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PERFORMANCE COMPARISON OF VACUETTE® CAT SERUM SEPARATOR CLOT ACTIVATOR AND LH LITHIUM HEPARIN TUBES WITH TWO DIFFERENT GEL TYPES ON SIEMENS ATELLICA® ANALYZER – A BICENTRIC STUDY

POREĐENJE PERFORMANSI VACUETTE® CAT EPRUVETA ZA SERUM SA SEPARATOROM I AKTIVATOROM KOAGULACIJE I LH LITIJUM-HEPARINSKIH EPRUVETA SA DVA RAZLIČITA GELA NA SIEMENS ATELLICA® ANALIZATORU – BICENTRIČNA STUDIJA

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Summary

Background: Preanalytical errors are the most common laboratory errors and are often related to manual steps in blood sample collection and handling. Blood collection devices, particularly tube materials and separator gels, are important sources of preanalytical variability. VACUETTE® CAT serum separator tubes (SSTs) and LH lithium heparin plasma separator tubes (PSTs) recently transitioned from one separator gel formulation (Reference Gel B) to the other (Gel 2.0). To understand whether and how this change affects the analytical performance of routine clinical chemistry and immunochemistry testing, we have compared the performance of tubes containing Gel 2.0 with that of tubes containing Reference Gel B.

Methods: This bicentric, retrospective study was conducted at two clinical laboratories during two observation periods: one using VACUETTE® CAT SSTs and LH PSTs with Reference Gel B, and a subsequent period using tubes with Gel 2.0. Centrifugation conditions routinely applied in participating laboratories were not

Kratak sadržaj

Uvod: Preanalitičke greške predstavljaju najčešći izvor grešaka u laboratorijskoj medicini i u velikoj meri su povezane sa manuelnim postupcima tokom uzimanja, transporta i obrade uzoraka krvi. U tom kontekstu, uređaji za uzimanje krvi, a posebno materijali epruveta i separacioni gelovi, mogu značajno doprineti preanalitičkoj varijabilnosti. VACUETTE® CAT serumske epruvete sa separator gelom (SST) i LH litijum-heparinske plazma epruvete sa separator gelom (PST) nedavno su prešle sa jedne formulacije separator gela (Referentni Gel B) na novu formulaciju (Gel 2.0). U cilju procene da li i u kojoj meri ova izmena može uticati na analitičke performanse rutinskih testova kliničke hemije i imunohemije, sprovedeno je poređenje performansi epruveta koje sadrže Gel 2.0 sa performansama epruveta koje sadrže Referentni Gel B.

Metode: Ova bicentrična retrospektivna studija sprovedena je u dve kliničke laboratorije tokom dva uzastopna perioda posmatranja. U prvom periodu korišćene su VACUETTE®

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aligned with the manufacturer's Instructions for Use (IFU), which are considered binding. This deviation was locally validated and accepted for scientific purposes, reflecting routine practices in a real-world laboratory environment. Routine testing on the Siemens Atellica® Solution clinical chemistry and immunoassay system was evaluated. Equivalence was assessed using the nonparametric Hodges–Lehmann estimate of the median difference. Haemolysis index (H-index) categories were compared using Chi-squared testing. Stable patient populations and sufficient sample sizes were assumed.
Results: A total of 253261 serum and 161486 plasma results were analysed. No significant differences were observed between gel types for any analyte, confirming analytical equivalence. Haemolysis frequencies in 24025 serum and 10807 plasma samples were comparable between periods, with no significant differences detected.
Conclusion: Gel 2.0 demonstrated equivalent analytical performance and preanalytical quality to Reference Gel B. Its implementation did not result in analyte drift or increased haemolysis, supporting its safe use in routine laboratory testing.

Keywords: preanalytical errors, blood collection tubes, separator gel, performance equivalence, VACUETTE®, Siemens Atellica®

CAT SST i LH PST epruvete sa Referentnim Gelom B, dok su u narednom periodu korišćene epruvete sa Gelom 2.0. Uslovi centrifugiranja koji su rutinski primenjivani u laboratorijama učesnicama nisu bili u skladu sa proizvođačevim Uputstvom za upotrebu (IFU), koje se smatra obavezujućim. Međutim, ovo odstupanje bilo je lokalno validirano i prihvaćeno za potrebe naučne analize, kako bi se obuhvatili uslovi rutinske laboratorijske prakse u realnom okruženju. Procena je obuhvatila rutinsko testiranje na sistemu Siemens Atellica® Solution za biohemijska i imunohemijska određivanja. Ekvivalentnost je ispitana primenom neparametarske Hodges–Lehmann procene razlike medijana, dok su kategorije indeksa hemolize (H-indeks) upoređene hi-kvadrat testom. U analizi je pretpostavljena stabilnost ispitivanih populacija pacijenata i adekvatna veličina uzorka.
Rezultati: Ukupno je analizirano 253 261 rezultata analize seruma i 161 486 rezultata analize plazme. Nisu uočene značajne razlike između ispitivanih tipova gela ni za jedan analizirani analit, čime je potvrđena njihova analitička ekvivalentnost. Učestalost hemolize, procenjena u 24 025 uzoraka seruma i 10 807 uzoraka plazme, bila je uporediva između posmatranih perioda, bez statistički značajnih razlika.
Zaključak: Gel 2.0 pokazao je ekvivalentne analitičke performanse i uporediv preanalitički kvalitet u odnosu na Referentni Gel B. Njegova primena nije bila povezana sa sistematskim pomeranjem vrednosti analita niti sa povećanjem učestalosti hemolize, što podržava njegovu bezbednu i pouzdanu primenu u rutinskom laboratorijskom testiranju.

