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# An Approach to Control Purity of the Drug Substance for Non-Clinical Study

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## Abstract

**Background: Purity of drug substance (API) used for clinical study must be the same or higher than that of API used for non-clinical study (NCAPI). It is important to allow flexibility in developing manufacturing process to design and control the purity of NCAPI. There are various ways to optimize the purity on purpose, such as addition of individual impurities on use of harsh chemical reactions.**

**In the present study, we established a method to ensure the desired purity of NCAPI by adding a separate set of API containing various species of impurities (IMAPI).**

**Methods: Firstly, the target purity of NCAPI was determined by the purity of API used for a two-week repeated dose toxicity study in the dog. Secondly, IMAPI was prepared in lab, and lab experiments were conducted to determine how much IMAPI needed to achieve the target purity of NCAPI at large-scale manufacturing. Thirdly, we conducted large-scale manufacturing by addition of IMAPI and confirmed whether the purity of NCAPI was within the desired one.**

**Results: The purity of API used in the dog toxicity study was 97.8%, so we set the target purity at 98%. IMAPI was synthesized with the purity of 82.2%, and added to the reaction mixture in large-scale production. Crystallization and filtration gave 37.4 kg of NCAPI with the purity of 99%, which is slightly higher than the target purity.**

**Conclusions: These results indicate that this method is useful for purity design of NCAPI.**

## Introduction

Various ways are known to optimize the purity and the impurity profile of drug substance (API) used for non-clinical study (NCAPI). We conducted this study to establish a new method which is easier than previous ones and convenient for large-scale production.

## Methods

1. *Target purity and impurity profile determination*
   API for a two-week repeated dose toxicity study in the dog was synthesized. Target purity and impurity profile of NCAPI were determined.
2. *Preparation of IMAPI*
   IMAPI was prepared by adding the residue of the filtrates, process intermediates, and degradate, which were prepared separately.
3. *IMAPI spike tests*
   Reaction mixture in the final manufacturing step was spiked IMAPI to determine where the appropriate process to add and how much IMAPI needed to optimize the purity and the target impurity profile of NCAPI at large-scale manufacturing.
4. *Manufacturing NCAPI*
   NCAPI was manufactured by adding IMAPI to the reaction process of the final manufacturing step.

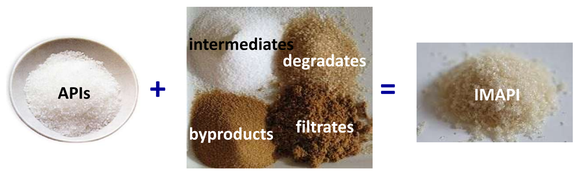
## Summary of results

1. The purity of API used in the dog toxicity study was 97.8%. Therefore, the target purity of NCAPI was set at 98%. Major impurities in this API were identified to determine the target impurity profile.
2. IMAPI was synthesized with the purity of 82.2% and major impurities were included.
3. Spike tests showed that adding 1.0 wt% IMAPI to the reaction process produced API with the purity of 98.0%, achieving the target purity profile. Adding IMAPI to the crystallization process did not affect the purity of the API.
4. NCAPI was manufactured by IMAPI. Adding IMAPI to the reaction process afforded 37.4 kg of NCAPI with the purity of 99.0%, which is slightly higher than the target purity. Impurities presented in NCAPI were as we anticipated.

## Conclusion

We established the IMAPI approach to control purity and impurity profile of NCAPI. This approach is applicable to the large-scale manufacturing.

## Comparison of Methods for Purity Optimization




| Methods for Purity Optimization | Comments |
|---|---|
| Conduct reaction in a harsh condition | ✓ **Has a risk that only the specified impurity will increase.**<br>✓ Undesired impurities may arise.<br>✓ Not appropriate for the large-scale production. |
| Add impurities individually to the process | ✓ **Each impurity must be synthesized.**<br>✓ Hard to add oily or gummy compounds because of their high viscosity.<br>✓ Need to investigate remaining rates individually. |
| Add IMAPI to the process | ✓ **Need not to synthesize all the impurities because impurities in IMAPI could be included from residue of the filtrates, degradates of API, or mix of APIs.**<br>✓ Easy to optimize the amount of impurities in API by controlling the amount of IMAPI to use.<br>✓ Easy to add oily or gummy compounds by means of being uniformly dispersed in IMAPI.<br>✓ Appropriate for the large-scale production. |

## Steps in conducting this study

**1. Synthesis of the API for a two-week repeated dose toxicity study in the dog**

Determine target purity of the NCAPI and identify impurities in the API to determine target impurity profile.

