

Certification Report

Certified Reference Material

BAM-S053

Hydrolytic Resistance of Borosilicate Glass

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Summary

This report describes preparation, analysis and certification of the glass reference material BAM-S053. The certified reference material (CRM) is available in the form of glass rods (length: 185 mm, diameter: 9 mm, weight: 27.5 g). It is intended for the quality control when applying ISO 719, ISO 720, USP<660>, Ph.Eur. 3.2.1 for the determination of hydrolytic resistance of borosilicate glass with the glass grains test.

The following properties have been certified:

Acid consumption according to	Consumption of 0.02M HCl per g in mL	Uncertainty in mL
ISO 720	0.0422	0.0030
USP<660>	0.0428	0.0025
Ph.Eur. 3.2.1	0.0429	0.0026

The certified values are based on the results of 15 laboratories which participated in the certification interlaboratory comparison. The test results according to ISO 719 had a too wide spread to certify this parameter. Therefore, it is given for information only.

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List of abbreviations

(if not explained elsewhere)

CRM	certified reference material
M	mean value
n	number of accepted data sets
s	standard deviation of an individual data set
s_M	standard deviation of laboratory means
s_{rel}	relative standard deviation
\bar{s}_i	square root of mean of variances of data sets under repeatability conditions
M_i	single result
RT	room temperature

1. Introduction

The European Pharmacopeia as well as the US Pharmacopeia require a test of the hydrolytic resistance of glass used for pharmaceutical containers. The container chosen for a given preparation shall be such that the glass material does not release substances in quantities sufficient to affect the stability of the preparation. Glass containers used in manufacturing are split into water-resistance classes, from Type I (highest resistance) to Type III. Glass containers with a hydrolytic resistance higher than that recommended for a specific purpose preparation may generally also be used beside the recommended type.

The test of hydrolytic resistance of glass is described in ISO 719, ISO 720, USP<660> and Ph.Eur. 3.2.1 [1-4]. For many years U.S. National Institute of Standards and Technology (NIST) sold Standard Reference Material 623 Borosilicate Glass for checking test methods and calibrating equipment for the determination of the Resistance of glass containers to chemical attack. NIST SRM 623 is not available anymore and will not be replaced by NIST.

This was the reason why BAM was asked to produce a reference material covering the applications of NIST 623. BAM-S053 succeeds the NIST material and is suitable for the same applications NIST 623 was before.

Certification of the reference material was carried out on the basis of ISO 17034 [5] and the relevant ISO-Guides [6,7].

2. Companies/laboratories involved

Manufacturing of the material

Schott AG, Mitterteich, Germany

Test for homogeneity

Schott AG, Mainz, Germany

Participants in the certification inter-laboratory comparison

Ardagh Glass GmbH, Nienburg, Germany

Cetim Grand Est, Schiltigheim, France

Corning European Technology Center (CETC), S&T European Laboratory, Fontainebleau, France

Corning Pharmaceutical Technology, NY, United States of America

Dorfner Anzaplan GmbH, Hirschau, Germany

Fraunhofer-Institut für Silicatforschung, Würzburg, Germany

Glass Technology Services Ltd, Sheffield, South Yorkshire, United Kingdom

NSG, Lathom, United Kingdom

Schott AG, Mainz, Germany

Schott AG, Analytical Services, Mitterteich, Germany

SG Lab Analytics, Stevanato Group S.p.A., Padova, Italy

Stazione Sperimentale del Vetro, Murano, Italy

T. Şişe ve Cam Fab. A.Ş. Science and Technology Center, Gebze Kocaeli, Turkey

TU Bergakademie Freiberg, Institut für Keramik, Glas- und Baustofftechnik, Freiberg, Germany

Zentrum für Glas- und Umweltanalytik GmbH, Ilmenau, Germany

Statistical evaluation of the data

Bundesanstalt für Materialforschung und -prüfung (BAM), Berlin, Germany

3. Candidate material

The candidate material foreseen for CRM BAM-S053 was produced by Schott AG, Mitterteich, Germany. In total a batch of 2000 kg of borosilicate glass was produced. From this batch glass rods with 185 mm length and a diameter of 9 mm were produced. The approximate weight of one glass rod is 27.5 g.

