
Guidance for Industry

Rheumatoid Arthritis:

Developing Drug Products for Treatment

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

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Clinical/Medical**

Revision 1

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Developing Drug Products for Treatment

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Guidance for Industry¹ Rheumatoid Arthritis: Developing Drug Products for Treatment

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to outline the FDA's current thinking on the principles of clinical development relevant to dose-selection and assessment of efficacy and safety to support the approval of drug products for the treatment of patients with rheumatoid arthritis (RA). It also addresses additional considerations for drug products developed as drug-device combination products. This guidance does not address nonclinical development, development of drug products for juvenile idiopathic arthritis, or development of biosimilar products.

This guidance revises the guidance for industry *Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)*, published in February 1999.² After it has been finalized, this guidance will replace the February 1999 guidance and will reflect the current thinking of the FDA on RA drug product development. The FDA's current thinking has been influenced by clinical development programs conducted for RA since the 1999 guidance published, and by changes in the standard of care for RA because of availability of many effective treatments. The revisions include:

- Dose(s) and dosing regimen(s) selection throughout the clinical development program
- Expectations for establishing efficacy in RA based on signs and symptoms and physical function domains

¹ This guidance has been prepared by the Division of Pulmonary, Allergy, and Rheumatology Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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- 39
- 40 • Use of efficacy endpoints such as clinical remission and prevention of structural damage
- 41 progression
- 42
- 43 • Limiting the use of placebo
- 44
- 45 • Use of active comparator for safety and efficacy trials
- 46
- 47 • Principles of safety assessment
- 48
- 49 • Development of drug-device combination products
- 50

51 This guidance does not discuss general issues of statistical analysis or clinical trial design. Those

52 topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical*

53 *Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.

54 This guidance focuses on specific drug product development and trial design issues that are

55 unique to the study of RA.

56

57 FDA’s guidance documents, including this guidance, do not establish legally enforceable

58 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should

59 be viewed only as recommendations, unless specific regulatory or statutory requirements are

60 cited. The use of the word *should* in Agency guidances means that something is suggested or

61 recommended, but not required.

62

63

64 **II. CLINICAL DEVELOPMENT PROGRAM**

65

66 **A. Dose and Dosing Regimen Selection Considerations**

67

68 The selection of nominal dose(s) and dosing regimen(s) is a fundamental component of drug

69 product development. The recommended dose(s) and dosing regimen(s) should be based on

70 benefit-to-risk assessment and should be supported by all available data gathered throughout the

71 development program. It is important to find the appropriate nominal dose and dosing regimen

72 that produces efficacy with an acceptable long- and short-term safety profile. Many drug

73 products intended to treat RA have the potential to cause serious dose-related adverse reactions,

74 such as opportunistic infections and malignancy, which may not be apparent in short-term

75 clinical trials (see section II.C. for further discussion of the clinical safety database). Dose-

76 ranging exploration should begin early in the development program and often should continue

77 throughout definitive efficacy and safety study(ies). Smaller early dose-ranging exploratory

78 studies may not be adequate for selection of a single dose or a single dosing regimen.

79

80 The following should be considered for the design of dose-ranging studies:

81

- 82 • Studying a wide range of doses and dosing regimens based on pharmacokinetic and
- 83 relevant pharmacodynamic considerations.
- 84

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- 85 • Using endpoints sensitive to change to provide better discriminatory power for dose-
86 response assessment. A clinical endpoint such as the ACR20 response criteria may not
87 be optimal for this purpose,³ because it is a dichotomous endpoint, and using the
88 proportion of responders in a small group of patients could be unreliable. Endpoints such
89 as DAS28,⁴ hybrid ACR response,⁵ and other continuous variables may be more sensitive
90 to change and provide a more suitable alternative to ACR responder index. Supportive
91 pharmacodynamic markers can be considered if scientifically justified.
92
- 93 • Timing of evaluation — assessing at the steep part of the dose-response curve for dose-
94 response assessment. Endpoints should be evaluated at time points before the therapeutic
95 plateau is likely (e.g., weeks 2 through 8) to better capture possible differences between
96 doses. Later time points of evaluation (e.g., 12 weeks) may be informative in estimating
97 clinical effect with chronic use.
98

99 **B. Efficacy Considerations**

100
101 To meet the regulatory standards for approval under section 505(d) of the Federal Food, Drug,
102 and Cosmetic Act, sponsors must provide substantial evidence of efficacy in the enrolled patient
103 population and demonstrate an acceptable risk-benefit profile for their drug product (21 U.S.C.
104 355(d)). Studying more than one dose/dosing regimen or using an active comparator in
105 definitive studies can facilitate the interpretation of efficacy and the overall risk-benefit
106 evaluation. This section outlines the principles sponsors should follow to assess efficacy of drug
107 products for the treatment of RA.
108

- 109 1. Establishing efficacy in key RA domains. For marketing approval of drug products for
110 the treatment of RA, sponsors should demonstrate substantial evidence of efficacy in the
111 key RA domains: clinical response and physical function.
112
- 113 • Clinical response. ACR20 response criteria continues to be an accepted measure to
114 demonstrate reduction in RA disease activity. In addition, higher levels of response,
115 as measured by ACR50 and ACR70 response rates, and measures of low disease
116 activity, such as DAS28 less than 2.6, can be used as supportive evidence of efficacy
117 in the clinical response domain.
118

³ ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.

