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# **Mucopolysaccharidosis Type III (Sanfilippo Syndrome): Developing Drugs for Treatment Guidance for Industry**

## ***DRAFT GUIDANCE***

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

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Clinical/Medical**

# Mucopolysaccharidosis Type III (Sanfilippo Syndrome): Developing Drugs for Treatment Guidance for Industry

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2                   **Developing Drugs for Treatment**  
3                   **Guidance for Industry<sup>1</sup>**  
4  
5

6  
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
11 for this guidance as listed on the title page.  
12

13  
14  
15 **I. INTRODUCTION**  
16

17 The purpose of this guidance is to provide recommendations to sponsors regarding eligibility  
18 criteria, trial design considerations, and efficacy endpoints to enhance clinical trial data quality  
19 and foster greater efficiency in development programs for drugs<sup>2</sup> to treat mucopolysaccharidosis  
20 type III (MPS III; also called Sanfilippo syndrome).  
21

22 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
23 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
24 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
25 the word *should* in Agency guidances means that something is suggested or recommended, but  
26 not required.  
27

28  
29 **II. BACKGROUND**  
30

31 MPS III is a rare, autosomal recessive, inborn error of glycosaminoglycan (GAG) metabolism  
32 with an estimated incidence of 0.28–4.1 per 100,000 live births. It belongs to a group of genetic  
33 disorders called mucopolysaccharidoses, which are caused by different single enzyme defects  
34 affecting lysosomal GAG breakdown. MPS III is caused by deficient activity of any one of four  
35 enzymes involved in the breakdown of the GAG heparan sulfate (HS) in lysosomes. The disease  
36 is divided into four distinct subtypes based on the gene defect and corresponding enzyme  
37 deficiency as follows: MPS IIIA (*SGSH* (N-sulfoglucosamine sulfohydrolase) gene; heparan N-

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<sup>1</sup> This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research and by the Center for Biologics Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> For purposes of this guidance, unless otherwise specified, references to *drugs* include drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and biological products licensed under section 351 of the Public Health Service Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

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38 sulfatase deficiency), MPS IIIB (*NAGLU* (N-acetyl-alpha-glucosaminidase) gene; N-acetyl- $\alpha$ -  
39 glucosaminidase deficiency), MPS IIIC (*HGSNAT* (heparan- $\alpha$ -glucosaminide N-  
40 acetyltransferase) gene; acetyl CoA: $\alpha$ -glucosaminide N-acetyltransferase deficiency), and MPS  
41 IIID (*GNS* (N-acetylglucosamine-6-sulfatase) gene; N-acetylglucosamine 6-sulfatase deficiency)  
42 (Valstar et al. 2008). These enzymatic defects result in progressive intralysosomal accumulation  
43 of HS, which is believed to lead to or initiate a cascade of events leading to cellular damage and  
44 progressive tissue and organ dysfunction. Currently, there are no approved disease-modifying  
45 therapies for MPS III.

46  
47 The central nervous system is the organ primarily affected in MPS III. The natural history and  
48 rate of progression of the neurologic manifestations are not well characterized in any of the four  
49 MPS III subtypes. Some limited natural history information is available in MPS IIIA. In  
50 general, genotype alone does not appear to be a reliable sole predictor of disease severity or rate  
51 of neurological progression in MPS III (Valstar et al. 2008; Valstar et al. 2011). However, in  
52 MPS IIIA, patients with onset of signs and symptoms in early childhood may have a more  
53 rapidly progressive course (*severe* MPS IIIA) compared to patients diagnosed later in childhood  
54 or adolescence (*attenuated* MPS IIIA). In severe MPS IIIA, clinical symptoms manifest in early  
55 childhood (2–6 years of age) and include developmental delay (primarily of speech and  
56 language) and behavioral problems (e.g., hyperactivity, inattention, anxiety, autistic features,  
57 aggression, lack of fear). Other symptoms variably include the following: disturbance of the  
58 normal sleep cycle, frequent upper respiratory and ear infections, hearing and visual impairment,  
59 and motor deficits. Hepatomegaly is found in some patients (splenomegaly is rare), but it is  
60 generally much less common and less severe in MPS III compared to other  
61 mucopolysaccharidoses.

62  
63 The following describes the general disease trajectory in severely affected patients (also called  
64 rapid progressors) with MPS IIIA (Shapiro et al. 2016). Typically, a patient's initial period of  
65 normal or near normal development (up to 2 years of age) is followed by a period of slowing in  
66 developmental progression (between 2 and 4 years of age). Development appears to arrest  
67 around 4 years of age in severely affected patients with MPS IIIA. Subsequently, patients enter a  
68 phase of progressive neurocognitive decline characterized by developmental regression and loss  
69 of previously acquired skills, which eventually leads to complete loss of cognitive, language, and  
70 motor abilities culminating in dementia. Motor abilities are usually not affected until later in the  
71 disease course. Median age at death in MPS IIIA is reported as 15 years of age, ranging between  
72 8.5 and 25.5 years of age (Valstar et al. 2008). There is insufficient information regarding the  
73 general disease trajectory and natural history of manifestations in patients with MPS IIIB, IIIC,  
74 and IIID.

