Zydus
dedicated to life

Exemptia™
Adalimumab

Global Development of Biosimilar Adalimumab

Zydus has taken a Two Phased Approach to Developing Biologics

Exemptia
Adalimumab

Phase 1 : Develop Biosimilars – Recombinant Proteins and Monoclonal Antibodies

- **Build Capabilities**
- **Build a Development Engine**
- **Build a Biosimilars Pipeline**

Phase 2 : Develop Novel Biologics and Antibody Drug Conjugates

- **Incremental improvement Novel Biologics or Biobetters**
- **Novel Targets**
- **Mabs Discovery Engine**

Capabilities Built in Biologics: Bioreactor Process

Exemptia

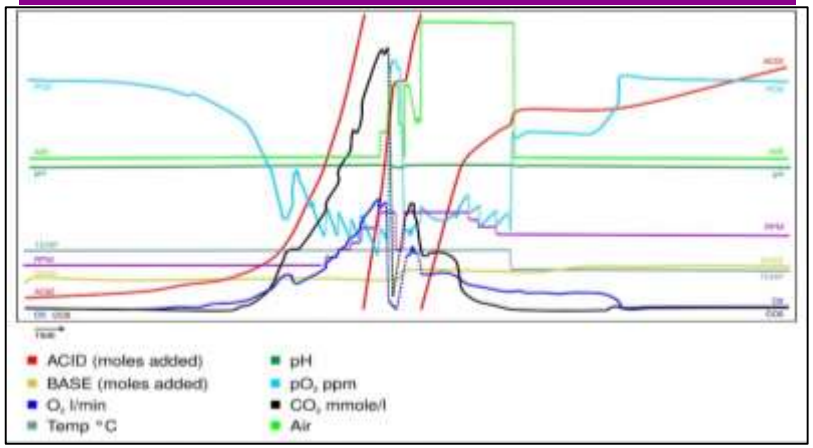
Process Iteration

Process Optimisation

Pilot Process

Scale-up

Process Controls



Comparable Toxicity between Zydus Adalimumab and Reference Product in the key comparability toxicity study in rats

Capabilities Built in Biologics: Protein Purification

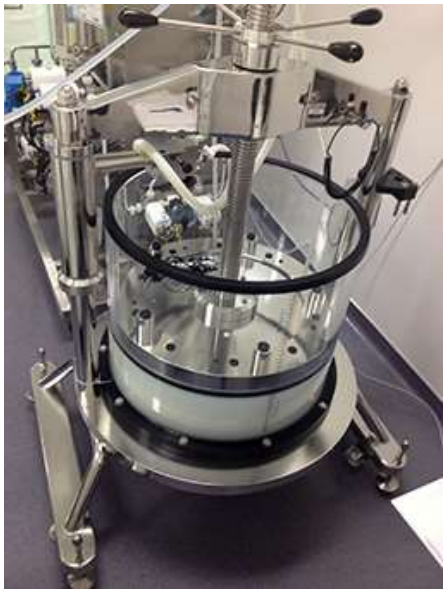
Exemptia

Purification Systems

Tangential Filtration

Columns

Centrifugation



Capabilities Built in Biologics: Characterization

Exemptia Adalimumab

UPLC/HPLC

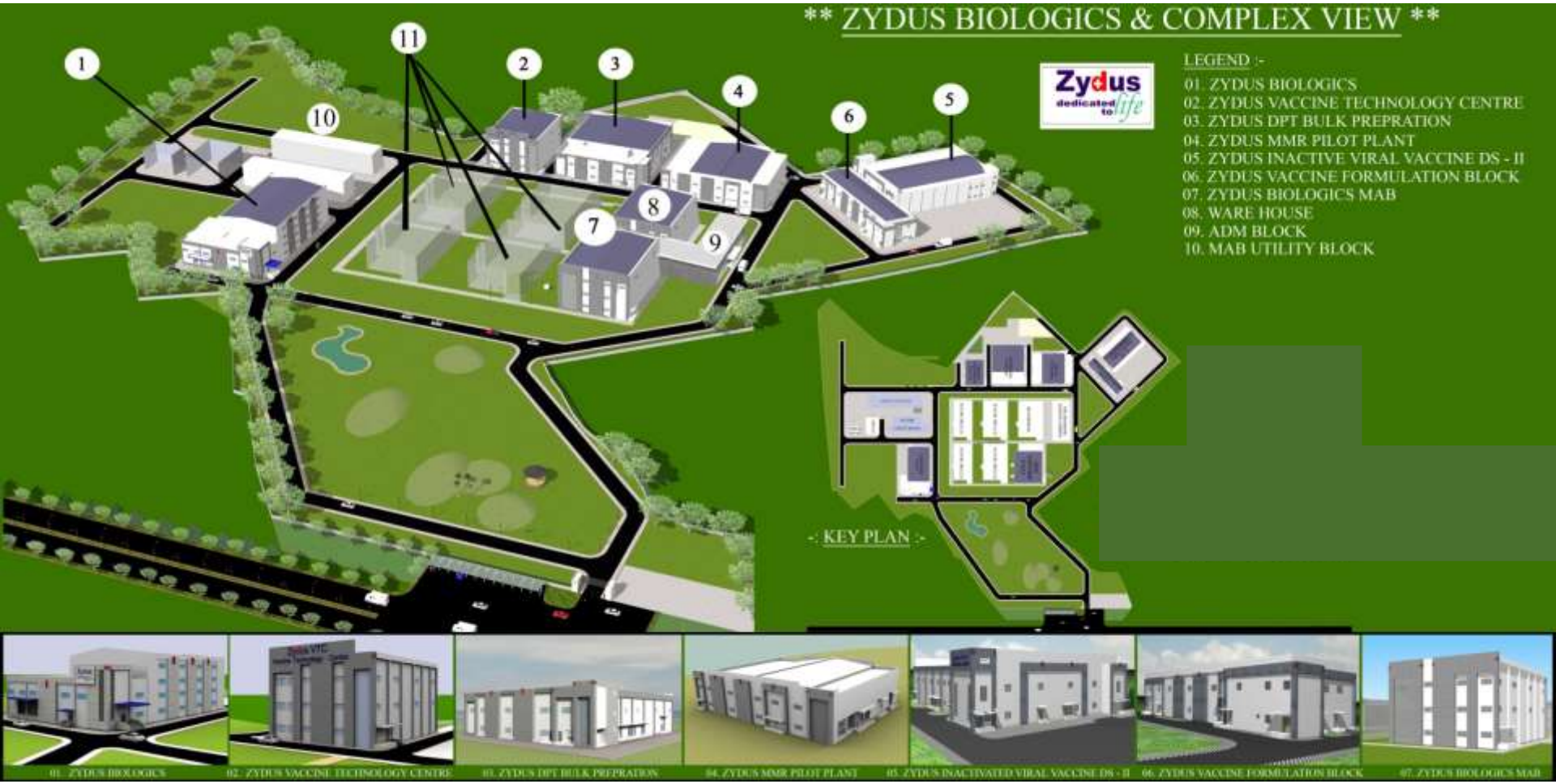
Gel Electrophoresis

Maldi Tof

Circular Dichroism

CZE

Zydus Biologicals Manufacturing Park: Biologics & Vaccines Manufacturing Facilities



Biologics Manufacturing Facilities at Ahmedabad

Exemptia Adalimumab

Unit I

- cGMP Drug Substance multi-product facility for Recombinant Proteins
- G-CSF, PEGG-CSF, IFN alpha 2b, PEG IFN alpha 2b, PTH and EPO
- Scale 20L; 400 RBs