Ključne reči: preanalitičke greške, epruvete za uzimanje krvi, separator gel, ekvivalentnost performansi, VACUETTE®, Siemens Atellica®

Introduction

Preanalytical errors represent the most frequent category of laboratory errors, accounting for approximately 46–68% of all laboratory-related medical errors, up to nearly 97% in the most recent reports, and affecting as many as 1.52% of specimens (1, 2). The potential consequences of preanalytical errors in healthcare are of paramount importance, as they can significantly affect patient outcomes and healthcare systems. The majority of preanalytical errors originate from manual steps in sample collection and handling (3). Among the most important sources of preanalytical variability in routine laboratory practice is the quality and performance of blood collection devices (4).

Blood collection tubes are not passive containers; they contain various additives designed for specific purposes, e.g., anticoagulants, surfactants, lubricants for rubber stoppers, clot activators, and separator gels. They are presumed not to increase total error or affect assay performance in any other way. Still, they may potentially affect laboratory test results (5).

According to the level of potential risk that blood collection tubes pose to the patients, in the European Union, they are classified under the In Vitro Diagnostic Medical Devices (IVD) Regulation (EU) 2017/746 as Class A IVDs, based on Annex VIII, Chapter II, Rule 5(c) (6). They must have performance evidence appropriate to the intended purpose to obtain the CE (Conformité Européenne) mark. In the United States (US), they are categorised as Class II medical devices by the US Food and Drug Administration (FDA) Regulations, i.e., they require special controls to assure their safety and effectiveness (7). These controls include an FDA-guided procedure and post-market surveillance (8).

Manufacturers should validate blood collection tubes across various clinical environments and on key instrument platforms, and examine whether there is any bias or inaccuracy in test results, particularly for serum indices and analytes that tend to be unstable over time, as these factors are crucial for clinical decision-making (9). Moreover, any alteration to the contents of a blood collection tube, such as changes to the separator gel, clot activator, or anticoagulant, must also be validated. However,

Manufacturers cannot feasibly test the performance of their products across every analytical platform and with all possible analytes used in laboratory test portfolios (5). This limitation underscores why post-market studies conducted in routine clinical laboratories are crucial; they provide valuable evidence on how blood collection tubes perform across various settings.

Serum separator tubes (SSTs) and plasma separator tubes (PSTs) make sample handling easier and help lower the risk of contamination from cells. It is well established that separator materials can interact with hydrophobic analytes, especially drugs, thereby reducing their concentration (10, 11). Additionally, some studies have observed fragments of separator gel or oil droplets in separated serum, which can sometimes interfere with sample pipetting and cause physical disruption in solid-phase immunoassay systems (12).

VACUETTE® CAT Clot Activator SSTs and LH Lithium Heparin PSTs (Greiner Bio-One GmbH, Kremsmünster, Austria) are made of PET (polyethylene terephthalate). They are closed with a cap made of PE (polyethylene) and bromobutyl rubber. Additionally, VACUETTE® CAT SSTs are coated with micronised silica particles that activate clotting when the tubes are gently inverted. Both tubes are designed with a barrier gel at the bottom. This gel has a specific gravity property that, after centrifugation, allows it to position between the blood clot and the serum, that is, between sedimented cells and plasma. In fact, during centrifugation, the barrier gel moves upward to the serum-clot/cells-plasma interface, forming a stable barrier that separates the serum from fibrin and cells, and plasma from cells. This design allows direct aspiration of serum/plasma from the collection tube, eliminating the need to transfer it to another container.

The VACUETTE® CAT Clot Activator SSTs and LH Lithium Heparin PSTs, introduced to the market in 2024, are identifiable by the suffix »A« in their item number. They contain the new Gel 2.0, which replaces the previous »Reference gel B«. The older tubes can be identified by their item numbers, which do not include the suffix »A«.

We hypothesised that VACUETTE® CAT Clot Activator SSTs and LH Lithium Heparin PSTs with Gel 2.0 will demonstrate equivalent performance to tubes with Reference Gel B in routine clinical chemistry and immunochemistry testing. Our aim was therefore to evaluate the performance equivalence of two gel types in a retrospective analysis of two consecutive observation periods, each utilising one of the two gel types, within routine laboratory operations on the Atellica® Solution clinical chemistry and immunoassay system (Siemens Healthineers, Erlangen, Germany). During these two periods, we aimed to compare values of clinical chemistry and immunochemistry parameters, and the frequency of haemolysis index values.

Although the comparison is based on two distinct observation periods, we assume that if the sample sizes are sufficiently large and the patient population remains stable across both periods, the two independent data sets can be reliably compared (13). This approach allows us to evaluate whether the implementation of Gel 2.0 results in a measurable shift in analyte values or increases the frequency of haemolysis.

Materials and Methods

Study design

A retrospective bi-centric study was conducted at the Laboratorio Clinico Generale con Aree Specialistiche, IRCCS Ospedale Galeazzi Sant'Ambrogio, Milan, Italy (for VACUETTE® CAT Clot Activator SSTs) and at the medical laboratories of the Salzkammergut Klinikum at two of three locations – namely Bad Ischl and Gmunden (VACUETTE® LH Lithium Heparin PSTs). The results were retrieved from the respective Laboratory Information Systems for the two observation periods specified in *Table I*.

Subjects

This study used anonymised data from routine laboratory analyses performed as part of standard patient care in the emergency department and hospital wards. As no additional blood collection or patient intervention was required, and all data were retrospectively collected and de-identified, informed consent and ethical committee approval were not required, in accordance with the hospital regulations.

