Snibe Diagnostic

CE REF 130265006M:100 tests/kit
130665006M: 50 tests/kit
130765006M: 30 tests/kit

MAGLUMI® EBV NA IgG (CLIA)

INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the qualitative determination of EBV NA IgG in human serum and plasma using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer and Biolumi series Integrated System, and the assay is used for an aid in the diagnosis of EB viral infection.

SUMMARY

Epstein-Barr virus (EBV) is an enveloped herpes virus with a 172-kb double-stranded DNA genome, and over 95% of the adult population worldwide are EBV seropositive[1]. In most cases primary infection occurs subclinically during childhood, often by spread between family members via salivary contact[2]. EBV targets oral epithelial cells and B cells, and the CD21 receptor of the B lymphocyte allows the EBV to enter the cell, being able to efficiently induce blast transformation and uncontrolled proliferation of infected B lymphocytes[1,3].

EBV is implicated in the pathogenesis of infectious mononucleosis (IM), Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma (NPC), gastric cancer, and a myriad of malignancies in individuals with inherited or acquired immunodeficiency[4,5]. Primary EBV infections whether or not accompanied by clinical signs of IM lead to the appearance of antibodies to various EBV-specific antigens[6],and antibodies to EBV nuclear antigen-1 (EBNA-1) and EA have also been found to be most complementary in detecting primary NPC[7].

Antibodies against the lytic antigens, viral capsid antigen (VCA) and early antigen (EA) can be demonstrated from as early as the third week of infection. Antibodies against the latent antigen, EBNA, usually only appear 1 to 6 months after primary infection (in the convalescent phase) or as part of the latency profiles of the various malignancies associated with EBV infection[8]. The main antibodies tested include immunoglobulin M (IgM) and IgG antibodies against the viral capsid antigen (VCA), IgG antibody against the nuclear antigen (NA), and IgG antibody against early antigen (EA)[9]. The determination of IgG antibodies to EBV-associated antigens is of diagnostic importance for infectious mononucleosis and EBV-associated tumors, as well as for the recognition of reactivation of latent EBV infection in patients with tumors and other diseases not related to EBV[10]. In general, it is not always necessary to definitively diagnose a cause for infectious mononucleosis, but specific antibody tests are available[11].

Using only three parameters (EBV VCA IgG, EBV VCA IgM and EBV NA IgG), it is generally easy to distinguish acute and past infections in immunocompetent patients, the presence of EBV VCA IgG and EBV VCA IgM in the absence of EBV NA IgG indicates acute infection, and the presence of EBV VCA IgG and EBV NA IgG in the absence of EBV VCA IgM is typical of past infection[12].

In EB NA IgG assays, it is important to point out that more sensitivity for detecting antibodies implies a greater ability to identify past infections (more specificity for identifying primary recent infection). More specificity for detecting EB NA IgG is related to an increased ability to identify primary recent infection (more sensitivity for this clinical classification)[13].

TEST PRINCIPLE

Indirect chemiluminescence immunoassay.

The sample, diluent, buffer, magnetic microbeads coated with EBV NA are mixed thoroughly and incubated, performing a wash cycle after a precipitation in a magnetic field. ABEI labeled with anti-human IgG antibody are then added and incubated, reacting to form immuno-complexes. After precipitation in a magnetic field, the supernatant is decanted and then a wash cycle is performed. Subsequently, the Starter 1+2 are added to initiate a chemiluminescent reaction. The light signal is measured by a photomultiplier as relative light units (RLUs), which is proportional to the concentration of EBV NA IgG present in the sample.

REAGENTS

Kit Contents

Component	Description	100 tests/kit	50 tests/kit	30 tests/kit
Magnetic Microbeads	Magnetic microbeads coated with EBV NA (~5.00 μg/mL) in PBS buffer, NaN_3 (<0.1%).	2.5 mL	1.5 mL	1.0 mL
Calibrator Low	A low concentration of EBV NA IgG in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
Calibrator High	A high concentration of EBV NA IgG in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
Buffer	BSA, NaN_3 (<0.1%).	12.5 mL	7.0 mL	4.8 mL
ABEI Label	ABEI labeled with anti-human IgG antibody (~5.00 ng/mL) in Tris-HCl buffer, NaN_3 (<0.1%).	12.5 mL	7.0 mL	4.8 mL
Diluent	BSA, NaN_3 (<0.1%).	25.0 mL	13.5 mL	8.0 mL
Negative Control	PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
Positive Control	A high concentration of EBV NA IgG (7.50 AU/mL) in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
All reagents are provided ready-to-use.				

