Analysis of Elemental Impurities in GLP-1 Receptor Agonist Oral Tablets by ICP-MS

Evaluation of an Agilent 7850 ICP-MS method compliant with USP <232>/<233> and ICH Q3D(R2)/ Q2(R2)

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Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists represent a rapidly expanding class of therapeutics for the management of type 2 diabetes and chronic weight management. While many approved GLP-1 receptor agonists are administered by subcutaneous injections, oral formulations are generating significant clinical and commercial interest. However, formulating peptide-based therapeutics as oral solid dosage forms introduces additional manufacturing complexity, including the need for permeation enhancers, excipients, and coating materials. Each of these components presents a potential source of elemental impurity contamination. International or national-based regulatory authorities are responsible for ensuring that pharmaceutical products are both effective and safe for use. Control of elemental impurities in drug products is governed by the International Council for Harmonisation (ICH) Guideline for Elemental Impurities, Revision 2 (Q3D(R2))[1] and United States Pharmacopeia (USP) <232>/<233> (Elemental Impurities — Limits and Procedures)[2,3] using ICP-OES- or ICP-MS-based instrumental methods.

The USP chapters classify 24 elemental impurities in three classes based on toxicity and probability of occurrence, with permitted daily exposure (PDE) limits defined by route of administration. Analytical method validation follows ICH Q2(R2) (Validation of Analytical Procedures, 2023)[4] and the harmonized USP <1225> (Validation of Compendial Procedures)[5], with system suitability criteria defined in USP <233>.[3] ICH Q2(R2) provides updated guidance on the validation of analytical procedures that is applicable to biological- and biotechnology-derived products. The revised guideline offers clearer guidance on complex therapeutics, such as peptide-based biotherapeutics, including GLP-1 receptor agonists—an area not specifically addressed in the earlier Q2(R1) framework.

In this study, an analytical method was developed and validated in accordance with USP <232>/<233> and ICH Q3D(R2)/Q2(R2). The method enables quantitative determination of all 24 regulated elemental impurities in an oral tablet of a GLP-1 receptor agonist using an Agilent 7850 ICP-MS. The instrument features an integrated fourth-generation Octopole Reaction System (ORS^4) collision cell, which was operated in helium (He) mode to provide robust suppression of matrix-derived polyatomic interferences affecting the analytes. Data were acquired to evaluate drift/stability, detectability, precision (repeatability and intermediate precision), specificity, accuracy, and linearity.

Experimental

System suitability tests

The sample preparation and method validation procedures defined in USP <233> were used to perform system suitability testing for the 7850 ICP-MS method.

The maximum level of elemental impurities in finished drug products is expressed as a maximum PDE. For materials that require digestion or dilution before analysis, the PDE limit (in µg/day) must be converted to a concentration limit (in µg/L) as measured in the prepared sample. This target concentration—referred to as the "J value" —defines the maximum permitted concentration limit for the analyte in the sample solution. It is calculated as follows:

$$J = PDE/(\text{Total Dilution} \times \text{Max Daily Dose})$$

Because the GLP-1 drug product is administered orally, the oral dosage PDE limits specified in ICH Q3D(R2) and USP <232> were used as reference limits. The J values for the 24 regulated elements are shown in Table 1 together with the instrument detection limit (IDL) for each element. J values are at least 500 times higher than the IDLs, indicating that the 7850 ICP-MS provides more than sufficient sensitivity for the application.

The J value defines calibration levels (0.5–1.5 J), detectability spikes (0.8 J for Limit Procedures), and spike recovery concentrations (50–150% J). The Agilent ICP-MS MassHunter software automatically calculates J values for each analyte based on the final dosage form and dilution factor, eliminating manual computation and enabling analysts to move from sample preparation to compliant results with minimal effort.

Table 1. Oral dosage PDEs, J values, and IDLs for 24 regulated elements (2500× dilution; 1 g/day max dose).

