06194   0.06998 =
        0.03238   0.00341  -0.00103   0.00990
C96         1   0.69911   0.75023   0.22476  11.00000   0.12417   0.10337 =
        0.03441   0.01537   0.02421   0.03314
C97         1   0.51941   0.75295   0.17732  11.00000   0.11897   0.11939 =
        0.02308  -0.01324  -0.00963  -0.00586
C98         1   0.40301   0.77268   0.23169  11.00000   0.06106   0.10242 =
        0.05463   0.00570  -0.01263  -0.00283
C99         1   0.45446   0.79193   0.33547  11.00000   0.05307   0.07089 =
        0.04982   0.00728  -0.00426  -0.01944
BR1         4   0.06011   0.52462   0.55140  11.00000   0.04153   0.05204 =
        0.07369  -0.00524   0.02434   0.00670
C2          1   0.25757   0.50395   0.49005  11.00000   0.02832   0.04536 =
        0.03350  -0.00752   0.01511   0.00763
C3          1   0.28921   0.45781   0.47911  11.00000   0.03135   0.03107 =
        0.04579   0.00145   0.00221  -0.00479
```

Fig. 5B

```
C4      1   0.42954   0.44393   0.43174  11.00000   0.03767   0.03461 =
 0.02980  -0.00320  -0.00151  -0.00125
C5      1   0.54674   0.47556   0.39943  11.00000   0.03535   0.02939 =
 0.03479  -0.00390   0.00647   0.00183
C6      1   0.51907   0.52242   0.41134  11.00000   0.04226   0.03479 =
 0.04333  -0.00172   0.00236   0.00188
C7      1   0.37213   0.53602   0.45794  11.00000   0.03598   0.02793 =
 0.04586  -0.00044   0.01652   0.00336
C8      1   0.64321   0.55824   0.38118  11.00000   0.03964   0.02453 =
 0.02719   0.00516   0.00457   0.00373
C9      1   0.68998   0.59645   0.46059  11.00000   0.03743   0.03694 =
 0.04454  -0.00375   0.01588   0.00649
N10     5   0.69097   0.58514   0.56581  11.00000   0.06070   0.03116 =
 0.04918  -0.00640   0.02020  -0.00054
C11     1   0.74090   0.61847   0.63822  11.00000   0.06804   0.05787 =
 0.04752  -0.00600   0.01695  -0.00669
C12     1   0.78515   0.66221   0.61053  11.00000   0.05480   0.04458 =
 0.05526  -0.02125   0.01554  -0.00787
C13     1   0.77550   0.67229   0.50132  11.00000   0.04463   0.03102 =
 0.05452   0.00407   0.01432  -0.00038
C14     1   0.73186   0.63955   0.42553  11.00000   0.04272   0.03021 =
 0.04282  -0.00243   0.01499   0.00270
N15     5   0.71451   0.55972   0.29408  11.00000   0.04979   0.02502 =
 0.03692   0.00975   0.01748   0.00775
C16     1   0.67500   0.52204   0.21324  11.00000   0.04463   0.02346 =
 0.04948  -0.00464   0.01738   0.00561
C17     1   0.75857   0.47996   0.26673  11.00000   0.04549   0.02673 =
 0.01954  -0.00693   0.00506  -0.00121
N18     5   0.70009   0.45973   0.35317  11.00000   0.03293   0.02806 =
 0.02597  -0.00088   0.00321   0.00207
C19     1   0.81334   0.42409   0.39181  11.00000   0.03678   0.02848 =
 0.03351  -0.00426   0.00585   0.00488
C20     1   0.93968   0.42402   0.32661  11.00000   0.03371   0.02802 =
 0.03711   0.00202   0.00106   0.00680
N21     5   0.90585   0.45925   0.25315  11.00000   0.04775   0.03416 =
 0.02231  -0.01051   0.01052  -0.00308
C22     1   0.79597   0.39511   0.48941  11.00000   0.03997   0.03711 =
 0.04548   0.01039   0.00508   0.00197
C23     1   0.74788   0.53407   0.10940  11.00000   0.05650   0.04712 =
 0.03514   0.00836   0.00449   0.00605
C24     1   0.68780   0.50047   0.01647  11.00000   0.08242   0.04077 =
 0.03001  -0.00046   0.01385   0.00523
C25     1   0.71419   0.51690  -0.09234  11.00000   0.06429   0.06543 =
 0.03392   0.00018   0.00559  -0.00499
O26     3   0.76261   0.55440  -0.11450  11.00000   0.12347   0.08282 =
 0.04188   0.01501   0.01658  -0.04001
O27     3   0.65910   0.48459  -0.16756  11.00000   0.10340   0.06919 =
 0.03191   0.00253   0.01824  -0.00449
C28     1   0.66642   0.49760  -0.27953  11.00000   0.19131   0.12699 =
 0.01390  -0.01417   0.02134  -0.05279
BR51    4   1.06737   0.71057   0.98743  11.00000   0.03812   0.08781 =
 0.06774   0.00566  -0.00531   0.00447
C52     1   0.84276   0.73306   0.93243  11.00000   0.03132   0.05952 =
 0.03819   0.00358   0.00226  -0.00263
C53     1   0.81293   0.77906   0.93249  11.00000   0.04627   0.06820 =
 0.03723  -0.00581   0.00481  -0.00474
C54     1   0.65043   0.79579   0.88269  11.00000   0.04551   0.03939 =
 0.04858  -0.00084   0.00376  -0.01071
C55     1   0.51946   0.76552   0.84226  11.00000   0.04294   0.03573 =
 0.03413   0.00062   0.00952  -0.00208
C56     1   0.54512   0.71765   0.84581  11.00000   0.02688   0.03659 =
 0.04586  -0.00025   0.00561   0.00047
C57     1   0.71139   0.70186   0.88914  11.00000   0.03105   0.04840 =
 0.04447  -0.00668  -0.00429   0.00504
C58     1   0.40956   0.68443   0.79765  11.00000   0.03348   0.02893 =
 0.04334   0.00070   0.00351   0.00421
```

Fig. 5C

C59	1	0.38048	0.64253	0.86694	11.00000	0.03165	0.03488 =
	0.04951	0.00002	0.00425	0.00528			
N60	5	0.42879	0.64650	0.97247	11.00000	0.03542	0.05694 =
	0.03178	0.00872	0.00154	0.00467			
C61	1	0.38962	0.61026	1.03529	11.00000	0.04457	0.06338 =
	0.05765	0.01416	0.00707	0.00171			
C62	1	0.30187	0.57202	0.98967	11.00000	0.06548	0.04957 =
	0.11303	0.03456	0.03582	0.00696			
C63	1	0.25733	0.56863	0.88018	11.00000	0.07395	0.04664 =
	0.09803	0.00115	0.01240	-0.01007			
C64	1	0.29561	0.60475	0.81590	11.00000	0.08355	0.04152 =
	0.05459	-0.00010	0.00128	-0.02308			
N65	5	0.31344	0.68797	0.70771	11.00000	0.03846	0.03072 =
	0.04952	-0.00160	0.00032	0.00597			
C66	1	0.33129	0.72953	0.64125	11.00000	0.03574	0.02676 =
	0.05519	0.00406	0.00580	0.00330			
C67	1	0.26347	0.76733	0.70231	11.00000	0.03803	0.03316 =
	0.04166	0.01528	0.00868	0.00029			
N68	5	0.35122	0.78274	0.79764	11.00000	0.03387	0.03259 =
	0.05055	0.00549	0.00427	0.00218			
C69	1	0.24763	0.81583	0.84108	11.00000	0.05345	0.03305 =
	0.04570	0.00005	0.02067	-0.00546			
C70	1	0.09873	0.81841	0.77077	11.00000	0.04465	0.03799 =
	0.06107	0.00794	0.01464	0.00936			
N71	5	0.10819	0.78841	0.68720	11.00000	0.03892	0.03266 =
	0.05306	0.00974	0.01063	0.00803			
C72	1	0.30218	0.84064	0.94469	11.00000	0.08091	0.04934 =
	0.08052	-0.01505	0.02392	-0.00661			
C73	1	0.22541	0.72388	0.52948	11.00000	0.04039	0.05583 =
	0.03295	0.00047	0.00724	-0.00165			
C74	1	0.30154	0.68566	0.46508	11.00000	0.05896	0.05343 =
	0.05504	-0.00576	0.00667	0.02016			
C75	1	0.18003	0.67204	0.36587	11.00000	0.05296	0.05447 =
	0.04241	0.00546	0.01355	0.00171			
O76	3	0.06782	0.69497	0.31818	11.00000	0.05552	0.07543 =
	0.05719	-0.00702	-0.00194	0.02108			
O77	3	0.22119	0.62976	0.33149	11.00000	0.08466	0.04267 =
	0.04376	-0.00714	0.00726	0.00488			
C78	1	0.10717	0.61220	0.23887	11.00000	0.06302	0.09312 =
	0.07465	-0.02449	0.02418	-0.00980			
H611	2	10.42342	10.61111	11.10933	11.00000	0.06582	
H621	2	10.27371	10.54835	11.03412	11.00000	0.09086	
H631	2	10.20282	10.54235	10.84949	11.00000	0.08585	
H641	2	10.26600	10.60396	10.74163	11.00000	0.07058	
H661	2	10.45616	10.73494	10.63683	11.00000	0.04658	
H701	2	10.00528	10.83765	10.77749	11.00000	0.05724	
H721	2	10.20390	10.85662	10.96784	11.00000	0.10482	
H722	2	10.39143	10.86250	10.93477	11.00000	0.10500	
H723	2	10.34863	10.81975	11.00178	11.00000	0.10479	
H731	2	10.22647	10.75279	10.49048	11.00000	0.05050	
H732	2	10.10462	10.71635	10.53573	11.00000	0.05107	
H741	2	10.41143	10.69632	10.44327	11.00000	0.06599	
H742	2	10.32279	10.65905	10.51273	11.00000	0.06616	
H571	2	10.73613	10.67093	10.88928	11.00000	0.04893	
H531	2	10.89874	10.79871	10.96543	11.00000	0.05990	
H541	2	10.63029	10.82681	10.87790	11.00000	0.05285	
H161	2	10.54702	10.51731	10.19609	11.00000	0.04687	
H201	2	11.03302	10.40374	10.33036	11.00000	0.03977	
H221	2	10.90306	10.37871	10.51025	11.00000	0.06107	
H222	2	10.77354	10.41394	10.54853	11.00000	0.06102	
H223	2	10.70245	10.37370	10.47387	11.00000	0.06087	
H231	2	10.71028	10.56434	10.08666	11.00000	0.05487	
H232	2	10.87494	10.53365	10.12431	11.00000	0.05471	
H241	2	10.56546	10.49241	10.01723	11.00000	0.06095	
H242	2	10.75795	10.47323	10.02815	11.00000	0.06099	
H111	2	10.74728	10.61186	10.71244	11.00000	0.06882	
H121	2	10.81997	10.68398	10.66349	11.00000	0.06182	

Fig. 5D

H131	2	10.79812	10.70154	10.48020	11.00000	0.05215
H141	2	10.72939	10.64544	10.35226	11.00000	0.04595
H71	2	10.35042	10.56684	10.46668	11.00000	0.04408
H31	2	10.21444	10.43638	10.50355	11.00000	0.04223
H41	2	10.44931	10.41280	10.42055	11.00000	0.04056
H891	2	10.44977	10.41481	9.93226	11.00000	0.09285
H881	2	10.39917	10.39332	9.75106	11.00000	0.09266
H871	2	10.12372	10.38356	9.66972	11.00000	0.10194
H861	2	9.88808	10.39388	9.76390	11.00000	0.11607
H851	2	9.94416	10.41466	9.94909	11.00000	0.08904
H951	2	10.86472	10.76918	10.35546	11.00000	0.06580
H961	2	10.78321	10.73544	10.18942	11.00000	0.10497
H971	2	10.48493	10.74055	10.10914	11.00000	0.10604
H981	2	10.28646	10.77378	10.20054	11.00000	0.08719
H991	2	10.37377	10.80653	10.37249	11.00000	0.07037
H781	2	10.14480	10.58182	10.22240	11.00000	0.11588
H782	2	10.11102	10.63197	10.17669	11.00000	0.11581
H783	2	9.98883	10.61082	10.25546	11.00000	0.11600
H711	2	10.01359	10.78308	10.62464	11.00000	0.05205
H211	2	10.98261	10.46785	10.19729	11.00000	0.04161
H281	2	10.62358	10.47180	9.67092	11.00000	0.11566
H282	2	10.59036	10.52501	9.70225	11.00000	0.11566
H283	2	10.79029	10.50514	9.71088	11.00000	0.11566

Fig. 6A

```
TITL 1142055    Compound CNS7056 form 2
CELL  0.71073  8.921 11.154 25.834  90.000  90.000  90.000
ZERR    4 0.0001 0.0002 0.0004 0.0000 0.0000 0.0000
LATT  -1
SYMM  X+0.500,-Y+0.500,-Z
SYMM  -X,Y+0.500,-Z+0.500
SYMM  -X+0.500,-Y,Z+0.500
SFAC C      2.3100  20.8439   1.0200  10.2075   1.5886   0.5687   0.8650 =
           51.6512   0.2156   0.0033   0.0016     1.15   0.7700  12.0110
SFAC H      0.4930  10.5109   0.3229  26.1257   0.1402   3.1424   0.0408 =
           57.7998   0.0030   0.0000   0.0000     0.06   0.3200   1.0079
SFAC BR    17.1789   2.1723   5.2358  16.5796   5.6377   0.2609   3.9851 =
           41.4328   2.9557  -0.2901   2.4595  1000.00   1.1000  79.9040
SFAC N     12.2126   0.0057   3.1322   9.8933   2.0125  28.9975   1.1663 =
            0.5826 -11.5290   0.0061   0.0033     1.96   0.7700  14.0067
SFAC O      3.0485  13.2771   2.2868   5.7011   1.5463   0.3239   0.8670 =
           32.9089   0.2508   0.0106   0.0060     3.25   0.7700  15.9994
SFAC S      6.9053   1.4679   5.2034  22.2151   1.4379   0.2536   1.5863 =
           56.1720   0.8669   0.1246   0.1234    53.20   1.1100  32.0660
UNIT  108. 100.   4.  16.  20.   4.