Warnings and Precautions

- For *in vitro* diagnostic use.
- For professional use only.
- Exercise the normal precautions required for handling all laboratory reagents.
- Personal protective measures should be taken to prevent any part of the human body from contacting samples, reagents, and controls, and should comply with local operating requirements for the assay.
- A skillful technique and strict adherence to the package insert are necessary to obtain reliable results.
- Do not use kit beyond the expiration date indicated on the label.
- Do not interchange reagent components from different reagents or lots.
- Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).
- All waste associated with biological samples, biological reagents and disposable materials used for the assay should be considered potentially infectious and should be disposed of in accordance with local guidelines.
- This product contains sodium azide. Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after disposal, flush with a large volume of water to prevent azide build-up. For additional information, see Safety Data Sheets available for professional user on request.

Note: If any serious incident has occurred in relation to the device, please report to Shenzhen New Industries Biomedical Engineering Co., Ltd. (Snibe) or our authorized representative and the competent authority of the Member State in which you are established.

Reagent Handling

- To avoid contamination, wear clean gloves when operating with a reagent kit and sample. When handling reagent kit, replace the gloves that have been in contact with samples, since introduction of samples will result in unreliable results.
- Do not use kit in malfunction conditions; e.g., the kit leaking at the sealing film or elsewhere, obviously turbid or precipitation is found in reagents (except for Magnetic Microbeads) or control value is out of the specified range repeatedly. When kit in malfunction conditions, please contact Snibe or our authorized distributor.
- To avoid evaporation of the liquid in the opened reagent kits in refrigerator, it is recommended that the opened reagent kits to be sealed with reagent seals contained within the packaging. The reagent seals are single use, and if more seals are needed, please contact Snibe or our authorized distributor.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.
- Use always the same analyzer for an opened reagent integral.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- For further information about the reagent handing during system operation, please refer to Analyzer Operating Instructions.

Storage and Stability

- Do not freeze the integral reagents.
- Store the reagent kit upright to ensure complete availability of the magnetic microbeads.
- Protect from direct sunlight.

Stability of the Reagents	
Unopened at 2-8°C	until the stated expiration date

Opened at 2-8°C	6 weeks
On-board	4 weeks

Stability of Controls	
Unopened at 2-8°C	until the stated expiration date
Opened at 10-30°C	6 hours
Opened at 2-8°C	6 weeks
Frozen at -20°C	3 months
Frozen and thawed cycles	no more than 3 times

SPECIMEN COLLECTION AND PREPARATION

Specimen Types

Only the specimens listed below were tested and found acceptable.

Specimen Types	**Collection Tubes**
Serum	Tubes without additive/accessory, or tubes containing clot activator or clot activator with gel.
Plasma	K2-EDTA, Na-heparin or Li-heparin

- The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. Follow tube manufacturers' instructions carefully when using collection tubes.

Specimen Conditions

- Do not use heat-inactivated samples or grossly hemolyzed/hyperlipidaemia specimens and specimens with obvious microbial contamination.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some serum specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the serum specimen is centrifuged before a complete clotting, the presence of fibrin may cause erroneous results.
- Samples must be free of fibrin and other particulate matter.
- To prevent cross contamination, use of disposable pipettes or pipette tips are recommended.

Preparation for Analysis

- Inspect all specimens for foam. Remove foam with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.
- Frozen specimens must be completely thawed before mixing. Mix thawed specimens thoroughly by low speed vortexing or by gently inverting. Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous. If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Specimens should be free of fibrin, red blood cells, or other particulate matter. Such specimens may give reliable results and must be centrifuged prior to testing. Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- The sample volume required for a single determination of this assay is 10 µL.

Specimen Storage

Specimens removed from the separator, red blood cells or clot may be stored up to 3 days at 10-30°C or 14 days at 2-8°C, or 6 months frozen at -20°C. Frozen specimens subjected to up to 5 freeze/thaw cycles have been evaluated.

Specimen Shipping

- Package and label specimens in compliance with applicable local regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

EBV NA IgG (CLIA) assay, control barcode labels.

Materials Required (But Not Provided)

- General laboratory equipment.
- Fully-auto chemiluminescence immunoassay analyzer Maglumi 600, Maglumi 800, Maglumi 1000, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000, Maglumi 4000 Plus, MAGLUMI X8, MAGLUMI X3, MAGLUMI X6 or Integrated System Biolumi 8000, Biolumi CX8.
- Additional accessories of test required for the above analyzers include Reaction Module, Starter 1+2, Wash Concentrate, Light Check, Tip, and Reaction Cup. Specific accessories and accessories' specification for each model refer to corresponding Analyzer Operating Instructions.
- Please use accessories specified by Snibe to ensure the reliability of the test results.