4. Homogeneity testing

Homogeneity testing was done by Schott AG, Mainz following the procedure according to USP<660>. 15 samples out of the total batch were taken randomly and analysed twice. The results are given in Table 1, the results of the statistical evaluation (ANOVA) in Table 2. The required sample intake in ISO 720 and Ph.Eur. 3.2.1 is the same as in USP<660>, the measurement procedures are very similar. Therefore, the results of the homogeneity test are also valid for ISO 720 and Ph.Eur. 3.2.1. For ISO 719 the sample intake is only 2 g, therefore it is not possible to take the results obtained with USP<660>. Since no independent homogeneity data was available for the acid consumption obtained with the procedure described in ISO 719, this parameter was only given for information with an uncertainty contribution from inhomogeneity estimated from the available data.

Table 1: Homogeneity testing results for BAM-S053

		1	2	3	4	5	6	7	8
Consumption of HCl per g	mL	0.035	0.036	0.036	0.035	0.036	0.036	0.037	0.034
Consumption of HCl per g	mL	0.034	0.037	0.037	0.034	0.036	0.037	0.038	0.034
Consumption of HCl per g	mL	0.037	0.036	0.036	0.037	0.035	0.034	0.036	0.034
		9	10	11	12	13	14	15	
Consumption of HCl per g	mL	0.035	0.035	0.036	0.035	0.036	0.034	0.037	
Consumption of HCl per g	mL	0.035	0.037	0.037	0.037	0.035	0.034	0.038	
Consumption of HCl per g	mL	0.035	0.033	0.036	0.033	0.037	0.034	0.036	

Table 2: ANOVA of the data obtained from homogeneity testing

ANOVA						
Sample	Number	Sum	Mean	Variance		
1	2	0.071	0.0355	4.5E-06		
2	2	0.073	0.0365	5E-07		
3	2	0.073	0.0365	5E-07		
4	2	0.071	0.0355	4.5E-06		
5	2	0.071	0.0355	5E-07		
6	2	0.071	0.0355	4.5E-06		
7	2	0.074	0.037	0.000002		
8	2	0.068	0.034	0		
9	2	0.07	0.035	0		
10	2	0.07	0.035	8E-06		
11	2	0.073	0.0365	5E-07		
12	2	0.07	0.035	8E-06		
13	2	0.072	0.036	2E-06		
14	2	0.068	0.034	0		
15	2	0.074	0.037	0.000002		
			0.0356333			
Source of variation	sums of squares (SS)	degrees of freedom	Mean squares (MS)	F-value	P-value	critical F-value
Between groups	2.55E-05	14	1.819E-06	0.727619	0.721171	2.4243644
Within groups	3.75E-05	15	0.0000025			
Total	6.3E-05	29				
within-sd	0.00158			status:	homogeneous	
effective n	2.00					
s_bb	0					
s_bb_min	0.00068					
u_bb	0.00068					
u_bb(rel.)	1.895978					

Table 8 shows the results of the uncertainty determinations.

5. Characterisation study

5.1 Analytical methods

16 laboratories participated in the certification inter-laboratory comparison. The laboratories were asked to analyse six subsamples (three on Day 1 and three on Day 2). All laboratories followed the procedures given in the respective standards. Although the procedures were prescribed there were a few variations between the laboratories (see Table 3).

