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Application Note

Comprehensive Biosimilar Comparability Assessment via Intact and Subunit RP-MS and IEX-UV-MS Using the Xevo™ G3 QTof System

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Abstract

With the increasing prevalence of biosimilar monoclonal antibodies (mAbs) in the drug development landscape, the need for robust liquid chromatography-mass spectrometry (LC-MS) instruments and streamlined characterization workflows is critical. The Xevo G3 QTof Mass Spectrometer coupled with an ACQUITY™ Premier UPLC™ offers the sensitivity, mass resolution, spectrum quality, and mass accuracy for large molecules to ensure accurate characterization of mAbs at intact and subunit levels. The hardware coupled with the waters_connect™ Informatics platform offers dedicated workflows for intact mAb analysis enabling streamlined reliable data analysis in a compliance-ready environment. This study demonstrates the use of Xevo G3 QTof platform to perform a comparability analysis for infliximab innovator Remicade® and three biosimilars (Inflectra®, Avsola®, and Renflexis®). The samples were analyzed at intact and IdeS subunit levels via reversed phase (RP) LC-MS and native ion exchange (IEX) LC-MS. The resulting data were processed with UNIFI™ and INTACT Mass applications within waters_connect. mAb product quality attributes such as N-glycosylation, C-terminal lysine variants, and charge variants were quantified and compared among the biosimilars.

Benefits

- Xevo G3 QTof offers updated ion optics, extended mass calibration range, and improved quantification capabilities for large molecule applications
- Confident profiling of product quality attributes at intact and subunit level using ACQUITY Premier BEH™ C4 and BioResolve™ SCX mAb Columns
- Flexibility of informatics platform for use in both GxP and non-GxP environments
- Use of intelligent data capture (IDC) improves spectral quality and reduces file size

Introduction

Over the decade, biosimilar monoclonal antibody (mAb) drug products have become increasingly prevalent as patents expire for blockbuster innovator molecules. The options for less expensive biosimilars are appealing for both patients and regulators. Regulatory agencies require analytical data, animal studies, and clinical studies to prove biosimilarity,[1–4] as minute differences can cause drastic changes in efficacy and safety of the drug product. Although biosimilars share the same amino acid sequence as the innovator, they could potentially have differences in their structure and/or product variant profiles arising from post-translational modifications (PTMs). These differences occur as a result of changes in the drug development and manufacturing processes such as cell line, protein expression, production conditions, and purification process. Some product variants, such as N-glycosylation, deamidation, and modification to the N- and C- termini, are significantly smaller in size compared to the total global structure of the mAb, and present in combinations. Thus, it can be challenging to reliably prove comparability in these complex molecules.

Intact mAb reversed phase (RP) LC-MS analysis provides an overall picture of N-glycoform distribution and can identify larger delta-mass product variants such as unprocessed C-terminal lysine. In addition, digesting the mAb into about 25 kDa subunits using IdeS enzyme allows for a more localized and detailed analysis of lower level variants. Native IEX-ultraviolet-mass spectrometry (UV-MS) may also be performed as a useful orthogonal technique that separates protein species by surface charge, creating a charge variant profile. These profiles are routinely used for characterization and monitoring of mAb drug products and coupling the IEX chromatographic separation with MS detection gives the additional benefit of investigating species under each charge variant

peak.

The Xevo G3 QTof (Figure 1) with its updated ion optics offers the sensitivity, mass resolution, and robustness required for implementation as an analytical workhorse for mAb characterization. The system is operated under compliance-ready waters_connect software, offering flexibility for deployment across both discovery and GxP environments. The system is also enabled with IDC[5], an acquisition processing option which adaptively lowers background noise and reduces the data file size. This application note showcases robust RPLC-MS and native IEX-UV-MS analyses using the Xevo G3 QTof MS Platform using streamlined workflows to simplify intact protein mass confirmation for characterization and comparability of infliximab biosimilars.

Figure 1. ACQUITY Premier UPLC coupled to Xevo G3 QTof mass spectrometer, operated under waters_connect workstation.

Experimental

Sample Description

Infliximab innovator (Remicade) and three biosimilars (Inflectra, Avsola, and Renflexis) were analyzed as intact, IdeS-digested subunits, and carboxypeptidase B-digested samples via UPLC-MS (both RPLC and IEX), coupled to a Xevo G3 QTof Mass Spectrometer. Data acquisition and processing were performed on the waters_connect platform using both the UNIFI App classic intact mass workflow and the new INTACT Mass application.

LC Conditions: Reversed Phase (RP)

LC system:	ACQUITY Premier UPLC
Detection:	TUV (280 nm)
Vials:	QuanRecovery™ with MaxPeak™ HPS 12 x 32 mm Screw Neck vial, 300 µL (p/n: 186009186)
Column(s):	ACQUITY Premier Protein BEH™ C4, 300 Å, 1.7 µm, 2.1 x 50 mm (p/n: 186010326)
Column temperature:	80 °C
Sample temperature:	6 °C
Injection volume:	2 µL of diluted 0.1 mg/mL sample (intact) 2 µL of diluted 0.1 mg/mL sample (subunit)
Flow rate:	0.4 mL/min for intact, 0.3 mL/min for subunit
Mobile phase A:	0.1% Formic acid in water
Mobile phase B:	0.1% Formic acid in acetonitrile

Gradient Table (RP Intact)

