# Case Study: Merck & Co., Inc.

## Use of In Vivo Pharmacokinetic Data to Develop a CRS for In Vitro Dissolution Testing

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# Implementing an in vivo study to support developing CRS -- Outline

- Background
- Objectives
- Methods
- Results
- Conclusions



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# A useful approach for designing CRS

## Manufacture tablets with different dissolution rates

- Fast, slow, target
- Target batch usually biobatch
- Target batch should be representative of Phase III supplies

## Compare in vivo performance in a clinical PK study

- Approach is ideal for BCS Class II and Class IV drugs
- Can be implemented pre- or post-approval

## Use results to set CRS

- If establish IVIVC, use model to set CRS
- If in vitro has no effect on PK, base CRS on a “safe space”



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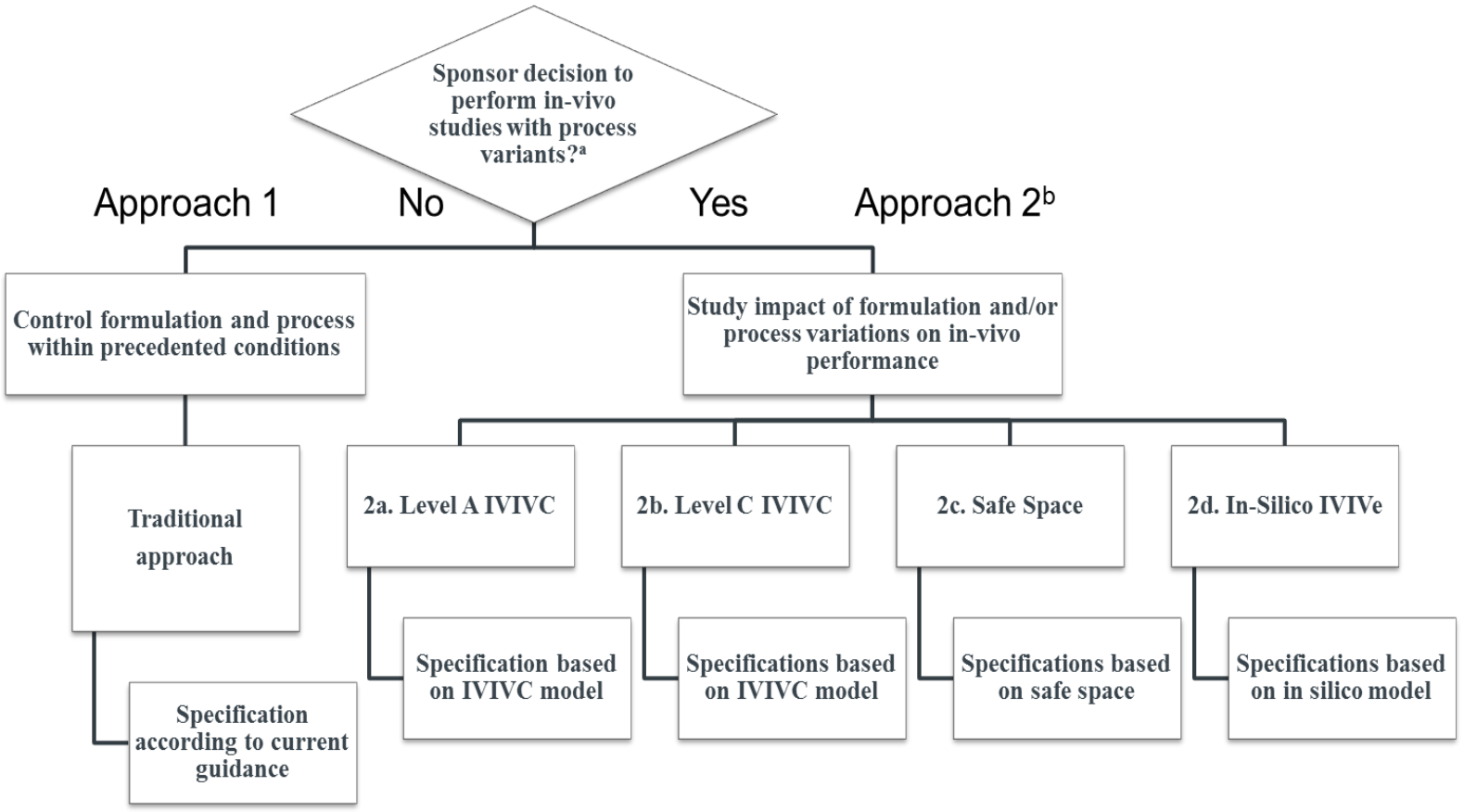
# Review of CRS Road-Map