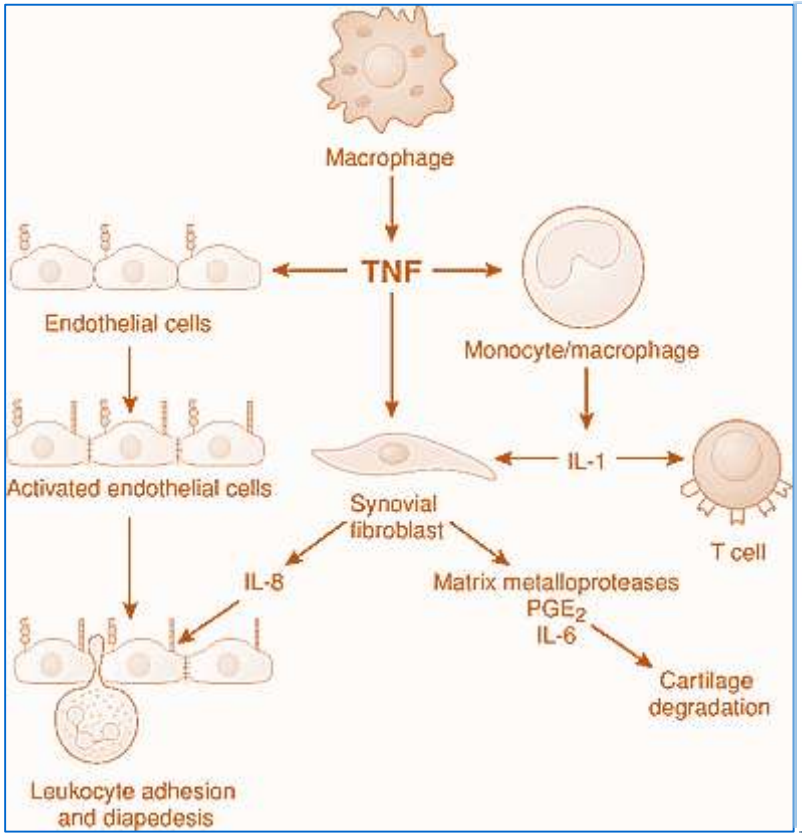
Unit II

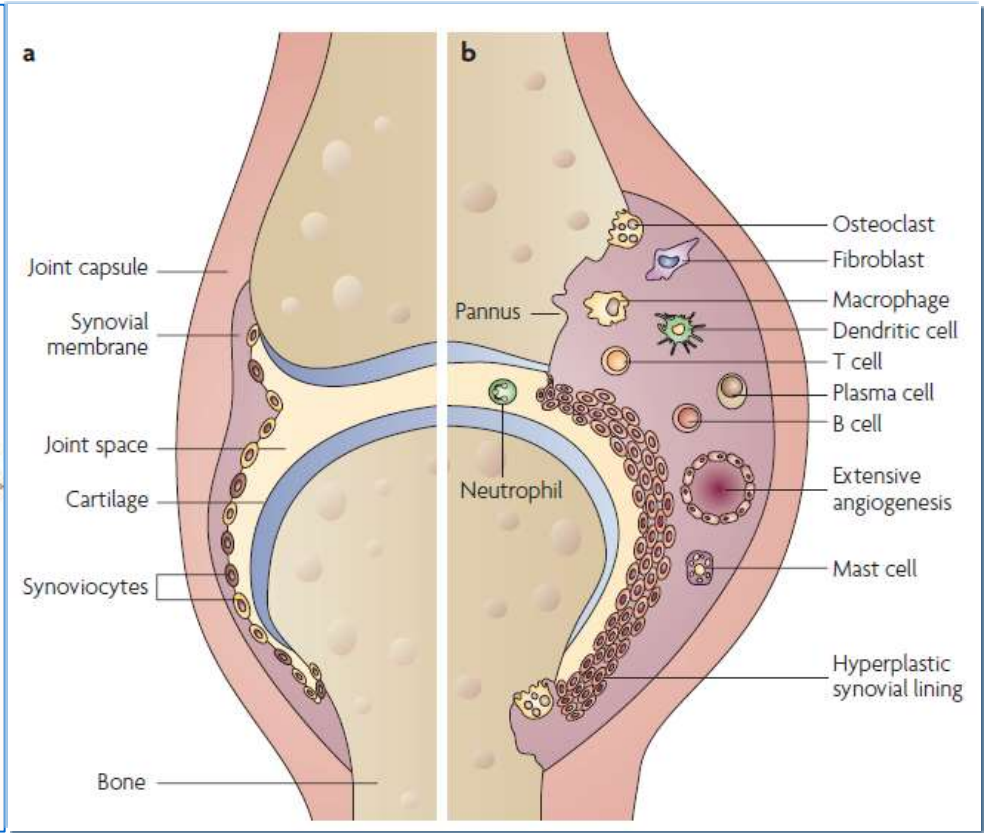
- cGMP Drug Substance multi-product facility for Monoclonal Antibodies
- Adalimumab, Trastuzumab, Bevacizumab and Rituximab etc.
- Two independent production streams with 2X 5KL and 1X 1KL bioreactors

Unit 9

- cGMP Drug Product multi-product facility for Biologics
- Liquid and lyophilized vials, PFS and Cartridges
- Liquid/Lyophilized vial line - 1; PFS line - 1; Cartridge line – 1

Adalimumab – A Product for TNF-mediated Disease





- **Adalimumab binds TNF-α so that it cannot bind to its receptor.**
- **Adalimumab is equipped to eliminate cells that produce TNF-α by ADCC/CDC or Apoptosis**

Biosimilars: EMA Guidelines

- "A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product)"

- "A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise."

- "…the success of developing a biosimilar will depend on the ability to produce a close copy to the reference medicinal product…"

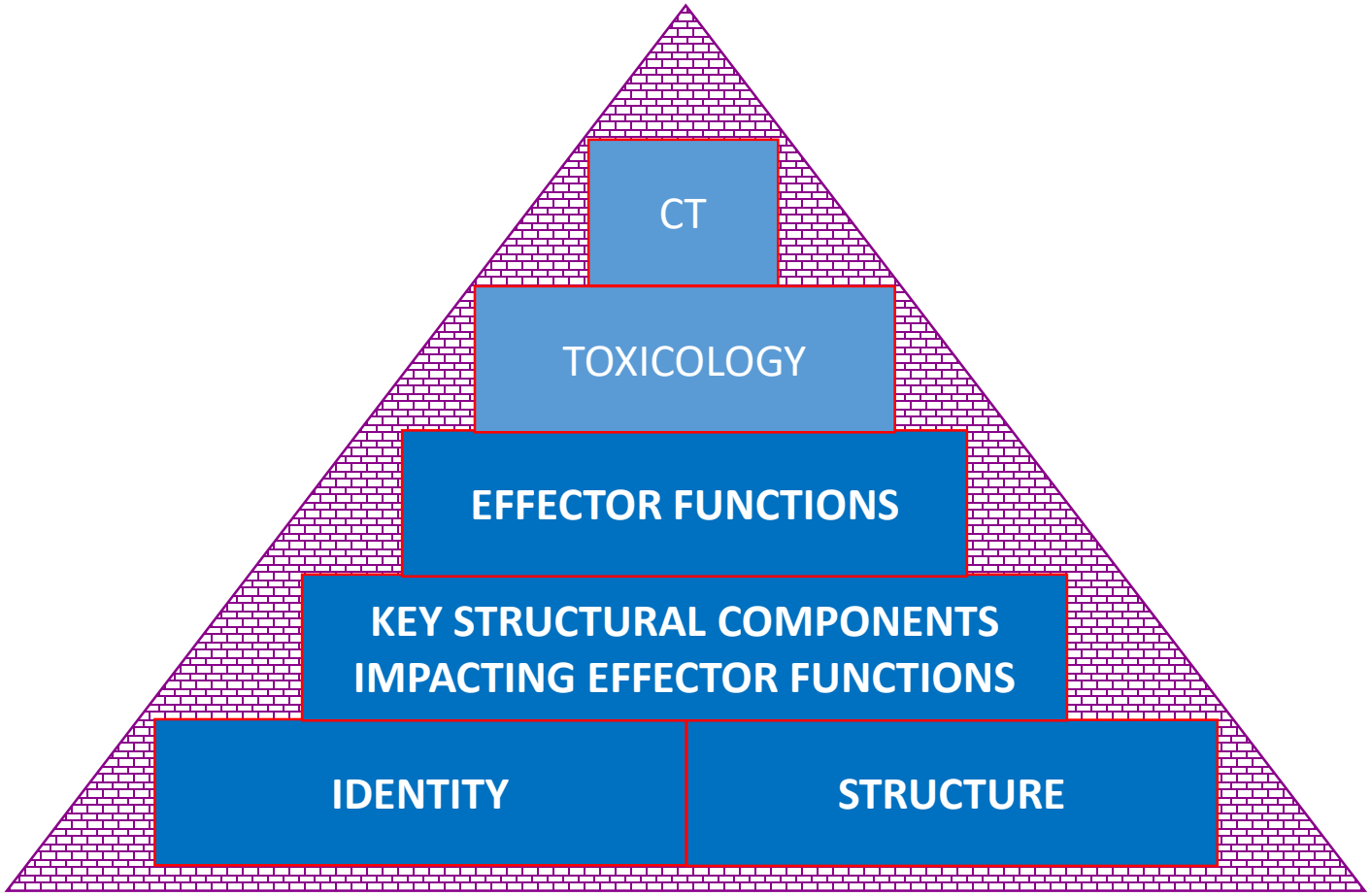
Biosimilars: US FDA Guidelines

- "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components"
- "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product"
- "The result of the comparative analytical characterization may lead to one of four assessments…: Not similar, Similar, Highly similar, or Highly similar with fingerprint-like similarity"

FDA on Fingerprint like Similarity: "…analytical similarity based on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences. …"

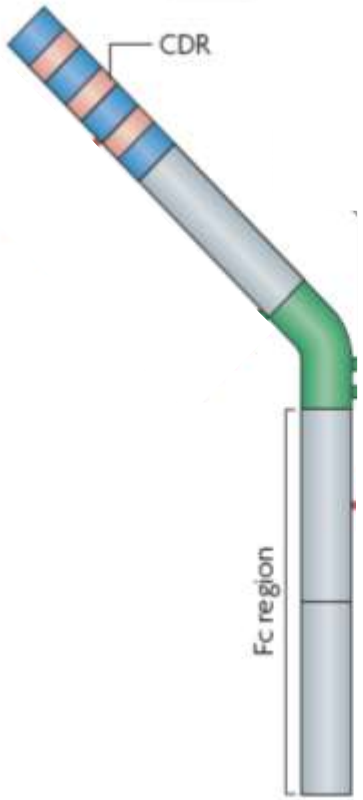
Adalimumab being a global program, we have designed it with a fingerprint like similarity to the reference product

Adalimumab – Process Adopted for Establishing Biosimilarity



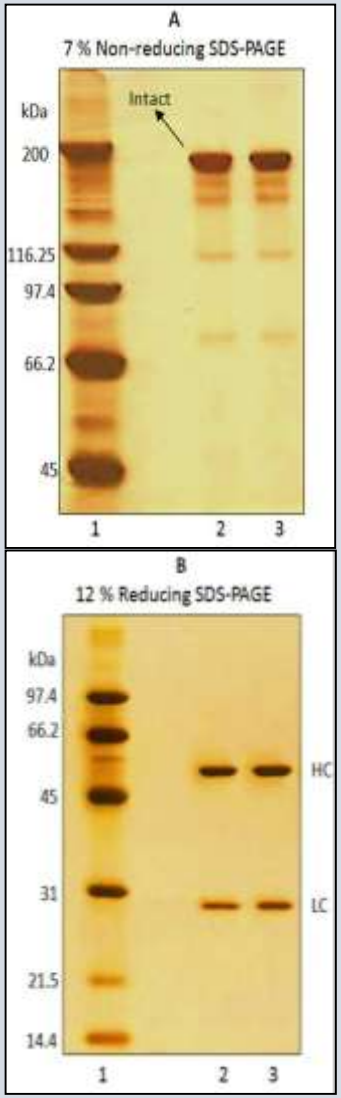
Build a Strong Foundation of Analytical Characterization to Minimize the Dependence on Clinical Data for Establishing Biosimilarity

Demonstration of Biosimilar IDENTITY by Comparing Product Profile



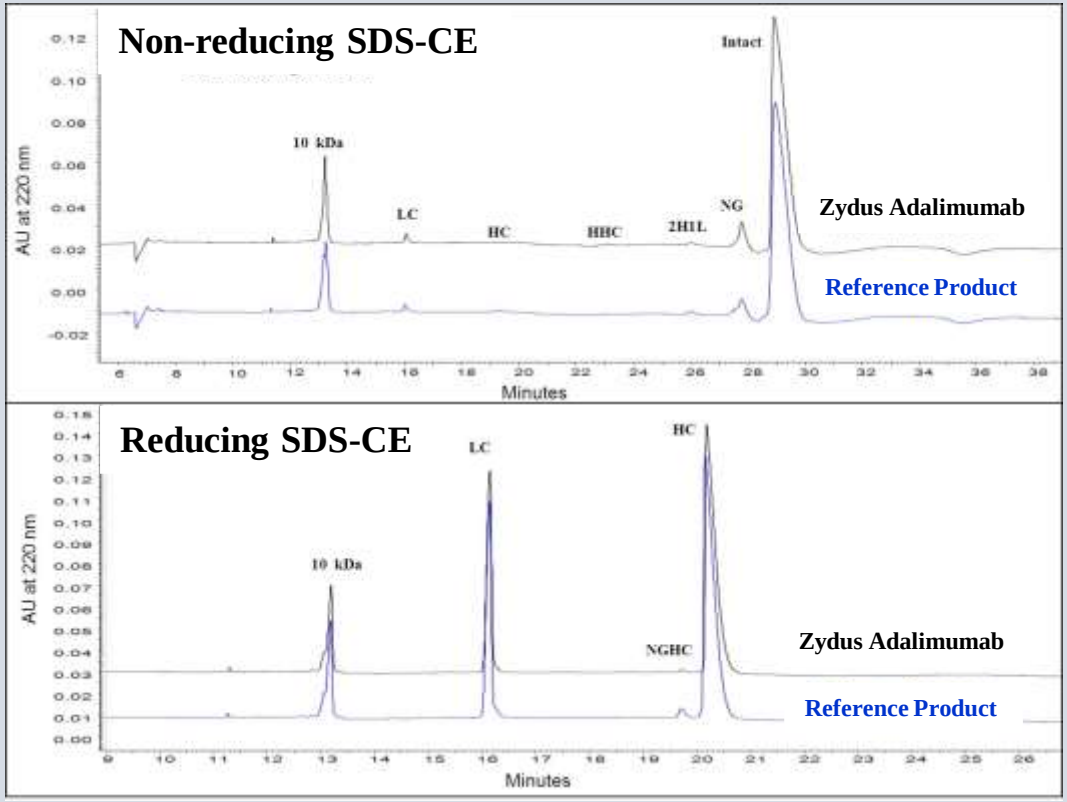
IDENTITY - Polypeptide Profile & Molecular Weight