Table 3a: Analytical conditions for ISO 719 used by the participating laboratories

Lab-No.	Sample intake	T in ° C	Titrimetric standard	Accreditation
1	2 g	22	Na ₂ CO ₃	yes
2	2 g	22		yes
3	2 g	23	TRIS	yes
4	2 g	RT		no
5	2 g	RT		yes
6	2 g	20		no
7	2 g	25		yes
8	2 g	25		yes
9	2 g	24.5		no
10	2 g	22		no
11	2 g	21		yes
12	2 g	22.2		yes
13	2 g	21	Na ₂ CO ₃	no
14	2 g	23		yes
15	2 g	27		yes
16	2 g	22		no

Table 3b: Analytical conditions for ISO 720 used by the participating laboratories

Lab-No.	Sample intake	T in ° C	Titrimetric standard	Waiting time in min	Accreditation
2	10 g	22		15	yes
3	10 g	23	TRIS	25-30	yes
5	10 g	RT		< 60	yes
6	10 g	20		< 60	no
7	10 g	25		21	yes
8	10 g	24,5		30	yes
9	10 g	24.5		30	no
10	10 g	22		15	no
11	10 g	22	K-hydrogen phthalate	1.5-6.4	yes
14	10 g	23			yes
15	10 g	26/28		30	yes

Table 3c: Analytical conditions for USP <660> used by the participating laboratories

Lab-No.	Sample intake	T in ° C	Titrimetric standard	Waiting time in min	Accreditation
2	10 g	22		15	yes
3	10 g	23	TRIS	25-30	yes
5	10 g	RT		< 60	yes
7	10 g	25		21	yes
8	10 g	25		30	yes
9	10 g	24.5		30	no
10	10 g	22		15	no
11	10 g	22	K-hydrogen phthalate	1.5-6.6	yes
12	10 g	22.5		60	yes
14	10 g	RT		40	yes
15	10 g	26/24		62/45	yes

Table 3d: Analytical conditions for Ph.Eur. 3.2.1 used by the participating laboratories

Lab-No.	Sample intake	T in ° C	Titrimetric standard	Waiting time in min	Accreditation
2	10 g	22		15	yes
3	10 g	23	TRIS	25-30	yes
5	10 g	RT		< 60	yes
7	10 g	25		22	yes
8	10 g	25		30	yes
9	10 g	24.5		30	no
10	10 g	22		15	no
11	10 g	24	K-hydrogen phthalate	1.35-6.6	yes
12	10 g	22.5		60	yes
14	10 g	RT		40	yes
15	10 g	27/28		27/35	yes

5.2 Analytical results and statistical evaluation

The analytical results of the certification inter-laboratory comparison are listed in Tables 4 to 7. These tables show the single results (M_i) of each laboratory, the respective laboratories' mean values (M), absolute and relative intra-laboratory standard deviation (s and s_{rel} , respectively), the standard deviation of laboratory means (s_M), and in addition the square root of mean of variances of data sets under repeatability conditions (\bar{s}_i), where n is the number of accepted data sets. The continuous line marks the certified value (mean of the laboratories' means), the broken lines mark the standard deviation, calculated from the laboratories' means. Single results highlighted blue are obtained on Day 1, results highlighted green on Day 2. Results highlighted in yellow were removed after statistical outlier tests.

In the related figures for each laboratory its mean value and single standard deviation is given.

Table 4: Results for the determination of the hydrolytic resistance of borosilicate glass according to ISO 719