Table I Observation periods of the study.

Type of blood collection tube	Reference Gel B	Gel 2.0
VACUETTE® CAT Clot Activator SSTs	1 April–31 May 2025	1 October–30 November 2025
VACUETTE® LH Lithium Heparin PSTs	1–30 September 2024	1–31 March 2025

SSTs – serum separator tubes; PSTs – plasma separator tubes.

Materials

The details of the blood collection tubes and centrifugation conditions used during each observation period are summarised in *Table II*. Centrifugation conditions applied in the participating laboratories were not aligned with the manufacturer's Instructions for Use (IFU), which recommend 1800–2200 g for 10–15 minutes and are considered binding. Instead, locally established protocols were used, which had been previously validated within each laboratory. This deviation was accepted for scientific purposes to enable evaluation under routine, real-world laboratory conditions.

In each observation period, blood collections were performed with CE-marked VACUETTE® CAT Clot Activator SSTs and LH Lithium Heparin PSTs, according to the local venous blood collection protocol. They were handled in accordance with the local standard operating procedures. SSTs were transported to the laboratory by a pneumatic tube system in less than 20 minutes. PSTs in Bad Ischl were delivered to the laboratory exclusively by courier service, while in Gmunden, they were delivered by both the pneumatic tube system (~30%) and courier service (~70%), in approximately 10–20 minutes in both hospitals.

Within each observation period, results of routine clinical chemistry and immunochemistry parameter determinations, as well as index values for haemolysis, were collected. All measurements were made from primary tubes on the Atellica® Solution clinical chemistry and immunoassay system (Siemens Healthineers, Erlangen, Germany). The list of parameters tested during this study is provided in *Tables IV* and *VI*.

Table II Blood collection tubes used in the study.

Product Name	Tube size	Nominal volume	Item no.	Separator gel	Centrifugation condition*
VACUETTE® CAT Clot Activator SSTs	13x100	5 mL	456018	Reference gel B	2400 g /10 minutes
			456018A	Gel 2.0	
VACUETTE® LH Lithium Heparin PSTs	13x75	3.5 mL	454083	Reference gel B	3600 g /10 minutes (Bad Ischl)
			454083A	Gel 2.0	3200 g /10 minutes (Gmunden)

SSTs – serum separator tubes; PSTs – plasma separator tubes. *Stated centrifugation conditions are not recommended by the manufacturer's IFU (see Disclaimer). The manufacturer-recommended centrifugation conditions are 1800–2200 g / 10–15 minutes.

Table III Manufacturer's specified concentrations of haemoglobin (H index) for the semiquantitative scale for H-index on Atellica® Solution.

Semiquantitative scale	H index
	Hemoglobin (g/L)
0	≤0.10
1	0.11–1.30
2	1.31–2.49
3	2.50–4.99
4	5.00–7.49
5	7.50–9.99
6	≥10

Statistical analysis

All clinical chemistry and immunochemistry parameters in both observation periods were initially included in the statistical analyses. Statistical analyses were conducted to test the null hypothesis (H0) that there is no clinically significant difference between measurements obtained using blood collection tubes containing Reference Gel B and Gel 2.0, against the alternative hypothesis (H1) that a difference exists.

All analyses were unpaired and performed at the analyte level. Statistical procedures included robust, nonparametric methods suitable for skewed biomarker distributions (13). They incorporated analyte-specific acceptance criteria based on Reference Change Values (RCV) (14).

The Shapiro-Wilk test was used to test for significant deviations from normality. Since the values for all analysed parameters did not follow a normal distribution, the differences in median results between the two observation periods, when the Reference Gel B and Gel 2.0 were used, were evaluated using non-parametric tests. For each parameter in each observation period, the median, 95% confidence interval (CI) of the median, and sample size were provided.

Results were tested for equivalence using the nonparametric Hodges-Lehmann (HL) estimate of median difference (15). Two-sided confidence intervals (95% CI) for the HL estimate were obtained from the Wilcoxon rank-sum procedure. The HL median differences with 95% CI for the two tube types were compared with analyte-specific clinically acceptable deviation limits. These limits were defined a priori using modified, maximum allowable

RCV values. Namely, instead of using the actual analytical variation for calculation, the modification involved using the desirable analytical performance specification (APS) for imprecision based on biological variation. This approach was chosen because direct comparisons of samples collected from the same patients at different time periods were not performed. Therefore, the RCV equation used for calculation was:

z – 1.96 for the confidence interval 95%

$$RCV = z \times \sqrt{2} \times \sqrt{CVI^2 + CVA_des^2}$$

CV_I – within-subject biological variation

CV_{A_des} – desirable APS for imprecision based on biological variation defined as $CV_I / 2$

The sources of within-subject biological variation and the desirable APS for imprecision were the EFLM Biological Variation Database, Chemical Pathology Analytical Performance Specifications of the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP), and Ricos Database of Biological Variation (16–18).

If the entire 95% CI of the observed difference between the two tubes (calculated using the HL estimate) was greater than the analyte-specific RCV-based equivalence limit, it was classified as a clinically relevant difference. Equivalence limit was calculated using the median value of the observation period when the Reference gel B tubes were used as the reference, according to the formula:

Equivalence limit = ± (Median (Reference Gel B) x (RCV/100))

The required sample size to perform an HL-estimate of the median difference with a 95% confidence level and power ≥90% was estimated using the FAST tool, which simulates different scenarios to determine the number of samples needed for reliable results (19). For each analyte, the tool repeatedly mixed and matched real data to determine the typical difference between the two types of blood collection tubes. It then checked whether the results would likely fall within a range where the tubes could be considered similar, aiming for high confidence (95%) and a strong chance of detecting a true similarity (at least 90%).