ICH/USP Class	Element	Mass	Oral PDE (µg/day)	J Value (µg/L, ppb)	7850 ICP-MS IDLs* (ng/L, ppt)
Class 1	As	75	15	6	12.18
	Cd	111	5	2	0.28
	Hg	202	30	12	1.82
	Pb	208	5	2	1.81
Class 2A	Co	59	50	20	0.72
	V	51	100	40	14.39
	Ni	60	200	80	0.65
Class 2B	Tl	205	8	3.2	0.16
	Au	197	300	120	19.82
	Pd	105	100	40	0.72
	Ir	193	100	40	1.24
	Os	189	100	40	4.22
	Rh	103	100	40	0.46
	Ru	101	100	40	0.61
	Se	78	150	60	15.65
	Ag	107	150	60	1.51
	Pt	195	100	40	0.34
Class 3	Li	7	550	220	23.14
	Sb	121	1,200	480	22.89
	Ba	137	1,400	560	5.79
	Mo	97	3,000	1,200	10.51
	Cu	63	3,000	1,200	8.38
	Sn	118	6,000	2,400	3.16
	Cr	52	11,000	4,400	3.52

**IDLs were calculated from the calibration graphs (3 x standard deviation (SD) of the concentration of the calibration blank, n=3)*

Sample preparation

USP <233> defines four sample preparation formats: neat, direct aqueous solution, direct organic solution, and indirect solution. Since GLP-1 oral tablets are not directly soluble, an indirect solution approach was used, employing closed-vessel microwave digestion with concentrated acids to bring the sample matrix into solution.

In this study, four GLP-1 oral tablets were pulverized into a fine, homogeneous powder using a tube mill. A 0.2 g aliquot was accurately weighed into a digestion tube, and 6 mL concentrated HNO_3 and 2 mL concentrated HCl were added. Six independent sample preparations were processed. The samples were then digested using a MARS 6 closed-vessel microwave digestion system (CEM Corporation, USA). The heating program is shown in Table 2. The 3:1 HNO_3:HCl ratio ensures effective decomposition of the organic matrix, while HCl stabilizes mercury (Hg) and the platinum group elements (PGEs) in solution. After cooling below 50 °C, the clear digest was diluted to a final volume of 500 mL with the 3% HNO_3/1% HCl diluent, giving a total dilution factor of 2500. Two digestion blanks were processed under identical conditions as the samples to check for contamination during sample preparation.

Table 2. Microwave digestion program used to prepare GLP-1 oral tablets.

Stage	Temp (°C)	Time (min)	Mode
1	200	15	Ramp
2	200	15	Hold
3			Vent and cool

For each sample, mixed standards containing all 24 regulated elements were prepared using Agilent ICH Q3D & USP 232 Orals Kit_v2. The standards were prepared at appropriate spike concentrations (0.5, 0.8, 1.0, and 1.5 J) in the digested sample based on the oral PDE limits.

Instrumentation

Elemental impurities were measured using an Agilent 7850 ICP-MS with ORS⁴ collision cell,[6] controlled via Agilent ICP-MS MassHunter software. The instrument was equipped with the standard sample introduction system comprising a MicroMist glass concentric nebulizer, a quartz spray chamber, a quartz torch with a 2.5 mm inner diameter (ID) injector, and nickel sampling and skimmer cones. An Agilent SPS 4 autosampler was used for sample introduction.

The ICH/USP preset method was selected in the ICP-MS MassHunter software, which automatically configured the operating parameters according to the target element list and applied QC criteria aligned with oral dosage PDE limits. Table 3 summarizes the key instrument parameters used in this study.

All elements were measured in He mode, which uses kinetic energy discrimination (KED) to attenuate polyatomic interferences. This approach is particularly advantageous for chloride-containing matrices, where the ORS⁴ He KED mode suppresses chloride-based species (for example, $ArCl^+$, which interferes with $^{75}As^+$), supporting the use of HCl for sample stabilization. HCl improves the chemical stability of Hg and PGEs and enhances the long-term stability of analytes such as osmium (Os) at higher concentrations.

Since He KED mode provides a robust, non-specific approach for multi-element interference control, it also enables the use of secondary (qualifier) isotopes to confirm analyte identity and the accuracy of results, in accordance with ICH Q2(R2), USP <233>, and USP <1225>.

Table 3. Agilent 7850 ICP-MS operating parameters.

