ORIGINAL ARTICLE

Factors to consider in developing individual pharmaceutical product quality risk profiles useful to government procurement agencies

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Received 23 June 2015; accepted 17 September 2015

KEY WORDS

Chinese essential medicine; Product-specific quality risk; Chemical stability; Dissolution; Risk assessment; US recall data

Abstract Governments that procure pharmaceutical products from an Essential Medicine List (EML) bear special responsibility for the quality of these products. In this article we examine the possibility of developing a pharmaceutical product quality risk assessment scheme for use by government procurement officials. We use the Chinese EML as a basis, and US recall data is examined as it is publically available. This is justified as the article is only concerned with inherent product quality risks. After establishing a link between Chinese essential medicines and those available in the US, we examine US recall data to separate product specific recalls. We conclude that, in addition to existing manufacturing based risks, there are two other product specific risks that stand out from all others, degradation and dissolution failure. Methodology for relative product risk for degradation is needed to be developed and further work is required to better understand dissolution failures which largely occur with modified-release solid oral products. We conclude that a product specific quality risk profile would be enhanced by including a risk assessment for degradation for all products, and in the case of solid oral products, dissolution.

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1. Introduction

Pharmaceutical product development and commercial manufacturing are subject to government regulation and oversight in virtually every country. This oversight includes review and approval of new products and site inspection for quality management (CGMP) of pharmaceutical production, packaging, storage, and distribution facilities, in addition to oversight of drug product promotional activities. Regulatory authorities charged with oversight of the pharmaceutical industry have limited resources with which to carry out their mission. As the pharmaceutical industry continues to grow and globalize, the issue of the resources available to regulatory authorities has become more critical. Many regulatory authorities have addressed the resources problem by introducing risk-based inspectional systems in which each facility is rated for relative risk and inspectional resources are preferentially directed to those facilities with high manufacturing risk profiles. For example, the European Medicines Agency (EMA) uses an assessment of Site Complexity, Process Complexity, and Product Complexity to generate an overall risk profile for a given facility.

While these risks based inspectional systems are appropriate where governments act primarily to oversee industry, they say nothing about individual products, only about product classes and/or facility types. For example, parenteral products are high risk because product failure generally has serious health consequences. However, for some governments their responsibilities extend to individual products in addition to the overall state of compliance of the industry. Countries that institute an Essential Medicine List (EML) must source EML products for use in the healthcare system. This raises the question of product quality based risk assessment in determining that individual sources of supply to government of EML products are in compliance and producing product that is fit for use.

At present the only product based risk assessment that has been widely applied is the Biopharmaceutics Classification System (BCS). This system classifies “bioequivalence risk” based on in vitro solubility and in vivo permeability of the drug. As such it is only applicable to immediate-release solid oral dosage forms. While this group represents the largest class of dosage forms, it does not help in assigning product risk factors to other dosage forms or to products in the same BCS class and subclass. The BCS system has been used to classify “bioequivalence risk” for products in WHO's model EML and top oral drugs in countries worldwide.

Not every orally administered drug has been assigned to a BCS class and some BCS class assignments are proposed based on in vitro measures of lipophilicity. These products still need in vivo permeability data to enable a BCS class assignment for regulatory purposes.

China has adopted an EML as part of the reform of the healthcare system that commenced in 2009. The intention of the EML is to reduce inappropriate use of drugs and to improve access to safe and effective drugs for the majority of treatment requirements. The government procures the supply of EML products and provides them to health-care institutions. Since the government makes the product acquisition decisions, the government bears more than the usual responsibility for these products being fit for use. For this reason regulatory authorities in countries where the government procures product for an EML have a special interest in assessing the state of compliance of EML product providers. Obviously such large supply contracts are very attractive to pharmaceutical manufacturing companies and competition to secure this business is fierce. Although government wants the best price, it must also ensure that the product it procures is good as the quality of EML drugs will have a major impact on healthcare outcomes. It would therefore be of interest to the relevant regulatory authority to be able to rank the relative “by product” quality risk profile for each of the products on the EML.

For the rest of this work the Chinese EML will be used as a reference point. However, this work is applicable to all countries where the government maintains an EML and procures EML products for use in the healthcare system.

2. Method

The Chinese government's EML was first promulgated in 2009 as part of a larger healthcare overhaul. The most recent version (2012 edition) of the list contains 317 chemical and biological drug products of a total of 520 where the other products are traditional Chinese medicines (TCMs). Although in theory risk assessment can be applied to TCM products, the focus in this assessment is on the chemical and biological products as many of these products are available in many other regulated markets whereas regulated TCM products are usually only available in China.

In order to find publically available data for analysis, the US FDA's Approved Drug Products with Therapeutic Equivalence Evaluation list, the so-called Orange Book, was used to determine how many of the products on the EML were also approved in the US. On the Chinese EML, chemical and biological products are listed as chemical ingredients by International Nonproprietary Names (INN) for their English names. The FDA Orange Book was searched for the English names of the Chinese Essential Medicines to see if they were also approved by FDA. This search found that two thirds of the products on the EML were also approved in the US.

Once we had determined from the Orange Book that the US market was representative of the Chinese EML products, we turned to sources of publically available information which might be used to judge the performance of individual products on the US market. There are two main sources, Adverse Drug Event (ADE) reporting and Drug Recalls. ADE data is massive but almost all reports do not contain enough data to determine whether an ADE is related to a specific product defect. Many ADEs are due to the specific pharmacological effects of drug ingredients rather than controllable product quality failures. For this reason, we decided to focus on the recall information.

