MSN SCIENTIFIC SPARKLES

MSN
Research for Better Medicines

MSN ABALOPARATIDE

MSNSS No: 00003

INTRODUCTION

Abaloparatide sold under the brand name Tymlos is an N-terminal analogue of parathyroid hormone-related protein (PTHrP) used to treat Osteoporosis in postmenopausal women and to increase bone density (anabolic agent) in men with Osteoporosis. Structurally, Abaloparatide is a synthetic 34 amino acid peptide approved by USFDA on April 28, 2017 and by European Medicines Agency on December 12, 2022. MSN filed USDMF (DMF No. 34697) in May 2020 and successfully addressed all the deficiencies received from USFDA. MSN offers Abaloparatide with consistent quality and with all necessary data packages such as SAMENESS STUDY with RLD, full Characterization of API and all relevant documentation in accordance with USFDA guidelines.

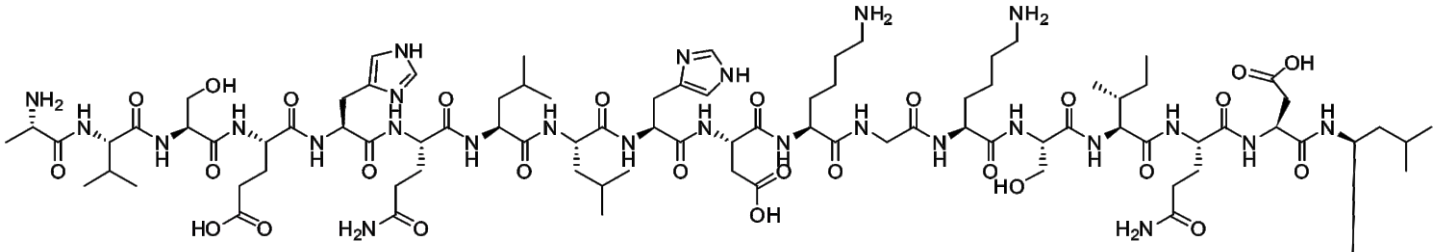
SYNTHESIS AND COMPLEXITY OF ABALOPARATIDE

The active substance of Abaloparatide is synthesized using SPPS (Solid Phase Peptide Synthesis) strategy with excellent optimized process conditions to control addition, deletion and chiral impurities with reproducible yields and consistent quality.

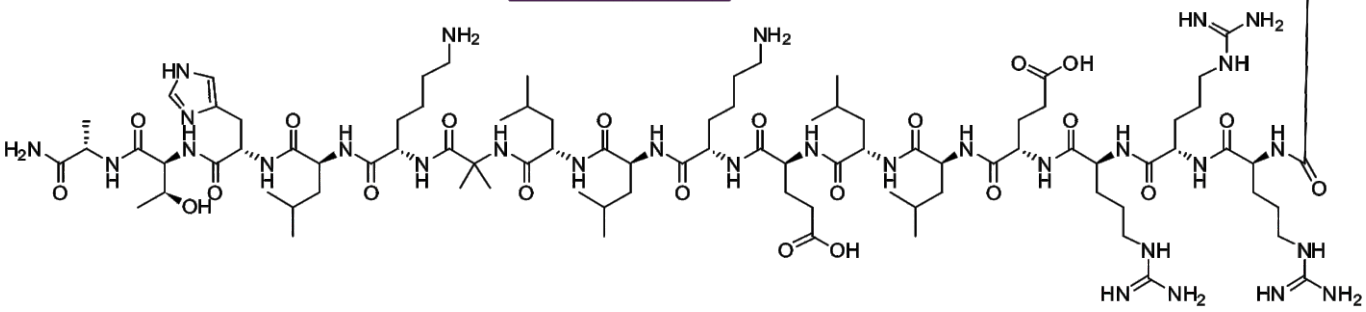
The complexity of Abaloparatide lies with purification. especially to remove isomeric impurities., It is also challenging to identify and characterize impurities. MSN has developed a robust and cost efficient purification process to control all racemic impurities below 0.1% along with consistent control of other impurities with desired specification.