If an analyte did not meet these standards using the FAST tool, a more detailed check was done using a full Wilcoxon/Hodges–Lehmann procedure (15, 20). Here, every simulated dataset was analysed using the Wilcoxon test to compute an exact Hodges-Lehmann confidence interval, ensuring the difference between tubes was definitely within the acceptable range. If a test still failed to meet the sample size and power requirements, it was not included in the final report. The occurrence of haemolysis was assessed by comparing Reference Gel B and Gel 2.0 blood collection tubes. Haemolysis was defined as a haemolysis (H) index of ≥1. The corresponding haemoglobin concentrations for each H index category, as specified by the manufacturer, are shown in *Table III*. The frequency of haemolysis was calculated as the percentage of samples with H≥1 out of the total number of collected samples. This frequency was compared between the two tubes containing the two different separator gels. A clinically acceptable difference between the two tube types was defined as <1%, according to the technical validation criteria set by the EFLM Working Group–Preanalytical Phase (9).

Statistical analysis was performed using R Studio, Version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

VACUETTE® CAT Serum Separator Clot Activator tubes

Clinical chemistry and immunochemistry

In total, 253261 measurements of clinical chemistry and immunochemistry parameters were conducted in both observation periods in VACUETTE® CAT Clot Activator SSTs, thereof 124335 measurements (49.1%) in observation period 1 with Reference Gel B, and 128926 (50.9%) in observation period 2 with Gel 2.0. During the observation periods, the results for 53 parameters were analysed using VACUETTE® CAT Clot Activator SSTs on the Atellica® Solution. Ten parameters (17-beta-estradiol, complement C3, complement C4, cortisol, digoxin, immunoglobulin A, immunoglobulin G, immunoglobulin M, and total and free prostate-specific antigen) were immediately excluded because there was insufficient data (fewer than 20 cases) available for this type of statistical analysis. Seven analytes (25(OH) Vitamin D, carcinoembionic antigen (CEA), free triiodothyronine (FT_3), free tyroxine (FT_4), folate, parathyroid hormone (PTH), and vitamin B12) had sample sizes below the HL-required thresholds for the 95% confidence level target for each observation period. However, even with the inadequate sample size, free thyroxine (FT_4), folate and vitamin B12 reached the power threshold of ≥90% to conclude equivalence. Consequently, it is anticipated that equivalence at the 95% confidence level for these three parameters would be demonstrated if the required sample size were attained in both observation periods. For CK-MB activity, ferritin, transferrin, vancomycin, and high-sensitivity cardiac troponin I (hs-cTnI), the program could not determine a suitable sample size. This means that the method could not reliably achieve the required equivalence power under the current settings or sample size, likely due to high data variability or

Table IV Equivalence assessment of median differences in the two observation periods in samples collected in VACUETTE® CAT Serum Separator Clot Activator tubes.

Parameter	Unit	Gel	Number of measurements	Required sample size	Median	95% CI of Median		Hodges-Lehmann median difference	95% CI of the difference[a]		RCV[b], %	Equivalence limit[d]	Equivalence assessment	Reached 95% confidence level and power ≥0.90?
						LL	UL		LL	UL				
ALP	U/L	B	492	170	73	71	77	0.0	-3.0	3.0	18.5	±13.5	Equivalent	yes
		2.0	593		72	69	74							
ALT	U/L	B	4644	210	22	21	22	-1.0	-2.0	-1.0	38.9	±8.6	Equivalent	yes
		2.0	4031		20	19	20							
AST	U/L	B	4662	190	25.5	25	26	-1.0	-1.0	0	26.6	±6.8	Equivalent	yes
		2.0	4054		25	24	25							
Albumin	g/L	B	1992	130	33.6	33.3	33.8	-0.2	-0.4	0.1	7.8	±2.6	Equivalent	yes
		2.0	2029		33.4	33.1	33.6							
Amylase	U/L	B	2415	330	58	57	60	-2.0	-4.0	-0.1	20.8	±12.0	Equivalent	yes
		2.0	1780		56	54	57							
CK	U/L	B	2842	350	110	104	116	-5.0	-10.0	0	43.6	±48.0	Equivalent	yes
		2.0	2899		105	100	112							
CK-MB	U/L	B	1281	NA	1.95	1.75	2.18	0.63	0.46	0.79	60.9[c]	±1.18	Equivalent	no
		2.0	1799		2.82	2.64	3.04							
CRP	mg/L	B	6195	150	33.5	32.3	34.9	0.5	-0.4	1.4	107.3	±35.9	Equivalent	yes
		2.0	6073		31.7	30.5	33.2							
Calcium	mmol/L	B	6583	1090	2.1	2.1	2.1	0.1	0.1	0.1	5.6	±0.1	Equivalent	yes
		2.0	6208		2.2	2.2	2.2							
Chloride	mmol/L	B	6693	130	106	106	106	-1.0	-1.0	-1.0	3.1	±3.3	Equivalent	yes
		2.0	7255		105	104	105							
Cholesterol	mmol/L	B	233	150	3.83	3.70	3.93	-0.08	-0.31	0.13	16.7	±0.64	Equivalent	yes
		2.0	261		3.78	3.574	3.98							
Cholinesterase	U/L	B	361	190	10652	10236	11070	722	258	1181	18.9[c]	±2014.3	Equivalent	yes
		2.0	404		11347	11000	11686							
Creatinine	µmol/L	B	7743	230	78.7	77.9	79.6	0.9	0	1.8	13.6	±10.7	Equivalent	yes
		2.0	7802		79.6	78.7	80.4							
Direct bilirubin	µmol/L	B	732	50	9.23	8.89	9.75	-0.51	-0.85	0	60.3	±5.57	Equivalent	yes
		2.0	704		9.06	8.72	9.58							
FT4	ng/L	B	88	950	11.6	11.1	12.6	0.68	-0.30	1.60	14.8	±1.7	Equivalent	no
		2.0	67		12.6	11.5	13.7							
Folate	µg/L	B	66	130	6.98	6.27	9.04	-0.12	-1.53	1.22	34.6	±2.41	Equivalent	no
		2.0	58		7.06	6.40	8.15							
GGT	U/L	B	3266	930	25	24	26	2.0	2.0	3.0	25.7	±6.4	Equivalent	yes
		2.0	2582		27	26	28							
Glucose	mmol/L	B	4809	90	5.6	5.6	5.6	0.1	0	0.1	14.6	±0.8	Equivalent	yes
		2.0	5315		5.6	5.6	5.7							
HDL cholesterol	mmol/L	B	231	110	1.16	1.11	1.22	0.02	-0.05	0.08	17.7	±0.21	Equivalent	yes
		2.0	258		1.16	1.14	1.22							
Iron	µmol/L	B	665	50	7.3	7.0	7.9	1.4	1.1	2.0	77.9	±5.7	Equivalent	yes
		2.0	512		9.1	8.6	9.5							