Time (min)	Flow (mL/min)	%A	%B	Curve
Initial	0.4	95.0	5.0	6
1.00	0.4	95.0	5.0	6
3.50	0.4	15.0	85.0	6
3.90	0.4	15.0	85.0	6
4.00	0.4	5.0	95.0	6
5.00	0.4	5.0	95.0	6
5.10	0.4	95.0	5.0	6
7.00	0.4	95.0	5.0	6

Gradient Table (RP Subunit)

Time (min)	Flow (mL/min)	%A	%B	Curve
Initial	0.3	80.0	20.0	Initial
10.00	0.3	60.0	40.0	6
10.30	0.3	20.0	80.0	6
11.30	0.3	20.0	80.0	6
11.60	0.3	80.0	20.0	6
15.00	0.3	80.0	20.0	6

LC Conditions: Ion Exchange (IEX)

LC system:	ACQUITY Premier UPLC
Detection:	TUV (280 nm)
Vials:	QuanRecovery with MaxPeak HPS 12 x 32 mm Screw Neck vial, 300 µL (p/n: 186009186)
Column(s):	BioResolve SCX mAb 3 µm, 2.1 x 100 mm (p/n: 186009056)
Column temperature:	30 °C
Sample temperature:	6 °C

Injection volume:	1 µL 10 mg/mL (intact), 2µL 5 mg/mL (Carboxypeptidase B digested) 4 µL 2.5 mg/mL (subunit)
Flow rate:	0.1 mL/min
Mobile phase A:	IonHance™ CX-MS Concentrate A (p/n: 186009280), diluted 10x with MilliQ water as directed (Final 50 mM Ammonium Acetate, 2% Acetonitrile, pH 5.0)
Mobile phase B:	IonHance CX-MS Concentrate B (p/n: 186009281), diluted 10x with MilliQ water as directed (Final 160 mM Ammonium Acetate, 2% Acetonitrile, pH 8.5)

Gradient Table (IEX Intact)

Time (min)	Flow (mL/min)	%A	%B	Curve
Initial	0.1	53.0	47.0	Initial
1.00	0.1	53.0	47.0	6
21.00	0.1	33.0	67.0	6
21.10	0.1	2.0	98.0	6
22.00	0.1	2.0	98.0	6
23.00	0.1	53.0	47.0	6
30.00	0.1	53.0	47.0	6

Gradient Table (IEX Subunit)

Time (min)	Flow (mL/min)	%A	%B	Curve
Initial	0.1	98.0	2.0	Initial
1.00	0.1	98.0	2.0	6
21.00	0.1	2.0	98.0	6
22.00	0.1	2.0	98.0	6
23.00	0.1	98.0	2.0	6
30.00	0.1	98.0	2.0	6

MS Conditions

MS system:	Xevo G3 QTof
Ionization mode:	Positive
Acquisition range:	50–5000 *m/z* (RP)
	400–8000 *m/z* (IEX)
Capillary voltage:	2.25 kV (intact RP)
	2.75 kV (subunit RP)
	3.00 kV (intact & subunit IEX)
Cone voltage:	150 V (intact RP, intact IEX, and subunit IEX)

	70 V (subunit RP)
Source temperature:	150 °C (intact RP) 125 °C (subunit RP) 120 °C (intact and subunit IEX)
Desolvation temperature:	500 °C (all)
Cone gas:	0 L/hr (RP) 50 L/hr (IEX)
Desolvation gas:	700 L/hr (RP) 600 L/hr (IEX)
Intelligent data capture (IDC) threshold:	Low (5)

Data Management

Chromatography software:	UNIFI (via waters_connect) v 2.1.1.13
MS software:	UNIFI (via waters_connect) v 2.1.1.13
Informatics:	UNIFI & INTACT Mass App v 1.9.13

Results and Discussion

In this study, samples of Remicade (innovator) and three biosimilars (Inflectra, Avsola, and Renflexis) were analyzed at intact and subunit levels via denaturing RPLC-MS and native IEX-UV-MS.

RPLC-MS

RPLC-MS was used to confirm mAb identity and perform relative quantitation of product variants arising from N-glycosylation, glycation, and C-terminal lysine processing. Mirror plots of combined raw spectra (Figure 2, left panel) and MaxEnt1 deconvoluted mass spectra (Figure 2, right panel) for intact Remicade and Renflexis. From this analysis, the most notable difference is the level of C-terminal lysine variants in Remicade (noted with blue asterisks) compared to Renflexis. In addition, there are subtle differences observed in the N-glycoforms: higher levels of Man5-containing species in Remicade, and the presence of A2-containing (biantennary) species in Renflexis.