Parameters	Settings
Plasma Mode	General Purpose
RF Power (W)	1550
Spray Chamber Temperature (°C)	2
Sampling Depth (mm)	10
Nebulizer Gas Flow (L/min)	1.03
Lens Tune	Autotune
Cell Mode	Helium
He Gas Flow (mL/min)	4.3
KED (V)	5

The shaded parameters are predefined by selecting the General Purpose plasma setting

Results and discussion

Before being used for limit or quantitative procedures, the analytical instrument and method must meet performance criteria defined in ICH Q2(R2) and USP <233>. System suitability—verified by confirming that results remain stable (drift ≤ 20%) throughout the analytical run—must be demonstrated on the day of analysis. Separately, USP <233> requires procedure validation to demonstrate fitness for purpose: detectability, precision, and specificity for Limit Procedures; and accuracy, precision/repeatability, intermediate precision (ruggedness), specificity, limit of quantitation, linearity and range (demonstrated across 0.5–1.5 J) for Quantitative Procedures.

Drift check and QC stability

Long-term stability is a critical system suitability requirement. Signal drift is assessed by comparing the results obtained for a standard at 1.5 J run before and after sample analysis; system suitability is obtained when drift does not exceed ±20% for each target element. The same 1.5 J standard also served as a QC check and was analyzed every 15 samples throughout the entire eight-hour batch run.

As shown in Figure 1, the 1.5 J drift check results remained within 90 to 110% over the eight-hour analysis, demonstrating the long-term stability performance of the 7850 ICP-MS.

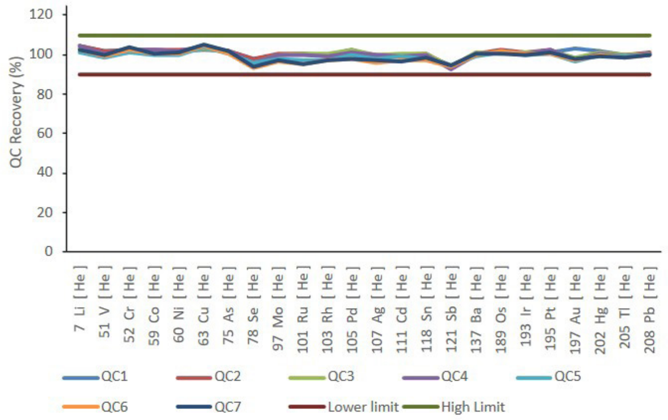

Figure 1. System suitability drift and QC stability check with 1.5 J standard throughout the eight-hour run.

The relative standard deviation (RSD) for each element across seven QC checks was less than 2.6% and below 1% for several critical Class 1 and Class 2A elements, including arsenic (As), mercury (Hg), lead (Pb), and nickel (Ni) (Table 4).

Together, the drift and QC stability results confirmed robust system suitability for this application.

Limit Procedures

Detectability

According to USP <233>, detectability is demonstrated by measuring samples spiked at 1 and 0.8 J and comparing results to a 1 J standard. Two criteria must be met: (1) the mean concentration of three independently prepared 1 J spiked samples must be within ±15% of the measured concentration of the 1 J standard, and (2) the mean concentration of the 0.8 J spiked samples must be lower than the measured concentration of the 1 J standard.

Both acceptance criteria were met for all 24 elements. Recoveries of the 1 J spiked samples relative to the 1 J standard ranged from 88.6 to 105.0%, well within the ±15% tolerance. The 0.8 J spike/1 J ratios ranged from 76.9 to 81.0%, confirming detectability at the specification limit (Table 5).

Table 4. QC stability for all regulated elements at 1.5 J during the eight-hour batch run.

Element	RSD (%) (n=7)	Element	RSD (%) (n=7)
Li	1.25	Ag	1.56
V	1.15	Cd	1.49
Cr	0.83	Sn	1.27
Co	1.02	Sb	0.86
Ni	0.75	Ba	0.69
Cu	0.96	Os	0.73
As	0.64	Ir	0.60
Se	1.86	Pt	0.68
Mo	1.62	Au	2.25
Ru	2.56	Hg	0.93
Rh	1.38	Tl	0.48
Pd	1.97	Pb	0.52

Precision (Repeatability)

USP <233> requires that the RSD for six independently prepared 1 J spiked samples (n=6) must not exceed 20%. As shown in Table 5, the precision results for all 24 elements were ≤ 2% RSD (n=6), far exceeding the acceptance criterion.