LDH	U/L	B	2642	790	228	223	232	-6.0	-11	-2.0	13.6	±31	Equivalent	yes
		2.0	2628		215	212	220							
Lipase	U/L	B	340	110	31	29	32	0	-3.0	2.0	23.5	±7.3	Equivalent	yes
		2.0	183		31	29	33							
Myoglobin	µg/L	B	617	150	50	46	53	4.0	0	7.0	43.0[c]	±21.5	Equivalent	yes
		2.0	785		54	52	57							
Magnesium	mmol/L	B	5130	70	0.78	0.78	0.79	0	0	0.01	8.4	±0.07	Equivalent	yes
		2.0	5134		0.79	0.79	0.79							
Inorganic phosphate	mmol/L	B	5202	50	1.10	1.10	1.13	0.02	0.02	0.02	23.9	±0.26	Equivalent	yes
		2.0	4939		1.12	1.12	1.15							
Potassium	mmol/L	B	8855	50	4.25	4.23	4.26	-0.03	-0.04	-0.02	12.1	±0.51	Equivalent	yes
		2.0	9314		4.22	4.21	4.23							
Procalcitonin	µg/L	B	1977	170	0.14	0.14	0.15	0	-0.01	0.01	60[d]	±0.08	Equivalent	yes
		2.0	1822		0.15	0.14	0.16							
Sodium	mmol/L	B	8769	50	141.5	141.5	141.6	-0.5	-0.5	-0.4	1.9	±2.6	Equivalent	yes
		2.0	9229		141.1	141.1	141.2							
TSH	mIU/L	B	275	130	1.55	1.35	1.76	-0.08	-0.28	0.10	55.0	±0.85	Equivalent	yes
		2.0	296		1.36	1.26	1.59							
Total bilirubin	µmol/L	B	2878	50	12.0	11.6	12.1	-0.5	-0.7	-0.2	62.4	±7.5	Equivalent	yes
		2.0	3009		11.6	11.3	11.8							
Total protein	g/L	B	1584	190	60	60	61	-1.1	-1.7	-0.5	8.0	±4.9	Equivalent	yes
		2.0	1861		59	59	60							
Triglycerides	mmol/L	B	229	50	1.08	0.96	1.17	0.11	0.01	0.20	61.2	±0.66	Equivalent	yes
		2.0	259		1.15	1.06	1.20							
Urea	mmol/L	B	6783	50	6.5	6.3	6.5	0	0	0.2	40.5	±2.6	Equivalent	yes
		2.0	6678		6.5	6.5	6.6							
Uric acid	µmol/L	B	273	90	333	317	351	0.6	-18.4	19.0	25.7	±85.6	Equivalent	yes
		2.0	458		331	317	341							
Vitamin B12	ng/L	B	67	570	447	373	514	-16.0	-90.0	59.0	22.2	±99.4	Equivalent	no
		2.0	49		407	353	503							
Hs-Troponin I	ng/L	B	986	NA	414.3	323.2	509.2	40.8	11.4	82.8	34.4	±142.3	Equivalent	no
		2.0	1181		638.9	525.8	753.3							

CI – confidence interval; LL – lower limit; UL – upper limit; RCV – maximum allowable
Reference Change Value, calculated as: $RCV = z \times \sqrt{2} \times \sqrt{CVI^2 + CVA_des^2}$
NA - the required equivalence power under the current settings or sample size could not be achieved, probably due to high variability of data or substantially different sub-populations
[a] Wilcoxon rank-sum test; [b] RCV calculated using CV_I and CV_A_des from the EFLM Biological Variation Database (16); [c] RCV calculated using CV_I and CV_A_des from Ricos Biological Variation Database (18); [d] Calculated as the percentage equal to the respective RCV of the median for the observation period 1 (when the VACUETTE® CAT Serum Separator Clot Activator tubes with the Reference Gel B were used): Equivalence limit = ± (Median (Reference Gel B) x (RCV/100)).

substantial differences across sub-populations. Even under these circumstances, existing data for CK-MB, vancomycin and hs-cTnI demonstrated equivalence. Finally, the 31 remaining clinical chemistry and immunochemistry parameters had an adequate sample size and power for the conducted statistical analysis. For all of those, the equivalence between the values obtained from blood collection tubes with Reference Gel B and Gel 2.0 was demonstrated. The results of statistical analysis data for each clinical chemistry and immunochemistry parameter included in the evaluation are listed in *Table IV*.