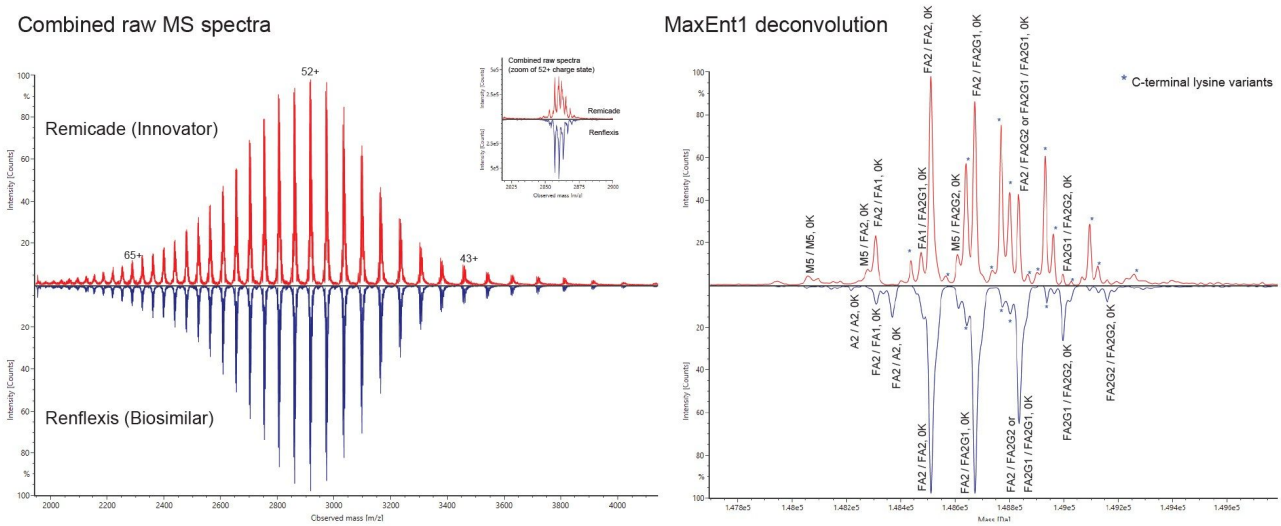

Figure 2. Mirror plots for Intact RP analysis of Remicade (red) vs Renflexis (blue) with inserted zoom of 52+ charge states. Left panel shows combined raw MS spectra and right panel shows MaxEnt1 deconvoluted and annotated spectra.

In order to simplify the relative quantitation of N-glycoform distribution, all samples were incubated with carboxypeptidase B enzyme to remove the C-terminal lysine variants prior to analysis using the same intact RPLC-MS method. The relative quantitation results for N-glycoform distribution are shown in Figure 3. Only minor differences are observed in the distribution of major N-glycoforms.

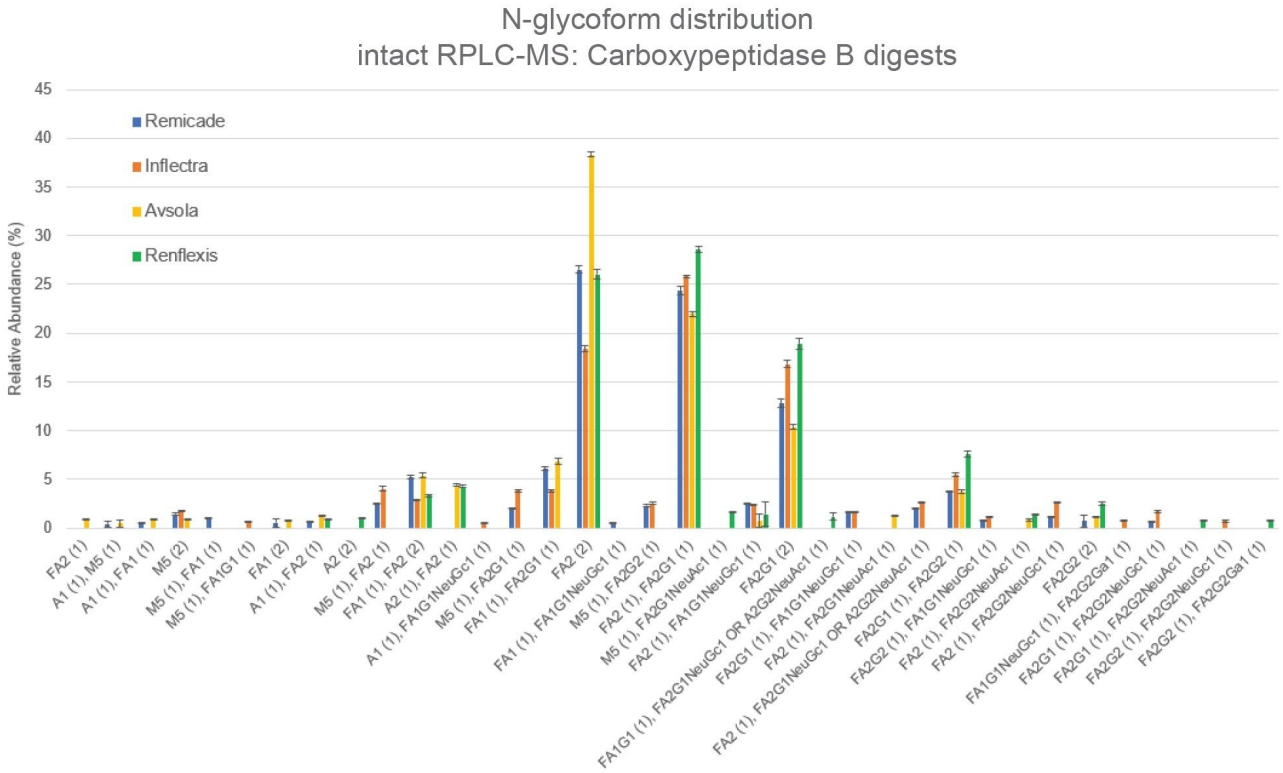

Figure 3. Intact RPLC-MS N-glycoform distribution. (Relative abundance calculation from carboxypeptidase B digested samples).