Intermediate precision

Intermediate precision was assessed by combining two sets of six independent 1 J spiked samples (n=12), obtained by different analysts on different days. ICH Q2(R2) defines intermediate precision as within-laboratory variability evaluated across factors such as days, analysts, and equipment. The intermediate precision results were ≤ 3.2% RSD (n=12) for all elements (Table 5), confirming the method's ruggedness and providing a robust baseline for drug lifecycle performance monitoring.

Table 5. Detectability, precision, and intermediate precision results.

Element	Mass	1 J Value (µg/L)	1 J Standard (µg/L)	1 J Spike (µg/L)	Recovery (%)	0.8 J Spike (µg/L)	0.8 J/1 J %	RSD% (n=6)	RSD% (n=12)
Li	7	220	218	210	96.3	168	80.0	0.99	2.38
V	51	40	39.9	39.3	98.5	31.4	79.9	0.89	0.68
Cr	52	4,400	4,368	4,344	99.5	3,443	79.3	0.93	1.33
Co	59	20	19.9	19.5	98.0	15.4	79.0	0.76	0.64
Ni	60	80	79.8	77.7	97.4	61.5	79.2	0.68	0.66
Cu	63	1,200	1,194	1,172	98.2	924	78.8	1.17	1.09
As	75	6	6.03	6.05	100.3	4.75	78.5	1.05	1.40
Se	78	60	61.9	62.1	100.3	48.9	78.7	1.66	1.70
Mo	97	1,200	1,218	1,194	98.0	954	79.9	1.30	1.63
Ru	101	40	40.8	38.6	94.6	30.8	79.8	1.05	1.35
Rh	103	40	41.2	38.9	94.4	31.5	81.0	1.03	1.78
Pd	105	40	39.9	38.5	96.5	29.6	76.9	1.91	2.68
Ag	107	60	63.9	56.6	88.6	43.5	76.9	1.88	2.51
Cd	111	2	2.06	1.94	94.2	1.56	80.4	1.17	2.15
Sn	118	2,400	2,448	2,391	97.7	1,901	79.5	1.13	1.55
Sb	121	480	490	485	99.0	388	80.0	1.05	1.44
Ba	137	560	573	557	97.2	444	79.7	1.23	1.71
Os	189	40	39.9	40.3	101.0	31.7	78.7	1.32	1.16
Ir	193	40	40.0	40.9	102.3	32.0	78.2	0.35	1.91
Pt	195	40	39.2	39.2	100.0	31.0	79.1	0.70	3.15
Au	197	120	119	125	105.0	100	80.0	0.72	1.27
Hg	202	12	12.0	12.2	101.7	9.60	78.7	0.54	1.20
Tl	205	3.2	3.18	3.20	100.6	2.52	78.8	0.66	0.72
Pb	208*	2	1.99	2.04	102.5	1.63	79.9	0.53	1.01

**Lead (Pb) was quantified using a built-in correction equation in ICP-MS MassHunter which sums the signals of* ^{206}*Pb,* ^{207}*Pb, and* ^{208}*Pb. This approach compensates for the natural variation in Pb isotopic abundances arising from the radiogenic origin of these isotopes, ensuring accurate total Pb determination regardless of the geological source of lead in the sample or standard.*

Specificity

According to ICH Q2(R2), specificity (also referred to as selectivity) is the ability of an analytical procedure to unequivocally assess the target analyte in the presence of components that may be expected to be present, including the sample matrix, degradation products, and other analytes. For ICP-MS, specificity is inherently provided by the measurement principle—each element is detected based on its unique isotopic mass free from direct overlap by any other element. Commonly occurring polyatomic ion interferences such as $^{40}\mathrm{Ar}^{35}\mathrm{Cl}^+$ on $^{75}\mathrm{As}$ and $^{40}\mathrm{Ar}^{40}\mathrm{Ar}^+$ on $^{80}\mathrm{Se}$ are effectively removed by the ORS^4 collision cell using He cell gas and KED.

He mode is a universal cell mode that also provides access to secondary or qualifier isotopes for most elements. These qualifier isotopes provide further confirmation of analyte identity and concentration, supporting the USP <233> and ICH Q2(R2) requirement for unequivocal analyte assessment.

Good agreement between primary and qualifier isotope results was confirmed for several elements (Table 6).