**2. Preparation of the IMAPI**

Prepare IMAPI with the residue of the concentrated filtrate of the final process, process intermediates, and degradate to mix the impurities in the target profile.

**3. IMAPI spike tests**

Spike IMAPI to the reaction mixture to determine where the appropriate process to add and how much IMAPI needed to optimize the purity and the target impurity profile of NCAPI at large-scale manufacturing.

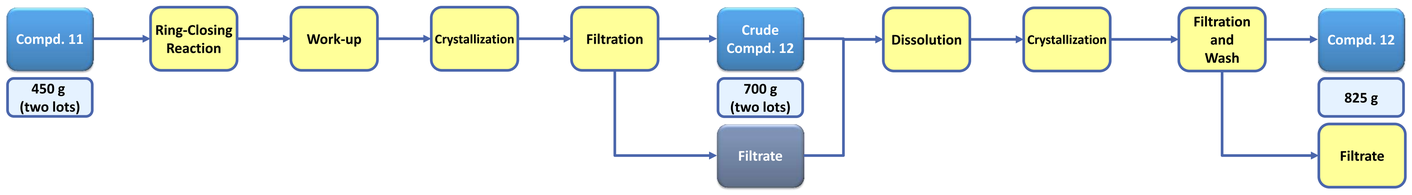
**4. Manufacturing the NCAPI**

Apply this approach in a large-scale production of NCAPI (35.0 kg scale at the final step).

## Synthetic Route of API (Compound 12)


## Result 1: Synthesis of the API for a two-week repeated dose toxicity study in the dog

1. Two lots of crude API crystal were prepared from compound 11, the final intermediate.
2. Crude APIs were dissolved in the filtrate and recrystallized to afford API for the dog toxicity study.

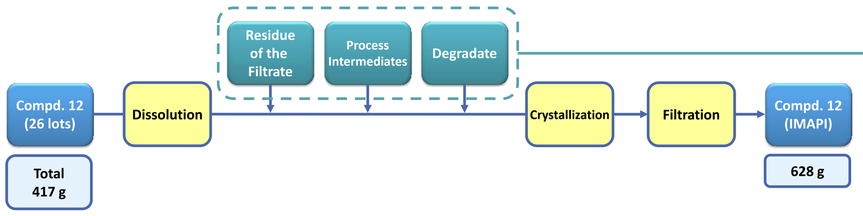



| API | Deg. A | Compd. 7 | Compd. 8 | Compd. 9 | Compd. 10 | Compd. 11 | Bypro. A | Bypro. B | Bypro. C | Bypro. D | Bypro. E | Bypro. F | Bypro. G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 97.770[a] | 0.057 | 0.177 | 0.014 | 0.085 | 0.283 | 0.009 | 0.091 | 0.056 | 0.008 | N.D. | 0.406 | 0.109 | 0.107 |

a. The content of each compound is expressed as a peak area% on HPLC chromatogram.

**Target purity was set to 98%.**
**Target impurity profile was determined.**

## Result 2: Preparation of IMAPI



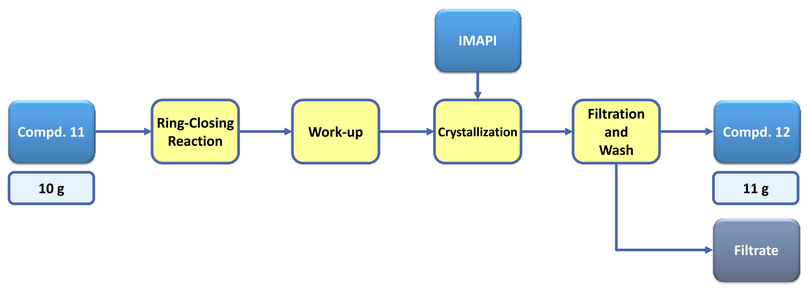

| Material | Impurities to add |
|---|---|
| Residue of the concentrated filtrate of the final process | Containing Compd. 11, Bypro. A, Bypro. B, Bypro. C, Bypro. D, Bypro. E, Bypro. F, and Bypro. G |
| Process intermediates | Compd. 7, 20 g; Compd. 8, 20 g; Compd. 9, 10 g; Compd. 10, 20 g |
| Degradate | Deg. A, which is a degradate identified in a photo stability test |

| API | Deg. A | Compd. 7 | Compd. 8 | Compd. 9 | Compd. 10 | Compd. 11 | Bypro. A | Bypro. B | Bypro. C | Bypro. D | Bypro. E | Bypro. F | Bypro. G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 82.224 | 0.110 | 2.380 | 5.347 | 1.646 | 2.639 | 0.110 | 1.884 | 0.011 | 0.148 | N.D. | 0.335 | 2.186 | 0.078 |