Additional PTM information can be achieved via the analysis of mAb subunits from an IdeS digest and reduction to generate three approximately 25 kD subunits, allowing for further localization of product variants and correlate their relative quantitation at this level. The infliximab biosimilars in this study were analyzed at subunit level to compare N-glycoform distribution and unprocessed C-terminal lysine on the Fc region (Figure 4), as well as the light chain and Fd subunit glycation levels. One key difference in N-glycosylation is the immunogenic N-glycans (those with N-glycolylneuraminic acid) detected in Remicade and Inflectra, which were not detected in Avsola and Renflexis. This is explained by the cell line used to manufacture each of the biosimilars[6]—Remicade and Inflectra are expressed in Sp2/0 cell lines, while Avsola and Renflexis are expressed in CHO (Chinese hamster ovary) cell lines.[4,7] Interestingly, light chain and Fd glycation were observed to be below 0.5% in Remicade, but ranged 2–3% each for Inflectra, Avsola, and Renflexis. Both intact and subunit RPLC-MS demonstrate excellent suitability for characterization, comparability, and monitoring of biologic drug products.

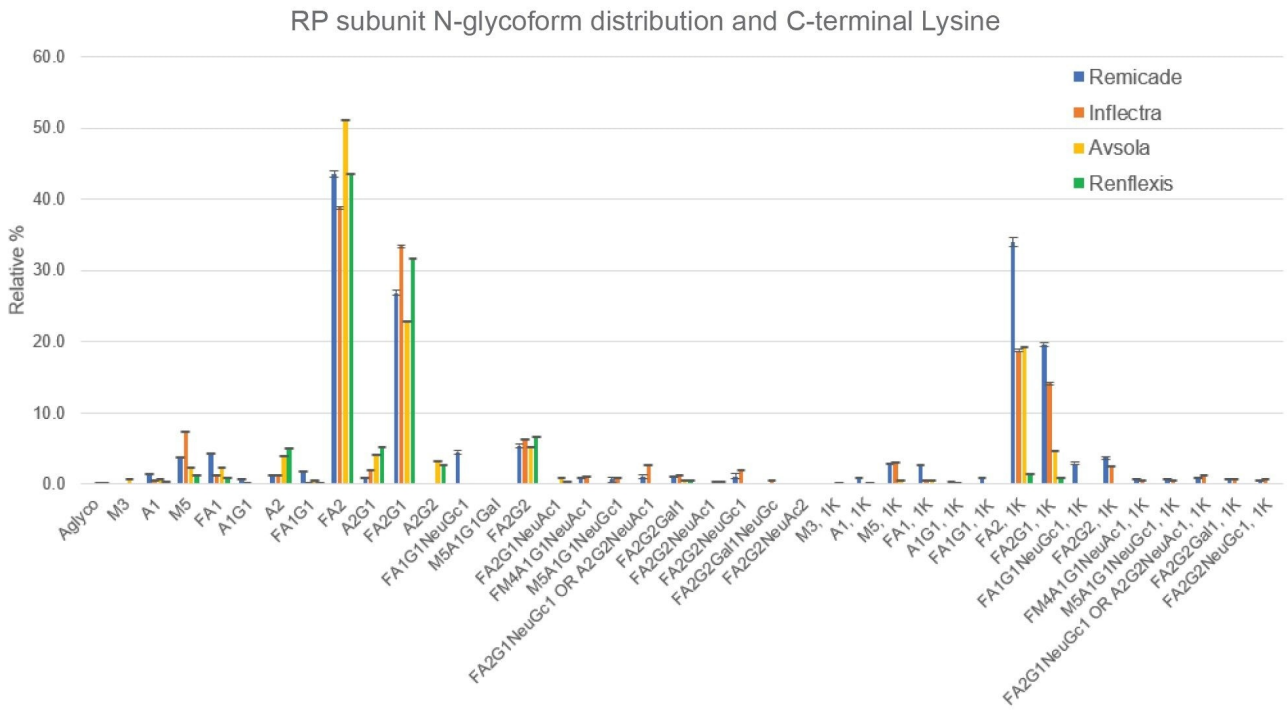

Figure 4. Relative quantitation of N-glycoforms and C-terminal lysine variants detected in subunit level RP analysis.

The waters_connect platform supports UNIFI App intact mass data processing, as well more streamlined and automated processing using the new INTACT Mass app, designed to improve usability when higher throughput rapid screening of numerous samples is desired. The app allows the user to perform data processing using both untargeted (discovery) and targeted (monitoring) approaches for intact mass analysis.

In this study, the biosimilar samples were treated as unknowns in an untargeted workflow with automatic data processing, which generated a list of deconvoluted masses allowing the user to assign the major N-glycoforms and unprocessed C-terminal lysine variants. Figure 5 displays the INTACT Mass app dashboard following data processing for this type of untargeted approach. The dashboard review tool allows a simple data quality review and clearly displays differences in the deconvoluted mass data, as shown in Figure 6. The user is able to quickly observe that the Renflexis biosimilar had a less complex product variant profile than the Remicade innovator and the other two biosimilars. These differences can be further investigated in either UNIFI or with a targeted approach within the INTACT Mass app to monitor each of the individual product variant peaks.

