ANNEX B

Metconazole

B.5 Methods of analysis
(Addendum August 2004)

B.5.1 Analytical methods for formulation analysis (Annex IIA 4.1; Annex IIIA 5.1)

B.5.1.2 Analytical methods for the determination of significant and/or relevant impurities and additives in the active substance as manufactured (Annex IIA 4.1.2 and 4.1.3)

Impurity method M-2479 still required additional validation for some impurities (precision for impurities 7, 11-12 and 14; full validation for impurities 3 and 13). New validation study addressing all process-related organic impurities was submitted in June 2004.

HRGC-FID method APL0423/02, which is based on method M-2479, is described (incl. validation data) in Addendum to Annex C, point C.1.2.4.1. Validation data are summarized in Table B.5.1.2-1.

Table B.5.1.2-1 : Validation of method APL0423/02 for determination of organic impurities (Foerster & Oberman, 2004b)

Impurity	**Specificity/ interferences**	**Linearity (R^2)**	**Repeatability**		**Accuracy**		**LOQ (%)**
			conc. level (% w/w)	**% RSD**	**conc. level (% w/w)**	**mean recovery (%)**	
1	demonstrated, no interferences	0.99990	0.05 0.36 1.75	1.60 2.17 2.09	~ 0.05 ~ 0.4 ~ 2	98.5 96.6 98.9	0.05
2	demonstrated, no interferences	0.99995	0.18 0.61 2.54	2.45 1.85 1.62	~ 0.2 ~ 0.5 ~ 2	92.1 95.2 100.9	0.05
3	demonstrated, no interferences	0.99998	0.04 0.32 1.58	3.29 2.83 1.16	~ 0.05 ~ 0.4 ~ 2	110.7 108.9 99.1	0.05
4	demonstrated, no interferences	0.99992	0.23 0.58 2.13	2.71 2.30 1.59	~ 0.2 ~ 0.5 ~ 2	94.2 92.3 99.6	0.05
5	demonstrated, no interferences	0.99985	0.21 0.60 2.31	3.37 2.60 1.78	~ 0.2 ~ 0.5 ~ 2	82.4 99.6 101.1	0.05
7	demonstrated, no interferences	0.99990	0.05 0.42 2.05	0.61 1.16 1.08	~ 0.05 ~ 0.4 ~ 2	107.7 102.7 100.9	0.05
8	demonstrated, no interferences	0.99994	0.08 0.41 1.87	2.32 2.49 1.54	~ 0.1 ~ 0.4 ~ 2	97.6 100.2 101.4	0.05
10	demonstrated, no interferences	0.99994	0.05 0.39 1.89	0.39 2.29 1.18	~ 0.05 ~ 0.4 ~ 2	106.0 105.4 102.1	0.05
11	demonstrated, no interferences	0.99992	0.05 0.39 1.88	1.49 1.35 1.42	~ 0.05 ~ 0.4 ~ 2	99.5 100.5 101.0	0.05
12	demonstrated, no interferences	0.99992	0.05 0.42 2.05	0.87 1.33 1.41	~ 0.05 ~ 0.4 ~ 2	102.9 101.4 101.2	0.05
13	demonstrated, no interferences	0.99991	0.07 0.48 2.31	1.33 2.74 1.42	~ 0.05 ~ 0.4 ~ 2	96.2 95.6 98.7	0.05
14	demonstrated, no interferences	0.99995	0.05 0.38 1.82	0.56 2.68 1.64	~ 0.05 ~ 0.4 ~ 2	99.5 95.2 98.1	0.05

Accuracy : determined by analyzing 5 fortified metconazole samples at 3 concentration levels (i.e. n=5 fort. x 2 inj. at each level); fortification levels are ca. 0.05%, 0.4% and 2% w/w resp.
Note : conc. level in table represents the nominal conc. after fortification, i.e. amount present in unfortified matrix + fortified amount

Repeatability : determined by 5-fold analysis of one fortified metconazole sample at each concentration level (i.e. n=5 repl. x 2 inj. at each level); acceptability of %RSD values was proved by modified Horwitz equation

Linearity : n = 4x2; range ca. 4 – 100 mg/L; peak area ratio vs. amount ratio

Specificity/interferences : identity of different component peaks is confirmed by MS detection; no interfering peaks; no co-eluting

Conclusion :

Method APL0423/02, which is based on method M-2479.02, is suitable for determination of metconazole-related organic impurities in technical metconazole. Acceptable validation data package is available for all impurities.

For the sake of completeness (and in reply to a comment made by EFSA), validation data of method M-2689.01 (HRGC-FID), which were reported in Annex C point C.1.2.4.2 of the DAR, are summarized in Table B.5.1.2-2.

Table B.5.1.2-2 : Validation of method M-2689.01 for determination of residual solvents (Ahuja, 1997b)

Impurity	**Specificity/ interferences**	**Linearity (R^2)**	**Repeatability (% RSD)**	**Reproducibility (% RSD)**	**Accuracy**		**LOQ (%)**
					fortif. level	**recovery (%)**	
6	demonstrated; no interferences	0.9995	1.9 (conc. 0.4849%)	2.4 (conc. 0.5032%)	~0.5%	96.63	0.01
9	demonstrated; no interferences	1.0000	1.7 (conc. 0.4923%)	4.2 (conc. 0.5299%)	~0.5%	95.86	0.01
15	demonstrated; no interferences	0.9999	1.8 (conc. 0.4793%)	4.0 (conc. 0.5062%)	~0.5%	96.43	0.02
16	demonstrated; no interferences	0.9985	3.0 (conc. 0.4818%)	5.0 (conc. 0.5082%)	~0.5%	105.25	0.1
17	demonstrated; no interferences	0.9979	2.5 (conc. 0.5324%)	2.4 (conc. 0.5522%)	~0.5%	106.21	0.09

Repeatability : n=5 (within-day); corresponding average conc. is mentioned between brackets

Reproducibility : n=25 (2 analysts, 2 resp. 3 days, n=5 per day); corresponding average conc. is mentioned between brackets

Linearity : n = 3x2; range ca. 10 – 100 µg/mL (corresponding with ca. 0.1 – 1%)

LOQ : determined as the lowest concentration which will produce a signal that is 10 times higher than the noise level

B.5.6 References relied on

B.5.6.1 Analytical methods for the active substance

Annex point(s)	**Author(s)**	**Year**	**Title** **Source** **BASF Document No.** **GLP or GEP status** **Published or not**	**Data Protection Claimed Y/N**	**Owner**
EG:AIIA-4.1.2 and 4.1.3 (< Doc. J)	Foerster, R. Obermann, M.	2004b	Validation of analytical method APL0423/02 : Gaschromatographic determination of the minor components of BAS 555 F (Metconazole) BASF AG, Agricultural Center Limburgerhof, Germany DocID 2004/1013199 yes unpublished	Y	BASF