In the United States, drug recalls are almost always voluntary actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request or by FDA order under statutory authority. Drug recalls are classified into three classes determined by the possible health consequences of the particular product failure. Recalls of Foods, Drugs, Biologics and Devices are published weekly on the FDA website. We collected drug recall information from calendar years 2011, 2012 and 2013. An event ID is assigned by FDA to every specific recall event and used for tracking purposes.

A recall event may include more than one recalled product. Where applicable, each recall event was further divided into individual recalled products. For each of the recalled products, a recall reason description of one or two sentences is given following a generalized phrase on the FDA website. Recalled products were examined individually to see if the recall reasons were detailed and clear enough for further analyses to determine the underlying cause of the recall. Four classes of recalled products

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1. The Chinese Essential Medicine List consists of 317 chemical and biological products, 203 traditional Chinese medicines and includes all other herbal slices or flakes not specifically listed.
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from the original list were excluded before further analyses as the reason for recall was not specific to the product but rather general in nature. Compounded products were also excluded as these are not produced by conventional commercial manufacturing and would not or should not be used as sources for EML procurement.

These recalled products were then divided into eight major groups based on more detailed causes as defined from the descriptions given by FDA. Products related to packaging were excluded because it is not viewed as a product specific factor. Recalled products related to CGMP failures, contamination, or temperature abuse were excluded because they are categorized as facility related and general to all drug products. For the recalled products related to visual crystalline particulates due to inspection failures or upon reconstitution, it was not possible to tell if they were due to product formulation problems, so they were obviated from further analyses. We checked the drug types of the remaining chosen recalled products and products not relevant to the Chinese EML were excluded.

This analysis showed that stability caused impurities/degradation/subpotent effects is the most frequent product specific risk. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has released 6 guidelines on stability testing and EU, Japan and US have incorporated these guidelines on stability testing into regulation. However, these guidelines only give very general guidance on carrying out stability indicating tests to get new drug substances, products and dosage forms approved. The recall analyses identified that some products still failed degradation or impurities specifications in routine commercial manufacture although all of them must have passed this kind of testing during application for approval. In order to get the drugs approved, manufacturers carry out so-called accelerated or stressed degradation test which can include severe stress conditions. The purpose is to demonstrate that the analytical methodology can separate degradants that arise from chemical decomposition. For our purpose we need testing under normal or mild conditions which could better ascertain the real life chemical stability characteristics of drug products, in particular to tell whether a drug might degrade or appear stable under mild stress.

To determine if any research exists on stability testing methods under less harsh conditions, 8 drugs were randomly chosen from the EML that had also been recalled in the US from our analysis of the recall data. Using these 8 drugs, a literature search was conducted to see what could be determined about chemical stability and stability testing.

For the products recalled due to "presence of foreign substances" in parenteral solutions, many of these recalls suggested that the particulate matter was related to packaging components, e.g., glass vials, rubber stoppers and silicone lubricant. As it is not possible to tell if product specific factors, such as product formulation, were a causative factor in any of these recalls they were excluded.

Then dissolution is the second most frequent product specific risk. To assess the significance of the dissolution failures, IMS data on volume of product sold in the US market were categorized by dosage form type for the years 2011, 2012, and 2013, the same years as the recall data were analyzed. Some of the IMS data were excluded as it did not identify dosage form, did not specify that it was a drug, or was otherwise not relevant (products simply listed as sodium, magnesium and calcium; botanicals; nutrients; probiotics; drugs for pets; minerals; cosmetics; undefined). There is little difference between the 2011, 2012, and 2013 product volume data, so 2013 is taken as representative for the purpose of determining relative product volume market size for solid oral products.

3. Results

3.1. US market as a valid representative of the Chinese EML products

220 essential medicines out of the Chinese EML, total of 317 (69.4%) were also approved in the US which is taken to mean that product performance of marketed products in the US is representative of the Chinese EML.

3.2. Getting a fit-for-purpose list of recalled products

From calendar year 2011 through 2013, a total of 1070 recall events were collected from the US database. Dividing them into individual recalled products, yielded a total of 4062 products recalled. Individual recalled products in four classes of recalled products were excluded from the data pool because the recall reasons were general to all pharmaceutical products and not ascribable to the individual product. This left 1524 recalled products for further analyses. The number of recalled products and the reasons for which they were excluded are listed in Table 1.

As is shown in Table 2, the remaining recalled products were divided into eight major groups based on more specifically identified causes. 501 recalled products related to packaging, 331 related to CGMP failures, 174 for contamination, 10 for storage temperature failures, 8 related to visual crystalline particulates and 2 reconstitution failures were excluded from the study database. The remaining products were then classified as 274 stability failures and 224 manufacturing failures most probably due to drug product specific problems. These 498 recalled products became the working database for the study and then each was evaluated to determine if there are actual product specific causes for each product in these two major groups. 41 products in product types that are not included in the EML (dental care products, sun screen products, cosmetics such as for acne treatment, animal medicine and first aid kits) were excluded resulting in a final list/ data pool of 457 products for further evaluation.

3.3. Stability-caused impurities/degradation/subpotent as the most frequent and significant product specific risk

The remaining 457 recalled products were reorganized into groups based on the actual underlying cause of the recall as it was determined. As shown in Table 3, 140 recalled products were recalled due to stability failures for impurities/degradation/subpotent reasons, which ranked first among all the recall reasons, approximately 31% of the total number.

