

Supplementary material

Supplementary Table 1. Definitions of disease modification and/or disease modifying treatments across multiple therapeutic areas.

Condition	Definition
Rheumatological disorders	
<i>General rheumatological disorders</i>	<ul style="list-style-type: none"> • “Disease modification is the improvement of symptoms (disease process) in conjunction with the change of the disease course (disease outcome)”[1]
<i>Rheumatoid arthritis</i>	<ul style="list-style-type: none"> • “A DMARD is defined as a medicine that interferes with signs and symptoms of rheumatoid arthritis, improves physical function, and inhibits progression of joint damage”[2] • EULAR: “The concept of ‘disease modification’ comprises a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work capacity; and most characteristically the inhibition of occurrence of progression of structural damage to cartilage and bone”[3] • ACR: “Agents that apparently alter the course and progression of rheumatoid arthritis, as opposed to more rapidly acting substances that suppress inflammation and decrease pain, but do not prevent cartilage or bone erosion or progressive disability”[4]
<i>Systemic sclerosis</i>	<ul style="list-style-type: none"> • “Ideal DMT should halt the progression of the disease and hopefully induce remission, and preferably also reverse some of the major organ complications... It is reasonable to expect a DMT to stabilize organ function without any further worsening of other domains”[5]
Neurodegenerative disorders	
<i>General neurodegenerative disorders</i>	<ul style="list-style-type: none"> • “A disease-modifying therapy is an intervention that produces an enduring change in the trajectory of clinical decline of a neurodegenerative disorder by impacting the disease processes leading to nerve cell death”[6] • EMA: “For regulatory purposes, a disease modifying effect will be considered when a pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by improvement in clinical signs and symptoms of the dementing condition”[7]
<i>Alzheimer’s disease</i>	<ul style="list-style-type: none"> • “Disease modification can be defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of Alzheimer’s disease”[8] • “A disease-modifying therapy is as an intervention that produces an enduring change in the clinical progression of Alzheimer’s disease by interfering in the underlying pathophysiological mechanisms of the

	<p>disease process that lead to cell death”[9]</p> <ul style="list-style-type: none"> • EMA: “A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes. This can be demonstrated by results that show slowing in the rate of decline of clinical signs and symptoms and when these results are linked to a significant effect on adequately validated biomarkers. Such biomarkers should reflect key pathophysiological aspects of the underlying disease process based on a plausible disease model. The choice of biomarker as well as the type of analysis is left open, although more weight will be given to those biomarkers showing not only target engagement, but also an effect on the downstream disease mechanisms”[10] • FDA: “Permanently altering the course of Alzheimer’s disease through a direct effect on the underlying disease pathophysiology; the effect persists in the absence of continued exposure to the drug”[11] • PMDA: “Medical agents that delay neurodegeneration and neuronal cell death by acting on the pathological mechanism of Alzheimer’s disease and, as a result, inhibit the progression of clinical symptoms”[12]
<i>Epilepsy</i>	<ul style="list-style-type: none"> • “According to the definition of epileptogenesis, ‘disease modification’ refers to every clinically relevant therapeutic outcome which does not necessarily prevent epilepsy onset but significantly improves the disease course by reducing seizure burden and/or decreases concomitant comorbidities”[13]
<i>Multiple sclerosis</i>	<ul style="list-style-type: none"> • Disease-modifying therapies are “drugs targeted to prevent relapses of the disease, and consequently, progression of disability”[14]
<i>Parkinson’s disease</i>	<ul style="list-style-type: none"> • “A disease-modifying therapy... slows or stops disease progression”[15]
Respiratory diseases	
<i>COPD</i>	<ul style="list-style-type: none"> • “An improvement in, or stabilization of, structural or functional parameters as a result of reduction in the rate of progression of these parameters which occurs whilst an intervention is applied and may persist even if the intervention is withdrawn”[16]
<i>Emphysema</i>	<ul style="list-style-type: none"> • “Disease modification is a sustained improvement in disease state following therapeutic intervention that persists when therapy is discontinued”[17]

ACR, American College of Rheumatology; COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; DMT, disease-modifying therapy; EMA; European Medicines Agency; EULAR, European Alliance of Associations for Rheumatology; FDA, US Food and Drug Administration; PMDA, Japanese Pharmaceuticals and Medical Devices Agency

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