Polypeptide Profile by SDS-PAGE



Lane 1 – Molecular weight marker
Lane 2 – Reference Product
Lane 3 – Zydus Adalimumab

Profile By SDS-CE

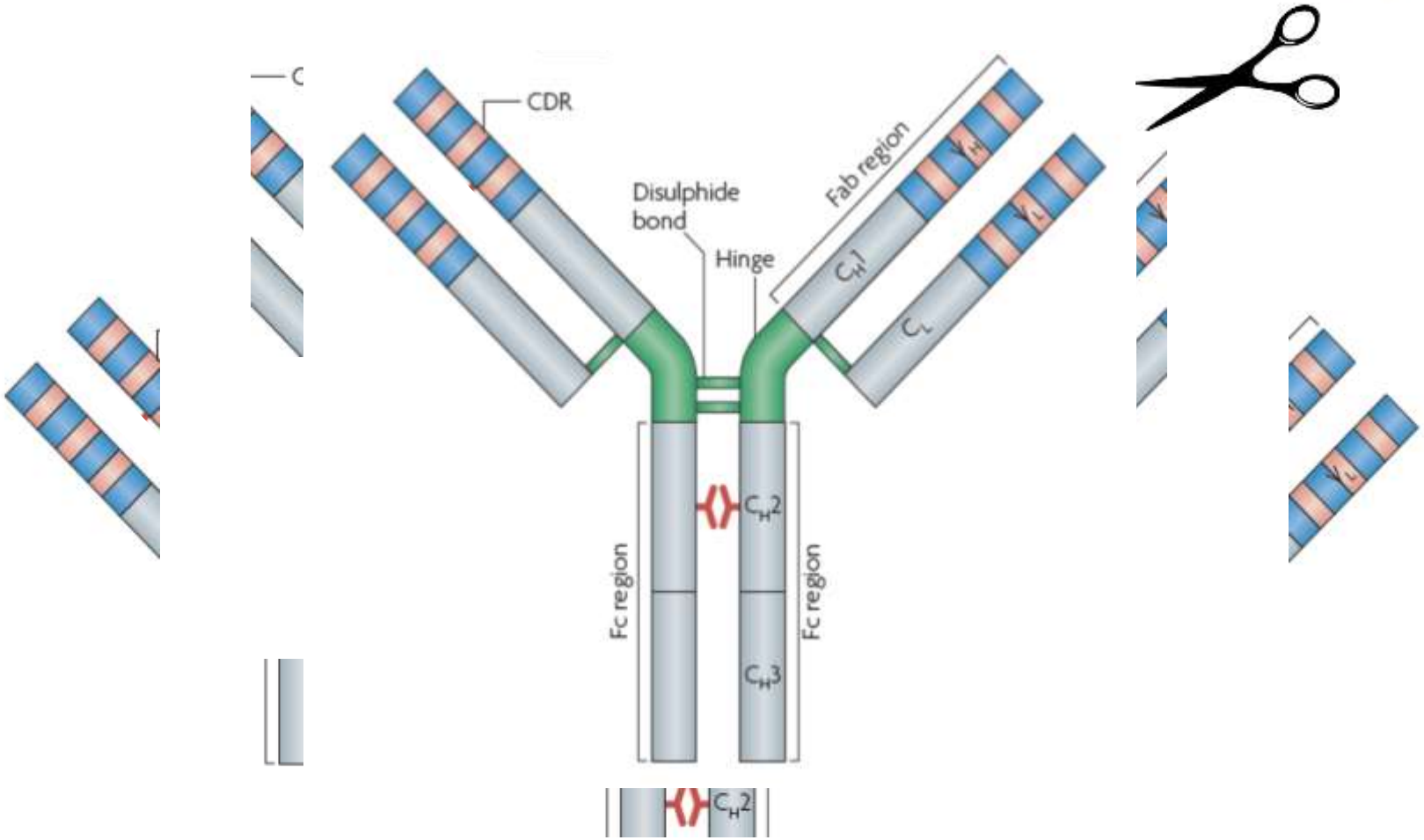


Molecular Weight by Maldi-Tof

Samples	Intact mass (kDa)	Heavy-chain mass (kDa)	Light-chain mass (kDa)
Reference Product	148.3	50.5	23.2
Zydus Adalimumab	148.3	50.5	23.2

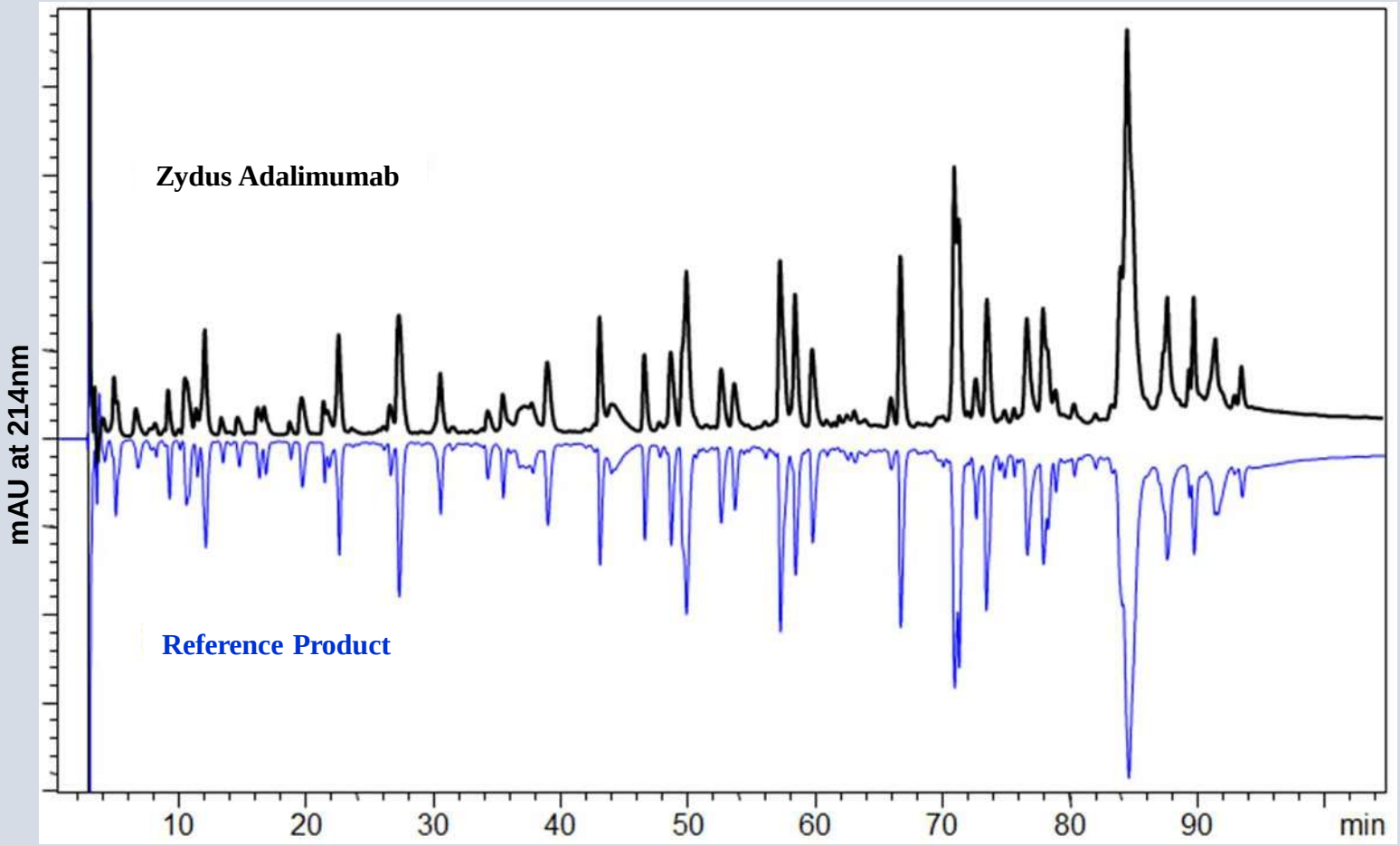
Highly Comparable Polypeptide Profile and Molecular Weight