Table 4(a) shows the 22 drug products recalled due to stability failures for impurities/degradation/subpotent that are also on the Chinese EML. Eight of these products were chosen at random to conduct a literature search to see if any methodology exists for testing pharmaceutical product stability under normal or less harsh conditions.

The literature search results are summarized in Table 5. The stability indicating methods generally use separative chromatographic methodologies such as HPLC, DAD, TLC, UPLC, LC, HPTLC and HPTL, and are used singly or in combinations to
carry out assay and related substance/degradation product determinations. The corresponding method parameters, such as column type, flow rate, mobile phase, detection wavelength and run time, etc. are optimized. The linearity, ranges, precision, accuracy, selectivity, detection and quantification limit, recovery rates and repeatability are validated. Then accelerated/stressed degradation tests are carried out under acid hydrolysis, alkali hydrolysis, oxidative degradation, dry heat degradation and photolytic degradation conditions. Such tests usually claim that they could resolve the degradants successfully.

However, as summarized in Table 5, these methods apply many and varied chemical stress conditions to carry out accelerated degradation tests. They thus yield diverse and sometimes contradicting results, even though the methodology claims to be validated according to the ICH guidelines. The literature search did not find any literature directed to determining the relative risk of drug substance or drug product degradation. There is a need for methodology that is predictive of chemical sensitivity of drugs and drug products so that a risk rating can be assigned to this failure mode for individual products.

### 3.4 Stability-caused dissolution failures as another frequent and significant product specific risk

Recalls listed as due to “presence of foreign substances” were excluded from the data pool because it is not possible to tell if product specific factors such as product formulation were a causative factor.

Stability related dissolution failures were then the second most frequent product specific risk. Table 4(b) shows the 15 products that were recalled for dissolution failure that are also on the Chinese EML. As shown in Table 6(b), an examination of the 52 products in the data pool that were recalled for dissolution related failures found that this issue is correlated to dosage form and most frequently happened to immediate- or extended-release oral dosage forms.

In order to analyze the significance of dissolution failures, the data from IMS Health on pharmaceutical products sold on the US
Table 2  Reclassification of the remaining 1524 recalls into 8 major groups.

| Group                | No. | Recall reason given on FDA website                                                                 | Group           | No. | Recall reason given on FDA website                                                                 |
|----------------------|-----|-----------------------------------------------------------------------------------------------------|-----------------|-----|--------------------------------------------------------------------------------------------------|
| Packaging/labeling   | 501 | • Label mix-up/misbranded/incorrect labeling/wrong barcode (226)                                    | Stability failures | 274 | • Impurities/degradation (82)                                                                    |
|                      |     | • Presence of foreign substances/particulate matter (81)                                            |                 |     | • Subpotent (67)                                                                                 |
|                      |     | • Lack assurance of sterility (66)                                                                  |                 |     | • Failed dissolution specifications (50)                                                          |
|                      |     | • Adulterated presence of foreign tablets/capsules (41)                                              |                 |     | • Stability data doesn’t support expiration date (24)                                            |
|                      |     | • Defective container/container leakage (33)                                                        |                 |     | • Product lacks stability/failed stability specifications (18)                                    |
|                      |     | • CGMP deviations (28)                                                                              |                 |     | • CGMP deviations (15)                                                                            |
|                      |     | • Miscalibrated/defective delivery system (7)                                                       |                 |     | • Presence of particulate matter (6)                                                              |
|                      |     | • Short fill (6)                                                                                   |                 |     | • Lack assurance of sterility (6)                                                                 |
|                      |     | • Unit dose mispackaging (4)                                                                       |                 |     | • Failed pH specifications (2)                                                                   |
|                      |     | • Superpotent (4)                                                                                  |                 |     | • Microbial contamination (1)                                                                    |
|                      |     | • Does not deliver proper metered dose (2)                                                         |                 |     | • Superpotent (1)                                                                                 |
|                      |     | • Impurities/degradation (2)                                                                       |                 |     | • Failed moisture limit (1)                                                                      |
|                      |     | • Discoloration (1)                                                                                |                 |     | • Failed tablets/capsules specifications (1)                                                      |
| CGMP failures        | 331 | • CGMP deviations (297)                                                                            | Manufacturing failures | 224 | • Presence of foreign substances/particulate matter (73)                                         |
|                      |     | • Lack assurance of sterility (18)                                                                 |                 |     | • Failed tablets/capsules specifications (44)                                                     |
|                      |     | • Impurities/degradation (4)                                                                       |                 |     | • Miscalibrated/defective delivery system (22)                                                    |
|                      |     | • Microbial contamination (3)                                                                      |                 |     | • Failed content uniformity specifications (19)                                                   |
|                      |     | • Subpotent (3)                                                                                    |                 |     | • Superpotent (18)                                                                               |
|                      |     | • Superpotent (2)                                                                                  |                 |     | • Subpotent (12)                                                                                 |
|                      |     | • Using materials not listed in FDA application (2)                                                 |                 |     | • Cross contamination/other products discoloration (11)                                          |
|                      |     | • Failed dissolution specifications (1)                                                            |                 |     | • Presence of precipitate (8)                                                                    |
|                      |     | • Incorrect product formulation (1)                                                                |                 |     | • Resuspension problems (5)                                                                     |
| Contamination        | 174 | • Microbial contamination (93)                                                                     |                 |     | • Crystallization (4)                                                                            |
|                      |     | • Chemical contamination (57)                                                                      |                 |     | • Tablet/capsules imprinted with wrong ID (4)                                                     |
|                      |     | • Lack assurance of sterility (13)                                                                 |                 |     | • Does not deliver proper metered dose (1)                                                        |
|                      |     | • Cross contamination (9)                                                                          |                 |     | • Defective product (1)                                                                          |
|                      |     | • Oversulfated chondroitin sulfate (2)                                                              |                 |     | • Discoloration (1)                                                                               |
|                      |     |                                                                                                    |                 |     | • Lack of assurance of sterility (1)                                                              |
| Temp abuse           | 10  | Temperature abuse (10)                                                                             |                 |     |                                                                                                  |
| Precipitate          | 8   | Crystallization (8)                                                                                |                 |     |                                                                                                  |
| Reconstitution       | 2   | Crystallization (2)                                                                                |                 |     |                                                                                                  |
### Table 3  Determined to be product specific risks.