Lab./Meth.	11	13	5	9	15	10	3	6	4	16	8	14	7	12	2		
M_i [mL]	0.013	0.020	0.030	0.030	0.030	0.035	0.034	0.0444	0.050	0.040	0.044	0.050	0.0560	0.054	0.060		n 14
	0.015	0.030	0.030	0.030	0.030	0.036	0.036	0.0424	0.040	0.050	0.043	0.040	0.0460	0.055	0.060		
	0.012	0.020	0.020	0.030	0.030	0.038	0.036	0.0399	0.040	0.030	0.042	0.040	0.0460	0.061	0.060		
	0.016	0.020	0.020	0.028	0.030	0.030	0.036	0.0325	0.040	0.050	0.041	0.040	0.0560	0.048	0.080		
	0.017	0.020	0.020	0.028	0.030	0.034	0.038	0.0394	0.039	0.030	0.044	0.040	0.0460	0.047	0.080		
	0.013	0.020	0.020	0.032	0.030	0.032	0.038	0.0221	0.030	0.050	0.042	0.050	0.0560	0.049	0.080		
M [mL]	0.0143	0.0217	0.0240	0.0297	0.0300	0.0342	0.0363	0.0368	0.0398	0.0417	0.0427	0.0433	0.0510	0.0523	0.0700		0.0356
s [mL]	0.0020	0.0041	0.0055	0.0015	0.0000	0.0029	0.0015	0.0082	0.0063	0.0098	0.0012	0.0052	0.0055	0.0054	0.0110	s_M [mL]	0.0109
s_{rel}	0.137	0.188	0.228	0.051	0.000	0.084	0.041	0.224	0.159	0.236	0.028	0.119	0.107	0.102	0.156	\bar{s}_i [mL]	0.0050
																	0.305

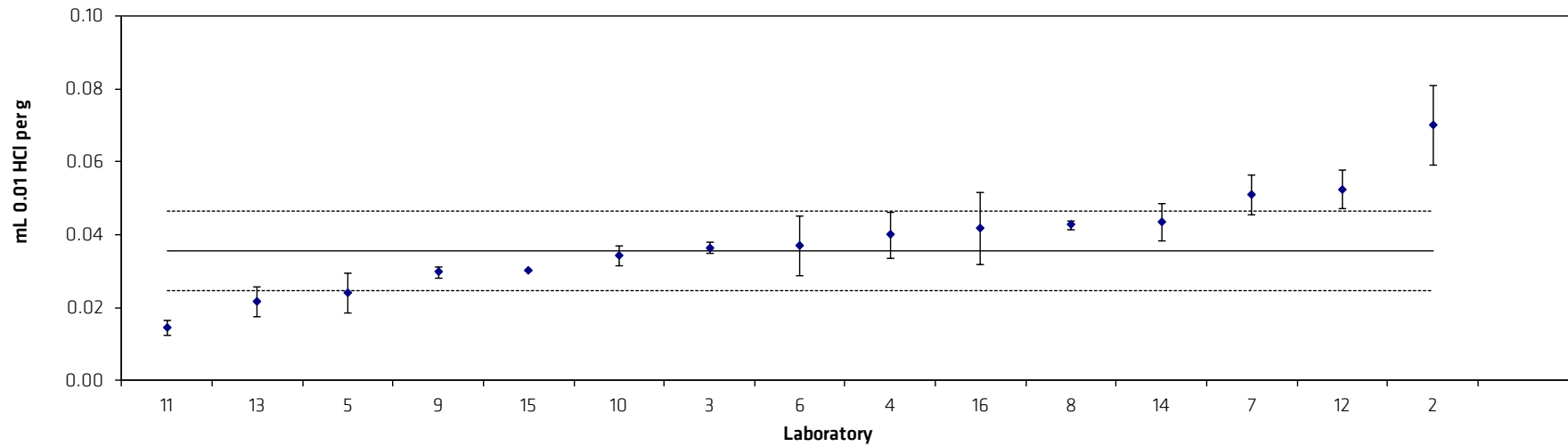


Table 5: Results for the determination of the hydrolytic resistance of borosilicate glass according to ISO 720