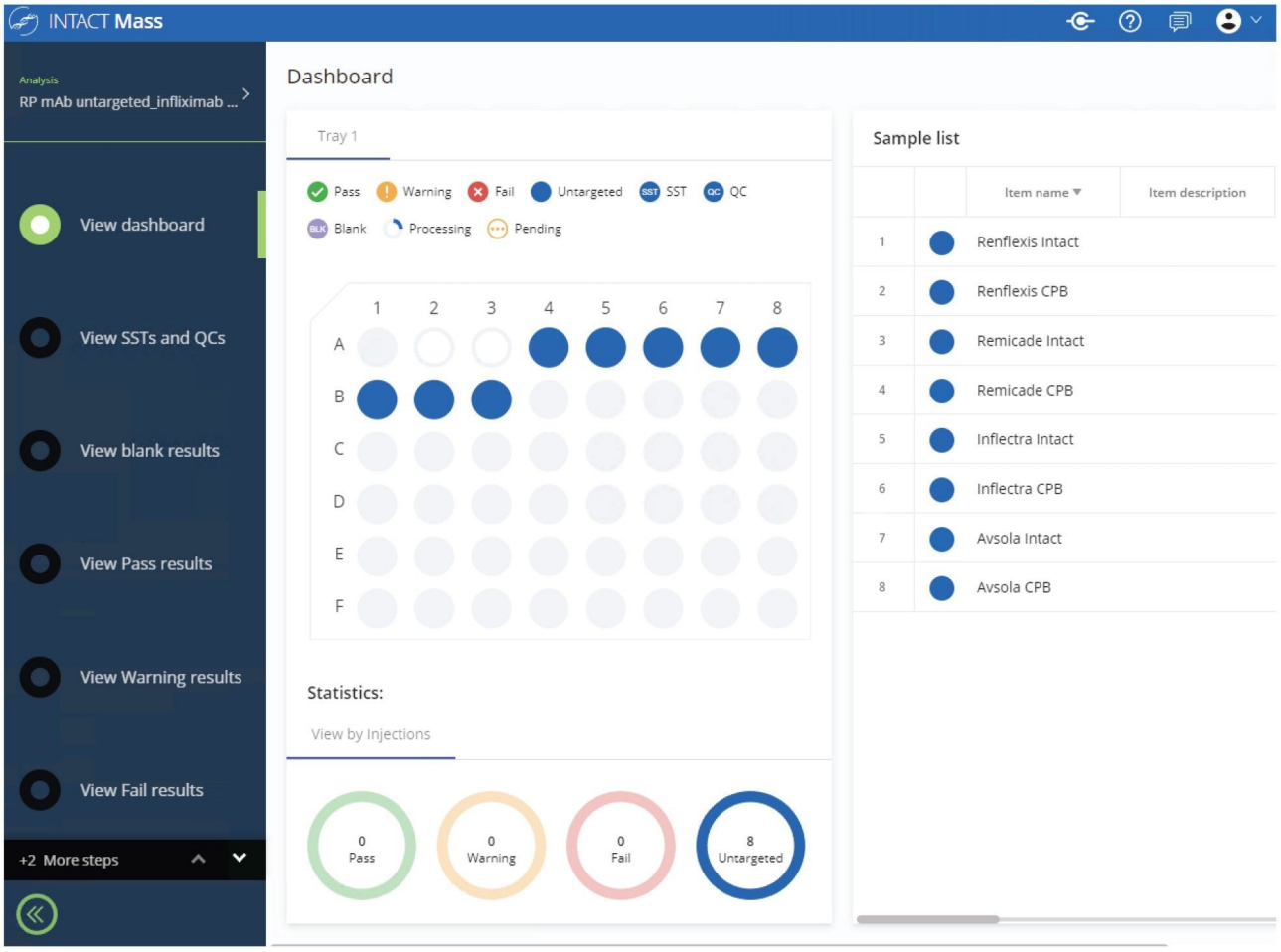

Figure 5. INTACT Mass app dashboard following data processing in an untargeted workflow.