| Essential recall reasons | Stability | Manufacturing | Laboratory impurity testing failure | Total |
|--------------------------|-----------|---------------|--------------------------------------|-------|
| Impurities/degradation/subpotent | 140       | 72            | 140                                  | 457   |
| Presence of foreign substances | 52       | 52            |                                      |       |
| Dissolution               | 4         | 13            |                                      |       |
| Tablet weight              | 50        | 50            |                                      |       |
| Content uniformity         | 12        | 12            |                                      |       |
| Peel force failure         | 11        | 11            |                                      |       |
| Cross contamination/other products discoloration | 10        | 10            |                                      |       |
| Subpotent                 | 9         | 9             |                                      |       |
| API precipitate            | 8         | 8             |                                      |       |
| Presence of particulate matter | 6       | 3             |                                      |       |
| Failed stability specifications | 8     | 8             |                                      |       |
| Superpotent                | 5         | 5             |                                      |       |
| Adhesion failure           | 4         | 4             |                                      |       |
| CGMP deviations            | 4         | 4             |                                      |       |
| Impurity                   | 4         | 4             |                                      |       |
| Leaking capsules           | 4         | 4             |                                      |       |
| Crystallization            | 4         | 4             |                                      |       |
| Friability                 | 4         | 4             |                                      |       |
| Logo incorrect             | 4         | 4             |                                      |       |
| Particle size              | 4         | 4             |                                      |       |
| AET failure                | 4         | 4             |                                      |       |
| Viscosity                  | 3         | 3             |                                      |       |
| Microbial contamination    | 3         | 3             |                                      |       |
| Packaging                  | 3         | 3             |                                      |       |
| PE failure                 | 2         | 2             |                                      |       |
| Sterility                  | 2         | 2             |                                      |       |
| Failed pH specification    | 2         | 2             |                                      |       |
| Logo illegible             | 4         | 4             |                                      |       |
| Failed unit weight         | 1         | 1             |                                      |       |
| Failed unit weight/osmality| 1         | 1             |                                      |       |
| Ink on tablets             | 1         | 1             |                                      |       |
| Presence of precipitate    | 1         | 1             |                                      |       |
| Resuspension problems      | 1         | 1             |                                      |       |
| Failed Moisture Limit      | 1         | 1             |                                      |       |
| Undecided                  | 1         | 1             |                                      |       |
| Total                      | 239       | 214           | 4                                    | 457   |

### Table 4  Drugs recalled due to stability failure for impurities/degradation/subpotent and stability caused dissolution specification failures that are also on the Chinese EML.