Lab./Meth.	9	3	8	6	10	15	14	5	2	11	7		
M_i [mL]	0.035	0.037	0.039	0.040	0.041	0.040	0.045	0.045	[0.058]	0.048	0.058		n 11
	0.035	0.037	0.038	0.042	0.041	0.039	0.042	0.044	0.046	0.046	0.053		
	0.039	0.036	0.040	0.040	0.040	0.042	0.043	0.045	0.046	0.045	0.050		
	0.035	0.039	0.039	0.040	0.040	0.042	0.044	0.044	0.044	0.045	0.048		
	0.037	0.039	0.039	0.039	0.040	0.040	0.044		0.044	0.048	0.046		
	0.037	0.038	0.039	0.039	0.042	0.042	0.043		0.044	0.044	0.048		
M [mL]	0.0363	0.0377	0.0390	0.0399	0.0407	0.0408	0.0435	0.0445	0.0448	0.0460	0.0505		0.0422
s [mL]	0.0016	0.0012	0.0006	0.0009	0.0008	0.0013	0.0010	0.0006	0.0011	0.0017	0.0044	s_M [mL]	0.0041
s_{rel}	0.045	0.032	0.016	0.023	0.020	0.033	0.024	0.013	0.024	0.036	0.087	\bar{s}_i [mL]	0.0017
													0.098

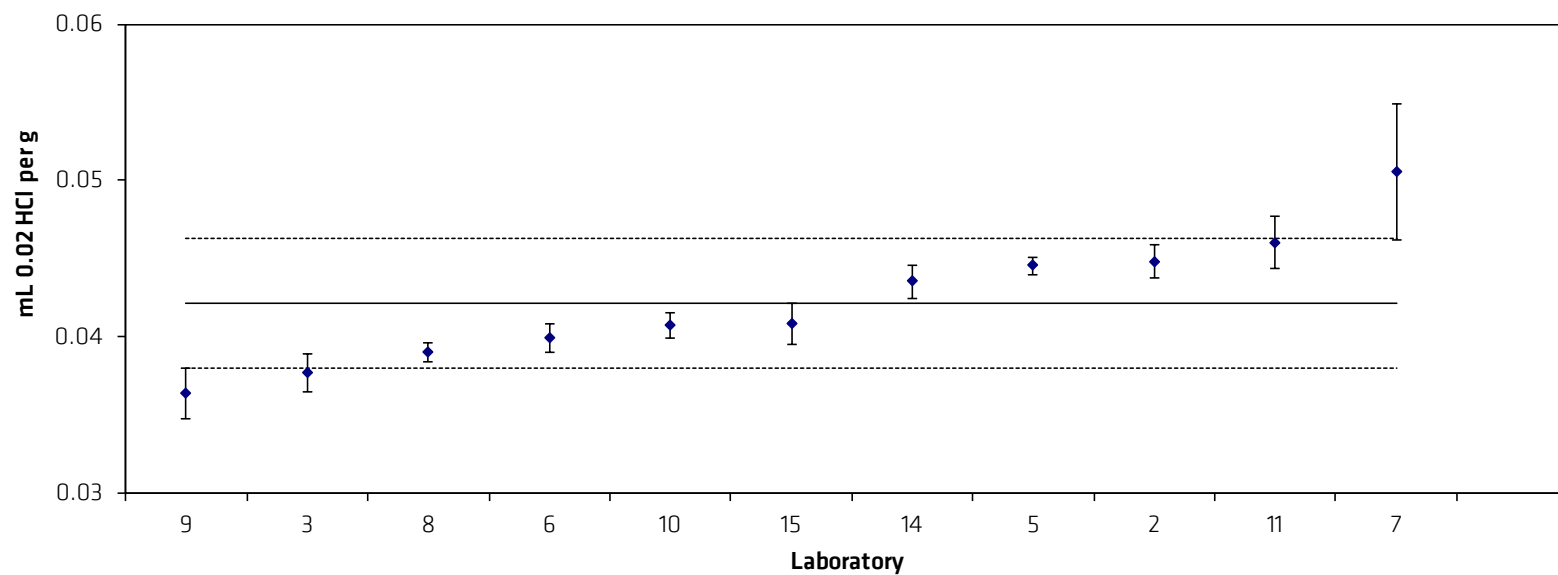


Table 6: Results for the determination of the hydrolytic resistance of borosilicate glass according to USP<660>