BR1          3  -0.04819  -0.10880  -0.27710  11.00000   0.07032   0.03277 =
        0.03090   0.00144  -0.01238  -0.02224
C2           1  -0.15018  -0.21830  -0.32054  11.00000   0.02777   0.02177 =
        0.02345  -0.00009  -0.00209  -0.00471
C3           1  -0.17401  -0.18875  -0.37205  11.00000   0.02963   0.01861 =
        0.02702   0.00623   0.00188  -0.00107
C4           1  -0.24491  -0.26965  -0.40362  11.00000   0.02825   0.02442 =
        0.01718   0.00327   0.00106  -0.00145
C5           1  -0.29275  -0.37943  -0.38401  11.00000   0.02223   0.01822 =
        0.01875  -0.00067   0.00141   0.00066
C6           1  -0.27139  -0.40894  -0.33163  11.00000   0.02028   0.01967 =
        0.01926   0.00182   0.00105  -0.00153
C7           1  -0.20042  -0.32532  -0.29979  11.00000   0.02809   0.02763 =
        0.01685   0.00206   0.00190  -0.00055
C8           1  -0.32197  -0.52600  -0.30927  11.00000   0.01670   0.02233 =
        0.01945   0.00135  -0.00476  -0.00144
C9           1  -0.39853  -0.52353  -0.25770  11.00000   0.01623   0.02317 =
        0.01584   0.00259  -0.00384  -0.00281
N10          4  -0.46099  -0.41943  -0.24363  11.00000   0.02251   0.02613 =
        0.02353  -0.00189   0.00408   0.00155
C11          1  -0.52777  -0.41652  -0.19697  11.00000   0.02617   0.03441 =
        0.02357  -0.00451   0.00365   0.00346
C12          1  -0.53610  -0.51390  -0.16425  11.00000   0.02740   0.04329 =
        0.02040  -0.00335   0.00652  -0.00779
C13          1  -0.47518  -0.62062  -0.17997  11.00000   0.03584   0.03200 =
        0.02405   0.00767   0.00645  -0.00687
C14          1  -0.40334  -0.62685  -0.22730  11.00000   0.02879   0.02223 =
        0.02565   0.00090   0.00272  -0.00057
N15          4  -0.30040  -0.62781  -0.33049  11.00000   0.02151   0.02416 =
        0.01713   0.00287  -0.00002   0.00182
C16          1  -0.21928  -0.62991  -0.38036  11.00000   0.02330   0.02286 =
        0.01602   0.00057   0.00417   0.00450
```

Fig. 6B

```
C17       1  -0.32510  -0.57975  -0.41920  11.00000   0.02824   0.02308 =
   0.01704  -0.00121   0.00336  -0.00285
N18       4  -0.36294  -0.46298  -0.41818  11.00000   0.02482   0.02037 =
   0.01483   0.00150  -0.00070   0.00079
C19       1  -0.46920  -0.44117  -0.45641  11.00000   0.03022   0.02725 =
   0.01634   0.00325   0.00039  -0.00224
C20       1  -0.49445  -0.54753  -0.47911  11.00000   0.03071   0.03401 =
   0.01669   0.00110  -0.00174  -0.00215
N21       4  -0.40440  -0.63226  -0.45591  11.00000   0.03619   0.02354 =
   0.02146  -0.00463   0.00147  -0.00154
C22       1  -0.54310  -0.32298  -0.46595  11.00000   0.03636   0.03429 =
   0.03074   0.00778  -0.00982  -0.00011
C23       1  -0.15995  -0.75547  -0.39193  11.00000   0.03430   0.02640 =
   0.01793  -0.00359   0.00177   0.00554
C24       1  -0.06166  -0.79435  -0.34621  11.00000   0.04707   0.03881 =
   0.02350   0.00041   0.00034   0.01530
C25       1   0.06625  -0.87542  -0.35603  11.00000   0.03182   0.02650 =
   0.01948   0.00340  -0.00125  -0.00016
O26       5   0.17233  -0.88334  -0.32760  11.00000   0.03778   0.06570 =
   0.03313  -0.01160  -0.01173   0.00417
O27       5   0.05245  -0.94265  -0.39885  11.00000   0.03130   0.03874 =
   0.02467  -0.00799  -0.00330   0.01418
C28       1   0.17574  -1.02443  -0.40865  11.00000   0.05622   0.08123 =
   0.03697  -0.01153  -0.00496   0.04396
S80       6  -0.94275  -0.52899  -0.49624  11.00000   0.03340   0.02679 =
   0.02442   0.00000   0.00210  -0.00075
O81       5  -0.83867  -0.47114  -0.53020  11.00000   0.05118   0.08336 =
   0.03575   0.02297  -0.00622  -0.02476
O82       5  -1.08156  -0.46260  -0.49186  11.00000   0.04015   0.07788 =
   0.05503  -0.01022  -0.00539   0.01721
O83       5  -0.97025  -0.65272  -0.50726  11.00000   0.13945   0.03230 =
   0.06071  -0.01467   0.01447  -0.00725
C84       1  -0.86288  -0.52210  -0.43343  11.00000   0.02735   0.05893 =
   0.02832   0.01509   0.00686  -0.00534
C85       1  -0.87781  -0.41462  -0.40588  11.00000   0.03763   0.08695 =
   0.03855  -0.01799   0.00427  -0.00754
C86       1  -0.81420  -0.39965  -0.35764  11.00000   0.05438   0.16315 =
   0.04455  -0.02905   0.00147  -0.02905
C87       1  -0.73766  -0.49241  -0.33773  11.00000   0.06202   0.20226 =
   0.06481   0.03510  -0.02105  -0.05062
C88       1  -0.71885  -0.60444  -0.36221  11.00000   0.04217   0.17120 =
   0.11388   0.10762  -0.01320  -0.03729
C89       1  -0.78500  -0.61610  -0.41251  11.00000   0.03725   0.08786 =
   0.07642   0.05538  -0.00772  -0.01074
H891      2   9.22557   9.31210   9.56883  11.00000   0.08027
H881      2   9.33331   9.33306   9.65289  11.00000   0.13097
H851      2   9.06867   9.64846   9.57936  11.00000   0.06577
H861      2   9.17563   9.67239   9.66111  11.00000   0.10509
H161      2   9.86530   9.42517   9.62245  11.00000   0.02469
H111      2   9.42959   9.65626   9.81326  11.00000   0.03383
H121      2   9.41618   9.49292   9.86839  11.00000   0.03606
H131      2   9.51614   9.31066   9.84059  11.00000   0.03697
H141      2   9.64103   9.30191   9.76144  11.00000   0.03108
H231      2   9.89972   9.24922   9.57680  11.00000   0.03066
H232      2   9.75764   9.18723   9.60372  11.00000   0.03099
H241      2   9.87585   9.16237   9.67759  11.00000   0.04434
H242      2   9.97980   9.27746   9.67100  11.00000   0.04489
```

Fig. 6C

H281	2	10.15353	8.92912	9.56085	11.00000	0.08666
H282	2	10.18989	8.92278	9.62053	11.00000	0.08723
H283	2	10.26566	9.02166	9.58620	11.00000	0.08710
H201	2	9.44027	9.43682	9.49457	11.00000	0.03327
H221	2	9.36727	9.66624	9.51370	11.00000	0.05146
H222	2	9.52479	9.72860	9.51527	11.00000	0.05104
H223	2	9.43193	9.71611	9.56601	11.00000	0.05131
H41	2	9.73983	9.74902	9.56204	11.00000	0.02807
H31	2	9.85823	9.88568	9.61518	11.00000	0.03001
H71	2	9.81367	9.65791	9.73490	11.00000	0.02870
H871	2	9.30621	9.51762	9.69480	11.00000	0.13226
H211	2	9.59801	9.29339	9.53630	11.00000	0.03270

Fig. 7A

S80	O81	1.454(5)Å
S80	O83	1.432(6)Å
C84	C85	1.376(12)Å
C85	C86	1.408(14)Å
C86	C87	1.360(16)Å
C87	C88	1.310(15)Å
C88	C89	1.386(14)Å
C89	H891	0.932Å
S90	O92	1.454(6)Å
S90	C94	1.793(8)Å
C94	C99	1.354(11)Å
C95	H951	0.938Å
C96	H961	0.934Å
C97	H971	0.924Å
C98	H981	0.927Å
Br1	C2	1.886(6)Å
C2	C7	1.381(9)Å
C3	H31	0.928Å
C4	H41	0.937Å
C5	N18	1.454(8)Å
C6	C8	1.498(9)Å
C8	C9	1.500(9)Å
C9	N10	1.343(9)Å
N10	C11	1.345(10)Å
C11	H111	0.933Å
C12	H121	0.927Å
C13	H131	0.918Å
N15	C16	1.492(9)Å
C16	C23	1.511(9)Å
C17	N18	1.352(8)Å
N18	C19	1.400(8)Å
C19	C22	1.496(9)Å
C20	H201	0.927Å
C22	H221	0.958Å
C22	H223	0.953Å
C23	H231	0.962Å
C24	C25	1.470(11)Å
C24	H242	0.962Å
C25	O27	1.354(10)Å
C28	H281	1.000Å
C28	H283	1.000Å
C52	C53	1.366(11)Å
C53	C54	1.404(11)Å
C54	C55	1.383(10)Å
C55	C56	1.414(9)Å
C56	C57	1.396(9)Å
C57	H571	0.925Å
C58	N65	1.254(8)Å
C59	C64	1.391(10)Å
C61	C62	1.386(14)Å
C62	C63	1.355(15)Å

S80	O82	1.468(5)Å
S80	C84	1.784(7)Å
C84	C89	1.318(12)Å
C85	H851	0.927Å
C86	H861	0.936Å
C87	H871	0.934Å
C88	H881	0.935Å
S90	O91	1.459(5)Å
S90	O93	1.431(5)Å
C94	C95	1.383(11)Å
C95	C96	1.356(13)Å
C96	C97	1.428(17)Å
C97	C98	1.323(15)Å
C98	C99	1.409(13)Å
C99	H991	0.924Å
C2	C3	1.382(9)Å
C3	C4	1.358(10)Å
C4	C5	1.388(9)Å
C5	C6	1.398(9)Å
C6	C7	1.394(9)Å
C7	H71	0.926Å
C8	N15	1.274(8)Å
C9	C14	1.386(9)Å
C11	C12	1.379(11)Å
C12	C13	1.375(11)Å
C13	C14	1.351(10)Å
C14	H141	0.921Å
C16	C17	1.500(9)Å
C16	H161	0.988Å
C17	N21	1.315(8)Å
C19	C20	1.344(9)Å
C20	N21	1.376(8)Å
N21	H211	1.000Å
C22	H222	0.950Å
C23	C24	1.536(11)Å
C23	H232	0.969Å
C24	H241	0.971Å
C25	O26	1.202(10)Å
O27	C28	1.445(10)Å
C28	H282	1.000Å
Br51	C52	1.886(7)Å
C52	C57	1.412(10)Å
C53	H531	0.927Å
C54	H541	0.921Å
C55	N68	1.427(9)Å
C56	C58	1.489(9)Å
C58	C59	1.530(10)Å
C59	N60	1.314(9)Å
N60	C61	1.372(10)Å
C61	H611	0.918Å
C62	H621	0.928Å

Fig. 7B

C63	C64	1.378(13)Å
C64	H641	0.917Å
C66	C67	1.474(9)Å
C66	H661	0.982Å
C67	N71	1.334(8)Å
C69	C70	1.343(11)Å
C70	N71	1.366(10)Å
N71	H711	1.000Å
C72	H722	0.958Å
C73	C74	1.535(10)Å
C73	H732	0.967Å
C74	H741	0.972Å
C75	O76	1.185(9)Å
O77	C78	1.440(11)Å
C78	H782	0.966Å

C63	H631	0.932Å
N65	C66	1.485(8)Å
C66	C73	1.516(10)Å
C67	N68	1.354(9)Å
N68	C69	1.406(9)Å
C69	C72	1.484(12)Å
C70	H701	0.925Å
C72	H721	0.964Å
C72	H723	0.965Å
C73	H731	0.975Å
C74	C75	1.493(12)Å
C74	H742	0.977Å
C75	O77	1.360(9)Å
C78	H781	0.965Å
C78	H783	0.960Å

Fig. 8A

O81	S80	O82	111.0(3)°
O82	S80	O83	114.4(4)°
O82	S80	C84	106.2(3)°
S80	C84	C85	117.7(6)°
C85	C84	C89	118.3(8)°
C84	C85	H851	119.626°
C85	C86	C87	118.1(10)°
C87	C86	H861	121.303°
C86	C87	H871	119.251°
C87	C88	C89	119.3(10)°
C89	C88	H881	120.264°
C84	C89	H891	118.485°
O91	S90	O92	111.7(3)°
O92	S90	O93	113.5(3)°
O92	S90	C94	105.7(3)°
S90	C94	C95	120.6(6)°
C95	C94	C99	119.3(8)°
C94	C95	H951	118.566°
C95	C96	C97	118.4(10)°
C97	C96	H961	121.695°
C96	C97	H971	119.699°
C97	C98	C99	120.8(9)°
C99	C98	H981	120.094°
C94	C99	H991	119.276°
Br1	C2	C3	121.0(5)°
C3	C2	C7	120.5(5)°
C2	C3	H31	120.203°
C3	C4	C5	120.6(6)°
C5	C4	H41	118.766°
C4	C5	N18	119.6(5)°
C5	C6	C7	117.8(6)°
C7	C6	C8	118.8(6)°
C2	C7	H71	119.721°
C6	C8	C9	117.5(5)°
C9	C8	N15	115.9(6)°
C8	C9	C14	121.2(6)°
C9	N10	C11	115.5(6)°
N10	C11	H111	118.526°
C11	C12	C13	117.4(7)°
C13	C12	H121	121.289°
C12	C13	H131	119.499°
C9	C14	C13	118.3(6)°
C13	C14	H141	121.419°
N15	C16	C17	105.9(5)°
C17	C16	C23	112.4(5)°
C17	C16	H161	109.539°
C16	C17	N18	122.7(6)°
N18	C17	N21	106.5(5)°
C5	N18	C19	127.0(5)°
N18	C19	C20	105.2(5)°
C20	C19	C22	129.4(6)°

O81	S80	O83	112.9(4)°
O81	S80	C84	105.5(3)°
O83	S80	C84	106.0(4)°
S80	C84	C89	123.6(7)°
C84	C85	C86	120.0(9)°
C86	C85	H851	120.377°
C85	C86	H861	120.636°
C86	C87	C88	121.8(10)°
C88	C87	H871	118.984°
C87	C88	H881	120.392°
C84	C89	C88	122.5(10)°
C88	C89	H891	119.061°
O91	S90	O93	112.8(4)°
O91	S90	C94	104.5(3)°
O93	S90	C94	108.0(3)°
S90	C94	C99	120.1(6)°
C94	C95	C96	121.6(9)°
C96	C95	H951	119.820°
C95	C96	H961	119.911°