[a] Sponsor may reevaluate as more data become available and change which approach is most appropriate

[b] When pursuing Approach 2, aspects such as analytical method variability and manufacturing process history will also be taken into account when selecting the final specification within the established window of acceptable clinical performance.

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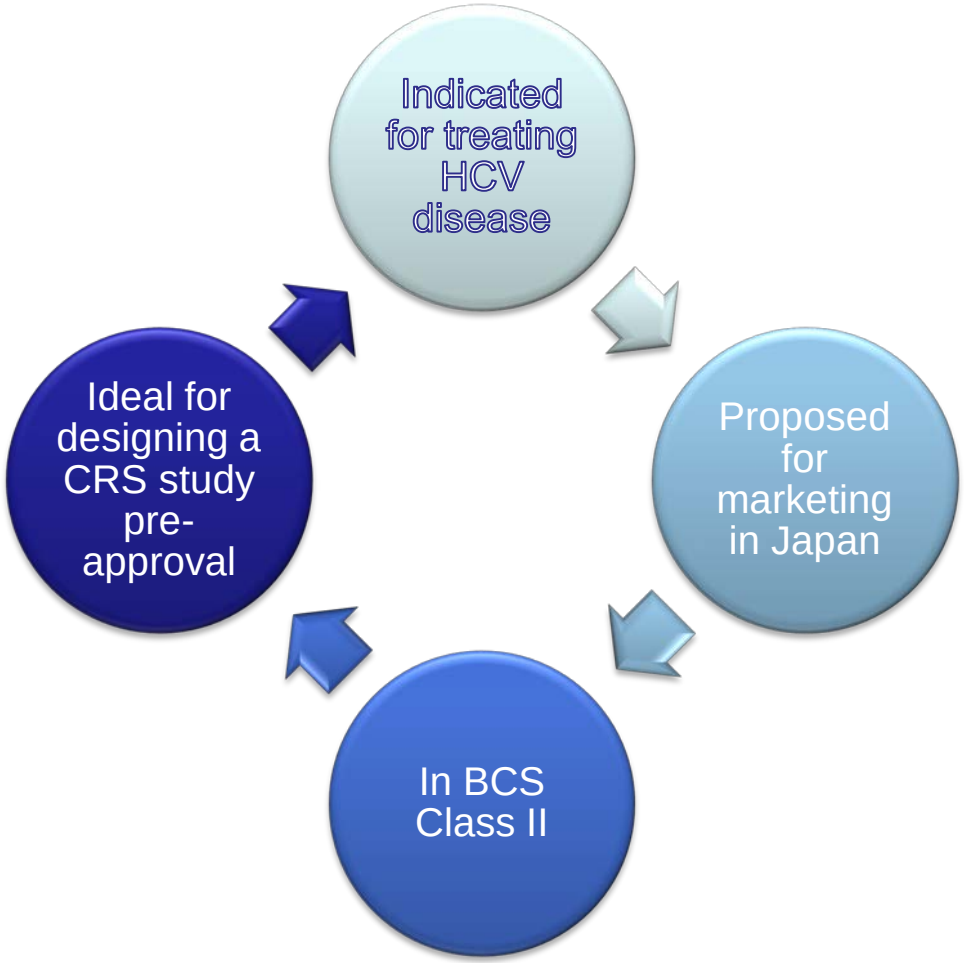
# Use of Approach 2 for establishing CRS for Grazoprevir (GZR) 50-mg Tablets