Lab./Meth.	9	3	8	12	15	14	5	7	2	10	11		
M_i [mL]	0.036	0.039	0.040	0.0412	0.039	0.044	0.045	0.046	[0.058]	0.045	0.046		n 11
	0.037	0.038	0.040	0.0410	0.040	0.042	0.044	0.044	0.046	0.045	0.050		
	0.038	0.036	0.040	0.0408	0.041	0.043	0.044	0.044	0.046	0.046	0.045		
	0.038	0.040	0.042	0.0419	0.045	0.044		0.043	0.044	0.050	0.047		
	0.039	0.038	0.042	0.0413	0.043	0.044		0.046	0.044	0.044	0.049		
	0.039	0.040	0.038	0.0412	0.044	0.043		0.044	0.044	0.050	0.046		
M [mL]	0.0378	0.0385	0.0403	0.0412	0.0420	0.0433	0.0443	0.0445	0.0448	0.0467	0.0472		0.0428
s [mL]	0.0012	0.0015	0.0015	0.0004	0.0024	0.0008	0.0006	0.0012	0.0011	0.0027	0.0019	s_M [mL]	0.0031
s_{rel}	0.031	0.039	0.037	0.009	0.056	0.019	0.013	0.028	0.024	0.057	0.041	\bar{s}_i [mL]	0.0015
													0.072