**Purity of IMAPI was 82.2%.**
**Major impurities were mixed.**

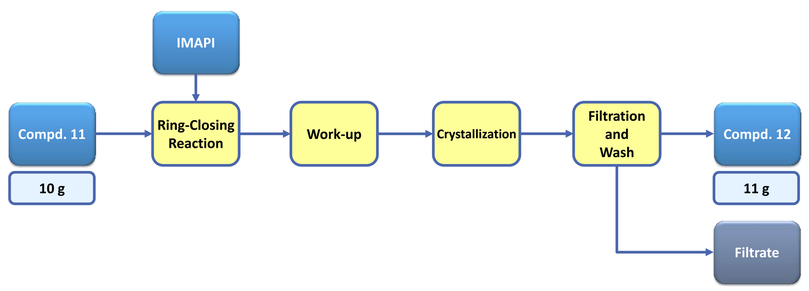
## Result 3: Spike tests of IMAPI

**A. To the crystallization process was added IMAPI.**




| | API | Deg. A | Compd. 7 | Compd. 8 | Compd. 9 | Compd. 10 | Compd. 11 | Bypro. A | Bypro. B | Bypro. C | Bypro. D | Bypro. E | Bypro. F | Bypro. G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| control | 98.729 | 0.029 | 0.053 | 0.045 | 0.156 | 0.132 | 0.016 | 0.040 | 0.035 | 0.129 | N.D. | 0.206 | 0.042 | 0.063 |
| 0.5 wt% | 98.709 | 0.023 | 0.039 | 0.078 | 0.143 | 0.136 | 0.015 | 0.035 | 0.024 | 0.130 | N.D. | 0.209 | 0.040 | 0.062 |
| 1.0 wt% | 98.628 | 0.043 | 0.081 | 0.077 | 0.158 | 0.142 | 0.016 | 0.041 | 0.035 | 0.130 | N.D. | 0.211 | 0.044 | 0.064 |
| 2.0 wt% | 98.626 | 0.028 | 0.041 | 0.134 | 0.143 | 0.162 | 0.016 | 0.036 | 0.023 | 0.126 | N.D. | 0.207 | 0.038 | 0.062 |

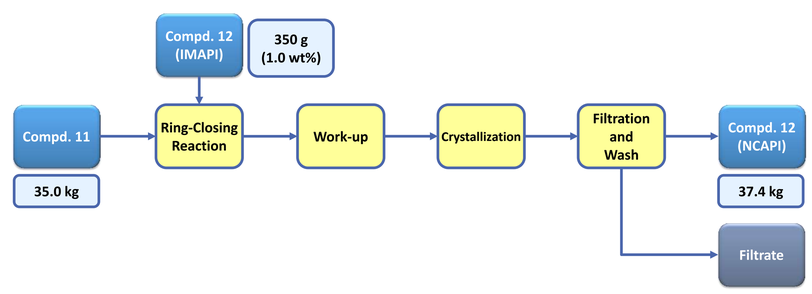
**B. To the reaction process was added IMAPI.**




| | API | Deg. A | Compd. 7 | Compd. 8 | Compd. 9 | Compd. 10 | Compd. 11 | Bypro. A | Bypro. B | Bypro. C | Bypro. D | Bypro. E | Bypro. F | Bypro. G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| control | 98.624 | N.D. | 0.082 | 0.041 | 0.251 | 0.130 | 0.015 | 0.084 | 0.047 | 0.114 | N.D. | 0.216 | 0.063 | 0.127 |
| 1.0 wt% | 98.042 | N.D. | 0.120 | 0.101 | 0.315 | 0.227 | 0.054 | 0.110 | 0.227 | 0.137 | 0.092 | 0.209 | 0.090 | 0.105 |

**Target purity and target impurity profile were achieved by 1.0 wt% IMAPI addition to the reaction process.**

## Result 4: Manufacturing NCAPI




| API | Deg. A | Compd. 7 | Compd. 8 | Compd. 9 | Compd. 10 | Compd. 11 | Bypro. A | Bypro. B | Bypro. C | Bypro. D | Bypro. E | Bypro. F | Bypro. G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99.046 | 0.088 | 0.028 | 0.082 | 0.097 | N.D. | 0.059 | 0.089 | 0.033 | 0.084 | N.D. | 0.020 | 0.030 | 0.101 |

**Purity of NCAPI was 99.0%.**
**Slightly higher than the target purity, however, impurity profile was similar to the desired one and each impurity was mixed without bias.**

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