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# Objectives of an in vivo PK study of GZR tablet formulations

To support a CRS strategy for in vitro dissolution testing of GZR 50-mg tablets by

Manufacturing tablets with different dissolution rates, and

Determining whether in vitro dissolution rate affects in vivo bioavailability (BA)



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# Three batches of Grazoprevir Tablets were manufactured for developing CRS

- ***Target:*** Same manufacturing conditions as the biobatch
- ***Fast:*** Rapid dissolution profile was achieved by compressing the tablets to a sufficiently low hardness that still passed the USP friability test but beyond the hardness level intended for commercial distribution
- ***Slow:*** Slow dissolution profile was achieved by compressing the tablets to a hardness a or near the plateau of the compression profile and to the maximum allowable force of the tooling



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# Methods: GRZ tablets processed to achieve $f_2$ (<50) dissimilar profiles to target

| Formulation (hardness) | $F_2$ similarity to target (20.3 kP) |
|---|---|
| Fast (15.2 kP) | 34 |
| Slow (25.5 kP) | 39 |



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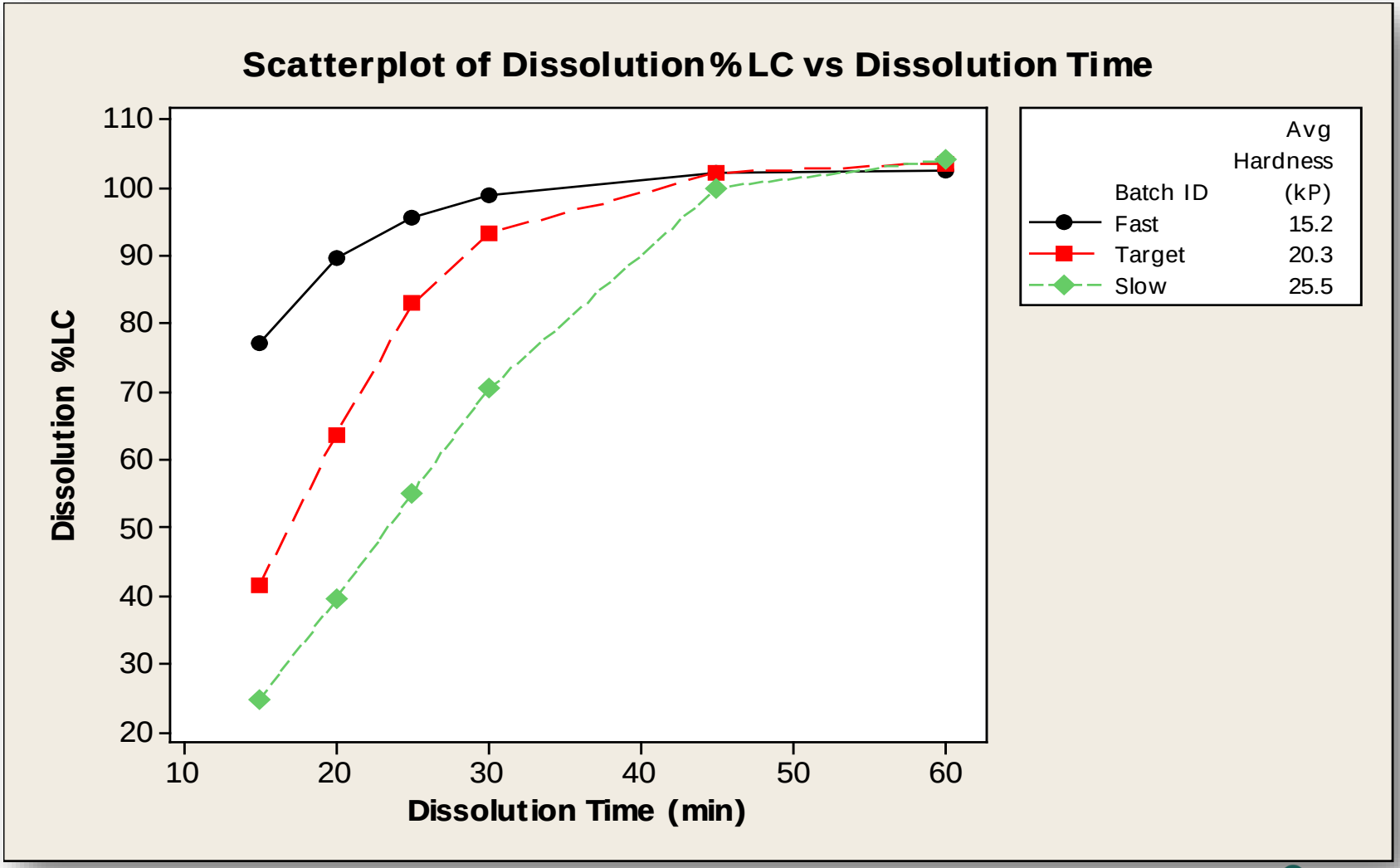
# Methods: dissolution profiles of 3 GZR formulation batches