IDENTITY - Peptide Mapping



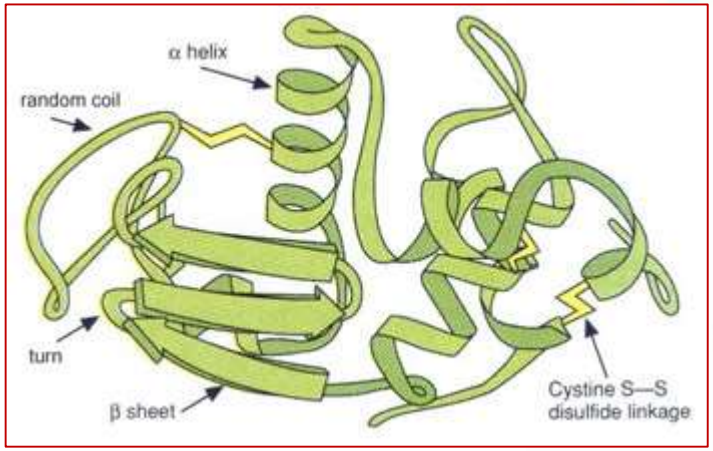
IDENTITY - Peptide Mapping

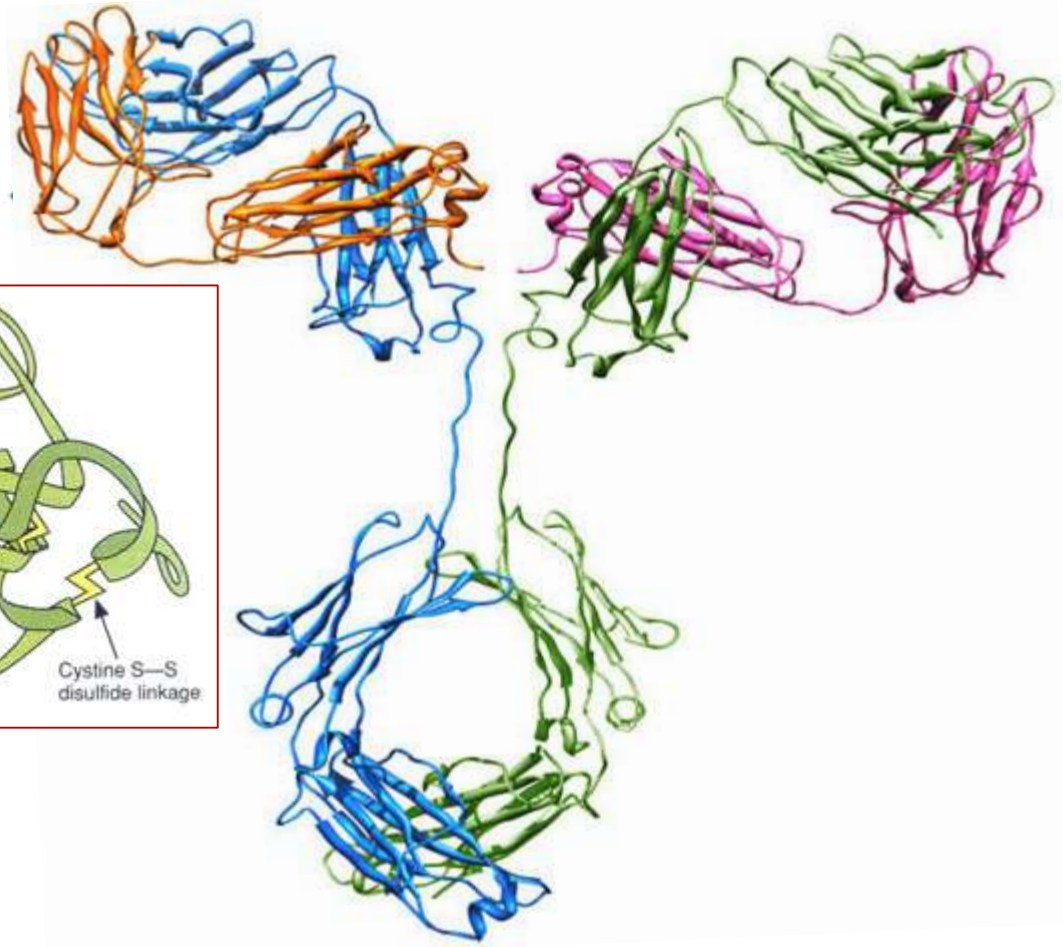
Peptide Mapping by RP-HPLC-UV Analysis of Tryptic Digests