75

76

### **77 III. IMPORTANT CONSIDERATIONS FOR CLINICAL TRIALS**

78

#### **79 A. Eligibility Criteria and Baseline Assessments**

80

81 All eligible patients should have clinical signs and symptoms consistent with a diagnosis of MPS  
82 III, which should be confirmed by both biochemical testing (HS concentration) and molecular  
83 genetic testing. Ideally, enrolled patients should be in the early stages of the disease (i.e., before

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84 irreversible neurological damage has occurred). For gene/enzyme-specific therapies targeting a  
85 specific MPS III subtype, enrolled patients should have the same MPS III subtype. If  
86 appropriate, (depending on the drug’s mechanism of action) sponsors can enroll in the same trial  
87 patients of different ages, patients with different MPS subtypes and/or patients who are at  
88 different stages of the disease. Baseline laboratory assessments should include, at a minimum,  
89 genotyping (if not already available) and assessment of HS concentration in relevant tissues  
90 (blood, urine, and/or cerebrospinal fluid (CSF)). As part of baseline laboratory assessments in  
91 enzyme replacement therapy and gene therapy trials, sponsors should collect and store blood (or  
92 other relevant tissues) for use in the assessment of cross-reactive immunologic material (CRIM)  
93 status. Baseline clinical assessments should include standard evaluations of hearing, vision,  
94 cognition, and adaptive behavior to ensure that enrolled patients are able to sufficiently complete  
95 trial assessments.

### **B. Trial Design**

96  
97  
98  
99 Because of the current paucity of natural history knowledge and the clinical heterogeneity of  
100 MPS III, appropriately designed and executed natural history studies could provide crucial  
101 information to help guide and inform essential aspects of a clinical development program.<sup>3</sup>  
102

103 Given the rarity of MPS III, a single adequate and well-controlled trial (as described in 21 CFR  
104 314.126), showing a clinically meaningful treatment effect on core disease manifestations,  
105 accompanied by additional confirmatory evidence can be used to support approval. Such  
106 confirmatory evidence could be based on different lines of evidence (e.g., data showing a  
107 treatment effect on disease-specific biochemical markers (e.g., CSF HS) in treated patients;  
108 nonclinical data showing biochemical and functional treatment effects in a well-characterized  
109 MPS III animal model).<sup>4</sup>  
110

111 If a large treatment effect and/or an effect on objective clinical measures (e.g., survival) are not  
112 expected within a specified trial duration, FDA strongly recommends a randomized, parallel-  
113 group trial design with an appropriate concurrent control group. Because of the uncertainties  
114 related to the lack of a well-characterized natural history, the variable rate of neurologic disease  
115 progression among patients, and the nonlinear developmental trajectory observed in many MPS  
116 III patients (Ghosh et al. 2017), such randomized, concurrently controlled trial design would  
117 provide the most informative and reliable data for an evaluation of efficacy in the most efficient  
118 and expedient way. Given the small patient population, sponsors should use randomization as  
119 early as in the first clinical trial involving MPS III patients to allow for maximal and most  
120 efficient use of efficacy data for regulatory purposes.

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<sup>3</sup> See the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019). When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>4</sup> We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

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121  
122 When natural history information becomes available and can reliably predict the disease course  
123 in a given patient cohort, and when a large treatment effect size is anticipated based on  
124 preliminary information, an externally controlled clinical trial may be acceptable. Sponsors can  
125 consider innovative and adaptive trial designs and should discuss these early in development  
126 with the appropriate review division.<sup>5, 6</sup>

127  
128 A patient's symptomatic treatment regimen (e.g., concomitant drugs, physical and occupational  
129 therapy, other interventions) should be optimized in advance of trial entry, and efforts should be  
130 made to maintain the stability of these background treatments during the trial. Any changes in  
131 the patient's background treatment regimen made during the trial should be carefully  
132 documented.