Haemolysis indices

The occurrence of H-indices within the two observation periods is presented in *Table V*. The frequency of any haemolysis (H-index≥1) was 0.96% (112/11725) with Reference Gel B tubes and 1.54% (190/12300) with Gel 2.0 tubes. Since the difference in haemolysis frequency was <1% (1.54–0.96 = 0.58%), this small difference in percentages is clinically irrelevant.

VACUETTE® LH Lithium Heparin Plasma Separator tubes

Clinical chemistry and immunochemistry

In total, 161486 measurements of clinical chemistry and immunochemistry parameters were conducted in both observation periods in VACUETTE® LH Lithium Heparin PSTs, thereof 76357 measurements (47.3%) in observation period 1 with Reference Gel B, and 85129 (52.7%) in observation period 2 with Gel 2.0. During the two observation periods, the results for 41 parameters were analysed in VACUETTE® LH Lithium Heparin PSTs using the Atellica® Solution.

Interleukin-6 was excluded from further analysis due to insufficient data availability (fewer than 20 observations). Five analytes (direct bilirubin, ethanol, magnesium, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and total human chorionic gonadotropin (total-hCG)) did not meet the HL sample size requirements for achieving a 95% confidence level in both observation periods. Despite the limited sample size, direct bilirubin, magnesium, NT-proBNP, and total-hCG achieved statistical power ≥90%, supporting equivalence. It is therefore anticipated that equivalence at the 95% confidence level would be demonstrated for these analytes if the required sample size were achieved. For parathyroid hormone (PTH) and high-sensitivity cardiac troponin I (hs-cTnI), the statistical model was unable to identify a suitable sample size, likely due to high data variability or substantial differences between sub-populations. Nevertheless, available data for hs-cTnI still supported the equivalence hypothesis. The remaining 33 clinical chemistry and immunochemistry parameters fulfilled both sample size and power requirements, and equivalence between blood collection tubes containing Reference Gel B and Gel 2.0 was demonstrated for all of them. The results of statistical analysis are listed in *Table VI*.

Table V Relative frequency of the occurrence of hemolytic samples in VACUETTE® CAT Serum Separator Clot Activator tubes in the two observation periods.

Semiquantitative scale	Haemolysis, N(%)	
	Reference Gel B	Gel 2.0
0	11613 (99.04)	12110 (98.46)
≥1	112 (0.96)	190 (1.54)
Total	11725 (100)	12300 (100)

N – number of samples

Table VI Equivalence assessment of median differences in the two observation periods in samples collected in VACUETTE® LH Lithium Heparin Plasma Separator tubes.

Parameter	Unit	Gel	Number of measurements	Required sample size	Median	95% CI of Median		Hodges-Lehmann median difference	95% CI of the difference[a]		RCV[b], %	Equivalence limit[c]	Equivalence assessment	Reached 95% confidence level and power ≥0.90?
						LL	UL		LL	UL				
ALP	U/L	B	3280	210	77	76	78	2	1	3	18.5	±14.3	Equivalent	yes
		2.0	3571		80	79	81							
ALT	U/L	B	3618	130	20	19	20	2	1	2	38.9	±7.8	Equivalent	yes
		2.0	3872		22	21	22							
AST	U/L	B	3552	310	19	18	19	2	2	3	26.6	±5.0	Equivalent	yes
		2.0	3779		20	20	21							
Albumin	g/L	B	974	230	36	36	37	-0.1	-0.6	0.5	7.8	±2.8	Equivalent	yes
		2.0	1084		36	36	37							
Amylase	U/L	B	909	530	58	56	61	4	2	7	20.8	±12.0	Equivalent	yes
		2.0	929		63	61	66							
CK	U/L	B	1319	150	74	71	79	3	-1	6	43.6	±32.3	Equivalent	yes
		2.0	1381		80	76	84							