Highly Comparable Tryptic Map & Sequence of the Tryptic Fragments

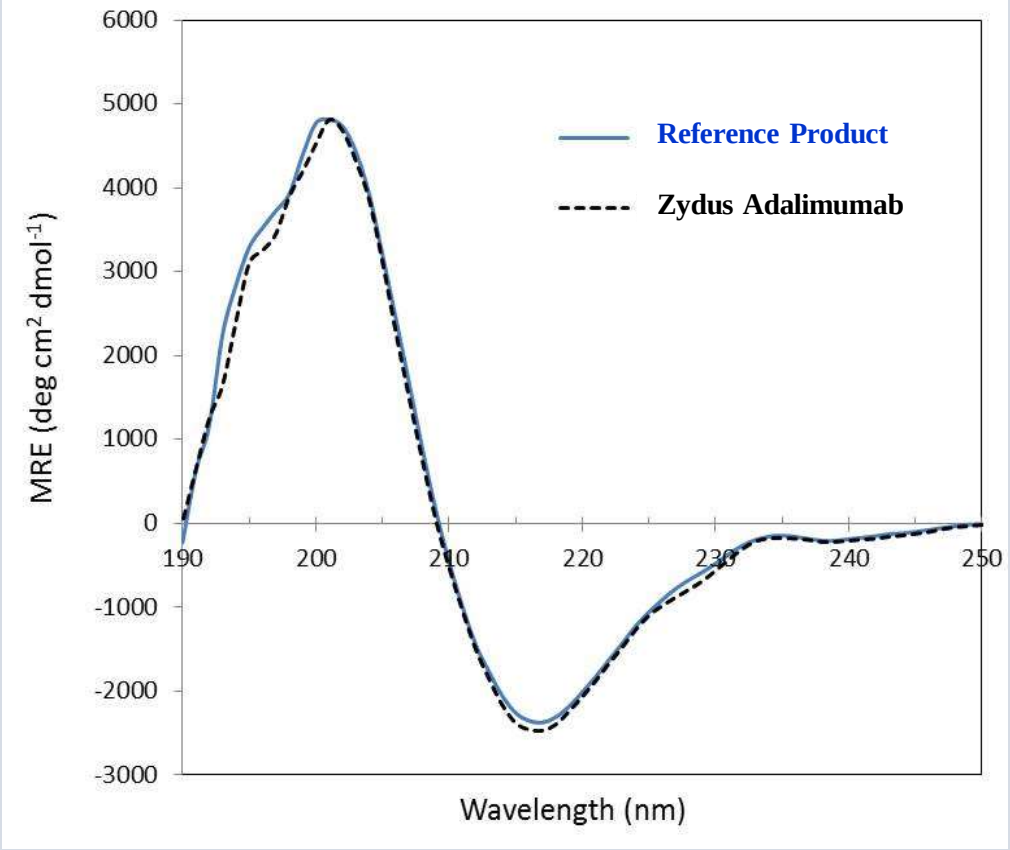
Demonstration of Biosimilar STRUCTURE



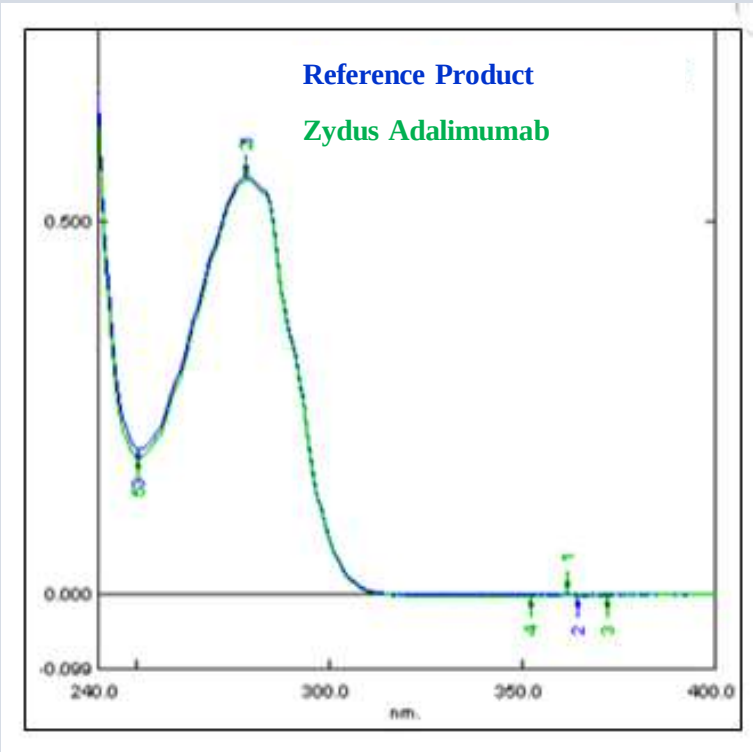


STRUCTURE – Secondary Structure and Overall Integrity

Circular Dichroism Analysis of Secondary Structure

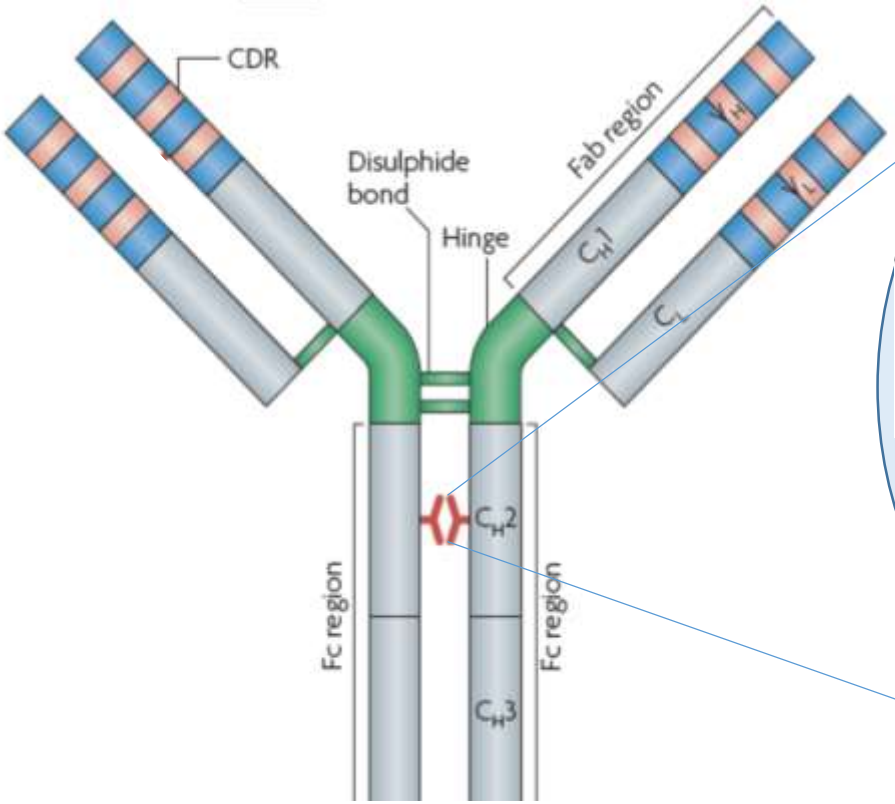


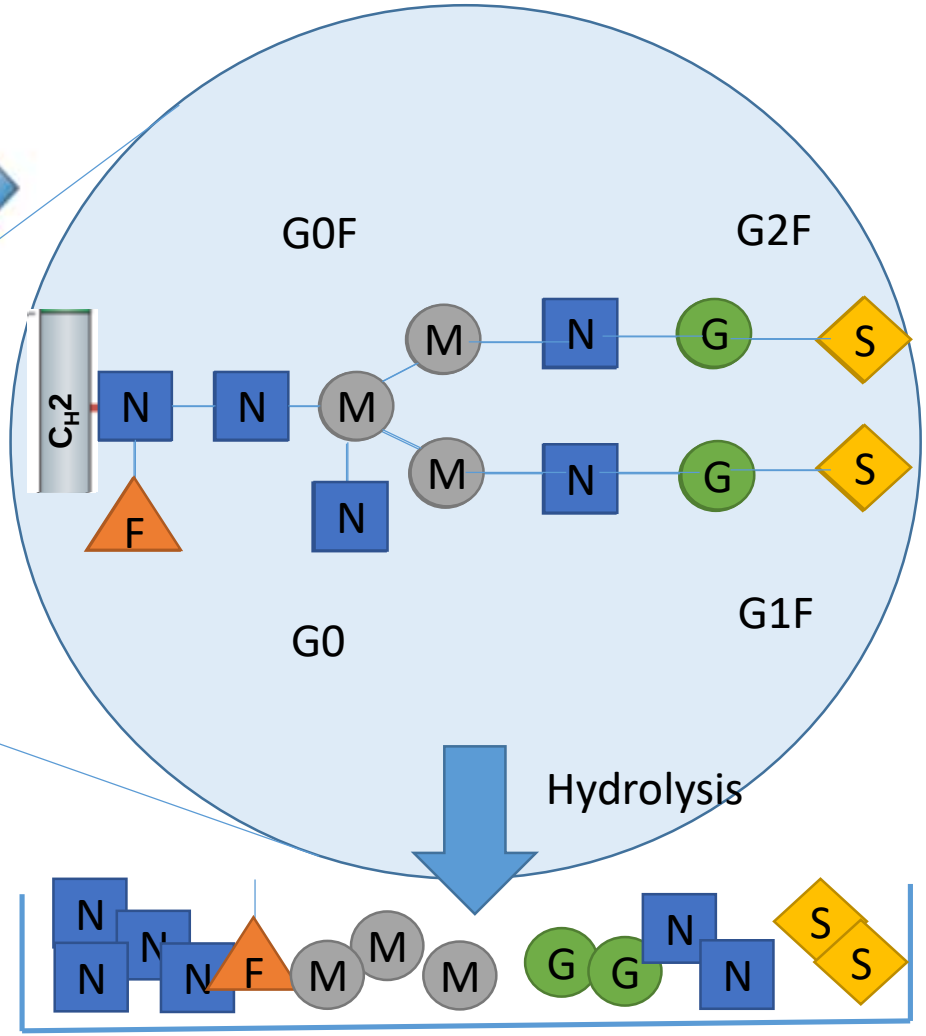
Near UV Analysis for Overall Integrity



Highly Comparable Secondary Structure & Overall Integrity. Further confirmed by Free Thiol and Disulphide Bridge Mapping

STRUCTURAL COMPONENTS – Structural Elements of Carbohydrate Tree

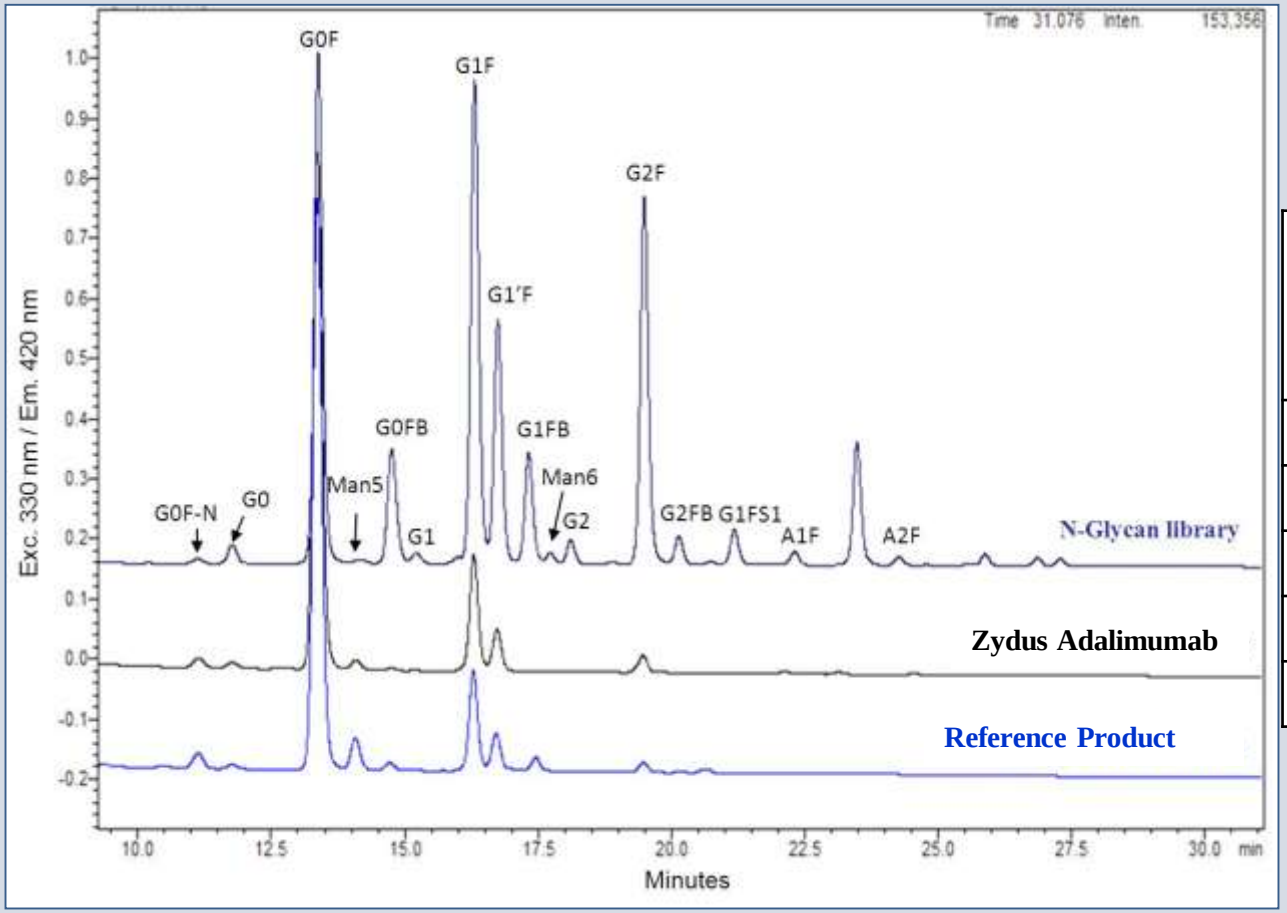




Carbohydrate structural elements directly impact Antibody Effector Function

Highly Comparable Carbohydrate Structural Elements

UHPLC



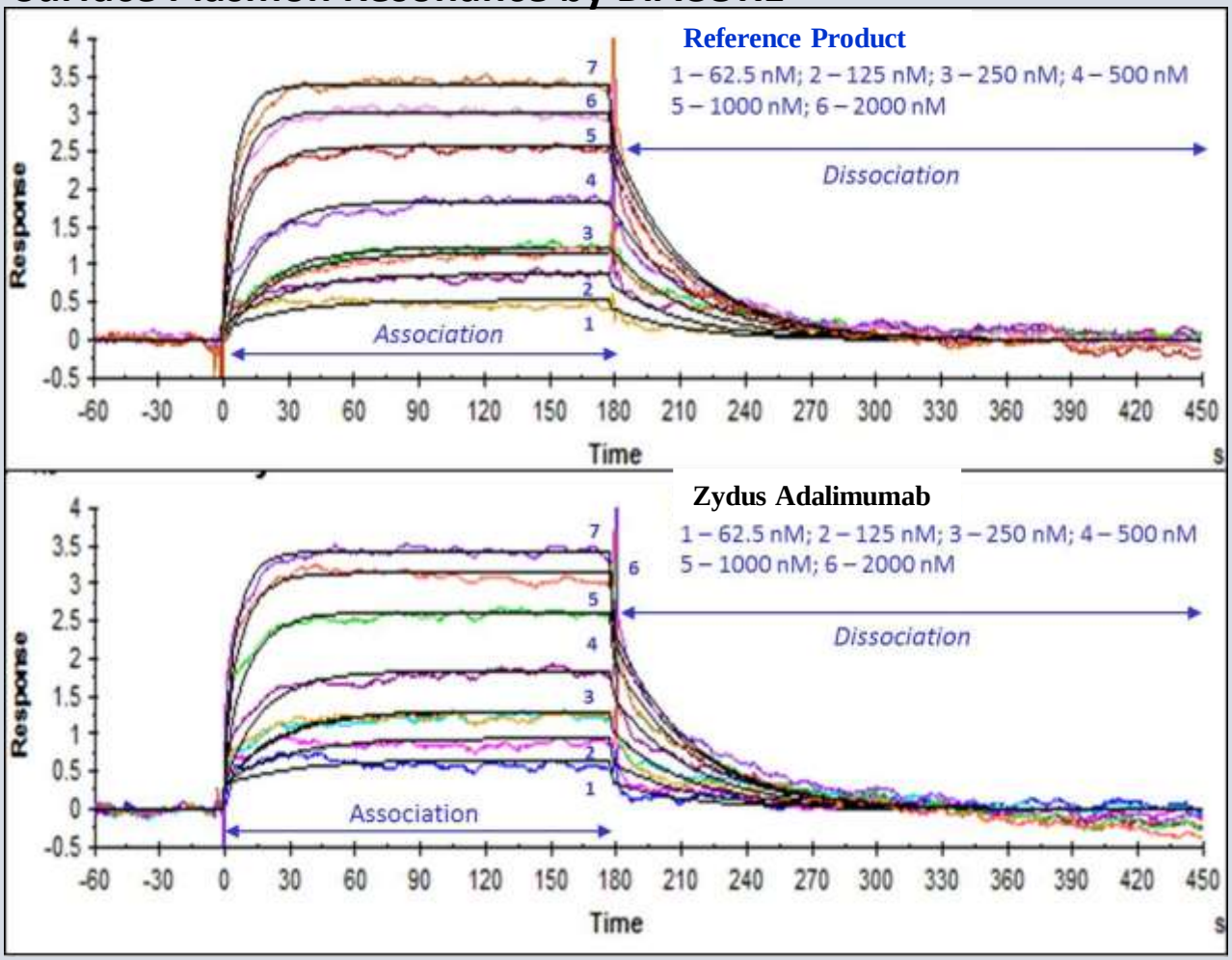
HPAEC-PAD

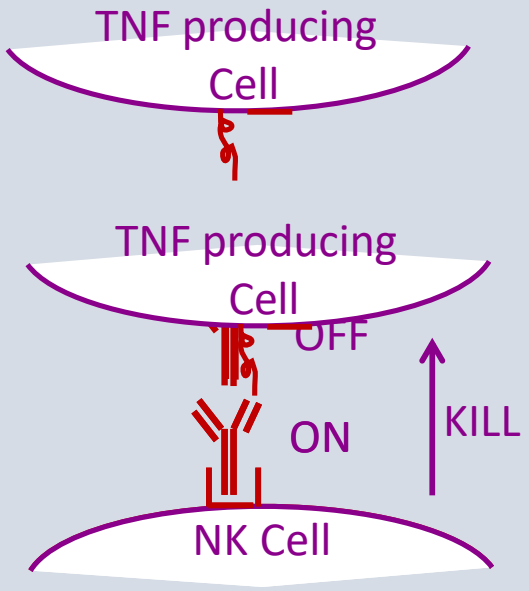
Sugar	µg sugar / mL protein	
	Reference Product	Zydus Adalimumab
Fucose	97	105
Galactosamine	< 12.5*	< 12.5*
Glucosamine	389	374
Galactose	25	30
Mannose	297	311