Assay Procedure

Preparation of the Reagent

- Take the reagent kit out of the box and visually inspect the integral vials for leaking at the sealing film or elsewhere. If there is no leakage, please tear off the sealing film carefully.
- Open the reagent area door; hold the reagent handle to get the RFID label close to the RFID reader (for about 2s); the buzzer will beep; one beep sound indicates successful sensing.
- Keeping the reagent straight insert to the bottom along the blank reagent track.
- Observe whether the reagent information is displayed successfully in the software interface, otherwise repeat the above two steps.
- Resuspension of the magnetic microbeads takes place automatically when the kit is loaded successfully, ensuring the magnetic microbeads are totally resuspended homogenous prior to use.

Assay Calibration

- Select the assay to be calibrated and execute calibration operation in reagent area interface. For specific information on ordering calibrations, refer to the calibration section of Analyzer Operating Instructions.
- Execute recalibration according to the calibration interval required in this package insert.

Quality Control

- When new lot used, check or edit the quality control information.
- Scan the control barcode, choose corresponding quality control information and execute testing. For specific information on ordering quality controls, refer to the quality control section of the Analyzer Operating Instructions.

Sample Testing

- After successfully loading the sample, select the sample in interface and edit the assay for the sample to be tested and execute testing. For specific information on ordering patient specimens, refer to the sample ordering section of the Analyzer Operating Instructions.

To ensure proper test performance, strictly adhere to Analyzer Operating Instructions.

Calibration

Traceability: This method has been standardized against the Snibe internal reference standard.

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the master curve.

Recalibration is recommended as follows:

- Whenever a new lot of Reagent or Starter 1+2 is used.
- Every 28 days.
- The analyzer has been serviced.
- Control values lie outside the specified range.

Quality Control

Controls are recommended for the determination of quality control requirements for this assay and should be run in singlicate to monitor the assay performance. Refer to published guidelines for general quality control recommendations, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24 or other published guidelines[14]

Quality control is recommended once per day of use, or in accordance with local regulations or accreditation requirements and your laboratory's quality control procedures, quality control could be performed by running the EBV NA IgG assay:

- Whenever the kit is calibrated.
- Whenever a new lot of Starter 1+2 or Wash Concentrate is used.

Controls are only applicable with MAGLUMI and Biolumi systems and only used matching with the same top eight LOT numbers of corresponding reagents. For each target value and range refer to the label.

The performance of other controls should be evaluated for compatibility with this assay before they are used. Appropriate value ranges should be established for all quality control materials used.

Control values must lie within the specified range, whenever one of the controls lies outside the specified range, calibration should be repeated and controls retested. If control values lie repeatedly outside the predefined ranges after successful calibration, patient results must not be reported and take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the package insert.
- If necessary, contact Snibe or our authorized distributors for assistance.

If the controls in kit are not enough for use, please order EBV NA IgG (CLIA) Controls (REF: 1602011002MT) from Snibe or our authorized distributors for more.

RESULTS

Calculation

The analyzer automatically calculates the EBV NA IgG concentration in each sample by means of a calibration curve which is generated by a 2-point calibration master curve procedure. The results are expressed in AU/mL. For further information please refer to the Analyzer Operating Instructions.

Interpretation of Results

The expected results for the EBV NA IgG assay was obtained by testing 230 EBV NA IgG positive patients and 660 EBV NA IgG negative people in China, gave the following expected value by ROC curve:

- Non-reactive: A result less than 4.00 AU/mL (<4.00 AU/mL) is considered to be negative.
- Reactive: A result greater than or equal to 4.00 AU/mL (≥4.00 AU/mL) is considered to be positive.

Results may differ between laboratories due to variations in population and test method. It is recommended that each laboratory establish its own reference interval. Clinical interpretation requires knowledge of the patient's medical history and clinical condition (signs and symptoms), as well as other diagnostic results including presence or absence of antibodies against VCA IgM and VCA IgG utilizing the MAGLUMI® EBV VCA IgM (CLIA) and MAGLUMI® EBV VCA IgG (CLIA) immunoassays.