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# Methods: clinical PK study of GZR formulation batches

| Parameter | Study conduct |
|---|---|
| Design | Single-dose, randomized, open-label, 3-treatment, 3-period, 6-sequence, 7-day washout |
| N | 24 healthy normal subjects |
| Dose | 50 mg tablet |
| Treatments | Fast, Target, Slow Tablets |
| PK metrics | $AUC_{0-t}$, $AUC\infty$, $C_{max}$, $T_{max}$, $t_{1/2}$ |
| Statistics | Ln-transformed PK parameters analyzed by linear mixed-effect model with fixed-effects terms for treatment and period |
| BA comparisons | Geometric mean ratios (GMRs) and 2-sided 90% Confidence Intervals (CIs) calculated for test = fast or slow versus reference = target |

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# Results: GZR in vivo BA from fast and slow tablets was comparable to target

| Test | Parameter | GMR, test/ref | 90% CI, test/ref |
|---|---|---|---|
| Fast Tablet | AUC | 0.99 | 0.92, 1.06 |
| | $C_{max}$ | 0.91 | 0.77, 1.08 |
| Slow Tablet | AUC | 0.98 | 0.91, 1.05 |
| | $C_{max}$ | 0.95 | 0.79, 1.15 |



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# Results: GZR arithmetic mean or median PK parameters for target, fast, slow tablets

| Parameter | Target tablets | | | Fast tablets | | | Slow tablets | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Arith mean | %CV, range | N | Arith mean | %CV, range | N | Arith mean | %CV, range |
| $AUC_{0-t}$, µM*hr | 23 | 0.240 | 46.1 | 23 | 0.232 | 38.7 | 20 | 0.230 | 51.0 |
| AUC∞, µM*hr | 23 | 0.290 | 47.2 | 23 | 0.284 | 59.1 | 20 | 0.285 | 51.9 |
| $C_{max}$, µM | 23 | 0.0175 | 48.3 | 23 | 0.0165 | 56.8 | 20 | 0.0173 | 83.3 |
| $T_{max}$, hr □ | 23 | 2.0 | 1, 6 | 23 | 3.0 | 1, 5 | 20 | 2.5 | 1, 5 |
| t½, hr | 23 | 38.43 | 39.0 | 23 | 40.44 | 41.2 | 20 | 41.56 | 40.5 |
| □Median and range are reported for $T_{max}$ | | | | | | | | | |