Highly comparable glycan structures and monosaccharide content between Zydus Adalimumab and Reference Product – Comparable effector functions of ADCC & CDC

Highly Comparable EFFECTOR FUNCTIONS – Binding to FcγRIII

Surface Plasmon Resonance by BIACORE





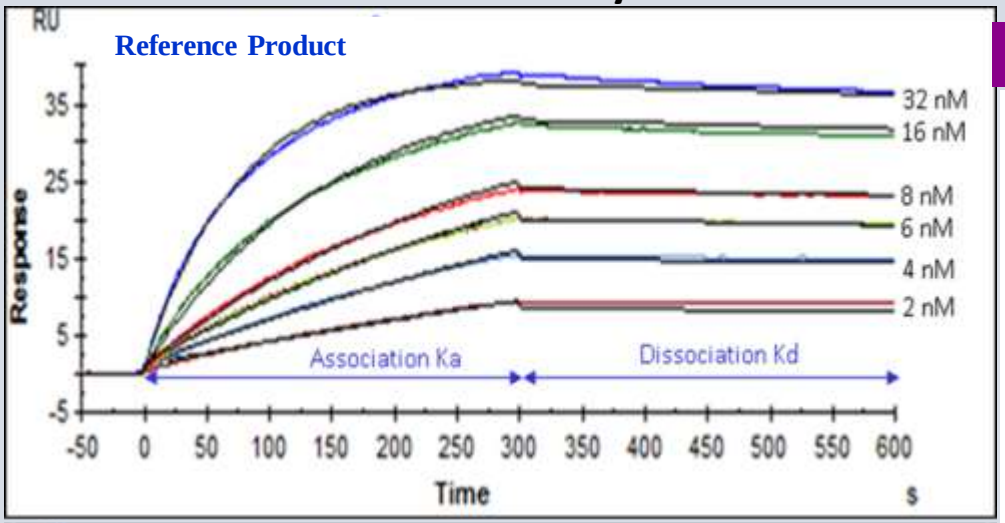
Reference Product – KD 4.47×10^{-7}

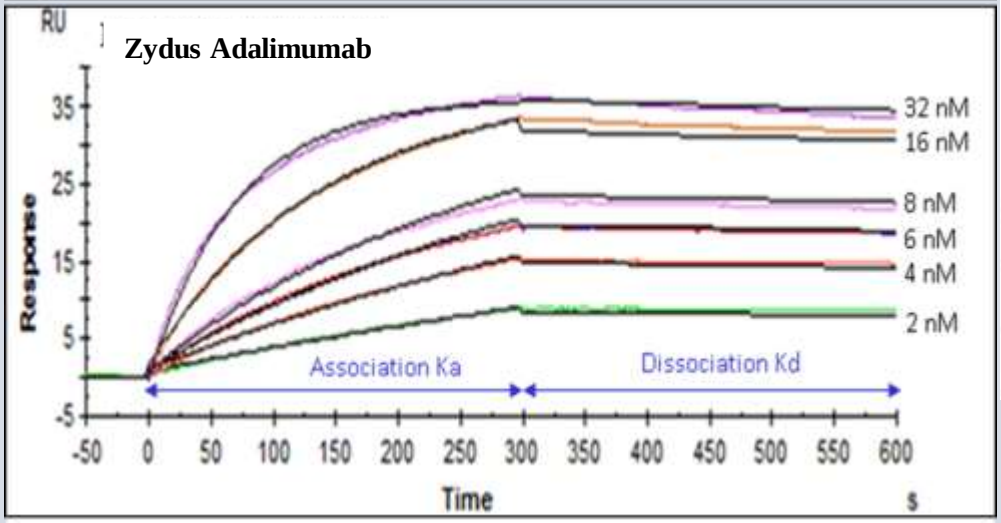
Zydus Adalimumab – KD 4.89×10^{-7}

Highly comparable ability to bind NK Cells – Comparable effector function of ADCC

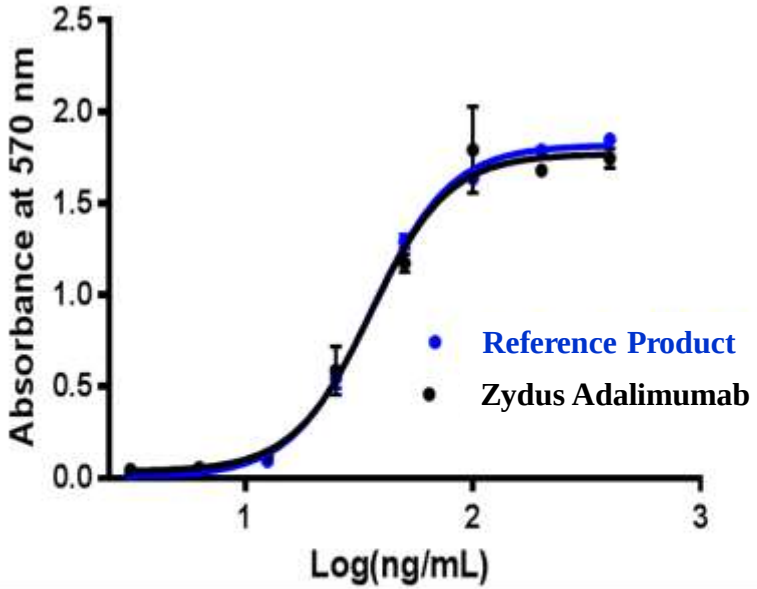
Highly Comparable EFFECTOR FUNCTIONS – Binding to TNF alpha

Surface Plasmon Resonance by BIACORE





Ability to Stop TNF-mediated killing of L929 cells

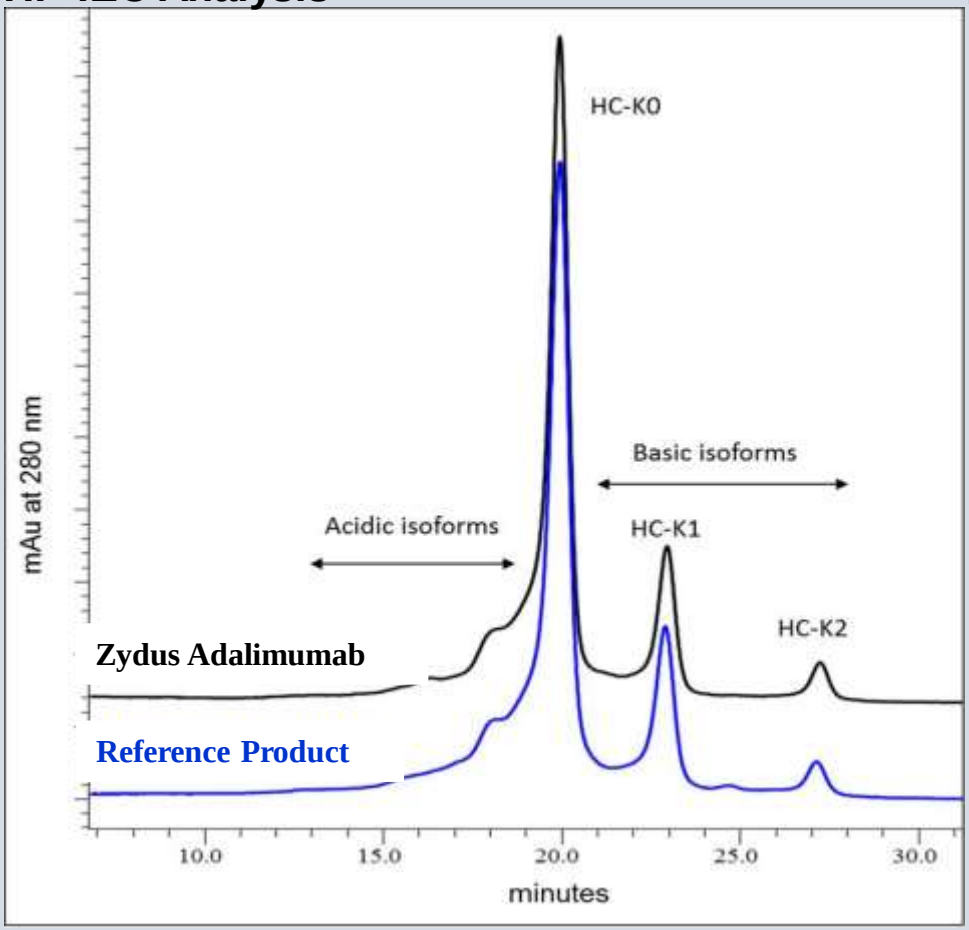


Samples	EC_{50} ng/mL	Relative Potency
Originator HUMIRA®	35.66	-
Biosimilar ZRC-3197	35.50	100.40%

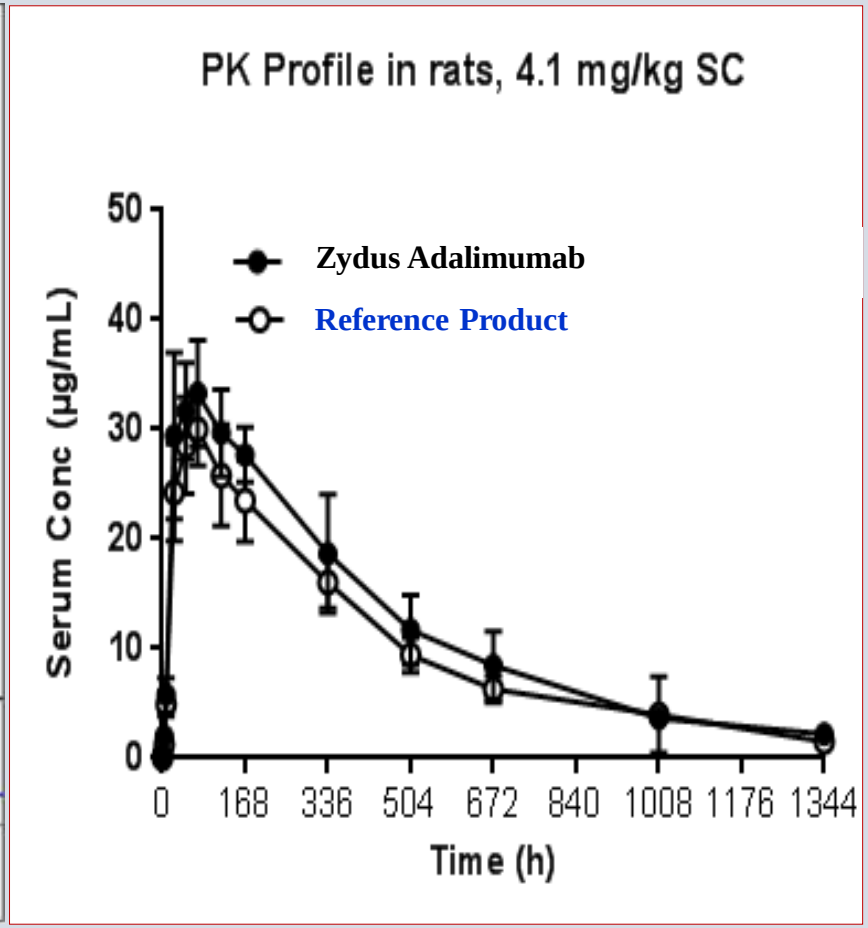
Highly comparable ability to bind & release TNF α – Comparable Neutralization