C96	C97	C98	119.9(8)°
C98	C97	H971	120.397°
C97	C98	H981	119.080°
C94	C99	C98	119.9(9)°
C98	C99	H991	120.819°
Br1	C2	C7	118.5(5)°
C2	C3	C4	119.7(6)°
C4	C3	H31	120.109°
C3	C4	H41	120.600°
C4	C5	C6	120.6(6)°
C6	C5	N18	119.8(6)°
C5	C6	C8	123.3(6)°
C2	C7	C6	120.6(6)°
C6	C7	H71	119.679°
C6	C8	N15	126.6(6)°
C8	C9	N10	114.9(6)°
N10	C9	C14	123.9(6)°
N10	C11	C12	124.4(7)°
C12	C11	H111	117.061°
C11	C12	H121	121.279°
C12	C13	C14	120.4(6)°
C14	C13	H131	120.125°
C9	C14	H141	120.274°
C8	N15	C16	118.0(5)°
N15	C16	C23	109.4(5)°
N15	C16	H161	110.723°
C23	C16	H161	108.851°
C16	C17	N21	130.3(6)°
C5	N18	C17	123.1(5)°
C17	N18	C19	109.8(5)°
N18	C19	C22	125.3(6)°
C19	C20	N21	108.0(5)°

Fig. 8B

C19	C20	H201	126.017°
C17	N21	C20	110.5(5)°
C20	N21	H211	124.681°
C19	C22	H222	109.778°
C19	C22	H223	110.905°
H222	C22	H223	109.018°
C16	C23	H231	109.392°
C16	C23	H232	108.378°
H231	C23	H232	108.825°
C23	C24	H241	109.968°
C23	C24	H242	108.195°
H241	C24	H242	108.752°
C24	C25	O27	109.4(7)°
C25	O27	C28	115.2(7)°
O27	C28	H282	109.261°
O27	C28	H283	109.465°
H282	C28	H283	109.476°
Br51	C52	C57	119.0(5)°
C52	C53	C54	118.9(7)°
C54	C53	H531	120.985°
C53	C54	H541	120.227°
C54	C55	C56	122.1(6)°
C56	C55	N68	118.5(6)°
C55	C56	C58	123.2(6)°
C52	C57	C56	120.2(7)°
C56	C57	H571	120.138°
C56	C58	N65	126.7(6)°
C58	C59	N60	116.3(6)°
N60	C59	C64	125.0(7)°
N60	C61	C62	121.7(8)°
C62	C61	H611	118.993°
C61	C62	H621	120.029°
C62	C63	C64	118.4(9)°
C64	C63	H631	121.124°
C59	C64	H641	120.844°
C58	N65	C66	118.2(6)°
N65	C66	C73	109.7(5)°
N65	C66	H661	109.122°
C73	C66	H661	112.017°
C66	C67	N71	130.3(7)°
C55	N68	C67	122.5(6)°
C67	N68	C69	108.7(6)°
N68	C69	C72	124.0(7)°
C69	C70	N71	109.1(6)°
N71	C70	H701	125.502°
C67	N71	H711	125.400°
C69	C72	H721	110.667°
H721	C72	H722	108.539°
H721	C72	H723	108.455°
C66	C73	C74	111.0(6)°

N21	C20	H201	126.026°
C17	N21	H211	124.840°
C19	C22	H221	109.508°
H221	C22	H222	108.808°
H221	C22	H223	108.786°
C16	C23	C24	112.3(6)°
C24	C23	H231	108.812°
C24	C23	H232	109.105°
C23	C24	C25	114.3(7)°
C25	C24	H241	110.030°
C25	C24	H242	105.346°
C24	C25	O26	126.4(7)°
O26	C25	O27	123.9(7)°
O27	C28	H281	109.674°
H281	C28	H282	109.475°
H281	C28	H283	109.476°
Br51	C52	C53	119.3(6)°
C53	C52	C57	121.7(7)°
C52	C53	H531	120.141°
C53	C54	C55	119.8(7)°
C55	C54	H541	120.000°
C54	C55	N68	119.4(6)°
C55	C56	C57	117.2(6)°
C57	C56	C58	119.5(6)°
C52	C57	H571	119.709°
C56	C58	C59	116.5(6)°
C59	C58	N65	116.8(6)°
C58	C59	C64	118.5(7)°
C59	N60	C61	116.1(7)°
N60	C61	H611	119.342°
C61	C62	C63	120.6(8)°
C63	C62	H621	119.353°
C62	C63	H631	120.452°
C59	C64	C63	118.1(8)°
C63	C64	H641	121.057°
N65	C66	C67	105.4(5)°
C67	C66	C73	111.5(6)°
C67	C66	H661	108.890°
C66	C67	N68	121.8(6)°
N68	C67	N71	107.4(6)°
C55	N68	C69	128.7(6)°
N68	C69	C70	105.5(6)°
C70	C69	C72	130.5(7)°
C69	C70	H701	125.444°
C67	N71	C70	109.2(6)°
C70	N71	H711	125.366°
C69	C72	H722	109.838°
C69	C72	H723	110.831°
H722	C72	H723	108.445°
C66	C73	H731	108.535°

Fig. 8C

C74	C73	H731	110.248°
C74	C73	H732	108.249°
C73	C74	C75	112.4(6)°
C75	C74	H741	109.125°
C75	C74	H742	108.578°
C74	C75	O76	126.2(7)°
O76	C75	O77	123.0(7)°
O77	C78	H781	109.214°
H781	C78	H782	109.923°
H781	C78	H783	109.026°

C66	C73	H732	110.751°
H731	C73	H732	108.042°
C73	C74	H741	108.496°
C73	C74	H742	108.155°
H741	C74	H742	110.035°
C74	C75	O77	110.7(7)°
C75	O77	C78	115.6(7)°
O77	C78	H782	109.848°
O77	C78	H783	109.687°
H782	C78	H783	109.127°

Fig. 9

Br1	C2	1.892(3)Å
C2	C7	1.383(5)Å
C3	H31	0.938Å
C4	H41	0.921Å
C5	N18	1.428(4)Å
C6	C8	1.497(4)Å
C8	C9	1.497(4)Å
C9	N10	1.338(4)Å
N10	C11	1.345(4)Å
C11	H111	0.935Å
C12	H121	0.948Å
C13	H131	0.936Å
N15	C16	1.478(4)Å
C16	C23	1.527(5)Å
C17	N18	1.346(4)Å
N18	C19	1.391(4)Å
C19	C22	1.494(5)Å
C20	H201	0.912Å
C22	H221	0.965Å
C22	H223	0.960Å
C23	H231	0.969Å
C24	C25	1.478(5)Å
C24	H242	0.988Å
C25	O27	1.342(4)Å
C28	H281	0.964Å
C28	H283	0.962Å
S80	O82	1.447(3)Å
S80	C84	1.774(4)Å
C84	C89	1.369(7)Å
C85	H851	0.932Å
C86	H861	0.943Å
C87	H871	0.934Å
C88	H881	0.925Å

C2	C3	1.387(5)Å
C3	C4	1.371(5)Å
C4	C5	1.392(5)Å
C5	C6	1.406(4)Å
C6	C7	1.395(5)Å
C7	H71	0.924Å
C8	N15	1.276(4)Å
C9	C14	1.395(5)Å
C11	C12	1.378(5)Å
C12	C13	1.370(5)Å
C13	C14	1.382(5)Å
C14	H141	0.934Å
C16	C17	1.487(5)Å
C16	H161	0.976Å
C17	N21	1.320(4)Å
C19	C20	1.342(5)Å
C20	N21	1.378(5)Å
N21	H211	0.854Å
C22	H222	0.966Å
C23	C24	1.534(5)Å
C23	H232	0.981Å
C24	H241	0.960Å
C25	O26	1.201(4)Å
O27	C28	1.451(5)Å
C28	H282	0.965Å
S80	O81	1.431(3)Å
S80	O83	1.430(3)Å
C84	C85	1.400(7)Å
C85	C86	1.380(7)Å
C86	C87	1.342(13)Å
C87	C88	1.410(13)Å
C88	C89	1.433(10)Å
C89	H891	0.940Å

Fig. 10

Br1	C2	C3	119.3(3)°
C3	C2	C7	121.8(3)°
C2	C3	H31	120.033°
C3	C4	C5	120.3(3)°
C5	C4	H41	120.261°
C4	C5	N18	118.9(3)°
C5	C6	C7	118.2(3)°
C7	C6	C8	119.5(3)°
C2	C7	H71	120.432°
C6	C8	C9	117.7(3)°
C9	C8	N15	117.9(3)°
C8	C9	C14	120.0(3)°
C9	N10	C11	116.7(3)°
N10	C11	H111	117.041°
C11	C12	C13	118.8(3)°
C13	C12	H121	120.783°
C12	C13	H131	120.694°
C9	C14	C13	118.1(3)°
C13	C14	H141	120.983°
N15	C16	C17	105.7(3)°
C17	C16	C23	115.7(3)°
C17	C16	H161	107.726°
C16	C17	N18	120.7(3)°
N18	C17	N21	108.0(3)°
C5	N18	C19	128.6(3)°
N18	C19	C20	105.7(3)°
C20	C19	C22	129.3(3)°
C19	C20	H201	127.007°
C17	N21	C20	108.7(3)°
C20	N21	H211	125.351°
C19	C22	H222	109.368°
C19	C22	H223	111.184°
H222	C22	H223	107.885°
C16	C23	H231	107.712°
C16	C23	H232	111.123°
H231	C23	H232	110.583°
C23	C24	H241	107.661°
C23	C24	H242	109.365°
H241	C24	H242	109.671°
C24	C25	O27	114.4(3)°
C25	O27	C28	115.2(3)°
O27	C28	H282	110.269°
O27	C28	H283	108.681°
H282	C28	H283	108.963°
O81	S80	O83	115.1(2)°
O81	S80	C84	106.30(18)°
O83	S80	C84	107.0(2)°
S80	C84	C89	122.1(4)°
C84	C85	C86	121.6(6)°
C86	C85	H851	119.275°
C85	C86	H861	121.859°
C86	C87	C88	124.9(7)°
C88	C87	H871	117.376°
C87	C88	H881	122.592°
C84	C89	C88	119.8(8)°
C88	C89	H891	120.078°

Br1	C2	C7	118.9(3)°
C2	C3	C4	119.0(3)°
C4	C3	H31	120.959°
C3	C4	H41	119.485°
C4	C5	C6	121.0(3)°
C6	C5	N18	120.1(3)°
C5	C6	C8	122.3(3)°
C2	C7	C6	119.7(3)°
C6	C7	H71	119.874°
C6	C8	N15	124.4(3)°
C8	C9	N10	116.6(3)°
N10	C9	C14	123.4(3)°
N10	C11	C12	123.7(3)°
C12	C11	H111	119.278°
C11	C12	H121	120.443°
C12	C13	C14	119.3(3)°
C14	C13	H131	119.952°
C9	C14	H141	120.942°
C8	N15	C16	117.6(3)°
N15	C16	C23	110.8(3)°
N15	C16	H161	107.681°
C23	C16	H161	108.910°
C16	C17	N21	131.2(3)°
C5	N18	C17	122.3(3)°
C17	N18	C19	109.0(3)°
N18	C19	C22	124.9(3)°
C19	C20	N21	108.6(3)°
N21	C20	H201	124.433°
C17	N21	H211	125.926°
C19	C22	H221	110.223°
H221	C22	H222	108.664°
H221	C22	H223	109.452°
C16	C23	C24	107.9(3)°
C24	C23	H231	110.073°
C24	C23	H232	109.430°
C23	C24	C25	118.8(3)°
C25	C24	H241	104.516°
C25	C24	H242	106.503°
C24	C25	O26	123.3(3)°
O26	C25	O27	122.4(3)°
O27	C28	H281	108.952°
H281	C28	H282	109.738°
H281	C28	H283	110.225°
O81	S80	O82	111.9(2)°
O82	S80	O83	111.2(3)°
O82	S80	C84	104.5(2)°
S80	C84	C85	117.6(4)°
C85	C84	C89	120.2(5)°
C84	C85	H851	119.148°
C85	C86	C87	117.5(8)°
C87	C86	H861	120.606°
C86	C87	H871	117.763°
C87	C88	C89	116.0(7)°
C89	C88	H881	121.435°
C84	C89	H891	120.080°

Fig. 11

Stability Data, CNS 7056 for Injection, 26 mg (Lot A01P310)

Product Name: CNS 7056 for Injection	**Date Manufactured: July 2009**				**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**		
Lot: A01P310							
		Storage Condition: 25 °C/60% RH					
Tests[a]	**Acceptance Criteria[a]**	**Time (Months)**					
		0	**1**	**3**	**6**	**9**	**12**	**18**
Appearance of Lyophilized Product	White to off white lyophilized powder.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Appearance of Reconstituted Product	A clear, colorless to pale yellow solution, free from visible particulates.	Clear, colorless solution, essentially free from particulates.	Clear, very pale yellow solution, essentially free from particulates.	Clear, very pale yellow solution, essentially free from particulates	Clear, very pale yellow solution, essentially free from particulates	Clear, very pale yellow solution, essentially free from particulates	Clear, very pale yellow solution, free from particulates	Clear, very pale yellow solution, essentially free from particulates
Time to Reconstitute (min)	NMT 2 min	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs
Osmolality	290 ± 30 mOsmol/kg	281	—	279	295	—	283	—
pH on Reconstitution	2.9 to 3.5	3.3	3.2	3.2	3.2	3.2	3.1	3.2
Moisture Karl Fischer (% w/w)	NMT 1.5	0.16	0.32	0.38	0.45	0.44	0.33	0.54
CNS 7056 Vial Content (mg/vial)	24.1 to 28.0 mg/vial	26.5	26.1	26.0	27.0	26.4	26.0	26.3
	92.5 to 107.5% nominal amount	102.0	100.5	99.9	103.9	101.4	100.0	101.0
Concentration on Reconstitution (mg/mL)	4.5 to 5.5 (Upright)	4.9	4.9	4.8	5.1	4.8	4.9	4.9
	4.5 to 5.5 (Inverted)	4.8	4.9	4.8	5.0	4.9	5.0	4.8
Subvisible particles	≥10 µm report per vial ≥25 µm report per vial	≥10 µm:79 ≥25 µm:1	—	—	≥10 µm:80 ≥25 µm:2	—	≥10 µm:344 ≥25 µm:6	—

Fig. 12

Stability Data, CNS 7056 for Injection, 26 mg (Lot A01P310) continued

Product Name: CNS 7056 for Injection		**Date Manufactured: July 2009**			**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**			
Lot: A01P310								**Drug Substance Lot: 11084**
					Storage Condition: 25 °C/60% RH			
Tests[a]	**Acceptance Criteria[a]**	**Time (Months)**						
		0	**1**	**3**	**6**	**9**	**12**	**18**
Related Substances (Area %):								
CNS 7054X	NMT 1.5%	0.06	0.10	0.09	0.14	0.13	0.14	0.17
RRT 0.67	NMT 0.4%	0.03	0.04	0.03	0.03	0.03	0.03	0.03
RRT 0.70	NMT 0.4%	0.06	0.05	0.06	0.05	0.06	0.06	0.05
RRT 0.92	NMT 0.4%	0.11	0.12	0.11	0.11	0.11	0.10	0.11
RRT 1.31	NMT 0.4%	0.23	0.24	0.24	0.24	0.25	0.24	0.24
RRT 1.82	NMT 0.4%	0.03	<LOQ	<LOQ	0.03	0.03	0.03	<LOQ
Total	NMT 2.0%	0.52	0.55	0.53	0.60	0.61	0.60	0.60
Chiral (%R)	NMT 0.5% R-enantiomer	0.27	—	0.28	0.28	—	0.25	—
Endotoxins USP <85>	NMT 0.5 EU/mg	<0.2 EU/mg	—	—	—	—	<0.2 EU/mg	—
Sterility USP <71>	Complies with test	Complies	—	—	—	—	Complies	—

[a] = These tests and acceptance criteria are based on a previous specification.

— = Not performed.