CRP	mg/L	B	4608	210	11.0	10.2	12.2	-0.5	-0.8	0	107.3	±11.8	Equivalent	yes
		2.0	5011		8.7	8.0	9.4							
Calcium	mmol/L	B	3945	290	2.37	2.36	2.37	0.08	0.07	0.08	5.6	±0.1	Equivalent	yes
		2.0	4347		2.44	2.44	2.45							
Chloride	mmol/L	B	3107	110	107	107	107	-1	-1	-1	3.1	±3.3	Equivalent	yes
		2.0	3450		107	106	107							
Cholesterol	mmol/L	B	2174	170	4.32	4.27	3.40	0.08	0	0.16	16.7	±0.7	Equivalent	yes
		2.0	2260		4.40	4.34	4.47							
Cholines-terase	U/L	B	2818	190	10174	9943	10337	-210	-396	-26	18.9[d]	±1923.9	Equivalent	yes
		2.0	2998		9912	9757	10062							
Creatinine	µmol/L	B	4200	210	84	84	85	2	0	3	13.6	±11.4	Equivalent	yes
		2.0	4574		86	84	87							
Direct bilirubin	µmol/L	B	47	90	15.73	14.36	19.03	-2.74	-5.30	-0.34	60.3	±9.5	Equivalent	no
		2.0	114		13.77	12.14	15.70							
FT3	ng/L	B	331	210	2.69	2.63	2.77	0.14	0.05	0.23	15.8	±0.4	Equivalent	yes
		2.0	482		2.88	2.83	2.96							
FT4	ng/L	B	414	70	12.8	12.5	13.1	-0.2	-0.5	0.1	14.8	±1.9	Equivalent	yes
		2.0	480		12.5	12.3	12.8							
Ferritin	µg/L	B	551	430	105	90	115	-2.0	-12.0	7.0	39.9	±41.9	Equivalent	yes
		2.0	583		96	84	106							
GGT	U/L	B	3552	490	30	29	31	-1	-2	0	25.7	±7.7	Equivalent	yes
		2.0	3813		30	29	31							
Glucose	mmol/L	B	2822	90	5.9	5.8	6.0	-0.01	-0.08	0.05	14.6	±0.9	Equivalent	yes
		2.0	2922		5.9	5.8	6.0							
HDL cho-lesterol	mmol/L	B	950	230	1.29	1.24	1.32	-0.08	-0.10	-0.05	17.7	±0.2	Equivalent	yes
		2.0	2259		1.22	1.21	1.24							
Iron	µmol/L	B	548	50	13.6	12.4	14.3	-0.7	-1.6	0	77.9	±10.6	Equivalent	yes
		2.0	589		12.5	11.8	13.2							
LDH	U/L	B	2532	1330	213	211	215	-21	-24	-19	13.6	±29.0	Equivalent	yes
		2.0	2833		192	189	194							
LDL cho-lesterol	mmol/L	B	949	190	2.66	2.56	2.72	-0.10	-0.18	-0.03	24.1	±0.6	Equivalent	yes
		2.0	2265		2.48	2.43	2.56							
Lipase	U/L	B	811	90	36	36	37	0	-1	1	23.5	±8.4	Equiva-lent	yes
		2.0	857		36	35	37							
Magne-sium	mmol/L	B	329	1090	0.84	0.83	0.86	0.04	0.02	0.06	8.4	±0.07	Equiva-lent	no
		2.0	304		0.88	0.86	0.91							

NT-proBNP	ng/L	B	614	1290	940	766	1163	-9.0	-85.0	70.0	30.1[d]	±290.6	Equivalent	no
		2.0	759		915	732	1160							
Inorganic phosphate	mmol/L	B	317	110	1.09	1.05	1.17	0.05	-0.01	0.11	23.8	±0.3	Equivalent	yes
		2.0	311		1.15	1.00	1.20							
Potassium	mmol/L	B	3772	50	3.98	3.96	3.99	0.01	-0.01	0.03	12.1	±0.5	Equivalent	yes
		2.0	4130		3.99	3.98	4.00							
Procalcitonin	µg/L	B	467	190	0.16	0.14	0.19	-0.01	-0.02	0.01	60.0[c]	±0.1	Equivalent	yes
		2.0	473		0.15	0.13	0.17							
Sodium	mmol/L	B	3848	290	140	140	140	1	1	1	1.8	±2.6	Equivalent	yes
		2.0	4248		140	140	141							
TSH	mIU/L	B	2549	70	1.59	1.54	1.64	0	-0.06	0.06	55.0	±0.8	Equivalent	yes
		2.0	2634		1.59	1.54	1.64							
Total bilirubin	µmol/L	B	3322	50	9.75	9.41	9.92	-0.3	-0.5	-0.2	62.4	±6.1	Equivalent	yes
		2.0	3603		9.41	9.23	9.58							
Total hCG	U/L	B	59	170	2.1	1.0	148.6	0.0	0.0	0.0	20.0[c]	±0.42	Equivalent	no
		2.0	73		1.0	1.0	1.0							
Total protein	g/L	B	2840	70	70.	70	71	-0.6	-1	-0.2	8.0	±5.6	Equivalent	yes
		2.0	3044		70	69	70							
Transferrin	g/L	B	541	50	2.11	2.05	2.16	0.01	-0.05	0.08	21.4	±0.4	Equivalent	yes
		2.0	579		2.14	2.09	2.19							
Triglycerides	mmol/L	B	2202	50	1.33	1.30	1.37	0.02	-0.01	0.06	61.2	±0.8	Equivalent	yes
		2.0	2261		1.37	1.34	1.40							
Urea	mmol/L	B	4032	70	2.5	2.5	2.6	0.1	0.1	0.2	40.5	±1.0	Equivalent	yes
		2.0	4421		2.7	2.6	2.7							
Uric acid	µmol/L	B	2487	70	327	321	333	5.9	0	11.9	25.7	±84.1	Equivalent	yes
		2.0	2622		337	333	342							
hs-Troponin I	ng/L	B	629	NA	11.1	9.1	12.5	-1.2	-2.3	0.0	34.4	±3.8	Equivalent	no
		2.0	679		8.9	7.1	10.4							

CI – confidence interval; LL – lower limit; UL – upper limit; RCV – maximum allowable Reference Change Value, calculated as:

$$RCV = z \times \sqrt{2} \times \sqrt{CVI^2 + CVA_des^2}$$

NA - the required equivalence power under the current settings or sample size could not be achieved, probably due to high variability of data or substantially different sub-populations

[a] Wilcoxon rank-sum test

[b] RCV calculated using CV_I and CV_A_des from the EFLM Biological Variation Database (16)

[c] RCV calculated using CV_I and CV_A_des from the RCPA Chemical Pathology Analytical Performance Specifications (17)

[d] RCV calculated using CV_I and CV_A_des from Ricos Biological Variation Database (18)

[e] Calculated as the percentage equal to the respective RCV of the median for the observation period 1 (when the VACUETTE® CAT Serum Separator Clot Activator tubes with the Reference Gel B were used): Equivalence limit = ± (Median (Reference Gel B) x (RCV/100)).