⁴ DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.

⁵ Hybrid ACR response is a continuous score of the mean improvement in the core set measures combining the ACR20, ACR50, and ACR70 response rates (American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007).

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119 • Physical function. Health Assessment Questionnaire-Disability Index (HAQ-DI) can
120 be used to demonstrate improvement in physical function.⁶
121

122 Data from 12-week placebo-controlled clinical trial(s) generally would be acceptable to
123 provide evidence of efficacy in clinical response and physical function domains.
124

125 2. Other domains. As noted in item 1 above, for marketing approval in RA, the
126 foundational demonstration of efficacy should include clinical response and physical
127 function using measures such as ACR20 response rates and HAQ-DI, respectively.
128 Demonstration of efficacy in other domains that are important to patients and health care
129 providers can provide further characterization of the efficacy of the drug product and its
130 utility in clinical practice. Other domains can include:
131

132 • Prevention of structural damage progression. Reduction in radiographic evidence of
133 structural damage progression is an important predictor of long-term benefits in
134 delaying or preventing the progression to disability related to RA. Radiographic data
135 using validated scoring methods have been used to demonstrate efficacy in this
136 domain. However, demonstration of prevention of structural damage progression on
137 radiographs has become increasingly difficult for several reasons:
138

139 – Use of placebo as a control in long-term trials (usually 6 months or longer for
140 trials done in the past to demonstrate effect on radiographic outcomes) is no
141 longer feasible (see item 3 below)
142

143 – The extent of progression in the placebo group is low during these short-term
144 trials, and thus the observed treatment effect size of the investigational drug
145 product is small and difficult to detect
146

147 – Limitations of the current analysis methods
148

149 Therefore, sponsors should consider alternative study designs (e.g., active comparator
150 studies), applying different measures (e.g., proportions of patients with radiographic
151 progression), and alternative analytical methods when assessing radiographic benefit.
152 Other imaging modalities, such as magnetic resonance imaging and ultrasonography,
153 may allow for demonstration of benefit on structural damage progression in
154 controlled studies that may be shorter than studies using radiographic data. However,
155 these modalities have not been validated as outcome measures in RA to date.
156

157 • Clinical remission. Remission is an important goal of RA treatment. The American
158 College of Rheumatology/European League Against Rheumatism (ACR/EULAR)
159 Provisional Definition of Remission criteria may be acceptable for use in RA clinical
160 development programs (ACR/EULAR 2011). Patients who achieve remission should
161 be followed to provide some information on the durability of the remission response.

⁶ HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

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- Other aspects of RA. Other outcome measures may be informative as additional endpoints in RA clinical development programs. Sponsors should provide supportive evidence on the development of the selected measure. Sponsors also should provide the justification for use of a given measure, which should include importance, clinical relevance, and nonredundancy of the proposed outcome with other measures.

3. Use of placebo. Assessment of efficacy in some domains may require long-term controlled clinical trial data. However, the availability of effective RA therapies and the shifting paradigm in the treatment of both early and established RA with a focus on early control of disease activity (Singh 2012) have provided a rationale for limiting the exposure of patients to placebo or ineffective therapies for a prolonged period of time (i.e., beyond 12 weeks) (American College of Rheumatology 2011). Therefore, studies longer than 12 weeks should include an active comparator as the control or provisions for escape to rescue treatment for patients with active disease.

C. Safety Considerations

The size of the safety database for drugs and biologic products should meet the minimum recommendations outlined in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*. However, drug products developed for RA may have potentially serious adverse effects that may cause concern. Unfortunately, the duration of trials that would support demonstration of efficacy may not be sufficient for an adequate safety assessment because the short duration of a placebo-controlled period (i.e., 12 weeks) would limit the amount of controlled safety data. Therefore, to better characterize the long-term safety profile of the investigational drug product and uncommon adverse events and events with longer latency periods, such as opportunistic infection and malignancy, we may request a premarket safety database of larger size and longer duration than recommended in ICH E1A for new molecular entities intended for the chronic treatment of RA.