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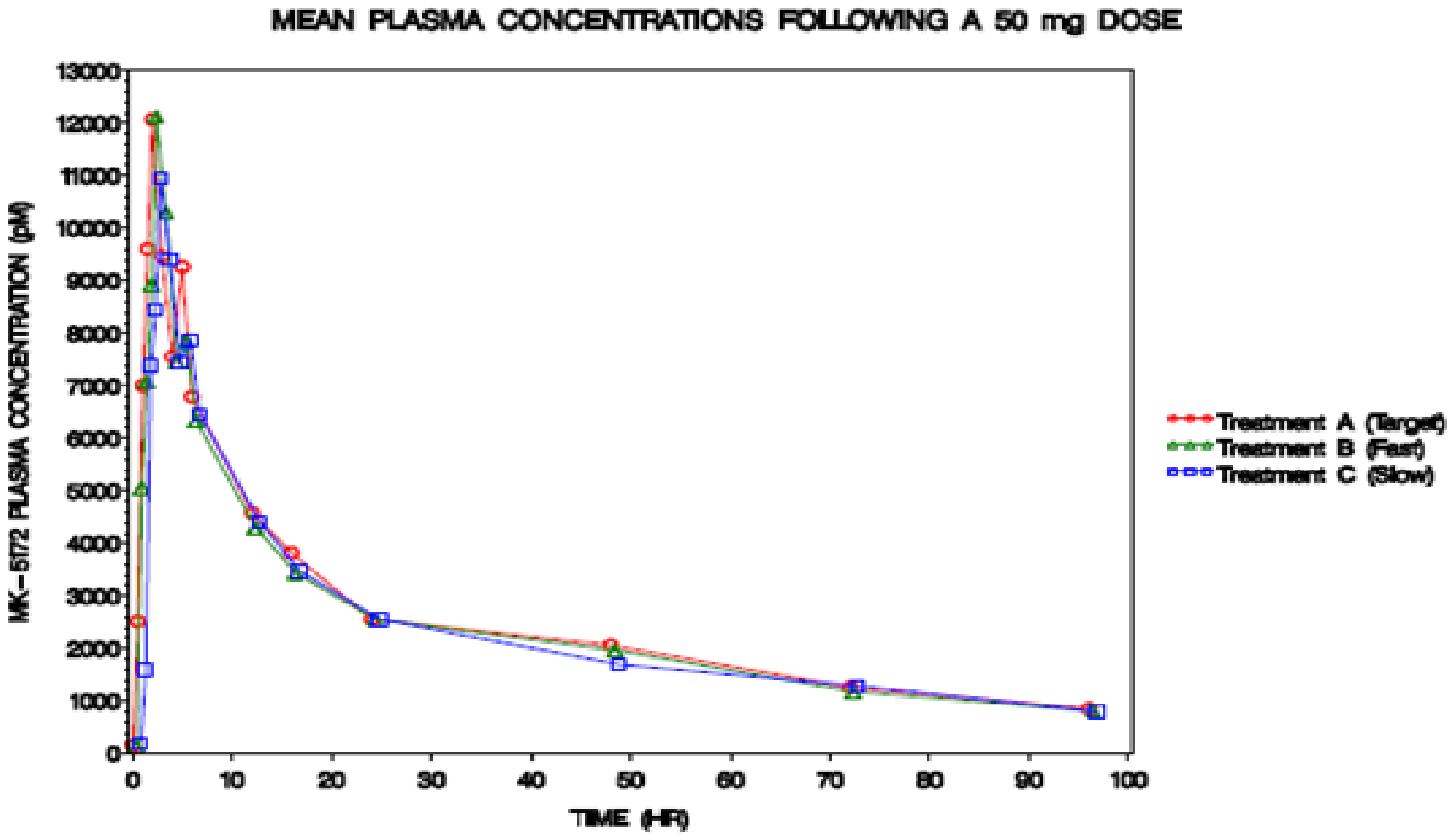
# Results: concentration versus time profiles, for target, slow, fast GZR tablets



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# Conclusions

- In vitro dissolution rate had no effect on GZR oral BA
- The three batches of GZR had comparable PK performance
- AUC and $C_{max}$ showed no apparent trend with dissolution rate



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# Conclusions (cont'd)

- The dissolution safe space identified in the PK study informed a Q value and sampling time
- These specifications were proposed at the time of filing the application for marketing in Japan
- The Japanese MHLW accepted the proposal
- The CRS proposed by Merck as defined by the in vivo safe-space PK study were incorporated into the GZR 50-mg tablet stability and quality controls program



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# Contributors

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