Fig. 13

Accelerated Stability Data, CNS 7056 for Injection, 26 mg (Lot A01P310)

Product Name: CNS 7056 for Injection	**Date Manufactured: July 2009**	**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**	
Lot: A01P310			**Drug Substance Lot: 11084**
		Storage Condition: 40 °C/75% RH	

Tests[a]	**Acceptance Criteria[a]**	**Time (Months)**			
		0	**1**	**3**	**6**
Appearance of Lyophilized Product	White to off white lyophilized powder.	Complies	Complies	Complies	Complies
Appearance of Reconstituted Product	A clear, colorless to pale yellow solution, free from visible particulates.	Clear, colorless solution, essentially free from particulates.	Clear, very pale yellow solution, essentially free from particulates.	Clear, very pale yellow solution, essentially free from particulates.	Clear, very pale yellow solution, 1 vial contained small fiber
Time to Reconstitute (min)	NMT 2 min	1–2 secs	1–2 secs	1-2 secs	1-2 secs
Osmolality	290 ± 30 mOsmol/kg	281	-	279	295
pH on Reconstitution	2.9 to 3.5	3.3	3.2	3.2	3.2
Moisture Karl Fischer (% w/w)	NMT 1.5	0.16	0.32	0.37	0.59
CNS 7056 Vial Content (mg/vial)	24.1 to 28.0 mg/vial	26.5	26.3	26.3	26.0
	92.5 to 107.5% nominal amount	102.0	101.0	101.3	99.8
Concentration on Reconstitution (mg/mL)	4.5 to 5.5 (Upright)	4.9	4.9	5.0	5.2
	4.5 to 5.5 (Inverted)	4.8	4.8	4.8	5.1
Subvisible particles	≥10 µm report per vial ≥25 µm report per vial	≥10 µm:79 ≥25 µm:1	—	—	—

Fig. 14

Accelerated Stability Data, CNS 7056 for Injection, 26 mg (Lot A01P310)					
Product Name: CNS 7056 for Injection			**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**		
Lot: A01P310					
			Storage Condition: 40 °C/75% RH		
Tests[a]	**Acceptance Criteria[a]**	**Time (Months)**			
		0	**1**	**3**	**6**
Related Substances (Area %):					
CNS 7054X	NMT 1.5%	0.06	0.14	0.18	0.33
RRT 0.67	NMT 0.4%	0.03	0.03	0.03	0.03
RRT 0.70	NMT 0.4%	0.06	0.05	0.05	0.05
RRT 0.92	NMT 0.4%	0.11	0.11	0.11	0.11
RRT 1.31	NMT 0.4%	0.23	0.24	0.25	0.25
RRT 1.82	NMT 0.4%	0.03	<LOQ	<LOQ	<LOQ
Total	NMT 2.0%	0.52	0.57	0.62	0.77
Chiral (%R)	NMT 0.5% R-enantiomer	0.27	—	0.28	0.28
Endotoxins USP <85>	NMT 0.5 EU/mg	<0.2 EU/mg	—	—	—
Sterility USP <71>	Complies with test	Complies	—	—	—
[a] =	These tests and acceptance criteria are based on a previous specification.				
— =	Not performed.				

Fig. 15

Long-Term Stability Data, CNS 7056 for Injection, 26 mg (Lot P310-01 (B))								
Product Name: CNS 7056 for Injection	**Date Manufactured: May 2009**	**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**						
Lot: P310-01 (B)					**Drug Substance Lot: 11084**			
		Storage Condition: 25 °C/60% RH						
Tests[a]	**Acceptance Criteria[a]**	**Time (Months)**						
		0	**1**	**3**	**6**	**9**	**12**	**18**
Appearance of Lyophilized Product	White to off white lyophilized powder.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Appearance of Reconstituted Product	A clear, colorless to pale yellow solution, free from visible particulates.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Clear, virtually colorless to very pale yellow solution, free from visible particulates. Several fibers visible not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related
Time to Reconstitute (Min)	NMT 2 min	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs
Osmolality	290 ± 30 mOsmol/kg	289	280	277	281	282	286	278
pH on Reconstitution	2.9 to 3.5	3.1	3.2	3.2	3.2	3.1	3.2	3.1
Moisture Karl Fischer (% w/w)	NMT 1.5	0.39	0.60	0.62	0.64	0.55	0.76	0.86
CNS 7056 Vial Content (mg/vial)	24.1 to 28.0 mg/vial	26.4	26.2	26.1	26.1	26.4	26.6	26.4

Fig. 16

Long-Term Stability Data, CNS 7056 for Injection, 26 mg (Lot P310-01 (B))

Product Name: CNS 7056 for Injection	**Date Manufactured: May 2009**	**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**
Lot: P310-01 (B)		**Drug Substance Lot: 11084**
		Storage Condition: 25 °C/60% RH

Tests[a]	**Acceptance Criteria**[a]	**Time (Months)**						
		0	**1**	**3**	**6**	**9**	**12**	**18**
	92.5 to 107.5% nominal amount	101.7	100.6	100.5	100.5	101.5	102.2	101.4
Concentration on Reconstitution (mg/mL)	4.5 to 5.5 (Upright)	5.0	5.0	4.9	4.9	5.1	4.9	5.1
	4.5 to 5.5 (Inverted)	5.0	4.9	4.9	4.9	5.1	4.9	5.0
Related Substances (Area %):								
CNS 7054X	NMT 1.5%	0.06	0.07	0.13	0.14	0.16	0.18	0.19
RRT 0.68	NMT 0.40%	0.03	0.03	0.03	0.03	0.03	0.03	0.04
RRT 0.70	NMT 0.40%	0.06	0.06	0.06	0.06	0.06	0.06	0.06
RRT 0.92	NMT 0.40%	0.11	0.12	0.12	0.12	0.10	0.11	0.11
RRT 0.94	NMT 0.40%	ND	0.03	ND	ND	ND	ND	ND
RRT 1.31	NMT 0.40%	0.24	0.24	0.24	0.25	0.24	0.25	0.24
RRT 1.85	NMT 0.40%	<LOQ	0.03	<LOQ	<LOQ	<LOQ	0.03	0.03
Total	NMT 2.0%	0.50%	0.58%	0.58	0.60	0.59	0.66	0.67
Chiral (%R)	NMT 0.5% R-enantiomer	0.25%	—	—	0.30	—	0.3	—

[a] = tests and acceptance criteria are based on a previous specification.

— = Not performed.

Fig. 17

Accelerated Stability Data, CNS 7056 for Injection, 26 mg (Lot P310-01 (B))							
Product Name: CNS 7056 for Injection		**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: P310-01 (B)					**Drug Substance Lot: 11084**		
		Storage Condition: 40 °C/75% RH					
Tests[a]	**Acceptance Criteria[a]**	**Time (Months)**					
		0	**1**	**3**	**6**	**9**	**12**
Appearance of Lyophilized Product	White to off white lyophilized powder.	Complies	Complies	Complies	Complies	Complies	Complies
Appearance of Reconstituted Product	A clear, colorless to pale yellow solution, free from visible particulates.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Clear, virtually colorless to very pale yellow solution free from visible particulates. Several fibers visible not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.	Very pale yellow, clear solution essentially free from particulates with several fibers not thought to be product related.
Time to Reconstitute (min)	NMT 2 min	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs	1–2 secs
Osmolality	290 ± 30 mOsmol/kg	289	281	274	281	284	281
pH on Reconstitution	2.9 to 3.5	3.1	3.3	3.2	3.1	3.1	3.2
Moisture Karl Fischer (% w/w)	NMT 1.5	0.39	0.51	0.58	0.84	0.82	0.82
CNS 7056 Vial Content (mg/vial)	24.1 to 28.0 mg/vial	26.4	26.0	26.3	26.3	26.2	26.5
	92.5 to 107.5% nominal amount	101.7	100.0	101.3	101.0	100.6	102.0

Fig. 18

Accelerated Stability Data, CNS 7056 for Injection, 26 mg (Lot P310-01 (B))							
Product Name: CNS 7056 for Injection		**Container Closure: Type I, Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: P310-01 (B)					**Drug Substance Lot: 11084**		
		Storage Condition: 40 °C/75% RH					
Tests [a]	**Acceptance Criteria [a]**	**Time (Months)**					
		0	**1**	**3**	**6**	**9**	**12**
Concentration on Reconstitution (mg/mL)	4.5 to 5.5 (Upright)	5.0	4.9	4.9	4.8	5.0	4.9
	4.5 to 5.5 (Inverted)	5.0	4.9	4.9	4.9	5.0	4.9
Related Substances (Area %):							
RRT 0.51	NMT 0.4%	<LOQ	<LOQ	0.03	<LOQ	<LOQ	<LOQ
CNS 7054X	NMT 1.5%	0.06	0.11	0.22	0.36	0.45	0.68
RRT 0.63	NMT 0.4%	<LOQ	<LOQ	0.03	0.03	<LOQ	<LOQ
RRT 0.68	NMT 0.4%	0.03	0.03	0.03	0.03	0.03	0.03
RRT 0.70	NMT 0.4%	0.06	0.06	0.06	0.06	0.06	0.06
RRT 0.92	NMT 0.4%	0.11	0.12	0.12	0.12	0.11	0.11
RRT 0.94	NMT 0.4%	ND	0.03	ND	ND	ND	ND
RRT 1.31	NMT 0.4%	0.24	0.25	0.24	0.25	0.25	0.25
RRT 1.85	NMT 0.4%	<LOQ	0.03	<LOQ	0.03	<LOQ	0.03
Total	NMT 2.0%	0.50	0.63	0.73	0.88	0.90	1.16
Chiral (%R)	NMT 0.5% R-enantiomer	0.25	—	0.3	0.3	—	0.3
[a] =		These tests and acceptance criteria are based on a previous specification.					
— =		Not performed.					

Fig. 19

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (026CNS27)									
Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**						
Lot: 026CNS27						**Drug Substance Lot: SOL12621/5**			
			Storage Condition: 25 °C/60% RH						
		Time (Months)							
Test	**Acceptance Criteria**	**0**	**1**	**2**	**3**	**6**	**9**	**12**	**18**
Appearance of Lyophilized Product	Record	White lyophilized plug with shrinkage. Although no layering evident, the bottom of the plug (2-3 mm) appeared to be slightly more shrunken	As initial	As initial	As initial	As initial	As initial	As initial	As initial
Completeness of Solution	A clear, colorless solution, free from visible particulates	A clear, colorless solution, free from visible particulates.	As initial	—	As initial	As initial	As initial	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	<1	<1	—	<1	<1	<1	<1	<1
pH on Reconstitution	2.9 to 3.5	3.1	3.1	—	3.1	3.1	3.1	3.2	3.1
Moisture Karl Fischer (% w/w)	NMT 1.5	0.12	0.20	0.30	0.34	0.42	0.48	0.40	0.59
CNS 7056 Vial Content (mg/vial)	23.1 to 26.9 mg/vial	25.4	25.2	24.8	25.8	25.9	25.5	25.4	25.2
	92.5 to 107.5% nominal amount	101.6	100.8	99.2	103.2	103.6	102.0	101.6	100.8
Concentration on Reconstitution (mg/mL)	4.5 to 5.5	4.6	—	—	4.7	4.7	4.6	4.8	4.9

Fig. 20

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (026CNS27)

Product Name: CNS 7056				**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: 026CNS27						**Drug Substance Lot: SOL12621/5**			
				Storage Condition: 25 °C/60% RH					
Test	**Acceptance Criteria**	**Time (Months)**							
		0	**1**	**2**	**3**	**6**	**9**	**12**	**18**
Related Substances (Area %):									
CNS 7054X	NMT 1.5%	1.12	1.12	1.12	1.14	1.14	1.13	1.18	1.20
RRT 0.68	NMT 0.4%	0.09	0.09	0.09	0.08	0.08	0.10	0.09	0.10
RRT 0.93	NMT 0.4%	0.13	0.13	0.12	0.14	0.13	0.12	0.10	0.16
RRT 0.94	NMT 0.4%	0.07	0.09	0.08	0.12	0.07	[a]	0.09	[a]
RRT 1.31	NMT 0.4%	0.24	0.23	0.24	0.23	0.22	0.23	0.22	0.23
Total	NMT 2.0%	1.65	1.66	1.65	1.71	1.64	1.58	1.68	1.69
Chiral (% R)	NMT 0.5% R-enantiomer	0.16	0.17	—	0.16	0.16	0.15	0.15	0.17

[a] = Peaks at RRT 0.94 not resolved from CNS 7056 peak.

— = Not performed.

Fig. 21

Accelerated Stability Data, CNS 7056 for Injection, 25 mg (Lot 026CNS27)						
Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**			
Lot: 026CNS27				**Drug Substance Lot: SOL12621/5**		
Bulk Batch Size: 800 mL			**Storage Condition: 40 °C/75% RH**			
Test	**Acceptance Criteria**	**Time (Months)**				
		0	**1**	**2**	**3**	**6**
Appearance of Lyophilized Product	Record	White lyophilized plug with shrinkage. Although no layering evident, the bottom of the plug (2-3 mm) appeared to be slightly more shrunken	As initial	As initial	As initial	As initial
Completeness of Solution	A clear, colorless solution, free from visible particulates	A clear, colorless solution, free from visible particulates.	As initial	—	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	<1	<1	—	<1	<1
pH on Reconstitution	2.9 to 3.5	3.1	3.1	—	3.1	3.1
Moisture Karl Fischer (% w/w)	NMT 1.5	0.12	0.28	0.46	0.54	0.64
CNS 7056 Vial Content (mg/vial)	23.1 to 26.9 mg/vial	25.4	25.4	24.8	24.8	25.1
	92.5 to 107.5% nominal amount	101.6	101.6	99.2	99.2	100.4
Concentration on Reconstitution (mg/mL)	4.5 to 5.5	4.6	—	—	4.7	4.9

Fig. 22

Accelerated Stability Data, CNS 7056 for Injection, 25 mg (Lot 026CNS27)						
Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**			
Lot: 026CNS27				**Drug Substance Lot: SOL12621/5**		
Bulk Batch Size: 800 mL			**Storage Condition: 40 °C/75% RH**			
Test	**Acceptance Criteria**	**Time (Months)**				
		0	**1**	**2**	**3**	**6**
Related Substances (Area %):						
CNS 7054X	NMT 1.5%	1.12	1.16	1.18	1.21	1.32
RRT 0.68	NMT 0.4%	0.09	0.09	0.09	0.08	0.08
RRT 0.93	NMT 0.4%	0.13	0.13	0.12	0.14	0.13
RRT 0.94	NMT 0.4%	0.07	0.09	0.09	0.11	0.07
RRT 1.31	NMT 0.4%	0.24	0.23	0.24	0.23	0.22
Total	NMT 2.0%	1.65	1.70	1.72	1.77	1.82
Chiral (% R)	NMT 0.5% R-enantiomer	0.16	0.17	—	0.16	0.16

— = Not performed.