Highly Comparable STRUCTURAL COMPONENTS Impacting EFFECTOR FUNCTIONS – Charge Variant Profile

HP-IEC Analysis

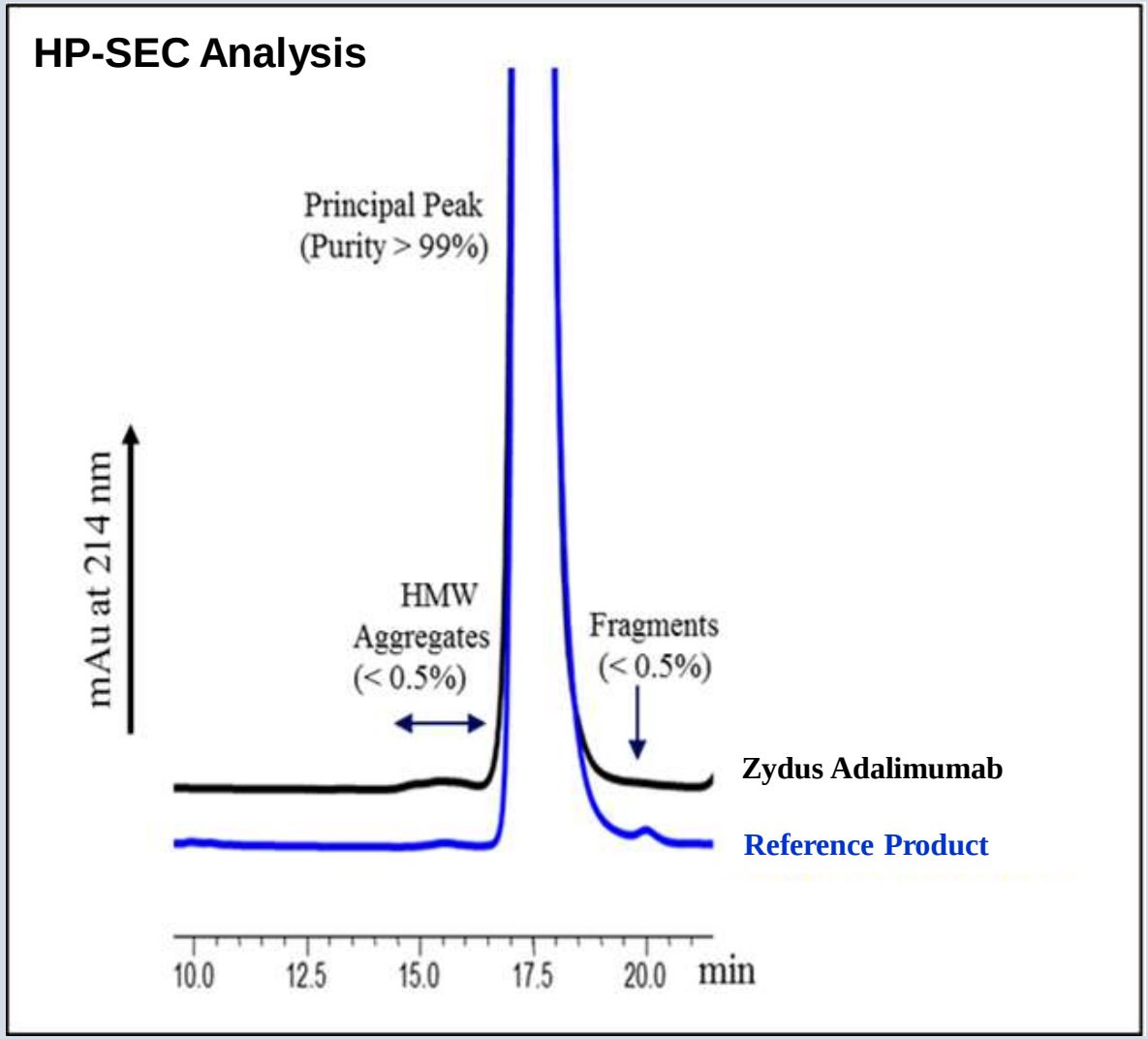


PK



Highly comparable charge variant profile also confirmed by LCMS-MS & cIEF – Comparable Molecular Stability and Bioavailability

Highly Comparable Molecular and Process PURITY



- Highly comparable purity; very low aggregate content – Low Immunogenicity
- High level of process purity and hygiene (low ppm of HCD and low pg/mg of HCD)

Highly Comparable Process PURITY– Virus Free Cell Banks

S.No.	Test name
1	Sterility
2	Mycoplasma by culture
3	Mycoplasma by PCR
4	Isoenzyme Analysis
5	Transmission Electron Microscopy
6	Embryonated egg assay by Allontoic route
7	Embryonated egg assay by Yolk sack route
8	In- vitro assay using MRC-5 detector cells
9	In- vitro assay using Vero detector cells

S.No.	Test name
10	In- vitro assay using CHO detector cells
11	In- vivo assay using Adult mice
12	In- vivo assay using Suckling mice
13	In-vitro assay for detection of Bovine virus
14	In-vitro assay for detection of porcine virus
15	Infectivity assay for retrovirus (S+L-)
16	Hamster Antibody Production
17	Gene Sequencing
18	Gene Copy number

A total of 18 *in vitro* and *in vivo* tests confirm cell banks to be free of viruses and any other adventitious agents [ICH Q5D and Q5A(R1)]

Comparable TOXICITY Findings

Study Title	Doses	Observations
Repeated Dose Toxicity Study in Rats by Subcutaneous Route	Zydus Adalimumab: 0, 4.1, 20.5 and 41 mg/kg/week ReferenceProduct: 4.1 mg/kg/week Weekly once for four weeks	• No mortality and adverse clinical signs of toxicity up to 41 mg/kg • Neurobehavioral & Ophthalmic Examination, Clinical examination, Body Weight & Feed Intake, Hematology, Serum Biochemistry & Urinalysis, Gross Pathology, Organ Weight, Bone marrow examination, Histopathology – All Normal up to the high dose of 41 mg/kg. • Comparable with Reference Product • Immunogenicity - Comparable between Adalimumab treated and reference product treated groups

Comparable Toxicity between Zydus Adalimumab and Reference Product in the key comparability toxicity study in rats

Comparable TOXICITY Findings

Exemptia
Adalimumab

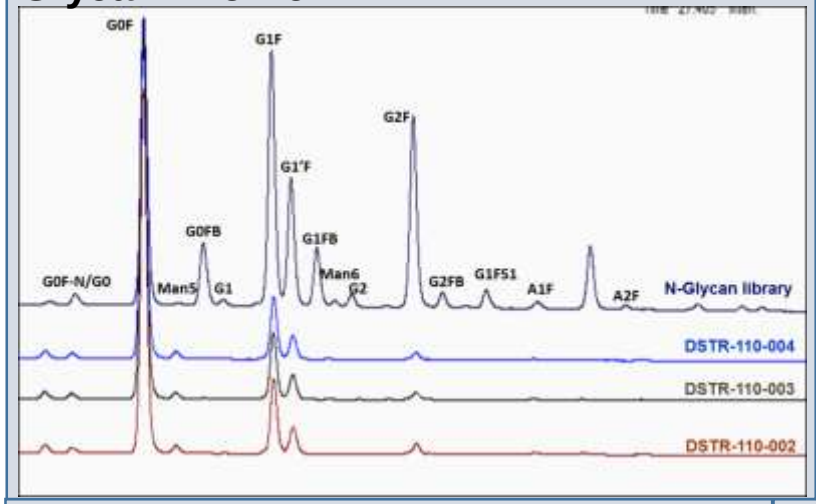
Similar Observations in the remaining Toxicity Studies

1. Acute Toxicity in Mice by Subcutaneous Route
2. Acute Toxicity in Rats by Subcutaneous Route
3. Acute Toxicity in Mice by Intravenous Route
4. Acute Toxicity in Rats by Intravenous Route
5. Skin Sensitization Study in Guinea Pigs
6. Comparability Study - Repeated Dose Toxicity & Immunogenicity in Rabbits by Subcutaneous Route

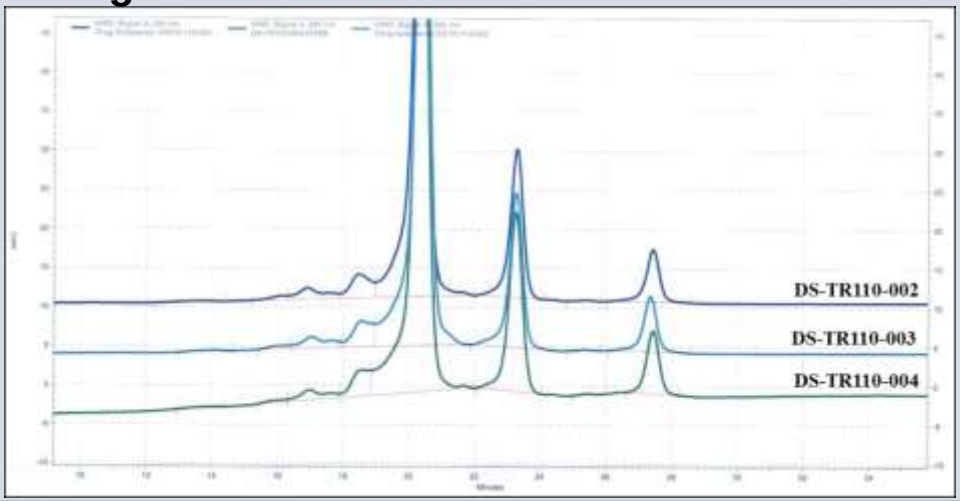
Zydus Adalimumab found to be safe and similar to the Reference Product