133  
134 As most drugs would be intended to slow or arrest the neurological disease progression rather  
135 than to reverse it, a clinical trial should be of sufficient duration, at least 2–3 years to observe an  
136 effect on neurological disease aspects. In addition, patients with different disease severity would  
137 be expected to have different rates of neurocognitive decline, which would necessitate different  
138 durations of observation to assess treatment effects on selected endpoints. For gene therapy  
139 products, sponsors should be aware of special considerations regarding the length of long-term  
140 follow-up.<sup>7</sup>

### 141 142 **C. Pharmacodynamic Endpoints**

143  
144 Assessment of changes in HS concentration in CSF could provide evidence of *in vivo* biological  
145 activity of the drug, demonstrate proof-of-concept, and help characterize the dose-response  
146 relationship in early phase trials. Changes in plasma or urine HS should be considered of limited  
147 utility given the neurologic nature of MPS III. Assessment of changes in organ volume (e.g.,  
148 liver, spleen) should be considered of limited utility given that organomegaly is not a common  
149 finding in MPS III patients and that changes in organ volume are of unclear clinical significance  
150 in a disease that is fundamentally neurologic. Quantitation of pharmacodynamic biomarkers  
151 (e.g., HS, HS derivatives, enzyme activity) should be conducted at a central laboratory using  
152 appropriately validated methods to ensure reliability of the results. Understanding the variability  
153 of the test(s) used is fundamental to the interpretation of any treatment effects on those  
154 biomarkers.

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<sup>5</sup> For sponsors interested in discussing complex innovative trial designs, see also the FDA Complex Innovative Trial Design pilot meeting program web page available at <https://www.fda.gov/drugs/development-resources/complex-innovative-trial-designs-pilot-program>.

<sup>6</sup> See the draft guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>7</sup> See the draft guidance for industry *Long Term Follow-Up After Administration of Human Gene Therapy Products* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

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### **D. Efficacy Endpoints**

156  
157  
158 Demonstration of a clinically meaningful treatment effect on neurological disease manifestations  
159 that are important to patients and their families can form the basis for traditional approval.  
160 Sponsors should assess multiple, distinct clinical endpoints in trials to provide a global  
161 characterization of treatment effects on disease manifestations. At this time, additional evidence  
162 should be provided to support the use of HS reduction in CSF or other tissues (blood or urine) as  
163 a surrogate endpoint reasonably likely to predict clinical benefit to support accelerated approval.<sup>8</sup>  
164

165 The selection and prioritization of efficacy endpoints should take into consideration patients' and  
166 parents'/caregivers' preferences to ensure that sponsors assess outcomes that are clinically  
167 meaningful to patients and their families. The selection of efficacy endpoint(s) should also  
168 consider the mechanism of action and anticipated clinical effects of the drug on the different  
169 disease manifestations. Furthermore, given the multiple clinical manifestations of MPS III,  
170 which may differentially affect patients' daily functioning, sponsors can consider the use of a  
171 multiple-endpoint strategy.<sup>9</sup> FDA strongly encourages sponsors to engage in early and  
172 continuous discussions with the appropriate review division regarding the selection of the most  
173 informative and clinically meaningful endpoint(s) for demonstration of efficacy.<sup>10</sup>  
174

175 Standardized clinical outcome assessment (COA) instruments should be used to evaluate  
176 treatment effects on major neurological disease aspects (e.g., cognition, behavior) (Janzen et al.  
177 2017). Appropriate standardized tests of cognitive performance should be selected based on  
178 patients' baseline level of functioning. When selecting COA instruments to evaluate cognitive  
179 performance, sponsors should also consider whether there may be anticipated floor effects of the  
180 particular instrument in the enrolled population as this could affect interpretability of the data.  
181 Sponsors should also consider that the selection of particular COA tests may also inform the  
182 frequency of the corresponding assessments (Van der Lee et al. 2017).  
183

184 All COA instruments should be administered by trained personnel who are familiar with the  
185 instruments and with the special challenges of MPS III patients as they relate to patients'  
186 behavioral problems, inattention, hyperactivity, sensory impairment (hearing, vision), speech and  
187 language deficits, fatigability, and motor impairment as those can interfere with test  
188 administration and interpretation of test results. Instructions, training materials, and case report  
189 forms should include detailed information on all specific methods that should be utilized when  
190 administering these tests. Assessments can be divided into multiple short sessions, and the  
191 trained personnel should allow adequate time for the completion of each assessment. In addition,  
192 assessments should be administered in an environment familiar to the patient, and the testing  
193 environment should be free of items that may cause distraction.  
194

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<sup>8</sup> See section 506(c) of the FD&C Act; 21 CFR part 314, subpart H; and 21 CFR part 601, subpart E.

<sup>9</sup> See the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>10</sup> See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic.



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195 The amount of time used and other contextual features of performance-based assessments should  
196 be recorded and accounted for in data analyses. Other factors that may affect patients'  
197 behavioral and cognitive performances, such as uncontrolled or insufficiently controlled seizures  
198 (which can be part of the underlying disease), should be carefully assessed and documented  
199 throughout the trial and should be considered in the interpretation of treatment effects. FDA  
200 strongly encourages sponsors to discuss all proposed COAs with the appropriate review division  
201 early in development (i.e., pre-investigational new drug application phase).  
202

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