Fig. 23

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (Lot G384)									
Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**						
Lot: G384						**Drug Substance Lot: SOL12621/5**			
			Storage Condition: 25 °C/60% RH						
Test	**Acceptance Criteria**	**Time (Months)**							
		0	**1**	**2**	**3**	**6**	**9**	**12**	**18**
Appearance of Lyophilized Product	Record	White lyophilized plug with shrinkage. Although no splitting evident, the bottom of the plug (2-3 mm) appeared to be slightly more shrunken.	As initial	As initial	As initial	As initial	As initial	As initial	As initial
Completeness of Solution	A clear, colorless solution, free from visible particulates	A clear, colorless solution, free from visible particulates.	As initial	As initial	As initial	As initial	As initial	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	<1	<1	<1	<1	<1	<1	<1	<1
pH on Reconstitution	2.9 to 3.5	3.3	3.3	3.4	3.3	3.3	3.3	3.3	3.3
Moisture Karl Fischer (% w/w)	NMT 1.5	0.10	0.22	0.30	0.31	0.43	0.50	0.45	0.60

Fig. 24

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (Lot G384)

Product Name: CNS 7056				**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: G384						**Drug Substance Lot: SOL12621/5**			
				Storage Condition: 25 °C/60% RH					
Test	**Acceptance Criteria**	**Time (Months)**							
		0	**1**	**2**	**3**	**6**	**9**	**12**	**18**
CNS 7056 Vial Content (mg/vial)	23.1 to 26.9 mg/vial	23.4	23.7	23.8	23.7	23.7	23.6	23.8	23.8
	92.3 to 107.5% nominal amount	93.6	94.8	95.2	94.8	94.8	94.4	95.2	95.2
Concentration on Reconstitution (mg/mL)	4.3 to 5.5	4.4[a]	—	4.5	—	4.8	—	4.6	4.5
Related Substances (Area %):									
CNS 7054X	NMT 1.3%	1.08	1.10	1.10	1.11	1.11	1.14	1.13	1.16
RRT 0.68	NMT 0.4%	0.09	0.09	0.09	0.09	0.10	0.10	0.08	0.08
RRT 0.93	NMT 0.4%	0.12	0.12	0.14	0.14	0.12	0.12	0.13	0.18
RRT 0.94	NMT 0.4%	0.07	0.09	0.10	0.10	[b]	[b]	<LOQ	[c]
RRT 1.31	NMT 0.4%	0.23	0.24	0.24	0.24	0.24	0.24	0.22	0.23
Total	NMT 2.0%	1.59	1.64	1.67	1.68	1.57	1.60	1.56	1.65
Chiral (% R)	NMT 0.5% R-enantiomer	0.16	0.16	—	0.16	0.17	0.15	0.14	0.16

[a] = See Section 7.2.13.1 for discussion.
[b] = Peak at RRT 0.94 not resolved from CNS 7056.
[c] = Peak not detected. Appeared to be unresolved from previous peak.
— = Not performed.

Fig. 25

Accelerated Stability Data, CNS 7056 for Injection, 25 mg (Lot G384)						
Product Name: CNS 7056		**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**				
Lot: G384			**Drug Substance Lot: SOL12621/5**			
		Storage Condition: 40 °C/75% RH				
Test	**Acceptance Criteria**	**Time (Months)**				
		0	**1**	**2**	**3**	**6**
Appearance of Lyophilized Product	Record	White lyophilized plug with shrinkage. Although no splitting evident, the bottom of the plug (2-3 mm) appeared to be slightly more shrunken	As initial	As initial	As initial	As initial
Completeness of Solution	A clear, colorless solution, free from visible particulates	A clear, colorless solution, free from visible particulates.	As initial	As initial	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	<1	<1	<1	<1	<1
pH on Reconstitution	2.9 to 3.5	3.3	3.3	3.4	3.4	3.3
Moisture Karl Fischer (% w/w)	NMT 1.5	0.10	0.48	0.44	0.50	0.69
CNS 7056 Vial Content (mg/vial)	23.1 to 26.9 mg/vial	23.4	23.6	23.8	23.7	23.7
	92.5 to 107.5% nominal amount	93.6	94.4	95.2	94.8	94.8
Concentration on Reconstitution (mg/mL)	4.5 to 5.5	4.4[a]	—	4.5	—	4.7

Fig. 26

Accelerated Stability Data, CNS 7056 for Injection, 25 mg (Lot G384)

Product Name: CNS 7056		**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**				
Lot: G384			**Drug Substance Lot: SOL12621/5**			
		Storage Condition: 40 °C/75% RH				
Test	**Acceptance Criteria**	**Time (Months)**				
		0	**1**	**2**	**3**	**6**
Related Substances (Area %):						
CNS 7054X	NMT 1.5%	1.08	1.14	1.14	1.18	1.28
RRT 0.68	NMT 0.4%	0.09	0.08	0.08	0.08	0.10
RRT 0.93	NMT 0.4%	0.12	0.12	0.14	0.14	0.12
RRT 0.94	NMT 0.4%	0.07	0.09	0.12	0.10	[δ]
RRT 1.31	NMT 0.4%	0.23	0.24	0.23	0.24	0.23
Total	NMT 2.0%	1.59	1.67	1.71	1.74	1.73
Chiral (% R)	NMT 0.5% R-enantiomer	0.16	0.14	—	0.16	0.16

[α] = See Section 7.2.13.1 for discussion.
[δ] = Peak at RRT 0.94 not resolved from CNS 7056.
— = Not performed.

Fig. 27

Long-Term Stability Data, CNS 7056 for Injection, 23 mg (Lot P02308)										
Product Name: CNS 7056				**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**						
Lot: P02308							**Drug Substance Lot: 11084**			
			Storage Condition: 25 °C/60% RH							
Test	**Acceptance Criteria**	**Time (Months)**								
		0	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance of Lyophilized Product	White to off-white lyophilized plug	Off-white lyophilized plug	As initial	As initial	As initial	As initial	As initial	As initial	As initial	As initial
Completeness of Solution	A clear, colorless to pale yellow solution, free from visible particulates	All vials - a clear , very pale yellow solution, free from visible particulates	As initial	As initial	As initial	As initial	As initial	As initial	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	<1	<1	<1	<1	<1	<1	<1	<1	<1
Subvisible Particulates	≥10 µm: report	66	65	—	93	—	24	16	13	40
	≥25 µm: report	1	0	—	<1	—	<1	<1	0	<1
Osmolality (mOsm/kg)	290 ± 30	280	283	292	288	289	287	282	284	288
pH on Reconstitution	2.9 to 3.5	3.1	3.1	3.1	3.2	3.2	3.1	3.2	3.1	3.1
Moisture Karl Fischer (% w/w)	NMT 1.5	0.27	0.27	0.36	0.50	0.47	0.46	0.62	0.59	0.68
CNS 7056 Vial Content (mg/vial)	21.3 to 24.7 mg/vial	23.6	23.6	23.4	23.6	23.6	23.5	23.5	23.4	23.4
	92.5 to 107.5% nominal amount	102.6	102.6	101.7	102.6	102.3	102.2	102.1	101.5	101.6

Fig. 28

Long-Term Stability Data, CNS 7056 for Injection, 23 mg (Lot P02308)

Product Name: CNS 7056					**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: P02308								**Drug Substance Lot: 11084**		
				Storage Condition: 25 °C/60% RH						
Test	**Acceptance Criteria**	**Time (Months)**								
		0	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**36**

Test	**Acceptance Criteria**	**Time (Months)**								
		0	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Concentration on Reconstitution (mg/mL)	4.5 to 5.5	4.9	5.1	5.0	5.0	5.1	5.0	5.1	5.1	5.0
Related Substances (Area %):										
CNS 7054X	NMT 1.5%	0.07	0.10	0.11	0.13	0.16	0.16	0.20	0.23	0.29
RRT 0.67	NMT 0.4%	0.03	0.03	0.04	0.03	0.03	0.03	0.03	0.03	0.03
RRT 0.71	NMT 0.4%	0.06	0.06	0.06	0.06	0.05	0.05	0.06	0.06	0.06
RRT 0.92	NMT 0.4%	0.12	0.12	0.12	0.11	0.12	0.12	0.11	0.11	0.11
RRT 0.96	NMT 0.4%	0.12	<LOQ	0.10	0.04	0.09	0.10	0.04	0.03	0.03
RRT 1.31	NMT 0.4%	0.25	0.27	0.25	0.25	0.25	0.26	0.26	0.25	0.25
RRT 1.80	NMT 0.4%	<LOQ	<LOQ	<LOQ	0.03	<LOQ	<LOQ	<LOQ	0.03	0.03
Total	NMT 2.0%	0.65	0.58	0.68	0.65	0.70	0.72	0.70	0.74	0.80
Chiral (% R)	NMT 0.5% R-enantiomer	0.26	0.27	—	0.27	—	0.27	0.27	0.26	0.28
Sterility	Complies	Complies	—	—	—	—	Complies	-	Complies	Complies

— = Not performed.

Fig. 29

Accelerated Stability Data, CNS 7056 for Injection, 23 mg (Lot P02308)							
Product Name: CNS 7056		**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: P02308				**Drug Substance Lot: 11084**			
		Storage Condition: 40 °C/75% RH					
Test	**Acceptance Criteria**	**Time (Months)**					
		0	**1**	**3**	**6**	**9**	**12**
Appearance of Lyophilized Product	White to off-white lyophilized plug	Off-white lyophilized plug.	As initial	As initial	As initial	As initial	As initial
Completeness of Solution	A clear, colorless to pale yellow solution, free from visible particulates	A clear, very pale yellow solution free from visible particulates.	As initial	As initial	As initial	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	<1	<1	<1	<1	<1	<1
Subvisible Particulates	≥10 µm: report	66	76	12	74	—	20
	≥25 µm: report	1	<1	0	<1	—	0
pH on Reconstitution	2.9 to 3.5	3.1	3.1	3.1	3.2	3.2	3.1
Osmolality (mOsm/kg)	290 ± 30	280	289	291	286	290	288
Moisture Karl Fischer (% w/w)	NMT 1.5	0.27	0.40	0.58	0.67	0.78	0.86
CNS 7056 Vial Content (mg/vial)	21.3 to 24.7 mg/vial	23.6	23.6	23.4	23.5	23.4	23.2
	92.5 to 107.5% nominal amount	102.6	102.6	101.7	102.2	101.7	101.0

Fig. 30

Accelerated Stability Data, CNS 7056 for Injection, 23 mg (Lot P02308)							
Product Name: CNS 7056		**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**					
Lot: P02308					**Drug Substance Lot: 11084**		
		Storage Condition: 40 °C/75% RH					
Test	**Acceptance Criteria**	**Time (Months)**					
		0	**1**	**3**	**6**	**9**	**12**
Concentration on Reconstitution (mg/mL)	4.5 to 5.5	4.9	5.2	5.0	5.0	5.1	5.1
Related Substances (Area %):							
CNS 7054X	NMT 1.5%	0.07	0.12	0.20	0.32	0.41	0.54
RRT 0.67	NMT 0.4%	0.03	0.03	0.04	0.03	0.03	0.03
RRT 0.71	NMT 0.4%	0.06	0.07	0.05	0.06	0.05	0.05
RRT 0.92	NMT 0.4%	0.12	0.12	0.12	0.11	0.12	0.12
RRT 0.96	NMT 0.4%	0.12	0.03	0.10	0.05	0.10	0.09
RRT 1.31	NMT 0.4%	0.25	0.27	0.27	0.28	0.29	0.29
RRT 1.80	NMT 0.4%	<LOQ	<LOQ	<LOQ	0.03	<LOQ	<LOQ
Total	NMT 2.0%	0.65	0.64	0.78	0.88	1.00	1.12
Chiral (% R)	NMT 0.5% R-enantiomer	0.26	0.27	0.27	0.27	—	0.27
Sterility	Complies	Complies	—	—	—	—	—
—= Not performed.							

Fig. 31

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (Lot 025CNS27)										
Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**							
Lot: 025CNS27						**Drug Substance Lot: SOL12621/5**				
			Storage Condition: 25 °C/60% RH							
Test	**Acceptance Criteria**	**Plug**	**Time (Months)**							
			0	**1**	**2**	**3**	**6**	**9**	**12**	**18**
Appearance of Lyophilized Product	Record	Unsplit	White lyophilized plug with shrinkage.	As initial	—	—	—	—	—	—
		Split	White lyophilized plug with shrinkage. 2 distinct layers evident.	As initial	As initial	As initial	As initial	As initial	As initial[a]	White lyophilized plug with shrinkage.
Completeness of Solution	A clear, colorless solution, free from visible particulates		The bulk of the plug dissolved rapidly. The resultant solution was clear, colorless, and free from visible particulates.	As initial	As initial	As initial	As initial	As initial	As initial	As initial
Time to Reconstitute (Min)	NMT 2 min	Unsplit	<1	<1	—	—	—	<1[b]	<1	<1[b]
		Split	<1	<1	<1	<1	<1		<1	
pH on Reconstitution	2.9 to 3.5	Unsplit	3.1	—	—	—	—	3.1[b]	3.1	3.2[b]
		Split	3.2	3.1	3.2	3.1	3.2		3.1	

Fig. 32

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (Lot 025CNS27)										
Product Name: CNS 7056			Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt							
Lot: 025CNS27						Drug Substance Lot: SOL12621/5				
			Storage Condition: 25 °C/60% RH							
Test	Acceptance Criteria	Plug	Time (Months)							
			0	1	2	3	6	9	12	18
Moisture Karl Fischer (% w/w)	NMT 1.5	Unsplit	0.36	0.31	—	—	—	0.79[b]	0.76	0.62[b]
		Split	0.83	0.78	0.86	0.87	0.87			
CNS 7056 Vial Content (mg/vial)	23.1 to 26.9 mg/vial	Unsplit	24.6	25.0	24.7	24.4	24.7	24.8	25.0	25.0
	92.5 to 107.5% nominal amount		98.3	100.0	98.7	97.6	98.7	99.2	100.0	100.0
Concentration on Reconstitution (mg/mL)	4.5 to 5.5	Unsplit	4.6	—	—	4.6	4.7	4.8	4.8	4.7
Related Substances (Area %):										
CNS 7054X	NMT 1.5%	Unsplit	1.08	1.09	—	—	—	—	—	—
RRT 0.68	NMT 0.4%		0.09	0.09	—	—	—	—	—	—
RRT 0.93	NMT 0.4%		0.12	0.13	—	—	—	—	—	—
RRT 0.94	NMT 0.4%		0.07	0.08	—	—	—	—	—	—
RRT 1.31	NMT 0.4%		0.22	0.24	—	—	—	—	—	—
Total	NMT 2.0%		1.58	1.628	—	—	—	—	—	—

Fig. 33

Long-Term Stability Data, CNS 7056 for Injection, 25 mg (Lot 025CNS27)

Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**						
Lot: 025CNS27						**Drug Substance Lot: SOL12621/5**			
			Storage Condition: 25 °C/60% RH						
Test	**Acceptance Criteria**	**Plug**	**Time (Months)**						
			0	**1**	**2**	**3**	**6**	**9**	**12**	**18**
Related Substances (Area %):										
CNS 7054X	NMT 1.5%	Split	1.08	1.09	1.12	1.14	1.15	1.20	1.20	1.16
RRT 0.68	NMT 0.4%		0.09	0.09	0.11	0.08	0.09	0.08	0.10	0.10
RRT 0.93	NMT 0.4%		0.12	0.13	0.20	0.12	0.14	0.12	0.12	0.13
RRT 0.94	NMT 0.4%		0.07	0.08	*c*	0.09	0.09	*d*	*d*	≤0.05
RRT 1.31	NMT 0.4%		0.22	0.23	0.24	0.24	0.24	0.23	0.24	0.24
Total	NMT 2.0%		1.58	1.62	1.67	1.67	1.71	1.63	1.66	1.63
Chiral (% R)	NMT 0.5% R-enantiomer	Unsplit	0.16	0.16	—	0.12	0.15	0.15	0.15	0.16

a = Two distinct layers evident in only 9 of 11 vials.
b = At 39 and 78 weeks, it is not known whether the vials used for the analysis were unsplit or split.
c = Peaks at RRT 0.93 and 0.94 are not resolved; total area remains the same.
d = Peak at RRT 0.94 not resolved from CNS 7056 peak.
— = Not performed.

Fig. 34

Accelerated Stability Data, CNS for Injection, 25 mg (Lot 025CNS27)									
Product Name: CNS 7056			Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt						
Lot: 025CNS27						Drug Substance Lot: SOL12621/5			
			Storage Condition: 40 °C/75% RH						
Test	Acceptance Criteria	Plug	Time (Months)						
			0	1	2	3	6	9	12
Appearance of Lyophilized Product	Record	Unsplit	White lyophilized plug with shrinkage.	As initial	As initial	As initial	As initial	As initial	As initial
		Split	White lyophilized plug with shrinkage. 2 distinct layers evident.	As initial	As initial	As initial	As initial	As initial	White lyophilized plug with shrinkage.