Although EBV serodiagnosis requires measurement of more than one analyte, universal agreement of a serological profile does not exist. Nonreactive results do not rule out the diagnosis of IM. The specimen may have been drawn before appearance of detectable antibodies. Nonreactive results in suspected early IM infection should be retested in 4–5 weeks. A serological profile used for diagnostic interpretation is shown below:

EBV VCA IgM	EBV VCA IgG	EBV NA IgG	Infection Stage
-	-	-	No Infection
+	-	-	Early phase acute primary infection
+	+	-	Acute primary infection
+	+	+	Transient infection
-	+	+	Past Infection
-	+	-	Isolated VCA IgG
-	-	+	Isolated NA IgG

LIMITATIONS

- Results should be used in conjunction with patient's medical history, clinical examination and other findings.
- If the EBV NA IgG results are inconsistent with clinical evidence, additional testing is needed to confirm the result.
- The presence of IgG antibodies in a single specimen is not sufficient to distinguish between active or past infection. For infection stage determination, results of the EBV NA IgG should be used in conjunction with the results of the EBV VCA IgM and the EBV VCA IgG. Caution should be used if interpreting a profile using more than one manufacturer's kits or different assay methods.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies[15,16]. Additional information may be required for diagnosis.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or animal serum products can be prone to this interference and anomalous values may be observed[17].
- Bacterial contamination or heat inactivation of the specimens may affect the test results.

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

Precision

Precision was determined using the assay, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): duplicates at two independent runs per day for 5 days at three different sites using three lots of reagent kits (n = 180). The following results were obtained:

Sample	Mean (AU/mL) (n=180)	Within-Run		Between-Run		Reproducibility	
		SD (AU/mL)	%CV	SD (AU/mL)	%CV	SD (AU/mL)	%CV
Serum Pool 1	1.495	NA	NA	NA	NA	NA	NA
Serum Pool 2	6.299	0.218	3.46	0.134	2.13	0.305	4.84
Serum Pool 3	12.158	0.399	3.28	0.105	0.86	0.581	4.78
Plasma Pool 1	1.506	NA	NA	NA	NA	NA	NA
Plasma Pool 2	6.031	0.169	2.80	0.141	2.34	0.288	4.78
Plasma Pool 3	12.179	0.380	3.12	0.145	1.19	0.482	3.96
Negative Control	0.504	NA	NA	NA	NA	NA	NA
Positive Control	7.290	0.217	2.98	0.111	1.52	0.398	5.46

Analytical Specificity

Interference

Interference was determined using the assay, three samples containing different concentrations of analyte were spiked with potential endogenous and exogenous interferents in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

Interference	No interference up to	Interference	No interference up to
Hemoglobin	1500 mg/dL	Heparin lithium salt	80 IU/mL
Intralipid	3000 mg/dL	Biotin	0.5 mg/dL
Bilirubin	50 mg/dL	Ribavirin	2 mg/mL
HAMA	40 ng/mL	Acyclovir	6.6 mg/dL
ANA	398 AU/mL	Interferon α	15000 IU/mL
Rheumatoid factor	2000 IU/mL	Levamisole	1.5 mg/mL
Human albumin	12 g/dL	Acetylsalicylic acid	0.65 mg/mL
Systemic Lupus Erythematosus Plasma	/	Ibuprofen	50 mg/dL
K2-EDTA	22.75 μmol/mL	Methylcobalamin	50 μg/mL
Heparin sodium salt	80 IU/mL	Ganciclovir	1000 μg/mL

Cross-Reactivity

The assay is highly specific for EBV NA IgG antibodies, with no observed cross-reactivity to Toxo IgG, CMV IgG, HSV-1 IgG, HSV-2 IgG, HHV-6 IgG, HHV-7 IgG, HHV-8 IgG, Rubella IgG, Anti-HAV IgG, Anti-HBs, HBeAb IgG, HBcAb IgG, Anti-HCV, Anti-HIV, Anti-Treponema pallidum, EBV EA IgG, EBV VCA IgG, EBV VCA IgM, EBV VCA IgA, EBV EA IgA, *M.Pneumoniae* IgG, *C.Pneumoniae* IgG, Parvovirus B19 IgG, VZV IgG, Influenza A virus IgG, Influenza B virus IgG, Adenovirus IgG and CVB IgG.

High-Dose Hook

No high-dose hook effect was seen for EBV NA IgG concentrations up to 5000 AU/mL.

Clinical Sensitivity

The clinical sensitivity of the EBV NA IgG assay was determined in China by testing 166 samples collected from expected positive population with commercial assay confirmation of EBV NA IgG positive result.