MANUFACTURING PROCESS ROBUSTNESS

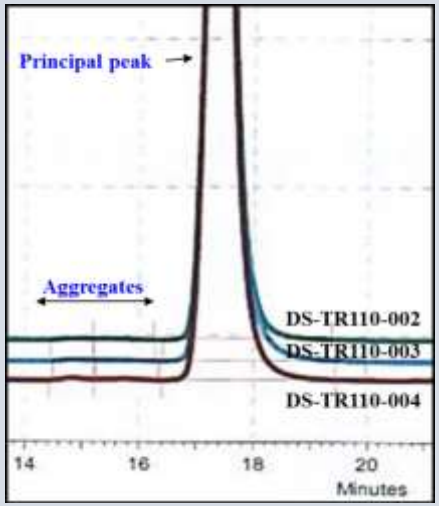
Glycan Profile



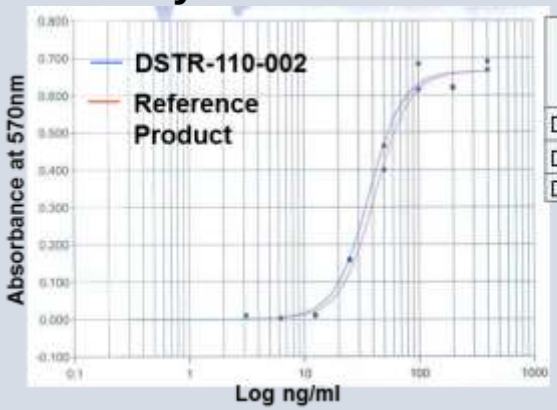
Charge Variant Profile



HP-SEC



Potency

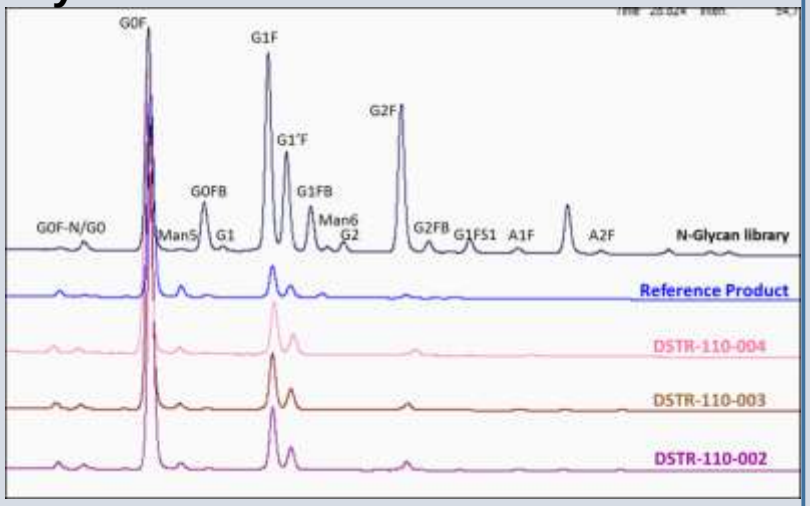


Batch	Relative Potency Limit (80 to 125 % of Reference Product)
DSTR-110-002	108%
DSTR-110-003	118%
DSTR-110-004	114%

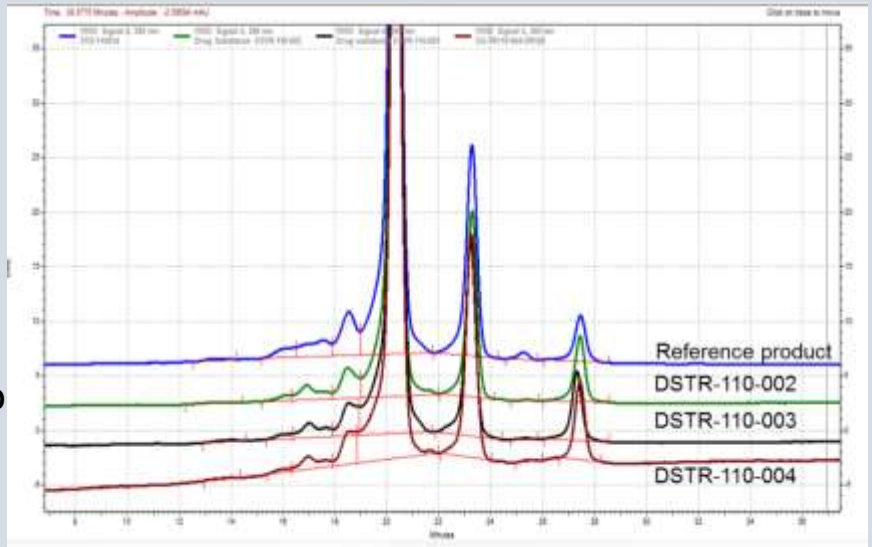
Robust Manufacturing Process is in Place

MANUFACTURING PROCESS ROBUSTNESS

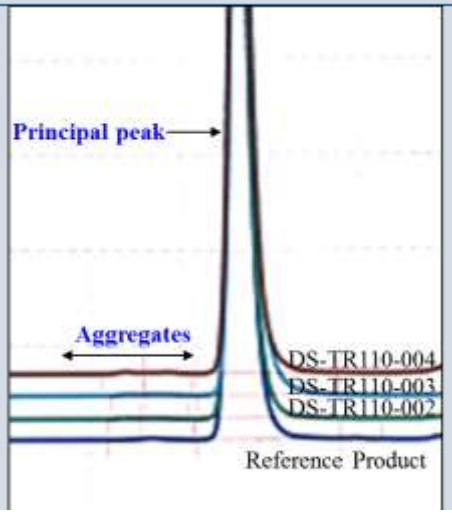
Glycan Profile



Charge Variant Profile



HP-SEC



Potency

Batch	Relative Potency Limit (80 to 125 % of Reference Product)
DSTR-110-002	108%
DSTR-110-003	118%
DSTR-110-004	114%

Robust Manufacturing Process is in Place

SUMMARY & CONCLUSIONS

Exemptia Adalimumab

- World's First Adalimumab Biosimilar
- Zydus is working with leading CROs to develop Adalimumab as a global product. India is the first country of launch
- Meeting with US FDA planned for Q1 2015
- Zydus Adalimumab is a highly biosimilar product developed to have a fingerprint-like match with reference product - established using a panel of more than 20 analytical assays
- A highly comparable animal toxicity has been established
- A highly comparable clinical profile has been established
- A highly robust manufacturing process has been established

Abridged Prescribing Information

COMPOSITION: Exemptia™ (Adalimumab) 40 mg /0.8 mL single use pre filled syringe and 20mg /0.4 mL single use pre filled syringe **DESCRIPTION:** EXEMPTIATM (Adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF-α).EXEMPTIATM is supplied as a sterile, preservative-free solution of Adalimumab for subcutaneous administration. The solution of EXEMPTIATM is clear and colorless. **MECHANISM OF ACTION**: Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Elevated levels of TNF-α is found in the synovial fluid of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. **INDICATIONS & DOSAGE:** Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis: The recommended dose of EXEMPTIATM for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg subcutaneously administered every other week. Methotrexate (MTX), other non-biologic DMARDs, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with EXEMPTIA™. Juvenile Idiopathic Arthritis: Exemptia™ dosing in JIA is based on weight; for 10 kg (22 lbs) to <15 kg (33 lbs): 10 mg s.c. every other week. For 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg s.c. every other week and for ≥ 30 kg (66 lbs): 40 mg s.c. every other week. Plaque Psoriasis or Non-Infectious Uveitis: Initial dose of 80 mg, followed by 40 mg every other week starting from week one after initial dose. Hidradenitis Suppurativa: 160 mg (Day 1) (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every week. Adult Crohn's Disease and Ulcerative Colitis: Initial dose (Day 1): 160 mg s.c. (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg. Two weeks later (Day 29): Begin a maintenance dose of 40 mg s.c. every other week. For patients with Ulcerative Colitis only: Only continue EXEMPTIA™ in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Pediatric Crohn's Disease: For weight 17 kg (37 lbs) to < 40 kg (88 lbs): Initial dose (Day 1): 80 mg s.c. (two 40 mg injections in one day). Second dose two weeks later (Day 15): 40 mg s.c.. Two weeks later (Day 29): Begin a maintenance dose of 20 mg s.c. every other week. For ≥ 40 kg (88 lbs): Initial dose (Day 1): 160 mg s.c. (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg s.c. (two 40 mg injections in one day).Two weeks later (Day 29): Begin a maintenance dose of 40 mg s.c. every other week. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients, Moderate to severe heart failure, Active tuberculosis or other severe infections such as sepsis and opportunistic infections. **SPECIAL WARNINGS AND PRECAUTIONS:** Serious and fungal infections: Do not start EXEMPTIA™ during an active infection. If an infection develops, monitor carefully, and stop EXEMPTIATM if infection becomes serious•Anaphylaxis or serious allergic reactions may occur• Hepatitis B virus reactivation: Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop EXEMPTIA™ and begin antiviral therapy• Demyelinating disease: Exacerbation or new onset, may occur• Heart failure: Worsening or new onset, may occur• Lupus-like syndrome: Stop EXEMPTIA™ if syndrome develops **USE IN PREGNANCY AND LACTATION**: Pregnancy Category B: Adequate and well controlled studies with EXEMPTIATM have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Lactation: No data is available on the absorption of adalimumab from breast milk in newborn or preterm infants. Caution should be exercised when EXEMPTIATM is administered to a nursing woman. **DRUG INTERACTION** Biological Products- Concomitant administration of EXEMPTIA™ with other biologic DMARDs (e.g., Anakinra and Abatacept) or other TNF blockers is not recommended •Live Vaccines- Avoid the use of live vaccines with EXEMPTIA™. •Cytochrome P450 Substrates- The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. Upon initiation or discontinuation of EXEMPTIA™ in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., Warfarin) or drug concentration (e.g., Cyclosporine or Theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **UNDESIRED EFFECTS**: The most serious adverse reactions include the following• Serious Infections- Tuberculosis and Opportunistic Infections •Malignancies. The Clinical experience has reported Upper Respiratory Tract Infection (URTI), Increased creatine phosphokinase, Headache, Rash, Sinusitis, Nausea, Urinary Tract Infection (UTI), Abdominal pain, Flulike syndrome, Hyperlipidemia, Back pain, Hypercholesterolemia, Hematuria, Hypertension, Increased alkaline phosphatase as common side effects. STORAGE CONDITION: Store between + 2°C and + 8 °C, in the carton to protect from light. Do not freeze Exemptia™. Do not use Exemptia™ if frozen, even if it has been thawed. Keep out of reach of children. PRESENTATION: a) Injection: 40 mg/0.8 mL in a single-use prefilled syringe b) Injection: 20 mg/0.4 mL in a single-use prefilled syringe.

Please refer to the full Prescribing Information before starting EXEMPTIA™.

Please consult full Prescribing Information before prescribing.

Zydus Cadila does not recommend the use of any product in any different manner than as described in the prescribing information.

Further information is available on request from:

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Exemptia
Adalimumab

Thank you

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dedicated to life