This request will likely include at least 1 year of controlled safety data for a new molecular entity with an active comparator arm to facilitate interpretation of these data. Safety data for a shorter duration may be considered if the drug product is not a new molecular entity. Reasonable comparator arms can include use of multiple doses of the investigational drug product or standard-of-care treatment in definitive clinical trials. Inclusion of more than one dose of investigational drug product can provide important dose-response information with regard to efficacy and safety. For safety issues of interest, sponsors should consider an independent adjudication process. The need for and details of specific monitoring may change as new data emerge. Sponsors are encouraged to discuss their plans for specific safety monitoring with the FDA during the early stages of drug product development.

The approach to the analyses of safety data should take into account the complexity of the study design (e.g., crossover by response or escape provision, or crossover by design). In addition, the approach to the analyses of integrated safety data should take into account (possible) differing patient populations and/or differing study designs from multiple studies.

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D. Drug-Device Combination Product Considerations

Therapies developed for the treatment of RA include drug products that may require parenteral administration and the use of an accessory delivery unit (e.g., an autoinjector). In these cases, the manufacturer of the drug product should ensure that the accessory delivery unit is approved or cleared for marketing through the device regulatory process (e.g., 510(k) process or premarket approval) by the Center for Devices and Radiological Health. If the accessory delivery unit is not already approved or cleared for marketing, then it should be approved or cleared at least concurrently with the drug product approval.

When the characteristics of the drug product and the delivery device are such that they meet the definition of a combination product under 21 CFR 3.2(e), the center with primary jurisdiction for premarket review and regulation for the combination product will be determined based on the procedure set forth in 21 CFR 3.4. For example, if the primary mode of action of the combination product is that of the drug product, the entire combination product is assigned to the Center for Drug Evaluation and Research. For such combination products, we generally need only one marketing application (e.g., a new drug application/biologics license application). Sponsors are encouraged to contact the Office of Combination Products with general questions regarding drug product jurisdiction and regulatory pathway for their drug-device combination products.

Generally, each drug-device combination product should have a complete chemistry, manufacturing, and controls database; device design and development; and a substantially complete clinical development program to support efficacy and safety of the entire combination product. We anticipate that the to-be-marketed drug-device combination product will be used in the pivotal studies supporting the efficacy and safety of the combination product for marketing approval. For information on drug-device injector development, see the draft guidance for industry and FDA staff *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*.⁷ This guidance includes information on issues such as root-cause analyses of device malfunction that may lead to potential improvements to the device itself. Likewise, current good manufacturing practice requirements for combination products are provided in 21 CFR part 4, subpart A.⁸

For the development of the RA drug delivery system, sponsors should take into consideration the characteristics of the intended user population and use environment. For products intended for self-administration by an RA patient, the device should be durable, and the dexterity and visual acuity required to use the device should be within the capability of RA patients. Human factor studies to assess use-related hazards should be conducted early in development, ideally before the conduct of key dose-ranging, safety, and efficacy studies. For further considerations on

⁷ 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 Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁸ See <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

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248 human factor studies, see the draft guidance for industry and FDA staff *Applying Human Factors*
249 *and Usability Engineering to Optimize Medical Device Design*.⁹

250
251 Ongoing evaluation of device performance should be incorporated into the pivotal studies for the
252 combination product. For example, the evaluation should include asking patients to report
253 devices they perceive to be broken or malfunctioning and to return any such device for
254 evaluation and identification of the problem. Device use and performance also can be evaluated
255 through directed questions defined in the protocols. In addition, a small number of devices (e.g.,
256 100) that are apparently functioning normally should be collected after use and evaluated by in
257 vitro performance testing to ensure device robustness.

258
259 Although use of the to-be-marketed formulation and drug-device combination product
260 throughout development is optimal, we acknowledge that changes to the drug product delivery
261 system may occur. Changes in the formulation, excipients, or device components may affect the
262 drug product delivery characteristics and clinical performance of the drug-device combination
263 product. The extent of clinical data needed to support such changes depends on the nature of the
264 change and the development stage. For example, a transition from a prefilled syringe to an
265 autoinjector delivery system involves the following, at a minimum: (1) human factor studies to
266 evaluate potential use-related risks of the modified combination product; (2) a pharmacokinetic
267 bridging study that demonstrates similar delivery of the drug product to the same biospace across
268 a range of body weights; and (3) real-life patient handling experience to assess device
269 performance as discussed above. Depending on the extent of the proposed changes, additional
270 clinical data may be needed to support efficacy and safety, including immunogenicity.

271
272 Sponsors are encouraged to discuss these types of issues and appropriate marketing applications
273 with the FDA as early in development as feasible.

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⁹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of this guidance, check the FDA Device guidance Web page at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm>. (When final, this guidance will supersede the guidance for industry and FDA premarket and design control reviewers *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*. For the most recent version of this guidance, check the FDA Device guidance Web page at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070271.htm>.)

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Singh, JA, 2012, Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis, *Arthritis Care Res.*, May;64(5):625-39.

Guidances

Draft guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*

Draft guidance for industry and FDA staff *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*

Guidance for industry and FDA premarket and design control reviewers *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*

ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*