N of samples	Reactive	Sensitivity	95% CI
166	164	98.80%	97.14%-100.00%

Clinical Specificity

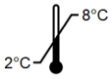
The clinical specificity of the EBV NA IgG assay was determined in China by testing 134 samples collected from expected negative population with commercial assay confirmation of EBV NA IgG negative result.

N of samples	Non-reactive	Specificity	95% CI
134	133	99.25%	97.80%-100.00%

REFERENCES

1. Bollard C M, Cooper L J, Heslop H E. Immunotherapy targeting EBV-expressing lymphoproliferative diseases[J]. Best Practice & Research Clinical Haematology, 2008, 21(3): 405–420.
2. Macsween K F, Crawford D H. Epstein-Barr virus—recent advances[J]. The Lancet Infectious Diseases, 2003, 3(3): 131–140.
3. Dolcetti R. B lymphocytes and Epstein–Barr virus: The lesson of post-transplant lymphoproliferative disorders[J]. Autoimmunity Reviews, 2007, 7(2): 96–101.
4. Dunmire S K, Verghese P S, Balfour H H. Primary Epstein-Barr virus infection[J]. Journal of Clinical Virology, 2018, 102: 84–92.
5. Perri F, Scarpati G D V, Giuliano M, et al. Epstein–Barr virus infection and nasopharyngeal carcinoma: the other side of the coin[J]. Anti-cancer drugs, 2015, 26(10): 1017-1025.
6. Färber I, Wutzler P, Wohlrabe P, et al. Serological diagnosis of infectious mononucleosis using three anti-Epstein-Barr virus recombinant ELISAs[J]. Journal of Virological Methods, 1993, 42(2–3): 301–307.
7. Chang K-P, Hsu C-L, Chang Y-L, et al. Complementary serum test of antibodies to Epstein-Barr virus nuclear antigen-1 and early antigen: A possible alternative for primary screening of nasopharyngeal carcinoma[J]. Oral Oncology, 2008, 44(8): 784–792.
8. Korsman S N J, Van Zyl G, Preiser W, et al. Virology E-Book: An Illustrated Colour Text[M]. Elsevier Health Sciences, 2012: 59
9. Ceraulo A S, Bytomski J R. Infectious Mononucleosis Management in Athletes[J]. Clinics in Sports Medicine, 2019, 38(4): 555–561.
10. Dölken G, Weitzmann U, Boldt C, et al. Enzyme-linked immunosorbent assay for IgG antibodies to Epstein-Barr virus-associated early antigens and viral capsid antigen[J]. Journal of Immunological Methods, 1984, 67(2): 225–233.
11. Lennon P, Crotty M, Fenton J E. Infectious mononucleosis[J]. BMJ, 2015, 350.
12. MD Paschale, Clerici P . Serological diagnosis of Epstein-Barr virus infection: Problems and solutions[J]. World Journal of Virology, 2012, 1(1):31-43.
13. de Ory F, Guisasola M E, Sanz J C, et al. Evaluation of Four Commercial Systems for the Diagnosis of Epstein-Barr Virus Primary Infections[J]. Clinical and Vaccine Immunology, 2011, 18(3): 444–448.
14. CLSI. Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions. 4th ed. CLSI guideline C24. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
15. Robert W. Schroff, Kenneth A. Foon, Shannon M. Beatty, et al. Human Anti-Murine Immunoglobulin Responses in Patients Receiving Monoclonal Antibody Therapy[J]. Cancer Research, 1985, 45(2):879-85.
16. Primus F J, Kelley E A, Hansen H J, et al. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine monoclonal antibodies for diagnosis and therapy[J]. Clinical Chemistry, 1988, 34(2):261-264.
17. Boscato L M, Stuart M C. Heterophilic antibodies: a problem for all immunoassays. Clin Chem 1988;34(1):27-33.

SYMBOLS EXPLANATIONS

	Consult instructions for use		Manufacturer
	Temperature limit (Store at 2-8°C)		Use-by date
	Contains sufficient for<n> tests		Keep away from sunlight
	This way up	EC REP	Authorized representative in the European Community
IVD	*In vitro* diagnostic medical device	CONTENTS	Kit component
REF	Catalogue number	LOT	Batch code
CE	CE marking		

Shenzhen New Industries Biomedical Engineering Co., Ltd.
No.23, Jinxiu East Road, Pingshan District, 518122 Shenzhen, P.R. China
Tel: +86-755-21536601 Fax:+86-755-28292740

EC REP

Shanghai International Holding Corp. GmbH (Europe)
Eiffestrasse 80, 20537 Hamburg, Germany
Tel: +49-40-2513175 Fax: +49-40-255726