| Drug product | No. | Dosage form          | Drug product | No. | Dosage form          |
|--------------|-----|----------------------|--------------|-----|----------------------|
| Stability failure for impurities/degradation/subpotent (a) | | | | | |
| Levothyroxine sodium | 21 | Tablet | Ciprofloxacin | 1 | Ophthalmic solution |
| Lorazepam | 7 | Tablet/solution | Hydrocortisone | 1 | Otic solution |
| Morphine sulfate | 6 | Extended-release capsule | Atropine sulfate | 1 | Injection |
| Risperidone | 5 | Tablet | Folic acid | 1 | Injection |
| Heparin sodium | 4 | Injection | Fluocinonide | 1 | Ointment |
| Amoxicillin, Clavulanate potassium | 3 | Tablet | Amoxicillin | 1 | Suspension |
| Oxytocin | 3 | Injection | Ethambutel hydrochloride | 1 | Tablet |
| Promethazine hydrochloride | 2 | Solution | Acetaminophen | 1 | Capsule |
| Amlodipine besylate | 2 | Tablet | Bupivacaine hydrochloride | 1 | Injection |
| Codeine phosphate | 1 | Solution | Epinephrine | 1 | Injection |
| Famotidine | 1 | Tablet | Fluorouracil | 1 | Cream |
| Stability caused dissolution specification failures (b) | | | | | |
| Fentanyl | 2 | Transmucosal/transdermal | Phenytin sodium | 1 | Extended-release capsule |
| Metformin hydrochloride | 2 | Tablet | Verapamil hydrochloride | 1 | Extended-release capsule |
| Quetiapine fumarate | 2 | Tablet | Diltiazem hydrochloride | 1 | Extended-release capsule |
| Ibuprofen | 2 | Tablet | Omeprazole | 1 | Delayed-release capsule |
| Sulfamethoxazole, Trimethoprim | 2 | Suspension | Allopurinol | 1 | Tablet |
| Albuterol sulfate | 2 | Extended-release tablet | Isoniazid | 1 | Tablet |
| Carbamazepine | 1 | Tablet | Alprazolam | 1 | Tablet |
| Drug product       | Ref. | Stability indicating method | Stability testing method | Acid hydrolysis                                                                 | Alkali hydrolysis                                                                 | Oxidative degradation                                                                 | Thermal degradation                                                                 | Photolytic degradation |
|-------------------|------|-----------------------------|--------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------|------------------|
| Lorazepam         | 27   | HPLC                        |                          | Stability of extemporaneously prepared lorazepam (from Mylan) suspension (1 mg/mL): 4°C for 91 days (recovery: 96.8%) | Stability of extemporaneously prepared lorazepam (from Mylan) suspension (1 mg/mL): 22°C for 91 days (recovery: 94.2%) | Stability of extemporaneously prepared lorazepam (from Watson) suspension (1 mg/mL): 4°C for 91 days (recovery: 99.4%) | Stability of extemporaneously prepared lorazepam (from Watson) suspension (1 mg/mL): 22°C for 91 days (recovery: 88.9%) | /                |
|                   | 28   | Spectrophotometry           |                          | 2.5 mg lorazepam: 25°C for 15 days, with blister                                | 2.5 mg lorazepam: 25°C for 15 days, without blister                                | /                                                                                     | /                                                                      |                  |
| Levothyroxine sodium | 29   | HPLC                        |                          | Storage condition 1: 60°C, 0% RH, 20.9% O₂                                       | Storage condition 2: 60°C, 75% RH, 20.9% O₂                                       | Stability of pentahydrate Form: 25°C/0% RH, 40°C/75% RH                              | Drug-excipient mixtures: excipients were weighed in 1:1, 1:10, or 1:100 w/w ratios to the drug; 5% moisture content; 60°C 1°C. |                  |
|                   | 30   | HPLC                        |                          | Storage condition 3: 60°C, 0% RH, 0% O₂                                        | Storage condition 4: RT, 0% RH, 20.9% O₂                                        | Stability of dehydrated Form: 25°C/0% RH and 40°C/0% RH                             | Stability with different excipients at different pH: 20% (w/v) aqueous slurries were prepared using 4 different excipients. The pH values were adjusted to 3, 5, 7, 9 and 11 using 0.1 mol/L HCl or 0.1 mol/L NaOH. | /                |
|                   | 31   | HPLC                        |                          | Stability and hygroscopicity: stored in open and closed vials at 40°C and 75% RH for a total of 6 months. | Stability with different excipients: 7 excipients individually mixed with 95% dibasic calcium phosphate; 20% (w/v) aqueous slurries. | Stability with different diluents: manufactured with dibasic calcium phosphate and different basic pH modifiers and acidic pH modifiers | Stability with pH modifiers: manufactured with dibasic calcium phosphate and different basic pH modifiers | /                |
| Risperidone (RSP) | 32   | RP-HPLC                     |                          | 100 mg RSP, 20 mL of 2 mol/L HCl, 45 min at 80°C (20.90% degradation)           | 100 mg RSP, 20 mL of 1 mol/L NaOH, 60 min at 80°C (12.70% degradation)            | 100 mg RSP, 20 mL of 6% H₂O₂, 2 h at 80°C (13.66% degradation)                      | 100 mg RSP, Petri dish placed in the hot air oven for 1 h at 80°C (no gradation) | 100 mg RSP, Petri dish placed in the UV chamber for 1 h (11.88% degradation) |
|                   | 33   | LC                          |                          | 100 mg RSP, 10 mL of 0.1 mol/L HCl, 12 h at RT (26.89% degradation).             | 100 mg RSP, 10 mL of 0.1 mol/L NaOH, 36 h at RT (17.53% degradation).             | 10 mL of 3% H₂O₂, 4 h at RT (68.54% degradation).                                    | 1 g RSP, petri dish kept in oven for 24 h at 80°C (30.09% degradation). | 1 g RSP, petri dish kept in 200 Wh/m² in UV light and 1.2 million lx·h in visible light for 36 h (26.62% degradation). |
| Drug product | Ref. | Stability indicating method | Stability testing method | Acid hydrolysis | Alkali hydrolysis | Oxidative degradation | Thermal degradation | Photolytic degradation |
|--------------|------|-----------------------------|--------------------------|----------------|-----------------|----------------------|---------------------|-----------------------|
| Oxytocin (OT) | 35   | HPLC                        | 0.02 U/mL OT in 1 mol/L HCl and heated at 90 °C for 1 h | 20 h (29.8% degradation) | / | / | / | / |
|              | 36   | HPLC                        | 20 h (97.9% degradation) | A 2 mL of 0.1 mol/L HCl was added to 8 mL of a 10 IU/mL solution of OT. This solution was allowed to stand for 1 h. | 2 mL of 0.1 mol/L NaOH, in a water bath at 90 °C for 30 min (Recovery: 64.32%) | / | / | / |
|              | 37   | HPLC                        | A 1 mL of 0.1 mol/L NaOH was added to 8 mL of a 10 IU/mL solution of OT. This solution was allowed to stand for 1 h. | 2 mL of 0.1 mol/L NaOH, in a water bath at 90 °C for 30 min (Recovery: 64.32%) | / | / | / | / |
| Amlodipine besylate (AML) | 38   | RP-HPLC                     | 1 mol/L HCl, in a water bath at 105 °C for 30 min (Recovery: 64.32%) | 1 mL of 0.1 mol/L HCl, in a water bath at 105 °C for 30 min (Recovery: 64.32%) | / | / | / | / |
|              | 39   | RP-HPLC                     | 0.1 mol/L NaOH, in a water bath at 80 °C for 1 h. (Recovery: 96.36%) | 0.1 mL of 0.1 mol/L NaOH, in a water bath at 80 °C for 1 h. (Recovery: 96.36%) | / | / | / | / |
|              | 40   | HPLC                        | Samples were kept in stability chamber at 40 ± 2 °C and 75 ± 5% relative humidity for 0, 1, 2, 3, 4,5 months | / | / | / | / | / |
|              | 41   | HPLC–DAD                    | 1 mol/L HCl, in a water bath at 90 °C for 10 min (Degradation 30%) | 1 mL of 0.1 mol/L NaOH, in a water bath at 60 °C for 10 min (Degradation 30%) | / | / | / | / |
| Famotidine   | 42   | HPTLC                       | Using 9 mL of AML and 0.5 mL of 5 mol/L HCl and keeping it overnight (0.1 mol/L HCl, negligible; 5 mol/L HCl 48.3% decrease in peak area) | Using 9 mL of AML solutions and 0.5 mL of 5 mol/L NaOH and keeping it overnight (0.1 mol/L NaOH, negligible; 5 mol/L HCl, negligible; 5 mol/L NaOH, 42.1% decrease in peak area) | / | / | / | / |
|              | 43   | RP-HPLC                     | To 0.49 mL of famotidine stock | To 0.49 mL of famotidine stock | / | / | / | / |