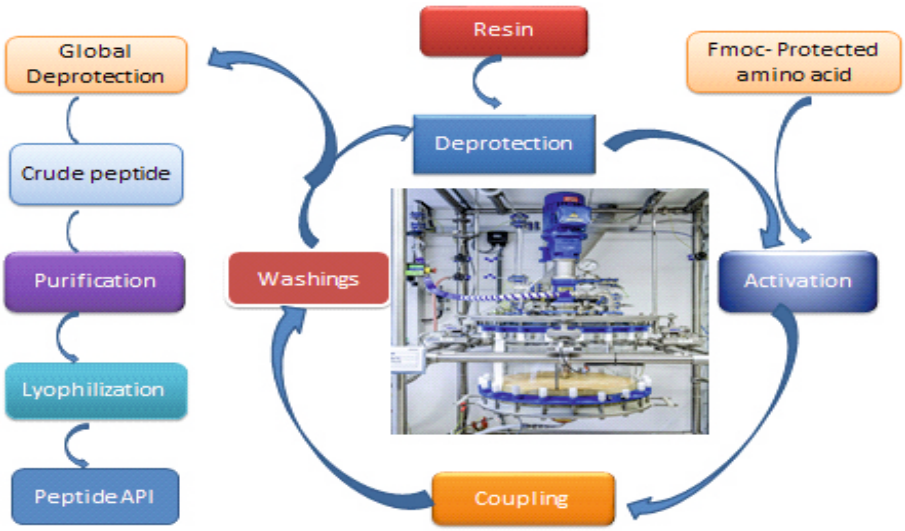
The most important part is the sameness study of the drug substance with the RLD (Tymlos) to ensure safety and efficacy as per USFDA guidelines. MSN Abaloparatide is comprehensively studied with various orthogonal analytical techniques to ensure similarity with RLD in physicochemical properties such as structure identification, purity and peptide content, self-association and aggregation studies and more. The following pictorials are demonstrating the process flow and Sameness study of MSN Abaloparatide with RLD.