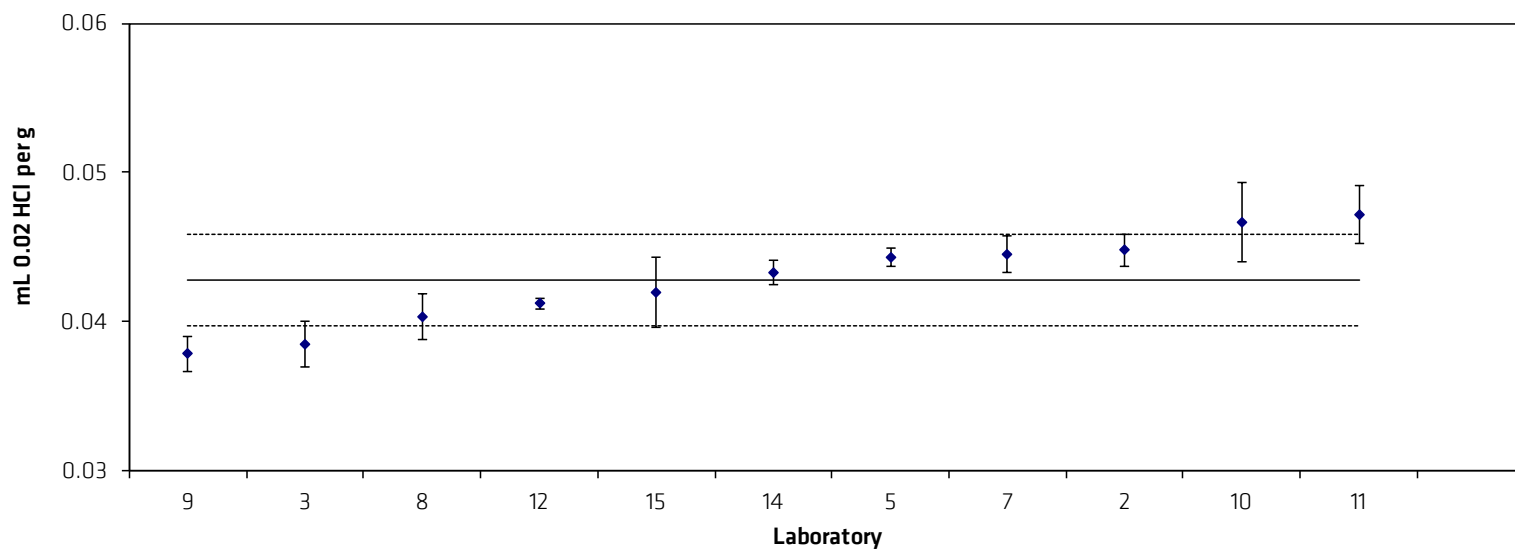
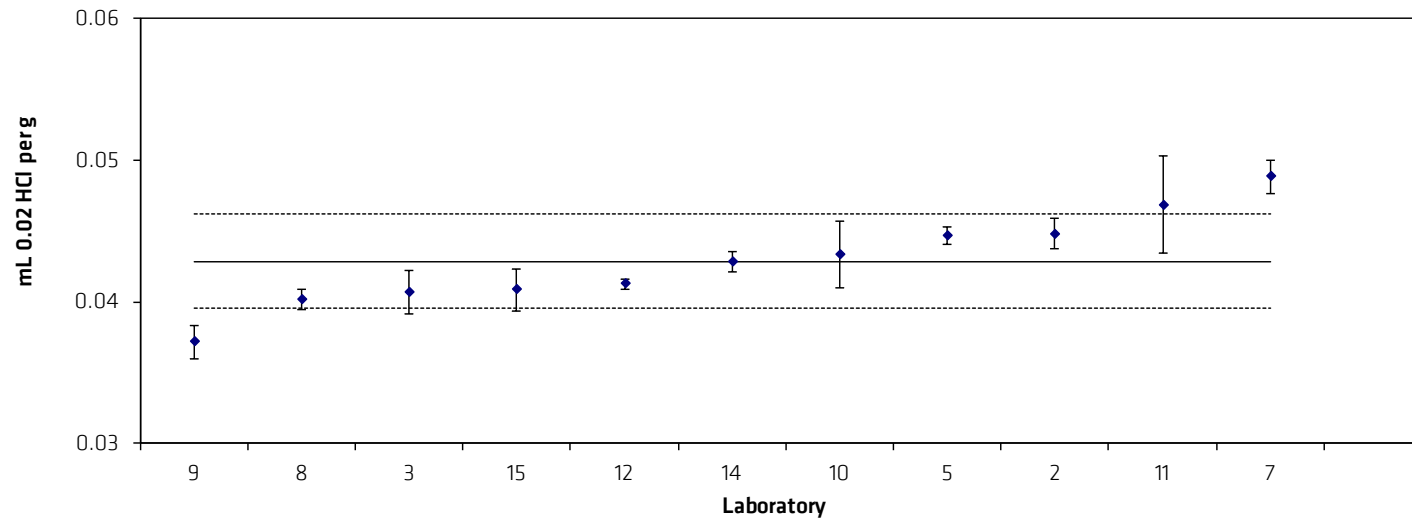


Table 7: Results for the determination of the hydrolytic resistance of borosilicate glass according to Ph.Eur. 3.2.1

Lab./Meth.	9	8	3	15	12	14	10	5	2	11	7		
M_i [mL]	0.037	0.040	0.039	0.039	0.0412	0.043	0.041	0.045	[0.058]	0.053	0.049		n 11
	0.038	0.041	0.039	0.039	0.0410	0.042	0.042	0.045	0.046	0.048	0.048		
	0.039	0.039	0.040	0.041	0.0408	0.043	0.046	0.044	0.046	0.046	0.048		
	0.037	0.040	0.042	0.042	0.0419	0.044	0.046		0.044	0.046	0.048		
	0.036	0.040	0.042	0.042	0.0413	0.042	0.041		0.044	0.043	0.049		
	0.036	0.041	0.042	0.042	0.0412	0.043	0.044		0.044	0.045	0.051		
M [mL]	0.0372	0.0402	0.0407	0.0408	0.0412	0.0428	0.0433	0.0447	0.0448	0.0468	0.0488		0.0429
s [mL]	0.0012	0.0008	0.0015	0.0015	0.0004	0.0008	0.0023	0.0006	0.0011	0.0034	0.0012	s_M [mL]	0.0033
s_{rel}	0.031	0.019	0.037	0.036	0.009	0.018	0.054	0.013	0.024	0.073	0.024	\bar{s}_i [mL]	0.0016
													0.077



The obtained data were evaluated statistically. Some of the datasets were removed on technical or statistical reasons. The certified values are calculated as mean values of the laboratories' means.