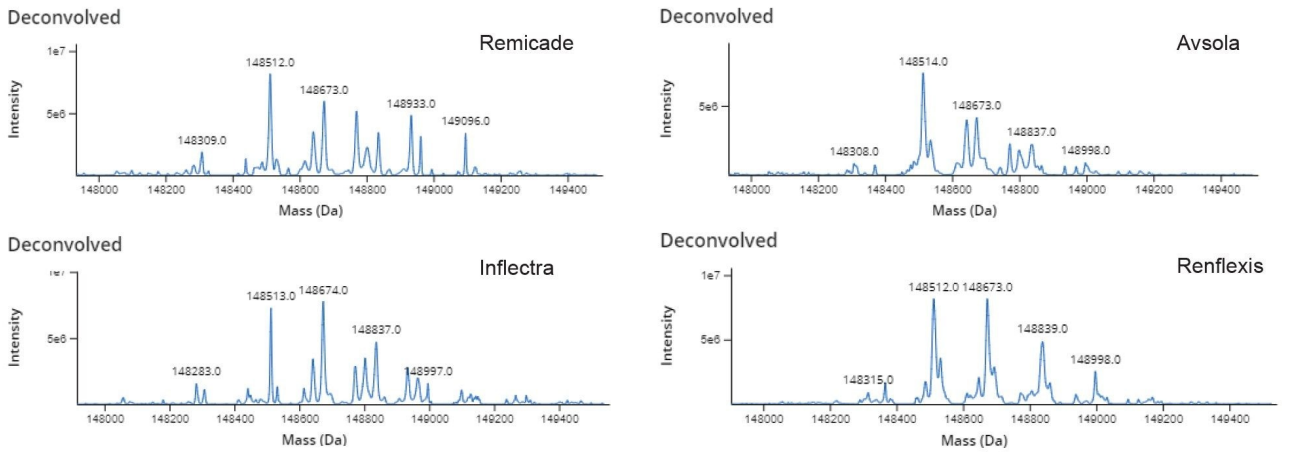

Figure 6. MaxEnt1 deconvoluted spectra from RP Intact analysis, generated with an untargeted mAb analysis in INTACT Mass app.

Charge variant profiling is used as an orthogonal approach to establish comparability and monitor stability of biosimilar drug products. An online IEX-UV-MS[8] approach enables qualitative and quantitative analysis of charge variants, generating the charge variant profile using relative %Area from the optical data, and MS detection to investigate species under each peak. Having the ability to directly investigate IEX peaks greatly reduces the need for time consuming fractionation and buffer exchange typically required to enable MS investigation of offline IEX analysis.

The infliximab biosimilars were analyzed by this method, and ACQUITY UPLC Tunable UV Detector 280 nm overlays of intact and subunit level IEX-UV-MS were generated (Figure 7 A and B, respectively). As seen from the RPLC-MS analysis, the infliximab innovator and biosimilars show a significant amount of unprocessed C-terminal lysine, resulting in basic variant species. Variants arising from unprocessed C-terminal lysine were confirmed in IEX through carboxypeptidase B digestion. The simplified profile overlay is shown in Figure 7A, inset. With online IEX-UV-MS, we were able to assign the Main, Basic 2 (B2), and B5 peaks as 0K, 1K, and 2K lysine variants, respectively.

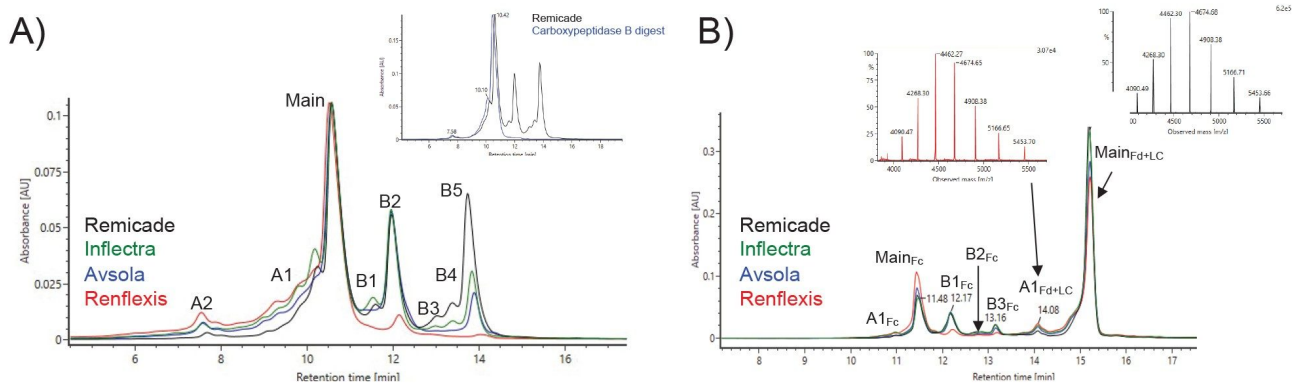

Figure 7. UV Overlay (280 nm) of (A) Intact IEX-MS analysis and (B) Subunit IEX-MS of Infliximab biosimilars. Inset of (A) shows Remicade digested with Carboxypeptidase B for removal of C-terminal lysine species as orthogonal method to confirm these variants. Insets of (B) show combined raw spectra for A1$_{Fd+LC}$ and Main $_{Fd+LC}$ peaks, MaxEnt1 deconvoluted masses of which are near isobaric.

Investigation of the remaining acidic and basic variants reveals a variety of species, including various N-glycoforms and likely deamidation. A selection of acidic and basic variants is displayed in Figure 8, including a zoomed view of the combined raw spectra for the 27+ charge states for the Main peak, two acidic variants, and one basic variant of Remicade (Figure 8A), and the resulting MaxEnt1 deconvoluted spectra (Figure 8B) for each. The acidic N-glycoforms observed for Peak A1 in Figure 8B were only observed in Remicade and Inflectra. Acidic and basic variants detected using intact IEX-UV-MS are summarized in Table 1.