ABALOPARATIDE STRUCTURE, SYNTHETIC PROCESS FLOW & SAMENESS WITH RLD

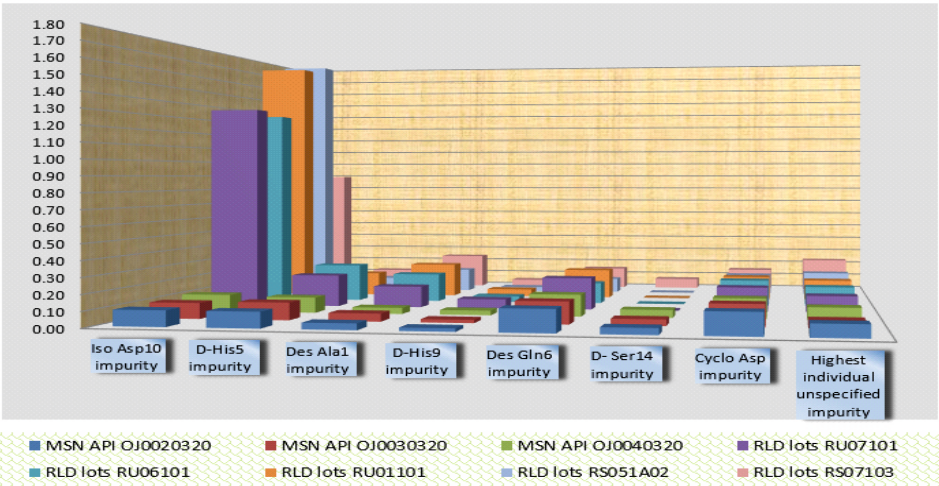


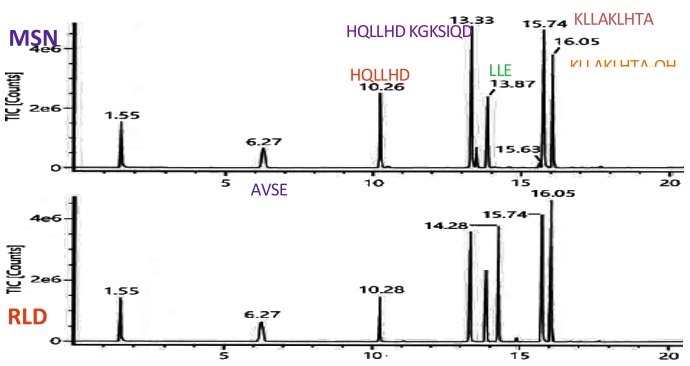
ABALOPARATIDE

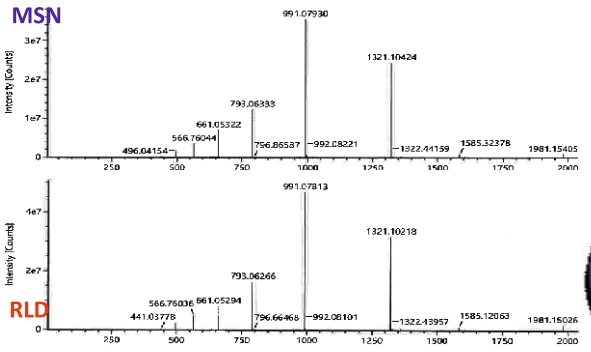


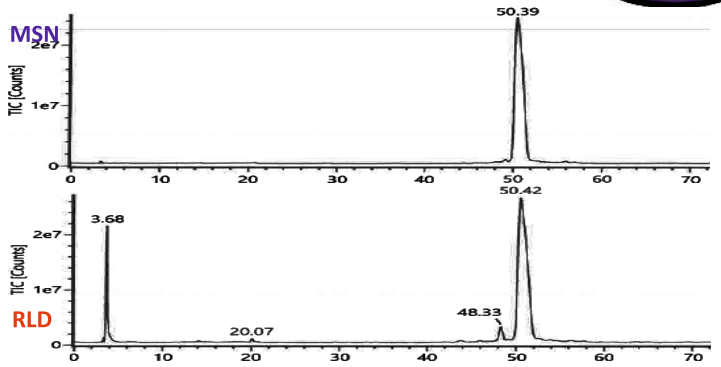


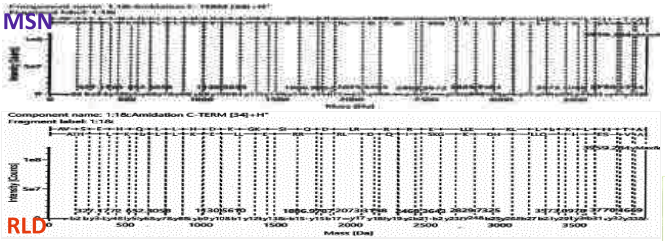
RLD Vs MSN API Impurity Profile

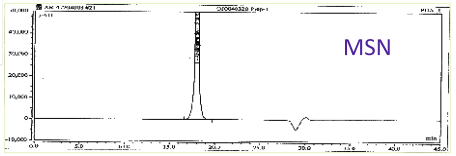


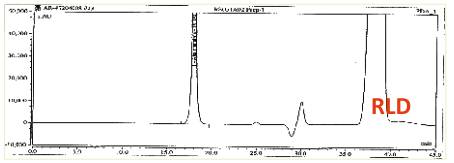

MSN
HQLLHD KGKSIQD
HQLLHD
LLE
KLLAKLHTA
AVSE
RLD

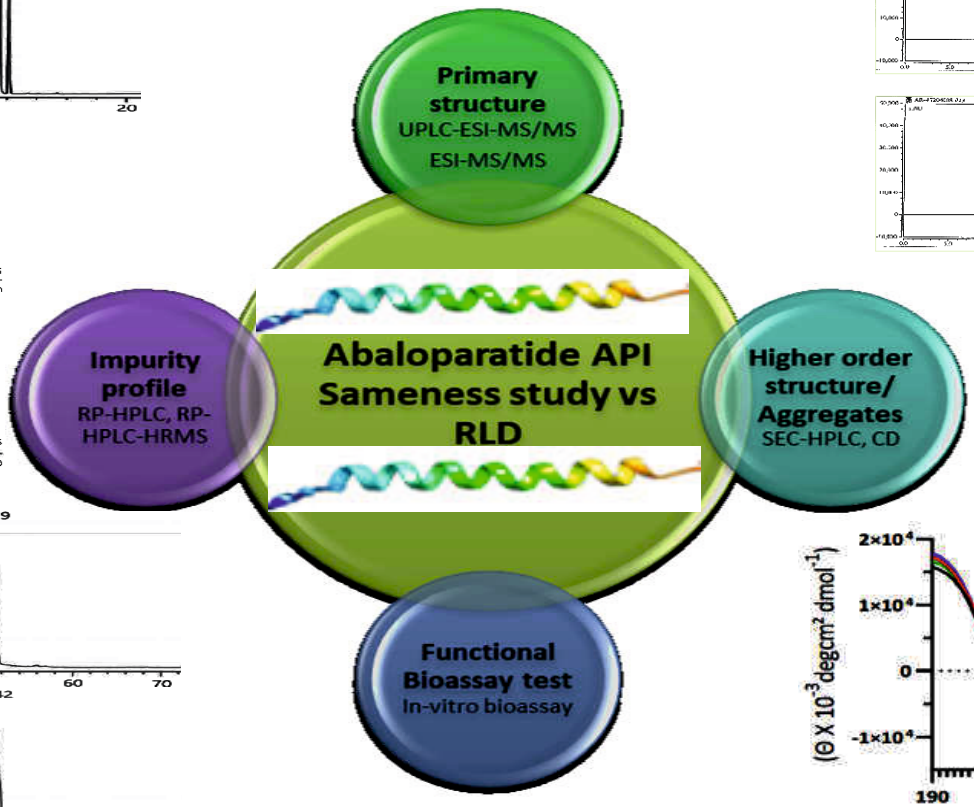

MSN
RLD

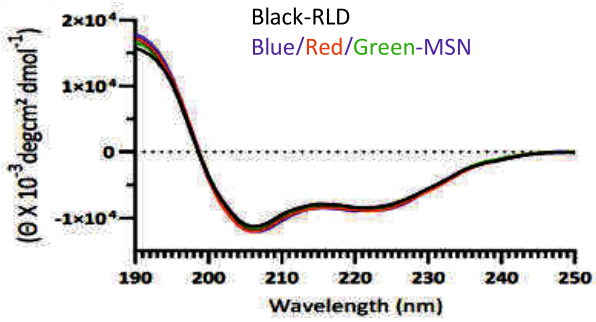

MSN
RLD


MSN
RLD


MSN


RLD


Primary structure
UPLC-ESI-MS/MS
ESI-MS/MS
Impurity profile
RP-HPLC, RP-HPLC-HRMS
Abaloparatide API Sameness study vs RLD
Higher order structure/ Aggregates
SEC-HPLC, CD
Functional Bioassay test
In-vitro bioassay


Black-RLD
Blue/Red/Green-MSN
Wavelength (nm)

CHARACTERIZATION AND OUTCOME OF THE SAMENESS STUDY

MSN applied multiple orthogonal analytical techniques to compare physico-chemical properties such as Intact mass, Peptide sequencing by MS-MS, 1H NMR, IR, UV, PXRD, DSC, TGA, SOR, CD, Chiral-GC, Solubility, pH, Residual solvents by GC etc, with RLD.

The sameness study successfully proved that MSN Abaloparatide has impurities content equal to or lower than those present in RLD (Tymlos). No new or higher than 0.10% level impurities are found in drug substance. The listed impurities are common between MSN Abaloparatide and RLD.

CAPABILITIES AND HIGHLIGHTS OF THE PROJECT

- MSN peptide team have capabilities to synthesize sensitive and complex peptide APIs for various regulated markets.
- MSN manufacturing facility has capability to produce grams to kilo grams of Abaloparatide annually.
- Innovative chromatographic purification techniques adopted and achieved high pure Abaloparatide API to comply with current regulatory requirements for peptides
- Identified, characterized and synthesized nearly 30 complex impurities to verify the quality the API.
- Successfully addressed multiple deficiencies raised by USFDA as part of their review process.
- Robust In-house analytical methods developed to qualify the purity, efficacy and safety of the Abaloparatide.
- Remarkable similarity of Abaloparatide has been proved with RLD with respective to impurity profile and physico-chemical properties.