Table 6. Comparison of primary and qualifier isotope results for selected elements in the 1.0 J spiked sample.

Element	Primary Isotope	Conc. (µg/L)	Qualifier Isotope	Conc. (µg/L)	Agreement (%)
Cu	63	1,172	65	1,169	99.7
Cr	52	4,344	53	4,323	99.5
Ba	137	557	135	564	101.2
Ir	193	40.9	191	40.4	98.7
Hg	202	12.2	200	12.2	100
			201	12.2	100

Quantitative Procedures

Accuracy

The accuracy of the quantitative procedure was demonstrated by measuring samples spiked at 0.5, 1.0, and 1.5 J in three independent sample preparations. USP <233> requires spike recoveries to be within 70–150% at each concentration level, after subtraction of any elements present in the unspiked sample.

As shown in Figure 2, the recovery of each element at each spike level (0.5, 1.0, and 1.5 J) was within 90–110%, substantially exceeding the acceptance criteria. This narrow recovery range readily satisfies more stringent statistical acceptance criteria. It also confirms the excellent accuracy and linearity of the 7850 ICP-MS method across the validated range for the GLP-1 oral tablet matrix.

The accuracy test also demonstrated performance for limits of detection (LODs), analytical range, and linearity. Figure 3 displays exemplary calibration curves of some elements, including the Class 1 elements (As, Cd, Hg, and Pb), the low-level Class 2A elements (Co, V, and Ni), and three Class 2B elements (Pd, Os, and Pt). For all elements, excellent linearity was achieved, with linear regression coefficients > 0.999. Background equivalent concentrations (BECs) and LODs were all at the ppt level.

Figure 2. Recoveries of spiked samples at 0.5 J (blue), 1 J (red), and 1.5 J (green) in three independent samples.

Speciation considerations for As and Hg

For some elements, toxicity is highly dependent on their chemical form. Of the analytes listed in the ICH/USP regulations, As and Hg are of particular concern. The PDE limit for both elements refers to their inorganic forms because inorganic As is the most toxic, and inorganic Hg is considered the most likely form to be present in pharmaceutical materials.

If the measured total As concentration exceeds the target concentration, USP <232> suggests that a speciation analysis is performed using LC-ICP-MS to allow independent quantification of inorganic As. If inorganic As is found to be below the limit, the material would be considered compliant even if total As exceeds the limit. The speciation of Hg should be established if the test material is likely to contain the more toxic methyl Hg species (for example, ingredients sourced from marine-derived materials). Otherwise, compliance is established by determining total Hg.

In this study, only trace-level Li (0.23 ppb) and Ni (0.07 ppb) were detected in the sample blank. All other elements were below the IDLs. Therefore, speciation analysis on As and Hg was not required. However, the 7850 ICP-MS can be easily integrated with an Agilent LC system for routine speciation analysis if needed.[7]