Completeness of Solution	A clear, colorless solution, free from visible particulates	Unsplit	The bulk of the plug dissolved rapidly. The resultant solution was clear, colorless and free from visible particulates.	As initial	As initial	As initial	As initial	As initial	As initial
Time to Reconstitute (min)	NMT 2 min	Unsplit	<1	<1	—	—	—	<1[a]	<1[a]
		Split	<1	<1	<1	<1	<1		
pH on Reconstitution	2.9 to 3.5	Unsplit	3.1	3.2	—	—	—	3.1[a]	3.1[a]
		Split	3.2	3.1	3.3	3.1	3.2		

Fig. 35

Accelerated Stability Data, CNS for Injection, 25 mg (Lot 025CNS27)									
Product Name: CNS 7056			**Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt**						
Lot: 025CNS27						**Drug Substance Lot: SOL12621/5**			
			Storage Condition: 40 °C/75% RH						
Test	**Acceptance Criteria**	**Plug**	**Time (Months)**						
			0	**1**	**2**	**3**	**6**	**9**	**12**
Moisture Karl Fischer (% w/w)	NMT 1.5	Unsplit	0.36	0.47	—	—	—	1.24[a]	0.82
		Split	0.83	1.18	1.00	0.78	1.11		
CNS 7056 Vial Content (mg/vial)	23.1 to 26.9 mg/vial	Unsplit	24.6	24.6	24.4	24.1	24.6	24.3	24.6
	92.5 to 107.5% nominal amount		98.5	98.4	97.5	96.4	98.3	97.0	98.4

Fig. 36

Accelerated Stability Data, CNS for Injection, 25 mg (Lot 025CNS27)										
Product Name: CNS 7056			Container Closure: Type I Glass Vials, 20 mL; Bromobutyl Rubber Stopper; and Aluminum Skirt							
Lot: 025CNS27			Storage Condition: 40 °C/75% RH			Drug Substance Lot: SOL12621/5				
Test	Acceptance Criteria	Plug	Time (Months)							
			0	1	2	3	6	9	12
Conc. on Reconst. (mg/mL)	4.5 to 5.5	Unsplit	4.6	4.6	4.5	4.6	4.6	4.9	[b]
Rel. subst. (Area %)									
CNS 7054X	NMT 1.5%	Unsplit	1.08	1.15	—	—	—	—[c]	—
RRT 0.68	NMT 0.4%		0.09	0.09	—	—	—	—[c]	—
RRT 0.93	NMT 0.4%		0.12	0.13	—	—	—	—[c]	—
RRT 0.94	NMT 0.4%		0.07	0.08	—	—	—	—[c]	—
RRT 1.31	NMT 0.4%		0.22	0.24	—	—	—	—[c]	—
Total	NMT 2.0%		1.58	1.67	—	—	—	—[c]	—
Rel. Sub. (Area %):									
CNS 7054X	NMT 1.5%	Split	1.08	1.15	1.24	1.25	1.36	1.40	1.51
RRT 0.68	NMT 0.4%		0.09	0.09	0.11	0.08	0.09	0.08	0.10
RRT 0.93	NMT 0.4%		0.12	0.13	0.20	0.12	0.13	0.11	0.12
RRT 0.94	NMT 0.4%		0.07	0.08	[d]	0.09	0.10	[d]	[d]
RRT 1.31	NMT 0.4%		0.22	0.24	0.24	0.23	0.24	0.23	0.23
Total	NMT 2.0%		1.58	1.69	1.79	1.77	1.92	1.82	1.96
Chiral (% R)	NMT 0.5% R-enantiomer	Unsplit	0.16	0.16	—	0.12	0.16	0.15	0.15

[a] = It is not known whether the vials used for the analysis were unsplit or split.
[b] = Not done due to shortage of vials stored at 40 °C/75% RH.
[c] = It is not known whether the vials used for the analysis were unsplit or split; aligned with split data for ease of comparison.
[d] = Peaks at RRT 0.93 and 0.94 were not resolved.
— = Not performed.

Fig. 37

Test (Release Specification and Shelf Life Specification)	Method	Results
		25°C/60%RH
Appearance of Lyophilised Product (White to off white lyophilised plug)	C/TE/8257	All vials off white lyophilised plug
Completeness of Solution (on reconstitution) (A clear, colourless to pale yellow solution free from visible particulates)	USP <641>	All vials - a clear, colourless to pale yellow solution, free from visible particulates
Time to reconstitute (NMT 2 minutes)	C/TE/8256	Vial 1: 38 secs Vial 2: 30 secs Mean : 34 secs
Identity CNS7056B UV (Absorbance maxima at 216±1nm and 230.5±1 nm)	QC058	NR
HPLC retention achiral method Identity CNS7056B (Retention time practically identical to reference standard)	ADP104 achiral HPLC	Retention time practically identical to reference standard
Identity CNS7056B HPLC retentiou chiral method (Retention time practically identical to reference standard)	ADP104 chiral HPLC	Retention time practically identical to reference standard
Sterility (Complies)	USP<71>	Sterile
Sub-visible particulates (≥10µm : Record ≥25µm : Record)	USP <788>	≥10µm : 40 particles ≥25µm : <1 particle

NR: Test not required as part of stability programme.

Fig. 38

Test (Release Specification)	Method	Results
		25°C/60%RH
pH on reconstitution (2.9 – 3.5)	USP<791>	Vial 1: pH 3.13 Vial 2: pH 3.15 Mean: pH 3.14
Osmolality (290 ± 30 mOsmol/Kg)	USP<785>	Vial 1: 289mOsm/kg Vial 2: 287mOsm/kg Mean: 288mOsm/kg
CNS 7056B Vial content/Recovery (Release 21.9 to 24.2 mg per vial, 95.0-105.0% of stated amount) (Shelf Life 21.3 to 24.7 mg per vial, 92.5-107.5% of stated amount)	ADP104 achiral HPLC	Vial 1: 23.2 mg per vial (101.0%) Vial 2: 23.5 mg per vial (102.2%) Mean: 23.4 mg per vial (101.6 %)
Chiral Purity (% area) (Release and Shelf Life NMT 0.5% R enantiomer)	ADP104 chiral HPLC	0.28%
Moisture by Karl Fischer (% w/w) (Release NMT1.0%) (Shelf Life NMT1.5%)	ADP104 KF	Vial 1: 0.71% Vial 2: 0.67% Vial 3: 0.67% Mean: 0.68%

NR: Test not required as part of stability programme.

Fig. 39

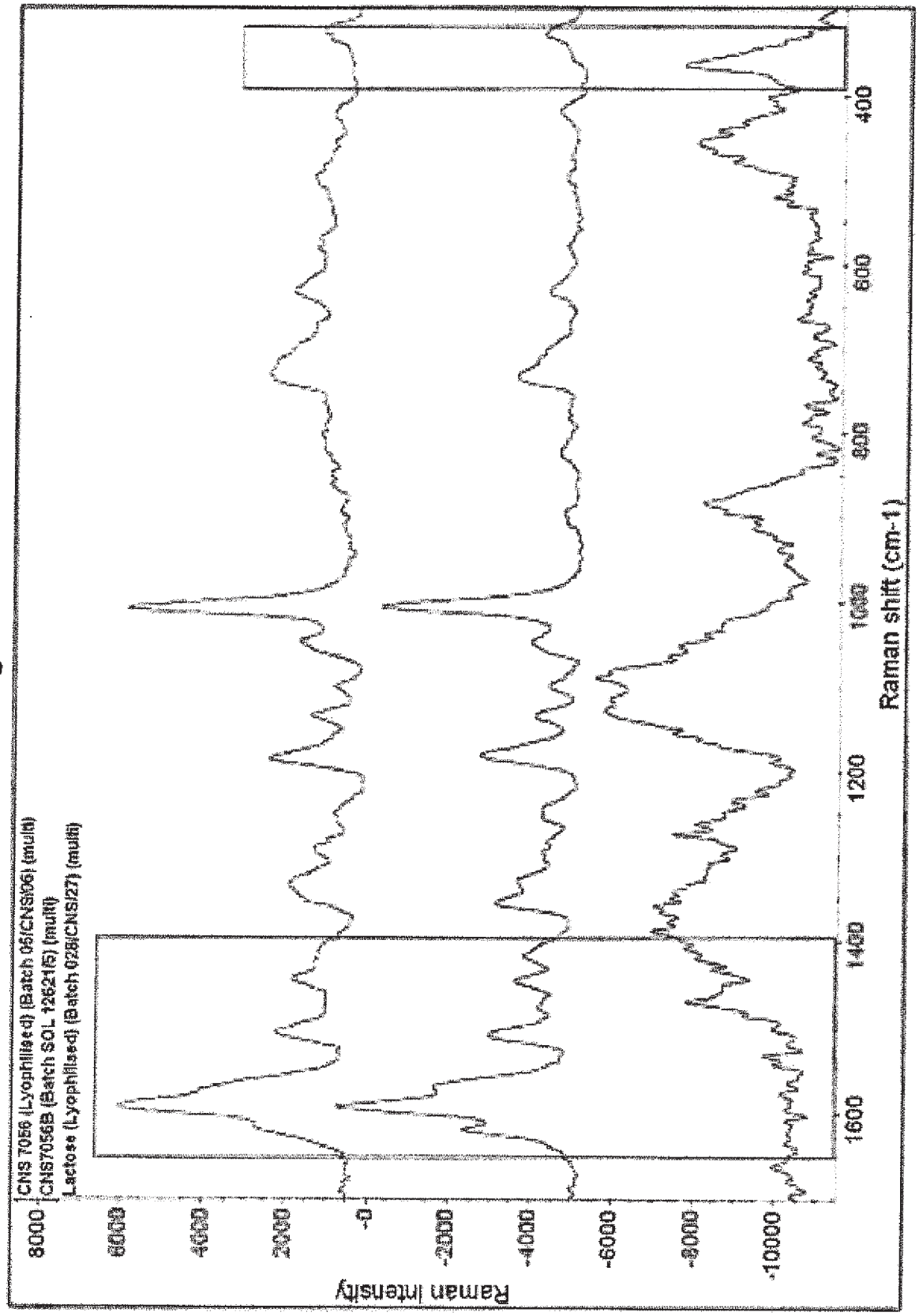

CNS 7056 (Lyophilised) (Batch 05/CNS056) (multi)
CNS7056B (Batch SOL 12621/5) (multi)
Lactose (Lyophilised) (Batch 028/CNS/27) (multi)
8000
6000
4000
2000
-0
-2000
-4000
-6000
-8000
-10000
Raman Intensity
1600
1400
1200
1000
800
600
400
Raman shift (cm-1)

Fig. 40

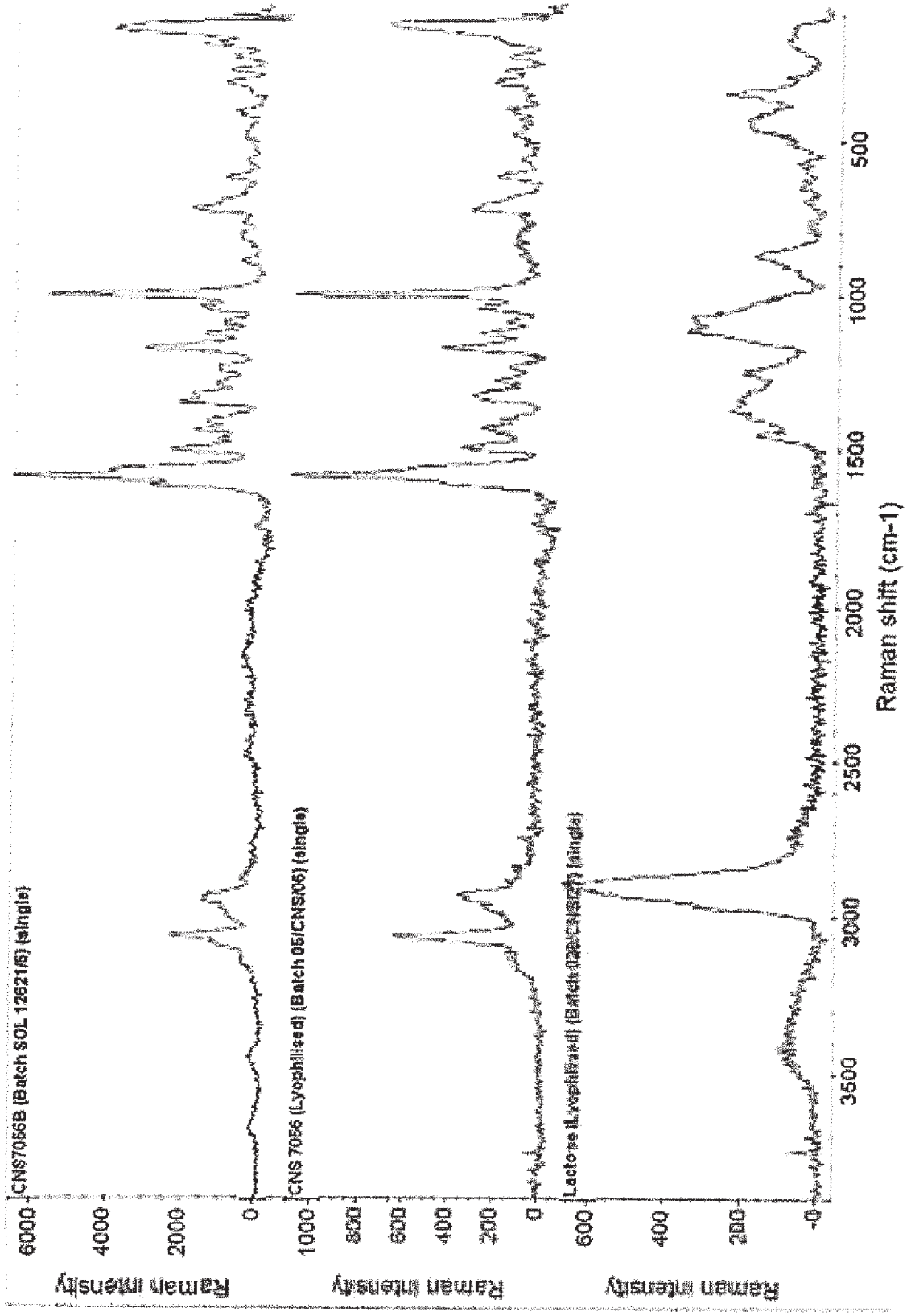

CNS7056B (Batch SOL 125215) (single)
CNS 7056 (Lyophilised) (Batch 05/CNS806) (single)
Lactobacillus (Lyophilised) (Batch 026/CNS807) (single)
Raman intensity
Raman shift (cm-1)
6000
4000
2000
0
1000
800
600
400
200
0
600
400
200
0
3500
3000
2500
2000
1500
1000
500

Fig. 41

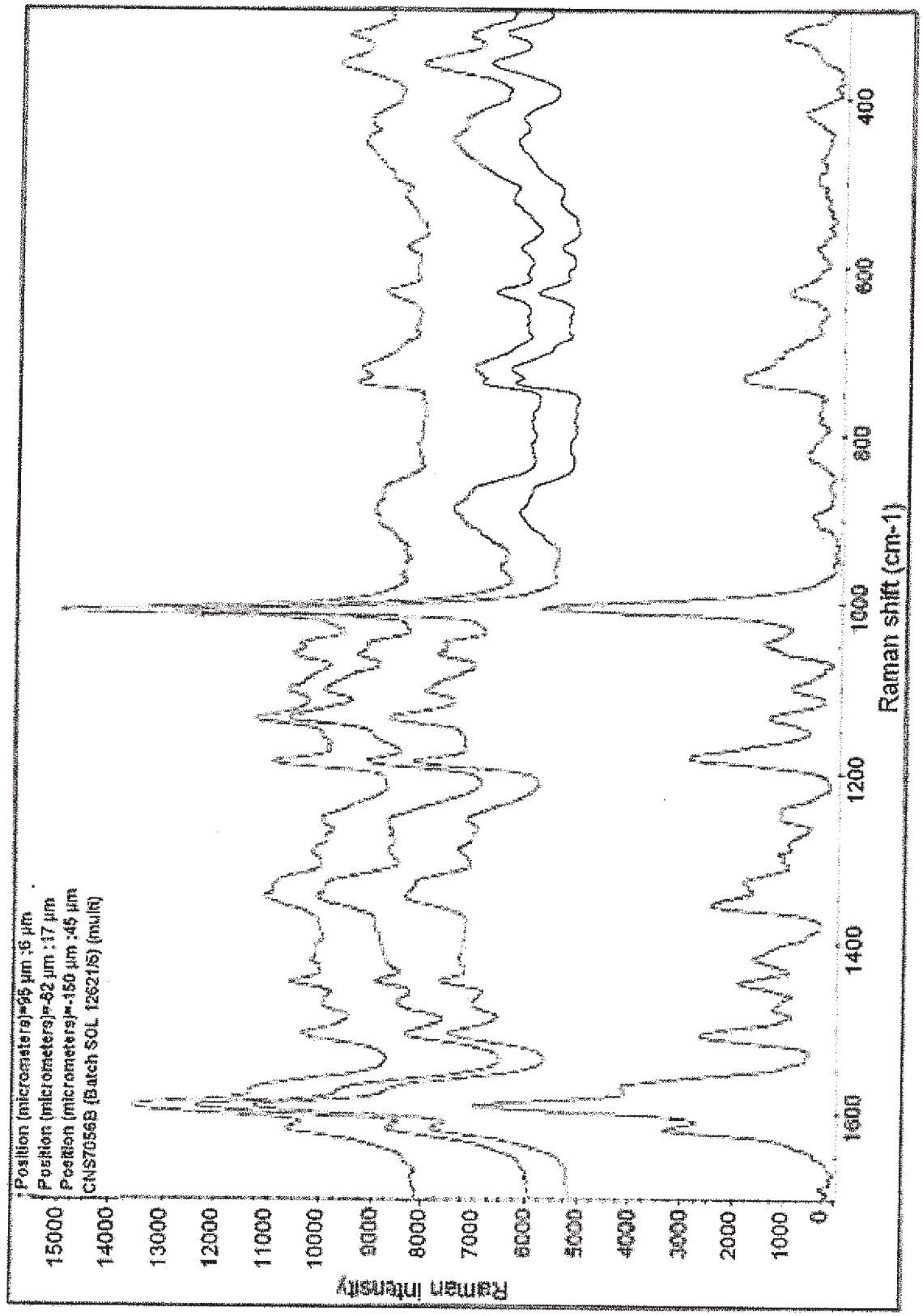

Position (micrometers)=95 µm :6 µm
Position (micrometers)=-62 µm :17 µm
Position (micrometers)=-150 µm :45 µm
CNS70556B (Batch SOL 12621/5) (mullit)
Raman Intensity
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1600
1400
1200
1000
800
600
400
Raman shift (cm-1)

Figure 42

Initial

Test Parameters	Specification	12PM529-8-2	12PM529-8-1	PM0237/12	12PM529-9-1
Appearance	White to off white powder	White powder	White powder	White powder	White powder
Assay (mg/vial)	24.94 – 27.66	25.97	26.11	26.25	N/A
% Assay	95%-105%	98.73%	99.29%	99.79%	98.75%
Total Impurities	2%	0.73%	0.67%	0.48%	0.97%
Impurities Above 0.045%	N/A	0.43%	0.39%	0.32%	0.76%
Moisture	1.5%w/w	0.24%	2.87%	0.34%	2.98%
Reconstitution Time	60 seconds	38.5s	30.5s	34.5s	-
Appearance after reconstitution time	A clear colourless to pale yellow solution free from visible particulates	clear very pale yellow solution	clear pale yellow solution	Clear colourless solution	-
XRPD	Assess whether crystalline material is present	No crystalline material detected	No crystalline material detected	No crystalline material detected	No crystalline material detected

Figure 43

4 Weeks

Test Parameters	Specification	12PM529-8-2 (40°C/75%RH)	12PM529-8-2 (55°C)	PM0237/12 (40°C/75%RH)	PM0237/12 (55°C)	12PM529-9-1 (40°C/75%RH)	12PM529-9-1 (55°C)
Appearance	White to off white powder	White Colour free flowing powder	White Colour free flowing powder	White Colour not free flowing powder	White Colour not free flowing powder	Off white colour free flowing powder	Light grey colour free flowing powder
Assay (mg/vial)	24.94 – 27.66	25.64mg/vial	25.72mg/vial	25.65mg/vial	25.72mg/vial	N/A	N/A
% Assay	95%-105%	102.56%	102.88%	102.61%	102.88%	95.51%	96.25%
Total Impurities	2%	0.92%	0.99%	0.61%	0.71%	2.56%	1.94%
Impurities Above 0.045%	N/A	0.89%	0.65%	0.40%	0.53%	2.35%	1.71%
Moisture	1.5%w/w	0.25%	0.36%	0.25%	0.23%	-	-
Reconstitution Time	60 seconds	42.5s	35.0s	35.0s	37.5s	-	-
Appearance after reconstitution time	A clear colourless to pale yellow solution free from visible particulates	Clear very pale yellow solution, free from visual particulates	Clear very pale yellow solution, free from visual particulates	Clear colourless solution free from visual particulates	Clear colourless solution free from visual particulates	-	-
XRPD	Assess whether crystalline material is present	No crystalline material detected	No crystalline material detected	No crystalline material detected	No crystalline material detected	-	-