Haemolysis index

Table VII displays the frequency of H-indices during the two observation periods. The frequency of any haemolysis (H-index ≥1) was 22.0% (1145/5203) with Reference Gel B tubes and 20.5% (1149/5604) with Gel 2.0 tubes. The difference in haemolysis frequency was >1% (22.0– 20.5=1.5%). Therefore, it can be considered clinically significant according to the adopted acceptance criteria, demonstrating better performance of Gel 2.0 tubes over Reference Gel B.

Table VII Relative frequency of the occurrence of hemolytic samples in VACUETTE® LH Lithium Heparin Plasma Separator tubes in the two observation periods.

Semiquantitative scale	Haemolysis, N(%)	
	Reference Gel B	Gel 2.0
0	4058 (78)	4455 (79.5)
≥1	1145 (22)	1149 (20.5)
Total	5203 (100)	5604 (100)

N – number of samples.

Discussion

The equivalence of the performance of Gel 2.0 and Reference gel B in VACUETTE® CAT Serum Separator Clot Activator and VACUETTE® LH Lithium Heparin Plasma separator tubes on Atellica® Solution was demonstrated through the comparison of clinical chemistry and immunochemistry parameters' values and the frequency of positive H-indices in two hospital centers for two retrospective observation periods within the routine laboratory work in which tubes with either Gel 2.0 or Reference gel B were used. Clinical chemistry and immunochemistry parameters across two observation periods were assessed for statistical and clinical significance using respective maximum allowable RCVs. In both serum and plasma samples, no clinically significant differences were found for any of the tested parameters with sufficient sample size for the applied statistical analysis.

Bayesian Hodges-Lehmann tests for assessing statistical equivalence between two independent (unpaired) samples, often involving distinct time periods or varying interventions, have historically been applied to general biomedical outcomes such as clinical endpoints (21, 22). However, these tests have not typically been used for laboratory assay comparisons. To the best of our knowledge, this study represents the first instance in which the Wilcoxon/Hodges-Lehmann median difference estimate has been employed to clinically evaluate modified blood collection tubes in the context of post-market surveillance.

The incidence of hemolysed samples differed between the two study sites. A clinically significant decrease was noted only in plasma samples. However, these findings cannot be interpreted as evidence of superior or inferior performance of either gel. Haemolysis is the most frequent preanalytical source of analytical interference. It may result from patient-related conditions (in vivo) or, more commonly, from preanalytical factors such as phlebotomy technique, collection devices, sample handling, transport, centrifugation, and storage conditions (23). As these factors were not assessed due to the study design, their potential contribution cannot be excluded.

The main limitation of this study is the relatively short observation periods, resulting in an insufficient sample size to detect clinically significant median differences for some parameters, particularly those less frequently encountered in everyday laboratory routine. Extended study periods could increase sample sizes, thereby reducing standard errors, narrowing confidence intervals, and enhancing the precision of estimates, especially when actual differences are small or negligible. Additionally, extended durations help stabilise inherent variability caused by factors such as seasonal changes, workflow adjustments, or analyser drift, and can mitigate transient influences such as reagent issues or operator variations. Increased sample size also helps reduce the effects of random noise, outliers, and biological variability. Conversely, if the true difference is clinically significant, a larger sample size will provide more precise confirmation (15). However, several parameters demonstrated equivalence even without reaching the required sample size and power for this kind of analysis, clearly supporting equivalence between the two serum/plasma separating gels.

A potential limitation of this study is that centrifugation conditions used in participating laboratories deviated from the manufacturer's IFU, which are considered binding. Although the applied protocols were locally validated, such deviations may have influenced preanalytical conditions and, consequently, the study outcomes. This approach was accepted strictly for scientific purposes to capture routine practice and support evaluation under real-world laboratory conditions, thereby increasing the external validity of the findings. However, the authors do not recommend deviation from IFU-defined handling conditions. Any modification of centrifugation protocols should be carefully validated within the local laboratory environment before implementation.

Conclusion

Both VACUETTE® CAT Serum Separator Clot Activator tubes and VACUETTE® LH Lithium Heparin Plasma Separator tubes containing the new Gel 2.0, even when centrifuged outside the IFU-recommended conditions, showed comparable performance to the corresponding Reference Gel B tubes across all routinely assessed parameters at participating study centres that were represented with sufficient sample sizes for Wilcoxon/Hodges-Lehmann median difference estimates in large datasets. This refers to 31 clinical chemistry and immunochemistry parameters in serum and 33 in plasma, tested using the Siemens Atellica® Solution. Additionally, the new gel type did not cause a significant increase in haemolysis frequency in either serum or plasma samples compared with the previously used separator gel. Consequently, the adoption of Gel 2.0 may be implemented without negatively affecting the results of standard laboratory tests. Alternative centrifugation conditions were accepted strictly for scientific purposes and are not recommended for routine implementation without proper validation.

Disclaimer

This information on off-label use is based on a study supported by Greiner Bio-One GmbH and is intended for scientific purposes only. The devices VACUETTE® CAT Serum Separator Clot Activator tubes and VACUETTE® LH Lithium Heparin Plasma Separator tubes have not been approved for use under stated centrifugation conditions.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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