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Table 5 (continued)
| Step | Method                  | Conditions                        | Results                                      |
|------|-------------------------|-----------------------------------|----------------------------------------------|
| 34   | RP-HPLC                 | 0.1 mol/L HCl for 24 h at TR     | 0.1 mol/L HCl was added and kept at normal condition for 90 min (1.51% degradation) |
| 35   | RP-HPLC                 | 0.1 mol/L NaOH for 24 h at TR    | 0.1 mol/L NaOH was added and kept at normal conditions for 90 min (1.28% degradation) |
| 36   | HPTLC                   |                                    | The drug (10 mg) was dissolved in 10 mL of 1 mol/L HCl solution and kept for 8 h at RT in dark. (96.02 ± 4.09% Recovery) |
| 37   | HPLC                    | 0.1 mol/L HCl, for 20 min        | /                                            |
| 38   | Fluocinonide LC         | 1 mol/L HCl, 48 h                 | 1 mol/L HCl, 48 h (86.5% of active substances) |
| 39   | Amoxicillin LC          |                                    |                                    |
| 40   | HPLC                    | 0.5 mol/L HCl (6.65% degradation) | /                                            |

*/ not applicable.
market was examined. As is shown in Table 7, for solid oral products, the products excluded from the data pool for the reasons described in Methodology amounted to about 7% of the total product volume for products designated as “ordinary” which means immediate-release, and about 0.25% for products designated as “long-acting” which means modified-release, over the 3 years. Modified-release product volume is about 8.9% of the total for solid oral product volume.

A total of 52 products had been recalled for dissolution failures that occurred during stability studies. Of these 48 were solid oral dosage forms (2 were suspensions, 1 was a transdermal product and 1 was a transmucosal product). Of the 48, 34 were modified-release dosage forms and 14 were immediate-release dosage forms. Based on simple number of products recalled, 71% (34/48) were extended-release dosage forms, however when weighted for 2013 corrected market volume, 96%\(^{(2)}\) of recalls were due to modified-release products. As might be expected, the vast majority of dissolution failures for solid oral products occur with modified-release products where the formulation seeks to exert control over drug release and dissolution.

Of the 14 recalls for dissolution failure of immediate-release solid oral products, 2 were extensions of other recalls making a total of 12 unique failures, as are shown in Table 8. All were tablets with no capsule product among the recalls. Three were brand products and 9 were generics, approximately the same ratio as marketed product volume. Eight of the 12 were high potency tablets (that is with a high API loading) including 4 very high potency products of high solubility drugs, indicating that tablet formulation is important in this type of product. This suggests that API solubility and tablet potency are not predictors of dissolution failure in immediate-release solid oral products. The high proportion of high and very high potency products suggests that formulation and possible changes in formulation on aging may be important predictors of dissolution failure.

The 38 recalls for dissolution failure of modified-release solid oral products contained 31 unique recalls, as shown in Table 9. Of these, 4 were delayed-release products and 27 were extended-release products. Eleven were capsule products and 20 were tablets with 8 brand products and 23 generics, approximately the same ratio as marketed product volume. Nineteen (61.3%) of these products are matrix type extended-release tablets, 8 (25.8%) are polymer coated multiparticulate type extended-release capsules, and of the delayed-release products 2 (6.4%) are tablets and 2 (6.4%) are polymer coated multiparticulate type capsules. There is no apparent pattern to the product type of these failures and the underlying causes of failure need more information than can be gleaned from the recall reason descriptions.

3.5. The generally regarded high risk profiles of sterile preparations are mostly due to compounding failures

Over the period 2011–2013, 1770 products (43.6% of total recalled products) were recalled due to compounding failures. Of all these 1770 recalled products, 850 (48.0%) were due to potential for penicillin cross contamination and 610 (34.5%) were due to lack assurance of sterility. These compounding recalls were fairly evenly spread across the 3 year time period strongly suggesting that compounding remains a significant public health threat.

Of the total 457 recalled products picked out due to potential product specific risks, only 7 were related to sterility. These were two due to lack of assurance of sterility, two because of microbial/mold contamination, and three for preservative efficacy failure. These results may indicate that the intensity of inspectional focus on high risk manufacturing is paying dividends.