Figure 44

13 Weeks

Test Parameters	Specification	12PM529-8-2 (40°C/75%RH)	12PM529-8-1 (40°C/75%RH)	PM0237/12 (40°C/75%RH)	12PM529-9-1 (40°C/75%RH)
Appearance	White to off white powder	White Colour free flowing powder	White Colour free flowing powder	White Colour not free flowing powder	Light beige colour free flowing powder
Assay (mg/vial)	24.94 – 27.66	25.69mg/vial	23.92mg/vial	25.48mg/vial	N/A
% Assay	95%-105%	102.76%	95.67%	101.92%	95.35%
Total Impurities	2%	0.78%	1.33%	0.57%	3.35%
Impurities Above 0.045%	N/A	0.49%	0.98%	0.41%	3.08%
Moisture	1.5%w/w	0.28%	2.96%	0.28%	-
Reconstitution Time	60 seconds	32.5s	37.5s	37.5s	-
Appearance after reconstitution time	A clear colourless to pale yellow solution free from visible particulates	Clear very pale yellow solution, free from visual particulates	Clear colourless solution free from visual particulates	Clear colourless solution free from visual particulates	-
XRPD	Assess whether crystalline material is present	No crystalline material detected	No crystalline material detected	No crystalline material detected	-

Figure 45

L10R5					
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**3 months 40°C±2°C / 75%±5% RH**	**3 months 25°C±2°C / 60%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off white cohesive cake, bright surface, some vials show cracks	Off white cohesive cake, bright surface, some vials show cracks	Off white cohesive cake, bright surface, some vials show cracks	Off white cohesive cake, bright surface, some vials show cracks	Off white cohesive cake, bright surface, some vials show cracks
Reconstitution time (V=4 mL)	30 s	35 s	72 s	63 s	38 s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	303 mOsm/Kg	-	-	-	-
Moisturecontent	0.29% (0.30%; 0.28%; 0.29%)	**0.69%** (0.69%; 0.64%; 0.75%)	**0.89%** (0.93%; 0.86%; 0.89%)	**0.56%** (0.62%; 0.51%; 0.53%)	**1.02%** (1.12%; 0.98%; 0.95%)
HPLC content/assay	20.4 mg/vial 102%	20.2 mg/vial 101%	20.1 mg/vial 101%	20.3 mg/vial 102%	20.2 mg/vial 101%
HPLC sum of RS & RS details	Total RS = 0.52% CNS7054X = 0.06% RRT 0.66 = 0.04% RRT 0.69 = 0.05% RRT 0.92 = 0.11% RRT 1.32 = 0.22% RRT 1.92 =0.03%	**Total RS = 0.60%** **CNS7054X =0,13%** RRT 0.66 = 0,03% RRT 0.68 = 0,05% RRT 0.92 = 0,11% **RRT 1.31 = 0,25%** RRT 1.91 = 0,03%	**Total RS = 0.74%** **CNS7054X = 0.28%** RRT 0.66 =0.03% RRT 0.69 = 0.05% RRT 0.92 = 0.11% RRT 1.31 = 0.24% RRT 1.91 =0.03%	Total RS = 0.57% **CNS7054X = 0.12%** RRT 0.66 =0.04% RRT 0.69 = 0.05% RRT 0.92 = 0.10% RRT 1.31 = 0.23% RRT 1.91 =0.03%	**Total RS = 0.93%** **CNS7054X = 0.53%** RRT 0.66 =0.03% RRT 0.67 = 0.04% RRT 0.92 = 0.10% RRT 1.31 = 0.23% RRT 1.93 <LOQ

Figure 46

L10R10			
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off-white cohesive cake, bright surface, irregular edge all around the cake	Off-white cohesive cake, bright surface, irregular edge all around the cake	Off-white cohesive cake, bright surface, irregular edge all around the cake
Reconstitution time (V=8 mL)	50 s	45 s	38s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	616 mOsm/kg	-	-
Moisturecontent	1.22% (1.29%; 1.16%)	**0.71%** (0.70%; 0.73%)	1.23% (**1.71%***; 0.74%)
HPLC content/assay	39.7 mg/vial 99%	39.1 mg/vial 98%	39.4 mg/vial 99%
HPLC sum of RS & RS details	Total RS = 0.57% CNS7054X = 0.05% RRT 0.66 = 0.05% RRT 0.69 = 0.07% RRT 0.92 = 0.13% RRT 1.32 = 0.25% RRT 1.92=0.03%	Total RS = 0.61% **CNS7054X =0,13%** RRT 0.66 = 0,04% RRT 0.68 = 0,05% **RRT 0.92 = 0,11%** RRT 1.31 =0,25% RRT 1.92=0,03%	**Total RS = 0.84%** **CNS7054X = 0.42%** RRT 0.67 = 0.03% RRT 0.71 = 0.05% RRT 0.92 = 0.10% RRT 1.32 = 0.24% RRT 1.97<LOQ (**)

(*) Sample partially melt

(**)Slight shift of the RRT, this RS has to be compared with RRT 1.92

Figure 47

L10R5S87					
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**3 months 40°C±2°C / 75%±5% RH**	**3 months 25°C±2°C / 60%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off white cohesive cake, bright surface, some vials show irregular edge only on a small part of the cake	Off white cohesive cake, bright surface, some vials show irregular edge only on a small part of the cake	Off white cohesive cake, bright surface, some vials show irregular edge only on a small part of the cake	Off white cohesive cake, bright surface, some vials show irregular edge only on a small part of the cake	Off white cohesive cake, bright surface, some vials show irregular edge only on a small part of the cake
Reconstitution time (V=4 mL)	30 s	38 s	68 s	41 s	40 s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	303 mOsm/Kg	-			-
Moisturecontent	0.56% (0.76%; 0.48%; 0.46%)	**0.75%** (0.78%; 0.73%; 0.76%)	**0.92%** (0.87%; 1..07%; 0.80%)	0.64% (0.74%; 0.57%; 0.61%)	**1.03%** (1.01%; 1.08%; 1.00%)
HPLC content/assay	20.7 mg/vial 104%	20.2 mg/vial 101%	20.2 mg/vial 101%	20.2 mg/vial 101%	20.2 mg/vial 101%
HPLC sum of RS & RS details	Total RS = 0.55% CNS7054X = 0.06% RRT 0.66 = 0.04% RRT 0.69 = 0.06% RRT 0.92 = 0.13% RRT 1.32 = 0.23% RRT 1.92=0.03%	Total RS = 0.61% **CNS7054X = 0,16%** RRT 0.66 =0,03% RRT 0.68 = 0,05% RRT 0.92 = 0,11% RRT 1.31 = 0,25% RRT 1.92= 0,03%	**Total RS = 0.74%** **CNS7054X = 0.28%** RRT 0.66 =0.03% RRT 0.69 = 0.05% RRT 0.92 = 0.11% RRT 1.31 = 0.24% RRT 1.91 =0.04%	Total RS = 0.57% **CNS7054X = 0.12%** RRT 0.66 =0.03% RRT 0.69 = 0.05% RRT 0.92 = 0.10% RRT 1.31 = 0.24% RRT 1.91 =0.03%	**Total RS = 1.10%** **CNS7054X = 0.69%** RRT 0.67 = 0.03% RRT 0.71 = 0.05% RRT 0.92 = 0.10% RRT 1.32 = 0.23% RRT 1.97 <LOQ(*)

(*) Slight shift of the RRT, this RS has to be compared with RRT 1.92

Figure 48

L20R5 (*)					
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**3 months 40°C±2°C / 75%±5% RH**	**3 months 25°C±2°C / 60%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off white cohesive cake, bright surface	Off white cohesive cake, bright surface (**some cakes were found to be shrunk**)	Off white cohesive cake, bright surface (**some cakes were found to be shrunk**)	Off white cohesive cake, bright surface	Off white cohesive cake, bright surface (**some vials were found to be charred**)
Reconstitution time (V=5 mL)	30 s	**34 s**	68 s	59 s	32 s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles (the charred cake was unsoluble)
Osmolality	-	-	-	-	-
Moisturecontent	0.22% (0.19%;0.23%;0.22%)	0.37% (0.36%; 0.37%; **5.40%****)	**0.76%** (0.44%; 1.07%(■■))	**0.63%** (1.01%; **4.85%(■);** 0.26%)	**0.53%** (0.52%; 0.52%; 0.55%)
HPLC content/assay	25.5 mg/vial 98%	26.9 mg/vial 103%	25.8 mg/vial 99%	25.6 mg/vial 98%	25.6 mg/vial 98%
HPLC sum of RS & RS details	Total RS = 0.58% CNS7054X = 0.07% RRT 0.66 = 0.05% RRT 0.69 = 0.06% RRT 0.92 = 0.12% RRT 1.32 = 0.24% RRT 1.92=0.03%	Total RS = 0.69% CNS7054X =0,25% RRT 0.66 = 0,03% RRT 0.68 =0,05% RRT 0.92 =0,11% RRT 1.32 = 0,24% RRT 1.92=0,03%	**Total RS = 1.02%** **CNS7054X = 0.51%** **RRT 0.61 = 0.03%** RRT 0.66 =0.03% RRT 0.69 = 0.05% RRT 0.92 = 0.11% RRT 1.31 = 0.23% RRT 1.91 =0.03% **RRT 2.07 = 0.03%**	**Total RS = 1.60%** **CNS7054X = 1.11%** **RRT 0.61 = 0.03%** RRT 0.66 =0.04% RRT 0.69 = 0.05% RRT 0.92 = 0.11% RRT 1.31 = 0.23% RRT 1.91 =0.03% **RRT 2.07 < LOQ**	**Total RS = 1.47%** **CNS7054X = 1.03%** RRT 0.64 = 0.03% **RRT 0.67 = 0.03%** RRT 0.71 = 0.05% RRT 0.92 = 0.10% RRT 1.32= 0.23% RRT 1.97 < LOQ (●)

(*) vials from clinical batch A01P310. Vials rejected after visual inspection;(**) Moisture content of a shrunk cake. This result wasn't considered in the average one as the other two results refer to cakes whose appearance didn't change from time 0. (***) Sample with a shrunk cake.(●)Slight shift of the RRT, this RS has to be compared with RRT 1.92; (■) result not included in the average; (■■) Only two vials available for the analysis, the other vials were found to be shrunk.