The resp. combined uncertainties were calculated from the spread resulting from the certification inter-laboratory comparison (u_{ilc}) and the uncertainty contribution (u_{hom}) from possible inhomogeneity of the material using Equation 3.

$$u_{combined} = \sqrt{u_{ilc}^2 + u_{hom}^2} \quad (3)$$

with

$$u_{ilc} = \sqrt{\frac{s_M^2}{n}} : \text{uncertainty contribution resulting from inter-laboratory comparison}$$

n : number of data sets used for calculating the certified mass fraction of each element

Table 8: Uncertainty calculation

	M	n	s_M	u_{hom}	$u_{combined}$	U
ISO 720	0.0422	11	0.0041	0.00080	0.0015	0.00295
USP	0.0428	11	0.0031	0.00081	0.0012	0.00248
Ph.Eur.	0.0429	11	0.0033	0.00081	0.0013	0.00257
ISO 719	0.0356	14	0.0109	0.00067	0.0030	0.00598

The expanded uncertainties U are calculated by multiplication of $u_{combined}$ with a coverage factor of $k = 2$ using Equation 4.

$$U = k \cdot u_{combined} \quad (4)$$

The calculated mass fractions and their resp. expanded uncertainties are given on Page 3 of this report. Rounding was done according to DIN 1333 [8].

7. Instructions for users and stability statement

The Reference Material is available in the form of glass rods (length: 185 mm, diameter: 9 mm, weight: 27.5 g). It is intended for quality control. According to ISO 719 the minimum sample intake is 2 g. For USP<660>, Ph.Eur. 3.2.1, and ISO 720 a minimum sample intake of 10 g is required. Before use, the surface of the material should be cleaned carefully.

One unit of BAM-S053 consists of ca. 2 kg of glass rods (ca. 73 rods).

The material will remain stable if it is not subjected to excessive heat or glass corrosive atmosphere. It has to be stored in a dry and clean environment at room temperature. Transport under normal ambient conditions.

8. Metrological Traceability

To ensure traceability of the certified mass fractions to the SI (Système International d'Unités) the acid used for titration was measured against pure substances for establishing the titration factor.

9. Information on and purchase of the CRM

Certified reference material BAM-S053 is supplied by

Bundesanstalt für Materialforschung und -prüfung (BAM)

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Each unit will be distributed together with a detailed certificate containing the certified values and their uncertainties, the mean values and standard deviations of all accepted data sets and the names of the participating laboratories.

Information on certified reference materials can be obtained from BAM, <https://www.bam.de>.

10. References

- [1] ISO 719:1985, Glass - Hydrolytic resistance of glass grains at 98 degrees C -- Method of test and classification
- [2] ISO 720:1985, Glass - Hydrolytic resistance of glass grains at 121 degrees C -- Method of test and classification
- [3] The United States Pharmacopeia USP 41 NF36 First Supplement; <660> Containers - Glass: Hydrolytic Resistance, Glass Grains Test - 2018-08
- [4] EUROPEAN PHARMACOPOEIA 9.5. 3.2.1. Glass containers for pharmaceutical use, Hydrolytic resistance, Test B: Glass Grains Test; 2018-07
- [5] ISO 17034, General requirements for the competence of reference material producers, 2016
- [6] ISO Guide 31, Reference materials - Contents of certificates, labels and accompanying documentation, 2015
- [7] ISO Guide 35, Reference materials - General and statistical principles for certification. Third edition, 2006
- [8] DIN 1333:1992-02 Zahlenangaben