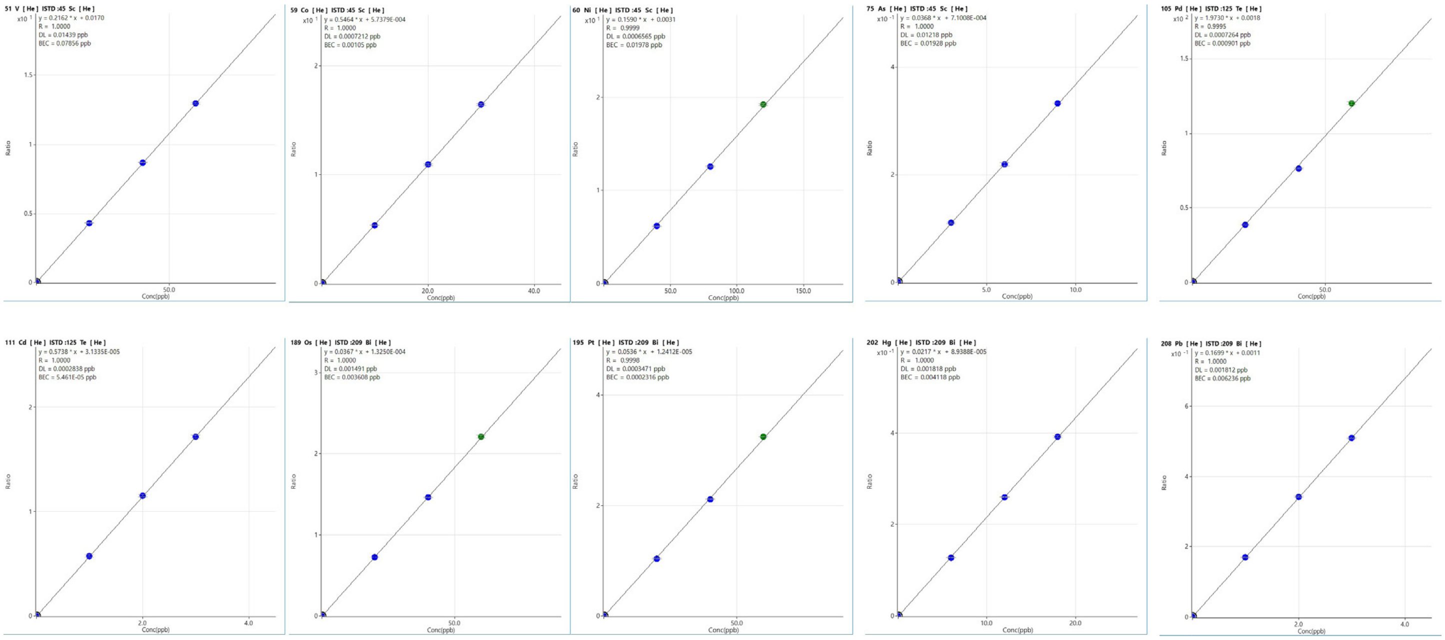

Figure 3. Calibration curves for As, Cd, Hg, Pb, Co, Ni, Pd, Os, and Pt demonstrating low LOQs, good linearity, and wide quantification range.

Conclusion

This study demonstrates the suitability of the Agilent 7850 ICP-MS for the identification and quantification of 24 regulated elemental impurities in a GLP-1 receptor agonist oral tablet formulation, prepared by microwave digestion. The instrument's ORS^4 collision cell was operated in helium mode, providing robust, non-specific attenuation of matrix-derived polyatomic interferences. The method successfully met the limit and accuracy requirements specified in USP <232>/<233> and ICH Q3D(R2)/Q2(R2) guidelines, ensuring reliable multi-element quantification of GLP-1 tablets without the need for element-specific method optimization.

For pharmaceutical QC laboratories, the Agilent ICP-MS MassHunter instrument control software assisted in developing the workflow, reducing the time and effort required to establish a compliant analytical method. The preset ICH/USP method template, automated J-value calculation, and built-in system suitability reporting eliminated manual configuration steps, making it easier for different analysts to use the instrument. The software also enables method transfer across sites. The demonstrated eight-hour signal stability performance of the 7850 ICP-MS further supports high-throughput batch testing in routine manufacturing QC environments.

As ICH Q2(R2) provides improved clarity for validating analytical procedures used with peptide based therapeutics, including GLP 1 receptor agonists, this application note provides a regulation-ready reference method. The workflow can be directly adopted or adapted for oral solid dosage forms containing active peptide ingredients, supporting faster regulatory submissions and reducing analytical development timelines.

References

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5. United States Pharmacopeia Validation of Compendial Procedures, Chapter <1225>, USP–NF. United States Pharmacopeial Convention, Rockville, MD, USA
6. Octopole Collision/Reaction Cell and Helium Mode, Agilent publication, 5994-1172EN
7. Meet The Growing Demand for Elemental Speciation, Agilent publication, 5991-4269EN

Products used in this application

Agilent products

Product Type	Description	Part Number
Sample Introduction	MicroMist glass concentric nebulizer (U-series)	G3266-80004
	Quartz torch, 2.5 mm injector	G3280-80053
Interface	Standard ICP-MS sampler cone, nickel tip with copper base	G3280-67040
	Standard nickel skimmer cone	G3280-67041
Tubing Kits	Peristaltic pump tubing (sample uptake)	5005-0020
	Peristaltic pump tubing (internal standard)	5005-0021
	Drain pump tubing	5005-0022
Standards	ICH Q3D & USP 232 Orals Kit_v2	5191-4553

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