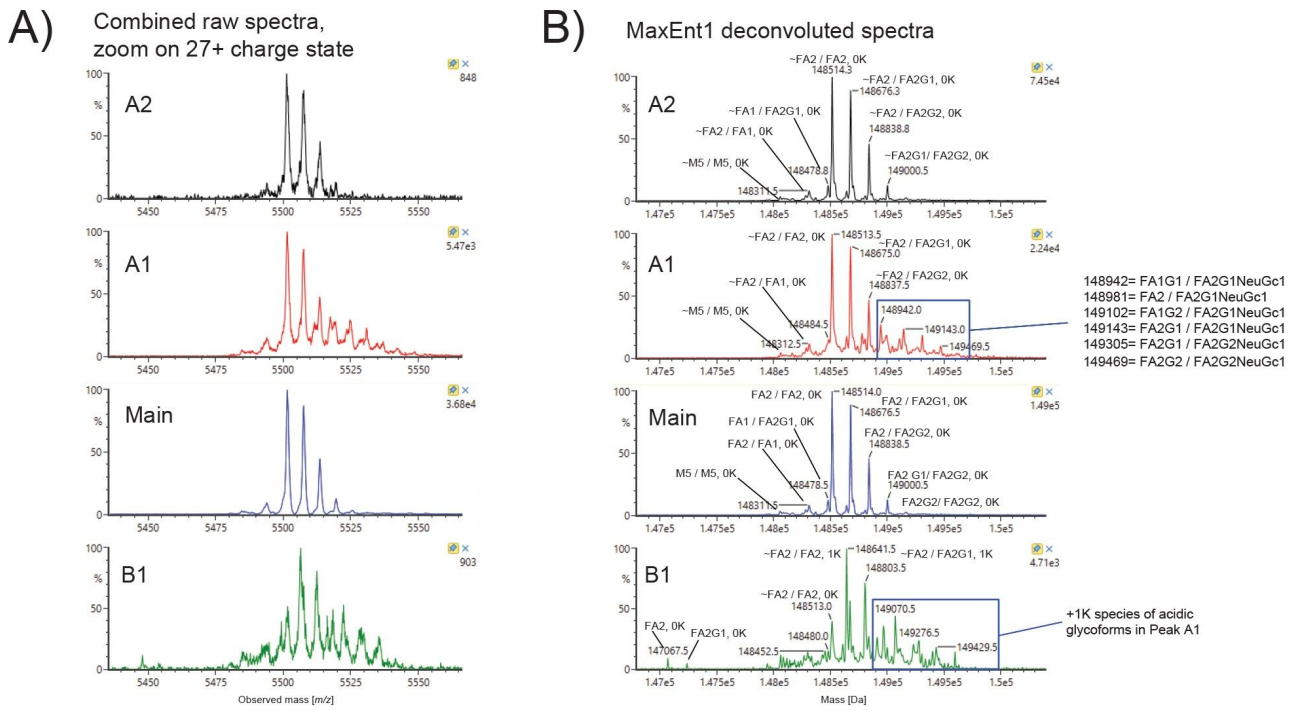

Figure 8. Intact Native IEX-MS: A) Combined raw spectra, zoom of 27+ charge state and B) MaxEnt1 deconvoluted spectra for selected acidic and basic species of Remicade (as labeled in Fig 5A).

Peak	Species detected via MS	UV Area (%) Remicade	UV Area (%) Inflectra	UV Area (%) Avsola	UV Area (%) Renflexis
A2	Deamidation* of Main peak (0K) species (all)	1.1	2.4	3.7	6.7
A1	▪ Deamidation* of Main peak (0K) species (all); ▪ [FA1/FA2G2NeuGc1, FA2/FA2G1NeuGc1, FA1G1/FA2G2NeuGc1, FA2G1/FA2G1NeuGc, ▪ FA2G1/FA2G2NeuGc, FA2G2/FA2G2NeuGc1]-Remicade and Inflectra only	15.4	26.0	19.6	31.6
Main	**FA2 (2), FA2/FA2G1, FA2G1 (2), FA2G1/FA2G2, FA2G2 (2), FA2/M5, FA2/FA1, FA2/A2, FA1/FA2G1**	**37.0**	**37.0**	**43.5**	**52.8**
B1	▪ Deamidation* of B2 peak (1K) species (all); ▪ FA2 (1), FA2G1 (1) (all); ▪ +1K species of all acidic glycoforms found in Peak A1- Remicade and Inflectra only	4.2	5.8	3.4	2.2
B2	**+1K species of all N-glycoforms in Main (0K) peak (all)**	**16.8**	**17.6**	**21.6**	**5.0**
B3	▪ Deamidation* of B5 peak (2K) species (Remicade, Inflectra & Avsola); ▪ +1K species of FA2 (1) & FA2G1 (1) found in B1 (Remicade, Inflectra, and Avsola)	3.0	1.5	1.0	0.5
B4	▪ Deamidation* of B5 peak (2K) species (Remicade, Inflectra & Avsola); ▪ +2K species of all acidic glycoforms found in Peak A1- Remicade & Inflectra only	4.0	2.1	1.0	0.3
B5	**+2K species of all N-glycoforms in Main (0K) peak (all)**	**18.5**	**7.7**	**6.1**	**0.8**

Table 1. Summary of Intact IEX-MS Results- assignment of species detected under each peak (as labeled in Fig. 5A) via MS analysis and comparison of UV area % for each infliximab sample (Average relative % from triplicate injections).

IEX-UV-MS analysis is also useful for the analysis of the IdeS-digested subunits, allowing the user to further localize important product variants. The IdeS enzyme cleaves the mAb into two main species—the covalently linked (Fd+LC) x 2 (~98 kDa) and the non-covalently associated N-glycosylated (Fc) x 2 (~50 kDa) species—which are easily separated by this IEX-UV-MS method (Figure 7B). The ability to differentiate acidic and basic variants of the Fd+LC species from the Fc species is crucial, as the Fd+LC species contains the CDR (complementary determining regions) of the mAb, which play an important role in binding. As such, modifications such as deamidation or isomerization in the CDRs may have a significant effect on binding affinity, and consequently, efficacy of the drug.