Figure 49

L4M110R5			
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off white cohesive cake, bright surface, some vials show cracks	Off white cohesive cake, bright surface, some vials show cracks	**Yellowish shrunk cake**
Reconstitution time (V=4 mL)	40 s	25 s	31 s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	292 mOsm/Kg	-	-
Moisturecontent	0.33% (0.34%; 0.33%)	**0.69%** (0.73%; 0.65%)	**1.05%** (1.10%; 1.01%)
HPLC content/assay	20.6 mg/vial 103%	20.3 mg/vial 102%	20.2 mg/vial 101%
HPLC sum of RS & RS details	Total RS = 0.56% CNS7054X = 0.07% RRT 0.66 = 0.04% RRT 0.69 = 0.06% RRT 0.92 = 0.13% RRT 1.32 = 0.23% RRT 1.92=0.03%	**Total RS = 0.66%** **CNS7054X =0,20%** RRT 0.66 = 0,03% RRT 0.68 = 0,04% RRT 0.92 = 0,11% RRT 1.32 = 0,25% RRT 1.92=0,03%	**Total RS = 1.33%** **RRT 0,36 = 0.03%** **CNS7054X = 0.90%** RRT 0.67 = 0.03% RRT 0.71 = 0.05% RRT 0.92 = 0.10% RRT 1.32= 0.24% RRT 1.97 <LOQ (*)
L4M110R10			
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off-white cohesive cake, irregular edge all around the cake	Off-white cohesive cake, irregular edge all around the cake	**Yellowish shrunk cake**
Reconstitution time (V=8 mL)	50 s	81 s	65 s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	596 mOsm/Kg	-	-
Moisturecontent	0.53% (0.54%; 0.52%)	**0.95%** (0.79%; 1.12%)	**0.98%** (0.95%; 1.01%)
HPLC content/assay	41.0 mg/vial 103%	40.1 mg/vial 100%	**39.7 mg/vial 99%**
HPLC sum of RS & RS details	Total RS = 0.55% CNS7054X = 0.06% RRT 0.66 = 0.04% RRT 0.69 = 0.06% RRT 0.92 = 0.12% RRT 1.32 = 0.24% RRT 1.92 = 0.03%	**Total RS = 0.61%** **CNS7054X =0,16%** RRT 0.66 =0,03% RRT 0.68 =0,06% RRT 0.92 = 0,11% RRT 1.32 = 0,25% RRT 1.92 <LOQ	**Total RS = 1.34%** **RRT 0.34 = 0.03%** **RRT 0.36 = 0.03%** **CNS7054X = 0.88%** RRT 0.67 = 0.03% RRT 0.71 = 0.06% RRT 0.92 = 0.10% RRT 1.32 = 0.24% RRT 1.97<LOQ (*)

Figure 50

L2M110R5			
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off white cohesive cake, surface less brighter than the other formulations, some vials show irregular edge all around the cake	Off-white cohesive cake **further shrunk**, irregular edge all around the cake, surface less brighter than the other formulations	**Yellowish shrunk cake**
Reconstitution time (V=4 mL)	50 s	43 s	45 s
Appearance of reconstitutedsolution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	329 mOsm/Kg	-	-
Moisturecontent	0.34% (0.31%; 0.36%)	**0.78%** (0.82%; 0.73%)	**0.83%** (0.73%; 0.92%)
HPLC content/assay	20.5 mg/vial 103%	20.2 mg/vial 101%	**19.9 mg/vial 100%**
HPLC sum of RS & RS details	Total RS = 0.58% CNS7054X = 0.08% RRT 0.66 = 0.05% RRT 0.69 = 0.06% RRT 0.92 = 0.13% RRT 1.32 = 0.24% RRT 1.92 = 0.03%	**Total RS = 0.68%** **CNS7054X =0,22%** **RRT 0,61 = 0.03%** RRT 0.66 = 0,03% RRT 0.68 = 0,05% RRT 0.92 = 0,11% RRT 1.32 = 0,23% RRT 1.92 = 0,03%	**Total RS = 1.76%** **RRT 0,34 = 0.05%** **RRT 0,36 = 0.05%** **CNS7054X = 1.21%** **RRT 0.64 <LOQ** RRT 0.67 = 0.03% RRT 0.71 = 0.06% RRT 0.92 = 0.10% RRT 1.32 = 0.24% **RRT 1.46 = 0.03%** RRT 1.97<LOQ (*)

Figure 51

L2M110R10			
Test	**Time 0**	**1 month 40°C±2°C / 75%±5% RH**	**1 month 55°C**
Appearance of the lyophilisate	Off-white cohesive cake, bright surface, irregular edge all around the cake, shrunk cake, surface less brighter than the other formulations	Off-white cohesive cake **further shrunk**, irregular edge all around the cake, surface less brighter than the other formulations	**Yellowish shrunk cake**
Recon. time (V=8 mL)	62 s	81 s	54 s
Appearance of recon solution	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles	Clear, pale yellow solution free of visible particles
Osmolality	648 mOsm/Kg	-	-
Moisturecontent	1.03% (1.16%; 0.91%)	1.00% (0.92%; 1.08%)	0.95% (0.96%; 0.94%)
HPLC content/assay	40.6 mg/vial 102%	40.5 mg/vial 101%	39.8 mg/vial 100%
HPLC sum of RS & RS details	Total RS = 0.58%% CNS7054X = 0.07% RRT 0.66 = 0.04% RRT 0.69 = 0.07% RRT 0.92 = 0.12% RRT 1.32 = 0.25% RRT 1.92 = 0.03%	**Total RS = 0.72%** **CNS7054X = 0,25%** **RRT 0,61 = 0,03%** RRT 0.66 = 0,03% RRT 0.68 = 0,05% RRT 0.92 = 0,11% RRT 1.32 = 0,25% RRT 1.92 < LOQ	**Total RS = 2.23%** **RRT 0,34 = 0.04%** **RRT 0,36 = 0.05%** **CNS7054X = 1.65%** RRT 0.64 = 0.03% RRT 0.67 = 0.03% RRT 0.71 = 0.07% RRT 0.92 = 0.10% RRT 1.32 = 0.24% RRT 1.97<LOQ (*)

(*)Slight shift of the RRT, this RS has to be compared with RRT 1.92

Figure 52

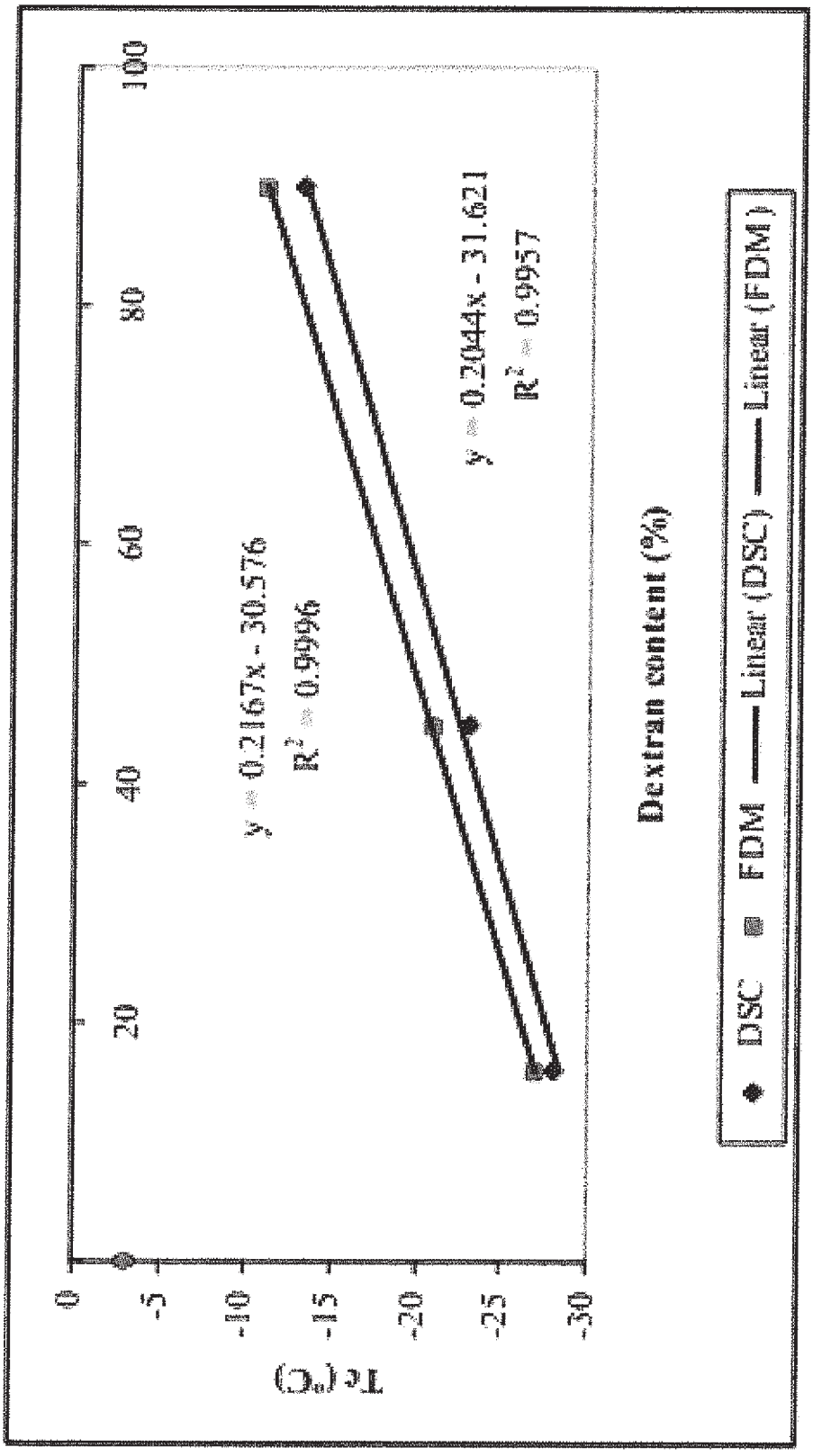
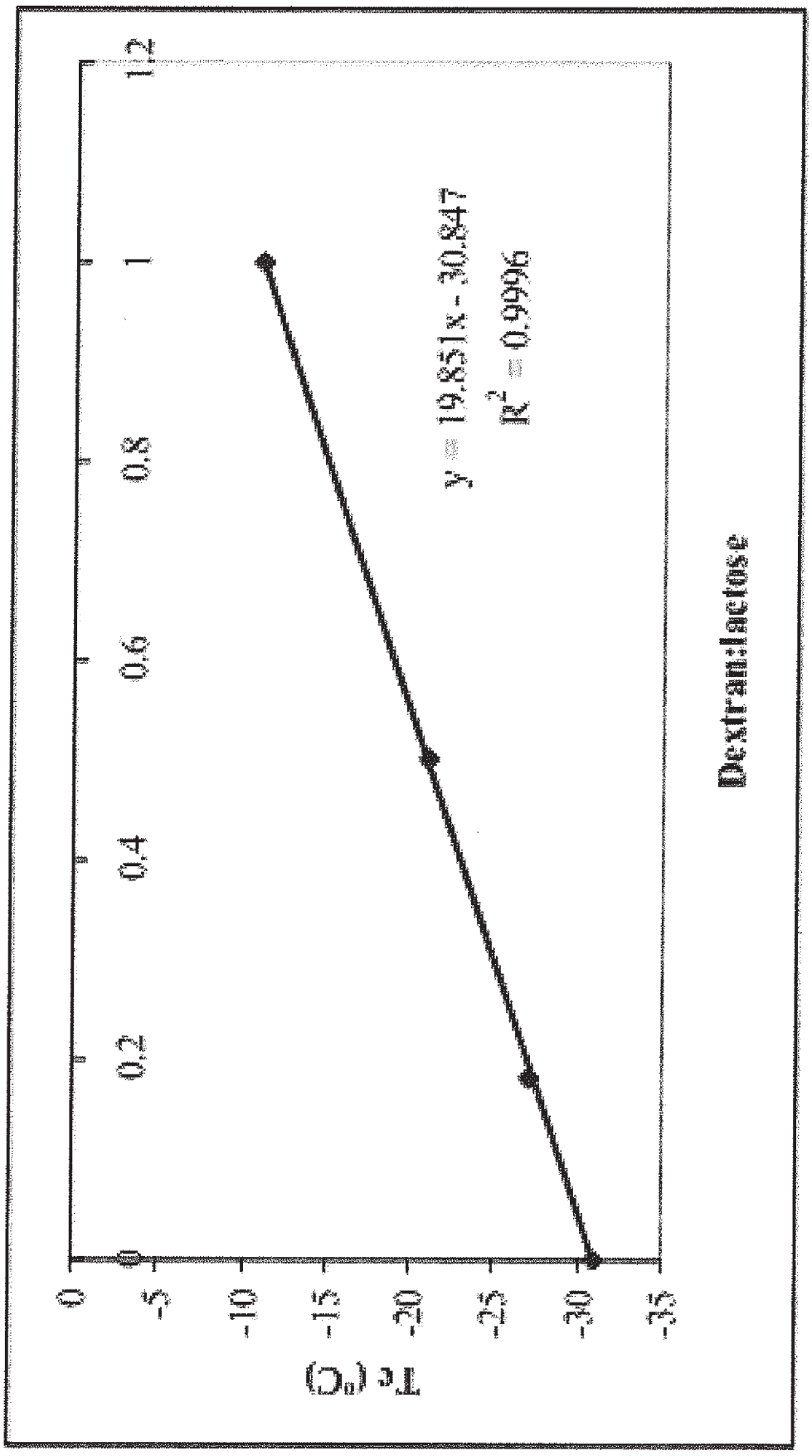

Tc (°C)
0
-5
-10
-15
-20
-25
-30
20
40
60
80
100
Dextran content (%)
y = 0.2167x - 30.576
R² = 0.9996
y = 0.2044x - 31.621
R² = 0.9957
DSC
FDM
Linear (DSC)
Linear (FDM)

Figure 53


Dextran:lactose
y = 19,851x - 30,847
R² = 0,9996
Tc (°C)
0
-5
-10
-15
-20
-25
-30
-35
0
0,2
0,4
0,6
0,8
1
1,2