3.6. Complex manufacturing processes lead to more problems

Among the 457 products recalled, the 12 peel force failures and 6 adhesion failures (in Table 3) were all related to transdermal delivery systems and summed to 18 which ranked 5th among all the recall reasons following impurities/degradation/subpotent, presence of foreign substances, dissolution and tablet weight. This disproportionate number of transdermal patch failures suggested that complex manufacturing processes did in fact lead to more problems.

4. Discussion

We set out to determine what would be required to establish a system of product specific risk profiles using the Chinese EML as a template for products, restricting our analysis to conventional chemical and biological drugs of commercial manufacture. Due to the reason that the marketed drug product problem information in China is not readily available publically, we turned to the US

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\[^{(2)}\](340.089)/(340.089+140.911) \times 100\% = 96\%.
market where data concerning marketed products is freely available on FDA’s website. First we determined from the Orange Book that the US market was in fact representative of the drug products on the Chinese EML, finding that 69.4% of the EML products were also approved in the US. We then turned to data about drug product market performance choosing to focus on recalls as the most fruitful source of data on marketed product problems. We analyzed recall data from calendar years 2011, 2012 and 2013, the most recent complete sets of recall data. Using the data, we expanded the FDA recalls into number of products recalled. This data was then reduced by excluding from the study product data pool that were not recalled for a product specific failure, products where we could not assign a specific recall reason, and product that were not relevant product types, for example dental products or cosmetics. This enriched the recall data set to those products where a product specific failure was the cause of the recall. Of the enriched data set of 457 product batches, we further analyzed the reason for recall and categorized them as stability related, manufacturing related, or laboratory testing related. Of the 239 product batches that exhibited stability failures, 192 were for two reasons, impurities/degradation/subpotent (140) and dissolution failures (52). The other product related stability failures were for reasons such as particle size (4), AET failure (3), viscosity (3), microbial contamination (2), pH specification failure (2), etc. So we conclude that for product specific risk factors, degradation and dissolution failures stand out well above all other causes which show only a slight signal of failure potential. Therefore methods of assessing the likelihood of degradation and assessing the causes behind the dissolution failures in modified-release products would add significantly to a scheme of product specific risk profiling.

A literature search based on a sample of 8 candidate drugs from the study product data pool did not reveal any methodology that is directed at predicting the relative chemical stability of drug

### Table 7  USA pharmaceutical product volume categorized based on dosage forms, 2013. Source: IMS Health

| Dosage form                  | Total      | After exclusion | Percentage (%) |
|------------------------------|------------|-----------------|----------------|
| Oral solid ordinary          | 202,145,656| 187,683,992     | 92.85%         |
| Oral solid long-acting       | 18,170,650 | 18,122,975      | 99.74%         |
| Oral liquid ordinary         | 20,912,828 | 14,993,005      | 71.69%         |
| Oral liquid long-acting      | 218,016    | 218,016         | 100.00%        |
| Parenteral ordinary          | 2,698,287  | 2,518,343       | 93.33%         |
| Parenteral long-acting       | 193,624    | 193,624         | 100.00%        |
| Rectal systemic              | 50,758     | 50,758          | 100.00%        |
| Nasal systemic               | 98,267     | 92,578          | 94.21%         |
| Other systemic               | 1,608,857  | 1,608,857       | 100.00%        |
| Transdermal                  | 743,270    | 743,270         | 100.00%        |
| Oral topical                 | 2,208,350  | 995,086         | 45.06%         |
| Topical, dermatological      | 51,420,649 | 26,091,630      | 50.74%         |
| Ophthalmic                   | 31,683,267 | 29,108,301      | 91.87%         |
| Otic                         | 1,887,305  | 1,879,664       | 99.60%         |
| Nasal topical                | 14,815,822 | 9,715,348       | 65.57%         |
| Lung administration          | 19,112,246 | 19,082,755      | 99.85%         |
| Vaginal/Intra-uterine        | 468,622    | 465,408         | 99.31%         |
| Non-human use and other      | N/A        | N/A             | N/A            |
| Unknown                      | N/A        | N/A             | N/A            |

N/A, not available.

*Products not identify dosage form, whether it is a drug or otherwise not relevant were excluded.

**Modified-release product volume is about 8.9% of the total for solid oral product volume, b/(b+c).

### Table 8  12 immediate-release solid oral products dissolution failures.

| Drug product                  | Strength (mg) | Recall No.     | Dosage form | Brand or generic | API solubility (mg/mL) | Tablet potency | Ref.   |
|-------------------------------|---------------|----------------|-------------|------------------|------------------------|----------------|--------|
| Valacyclovir hydrochloride    | 1000          | D-164-2011     | Tablet      | Generic          | 174 (very high)        | Very high      | 2      |
| Carbamazepine                | 200           | D-381-2011     | Tablet      | Generic          | 0.01–0.12 (low)        | High           | 2,51–54|
| Allopurinol                  | 300           | D-1280-2011    | Tablet      | Generic          | 0.1–0.5 (high)         | High           | 2,65   |
| Metformin hydrochloride       | 1000          | D-1113-2012    | Tablet      | Generic          | 100–300 (very high)    | Very high      | 2,56   |
| Moexipril hydrochloride       | 7.5           | D-007-2013     | Tablet      | Generic          | <0.1 (low)             | Low            | 57     |
| Quetiapine fumarate           | 25            | D-059-2013     | Tablet      | Generic          | 10 (low)               | Medium         | 2      |
| Isoniazid                    | 300           | D-174-2013     | Tablet      | Generic          | 125 (high)             | High           | 2      |
| Estradiol acetate            | 1.8           | D-851-2012     | Tablet      | Brand            | 0.01 (low)             | Low            | 2      |
| Potassium citrate            | 540           | D-867-2012     | Tablet      | generic          | 1540 (very high)       | High           | 58     |
| Alprazolam                   | 0.5           | D-1197-2012    | Tablet      | Brand            | 0.01–0.11 (low)        | Very low       | 2,59,60|
| Buprofen                     | 200           | D-1216-2012    | Tablet      | Brand            | 0.01–0.05 (low)        | High           | 2,64   |
products. Literature was all directed at the development of stability indicating analytical methods which used forced or stress degradation to produce samples for developing the method. The aim was to generate degradants no matter how severe the conditions applied. What is required for a product specific risk assessment is methodology that can predict how chemically fragile a drug substance and drug product are under conditions that it could reasonably be exposed to normal handling and use. It is possible that the drug products that have shown failures can be compared with those that have not shown failures to aid in developing suitable methodology.