Traditionally to achieve this level of detail to assess the CDR deamidation levels, a user must rely upon peptide mapping, a method requiring significantly longer sample preparation, LC-MS methods, and complex data analysis. Subunit level IEX-UV-MS can be utilized as a "first pass" screening method for Fd+LC acidic variants, proving a valuable time-saving alternative to numerous peptide mapping analyses. In addition, the chromatographic separation of the Fc C-terminal lysine variants can be used as an orthogonal method of quantitation, when integration of the optical data is applied. The full details of species identified for the infliximab biosimilar study are captured in Table 2.

Peak	RT (min)	Species detected via MS	UV Area (%) Remicade	UV Area (%) Inflectra	UV Area (%) Avsola	UV Area (%) Renflexis
$A1_{Fc}$	11.0	▪ Deamidation* of $Main_{Fc}$ species (all), ▪ [FA2/FA2G1NeuGc1, FA2G1/FA2G1NeuGc1, FA2G2/FA2G1NeuGc1, FA2G2/FA2G2NeuGc1]-Remicade and Inflectra only	2.5	5.2	2.5	6.3
$Main_{Fc}$	**11.5**	**FA2 (2), FA2/FA2G1, FA2G1 (2), FA2G1/FA2G2, FA2/A2 (all)**	**49.1**	**48.2**	**59.0**	**80.5**
$B1_{Fc}$	12.2	▪ +1K Species of all N-glycoforms in $Main_{Fc}$ (all); ▪ FA2/M5, FA2G1/M5, FA1/FA2, FA1/A2, FA1/A2G1, FA1/FA2G1, FA1/A2G2 (all)	27.0	29.0	27.9	7.9
$B2_{Fc}$	12.8	▪ M5 (2) (all); ▪ Deamidation* of main N-glycoforms of +2K species in $B3_{Fc}$ (all) ▪ +1K species of (FA2/M5, FA2G1/M5, FA1/FA2, FA1/A2, FA1/A2G1, FA1/FA2G1, FA1/A2G2 in $B1_{Fc}$) (all)	8.8	7.2	3.8	1.9
$B3_{Fc}$	13.2	▪ +2K Species of all N-glycoforms in $Main_{Fc}$ (all); ▪ FA2 (1), FA2G1 (1) (all)	12.6	10.5	6.8	3.3
$A1_{Fd+LC}$	14.1	Deamidation* of all $Main_{Fd+LC}$ peaks (all)	2.4	6.0	5.7	9.5
$Main_{Fd+LC}$	**15.2**	**$(Fd+LC)_2$, $(Fd+LC)_2$ + Glycation (all)**	**97.6**	**94.0**	**94.3**	**90.5**

Table 2. Summary of Subunit IEX-MS Results- assignment of species detected under each peak (as labeled in Fig. 5B) via MS analysis and comparison of UV area % for each infliximab sample (average relative % from triplicate injections) Fc peaks and Fd+LC peaks are grouped together for relative quantitation.

The results from RPLC-MS and IEX-UV-MS are in agreement regarding C-terminal lysine variants and N-glycoform distribution. For C-terminal lysine variants, both Remicade and Inflectra were observed with ~48% retained, Avsola was observed with ~35%, and Renflexis with only ~5% (based on relative MS quantitation from Intact RPLC-MS and UV integration of Fc species from subunit IEX-UV-MS). Overall N-glycoform distribution observed with intact RPLC-MS and intact/subunit IEX-UV-MS are comparable for each biosimilar. The generation of consistent results from orthogonal methodologies is looked favorably by reviewers, and provides

for future flexibility in establishing methods for lot release of the biosimilar product.

Conclusion

Robust and efficient comparability assessment is critical to ensure the safety and efficacy of biosimilar mAb drug products in support of their regulatory approval. This application note demonstrates the use of intact/subunit level RPLC-MS and IEX-UV-MS on the new Xevo G3 QTof System to assess comparability of infliximab innovator and three biosimilars.

The most notable differences observed between the infliximab biosimilars are unprocessed C-terminal lysine variants, N-glycoforms, and charge variant profiles. Such differences would be expected and would need to be risk-assessed as part of the biosimilar submission. There is good agreement between results from RPLC-MS and IEX-UV-MS analyses for C-terminal lysine variants and N-glycoform distribution. In addition, subunit level RPLC-MS provides additional detail of light chain and Fd glycation and Fc N-glycosylation. IEX-UV-MS at intact and subunit level offers traditional UV-based quantitation of charge variants with the added benefit of MS detection for further investigation of each charge variant profile. Overall, the advanced capabilities of the Xevo G3 QTof operated under control of the waters_connect informatics platform to perform intact/subunit RPLC-MS and IEX-UV-MS methods allows for detailed orthogonal characterization and comparability assessment of mAb drug products and biosimilars.

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ACQUITY UPLC Tunable UV Detector <https://www.waters.com/514228>

Xevo G3 QTof </nextgen/br/pt/products/mass-spectrometry-systems/xevo-g3-qtof.html>

Biopharmaceutical Platform Solution with UNIFI <https://www.waters.com/10195515>

waters_connect <https://www.waters.com/waters/nav.htm?cid=135040165>

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