To further assess the risk of dissolution failure the first step is to determine what type of modified-release formulations resulted in failures to see if some formulation types are more prone to this failure mode. We weighted the data from the drug recall information using the products volume data on US market and found that 96% of the dissolutions failures were related to modified-release oral dosage forms.

Analysis of the recall data for manufacturing and/or product class failures supports the idea that complex manufacturing methodologies lead to increased post marketing product problems. The number of recalls of transdermal products linked to failure of adhesives is a strong signal that complex products are more fragile and subject to relatively more on-market failures. Parenteral products yielded many failures for particulate matter, the origin of some ascribed to packaging components but many undefined. There were almost no sterility failures which might suggest that the intensive oversight of sterile product manufacturing has almost eliminated sterility issues in commercially manufactured product in the US. This is a conclusion that is not easily extrapolated to other areas where oversight and inspectional practices may vary considerably.

5. Conclusions

We established that there is a similarity in the set of drugs on the Chinese EML and the set of drugs registered in the US. Using US recall data from a 3 year period, we extracted recalls that are product specific, i.e., the product failure relates to a property of the specific product. We found two causes for product specific recalls over all others, degradation and dissolution failure. In addition, manufacturing complexity, an established risk factor, also results in a relatively high recall rate. Literature search failed to find any methodology for assessing relative risk of product degradation, so such methodology needs to be developed. Further work on dissolution failures targeted at determining the types of product that fail would enhance understanding of this important cause of product failure.

Acknowledgments

Sincere thanks to IMS Health for providing the pharmaceutical products volume data from 2009 to 2013 on the US market. We also thank the support of PKU-Hisun QbD Lab and PKU-Siyao Sterile GMP Lab.

### Table 9: 31 modified-release solid oral products dissolution failures.

| Drug products       | Strength (mg) | Recall no. | Dosage form       | Brand or generic |
|---------------------|---------------|------------|-------------------|------------------|
| Nisoldipine         | 25.5          | D-210-2011 | ER Matrix type    | Tablet Brand     |
|                     | 17            | D-211-2011 | ER Matrix type    | Tablet Brand     |
|                     | 17            | D-1398-2012| ER Matrix type    | Tablet Brand     |
| Alprazolam          | 2             | D-726-2011 | ER Matrix type    | Tablet Brand     |
|                     | 2             | D-1361-2012| ER Matrix type    | Tablet Brand     |
| Doxazosin mesylate  | 4             | D-1186-2012| ER Matrix type    | Tablet Brand     |
| Acamprosate calcium | 333           | D-1332-2012| DR Coated tablet  | Tablet Brand     |
|                     | 333           | D-291-2011 | DR Coated tablet  | Tablet Brand     |
| Potassium citrate   | 10            | D-773-2011 | ER Matrix type    | Tablet Generic   |
|                     | 5             | D-774-2011 | ER Matrix type    | Tablet Generic   |
| Albuterol sulfate   | 4             | D-884-2012 | ER Matrix type    | Tablet Generic   |
|                     | 4             | D-885-2012 | ER Matrix type    | Tablet Brand     |
| Bupropion hydrochloride | 300        | D-1328-2012| ER Matrix type    | Tablet Generic   |
|                     | 150           | D-1329-2012| ER Matrix type    | Tablet Generic   |
|                     | 300           | D-175-2013 | ER Matrix type    | Tablet Generic   |
|                     | 300           | D-248-2013 | ER Matrix type    | Tablet Generic   |
|                     | 300           | D-917-2013 | ER Matrix type    | Tablet Generic   |
|                     | 300           | D-855-2013 | ER Matrix type    | Tablet Generic   |
| Venlafaxine hydrochloride | 225      | D-1067-2013| ER Matrix type    | Tablet Generic   |
| Budesonide          | 3             | D-452-2013 | DR Polymer coated multiparticulate type | Capsule Generic   |
| Diltiazem hydrochloride | 360      | D-145-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
| Dextroamphetamine sulfate | 5         | D-171-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
|                     | 5             | D-172-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
|                     | 5             | D-173-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
| Methylphenidate hydrochloride | 20         | D-847-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
|                     | 30            | D-848-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
|                     | 40            | D-849-2013 | ER Polymer coated multiparticulate type | Capsule Generic   |
| Phenytoin sodium    | 100           | D- 66,014-001| ER Matrix type | Capsule Generic   |
| Verapamil hydrochloride | 180        | D-1116-2012| ER Polymer coated multiparticulate type | Capsule Generic   |
| Nifedipine          | 60            | D-449-2011 | ER Matrix type    | Tablet Generic   |
| Omeprazole          | 20            | D-009-2014 | DR Polymer coated multiparticulate type | Capsule Generic   |
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